

**AN ANALYSIS OF PROGNOSTIC, ENDOSCOPIC AND
TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SALVAGE
SHUNTING FACTORS INFLUENCING REBLEEDING AND DEATH
IN PORTAL HYPERTENSIVE PATIENTS WITH LIFE-
THREATENING VARICEAL BLEEDING**

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ABSTRACT

The management of refractory variceal bleeding constitutes one of the most difficult and complex life-threatening emergencies in surgical gastroenterology. Over the past four decades the treatment of variceal bleeding has evolved and improved with the consequence that mortality has decreased substantially to current rates of 15 to 20% at six weeks after the index variceal bleed. Significant advances have included new vasoactive drug combinations, improved endoscopic techniques with refinements in variceal ligation equipment using multi-band devices and the selective use of radiologically inserted transjugular intrahepatic portosystemic shunts (TIPS). While medical and endoscopic technical advances in treatment have reduced overall mortality, uncontrolled, recurrent and persistent refractory bleeding from recalcitrant varices and the consequences of progressive liver failure remain the leading causes of early death in portal hypertensive patients.

Despite progress in overall management, specific limitations in treatment and deficiencies in existing knowledge remain and represent areas where further research, analysis and clinical improvements are necessary. These investigations relate to the need for more accurate prognostic scoring in complex variceal bleeding, the lack of comparative efficacy outcome data for injection sclerotherapy and endoscopic ligation when treating active variceal bleeding, the long-term limitations of endoscopic ligation in eradicating varices, preventing variceal recurrence and rebleeding and crucially, improving the safety profile of variceal interventional endoscopy. In addition, there is a dearth of clinical and laboratory risk factors predicting in-hospital mortality and intermediate and long-term survival after salvage transjugular intrahepatic portosystemic shunting when used as a rescue method in patients who have endoscopically uncontrolled variceal bleeding.

These major clinical issues and deficiencies are addressed in this thesis which comprises a literature review and six clinical investigations.

A. The literature review component focusses on three main variceal bleeding themes.

These include:

1. Prognostic predictors of mortality in acute variceal bleeding including a comparative evaluation of existing Child-Pugh and MELD scores, the pathophysiology of variceal bleeding and the implications of altered oesophageal venous anatomy on endoscopic treatment of varices.
2. Endoscopic methods used in acute variceal bleeding including a historical perspective and the evolution of endoscopic variceal intervention, injection sclerotherapy and variceal ligation endoscopic techniques, and comparative studies evaluating the relative efficacies of endoscopic variceal intervention in the treatment of acute variceal bleeding and an analysis of oesophageal, regional and systemic adverse events after endoscopic variceal ligation for oesophageal varices.
3. A review of salvage transjugular intrahepatic portosystemic shunts (sTIPS) for uncontrolled oesophageal variceal bleeding, including a historical background, the evolution and development of sTIPS, indications and insertion technique, contra-indications and complications of TIPS insertion, and the results of sTIPS.

B. An assessment of the major unresolved clinical variceal bleeding-related issues indicated above are addressed in six clinical investigations which constitute the research component of this thesis.

1. Improvement of prognostic scoring: While the ideal prognostic score should be accurate, objective, functional on a continuous scale, validated worldwide, be able to guide treatment and easy to calculate, the currently available Child-Pugh and MELD scores

are flawed when used to assess severity of liver dysfunction and predict patient risk for in-hospital rebleeding and death. Neither score is ideal, and both have intrinsic limitations related to their development and inclusion of biochemical and clinical components. Study 1 in this thesis addresses these issues and proposes and validates a new 4-category recalibrated C-P score.

2. Endoscopic control of acute variceal bleeding. Immediate and durable endoscopic control of acute variceal bleeding is the objective of intervention and is crucial to survival. Study 2 in this thesis evaluated the relative efficacies of endoscopic ligation and injection sclerotherapy in arresting acute variceal bleeding in a matched controlled cohort study.
3. Determining the benefits and limitations of endoscopic banding in variceal bleeding. Although the utility of endoscopic therapy in controlling acute variceal bleeding has been widely reported, the long-term efficacy and safety of banding in a high-risk cohort of patients with active variceal bleeding is poorly defined and documented. Study 3 in this thesis assessed acute bleeding control, rebleeding, variceal eradication and recurrence after endoscopic banding in a prospective longitudinal observational study.
4. Identifying factors influencing in-hospital mortality for salvage TIPS in cirrhotic patients with recalcitrant variceal bleeding after failed endoscopic intervention.

TIPS is now established as the preferred rescue or salvage procedure for patients who have either uncontrolled or severe recurrent variceal bleeding unresponsive to medical and endoscopic treatment. Study 4 in this thesis investigated the outcome of sTIPS in patients who had life-threatening variceal bleeding resistant to standard treatments in order to identify clinical and laboratory risk factors that would predict in-hospital death during the index admission.

5. Intermediate and long-term outcomes after salvage TIPS for uncontrolled variceal bleeding. The reported long-term survival data after salvage TIPS placement are widely divergent due to differing inclusion criteria, population selection, timing of TIPS, severity of underlying liver disease and the experience of the faculty and the facility in the management of critically ill patients with end-stage liver disease. Accurate patient selection is an important consideration in the TIPS procedure. Study 5 in this thesis assessed intermediate and long-term survival after sTIPS to identify possible prognostic factors influencing prolonged survival.
6. Development of a novel CABIN prognostic score to predict in-hospital mortality after salvage TIPS and testing the efficacy of the new score against other established prognostic models. Several prognostic and risk scores have been developed to identify patients at risk for a poor clinical outcome after sTIPS insertion. Although these individual models have been correlated with TIPS outcome, their relative performances have not been assessed in a detailed analysis. Study 6 in this thesis assessed the accuracy of a newly developed and novel CABIN score and compared the CABIN score to existing established risk scores to predict in-hospital mortality after sTIPS placement.

The studies reported in this thesis are original, relevant and important and make a substantial contribution to the existing body of knowledge. As the six studies are clinically based and involve portal hypertensive patients with acute and life-threatening variceal bleeding which has a substantial mortality rate, any improvement in outcome will have a beneficial impact on existing patient care. The newly proposed 4-category recalibrated Child-Pugh score is easy to calculate at the bedside and can assist in guiding treatment and predicting the risk of in-hospital variceal rebleeding and death. In the matched controlled cohort study, endoscopic ligation has been shown to be the optimal method of controlling acute variceal bleeding, while

the long-term study defined the benefits and exposed the limitations of variceal ligation. The three salvage TIPS studies identified factors influencing in-hospital mortality in cirrhotic patients with recalcitrant variceal bleeding after failed endoscopic intervention, as well as intermediate and long-term outcomes and predictive risk factors. The development of a novel CABIN prognostic score designed to predict in-hospital mortality after salvage TIPS was shown to be an improvement over other established prognostic models and should be beneficial in future accurate patient selection for salvage TIPS.

In making recommendations for future research, new prognostic scoring systems incorporating artificial intelligence, machine learning algorithms and neural network models will need to be assessed and included as part of essential variceal bleeding clinical algorithms. Because published results are variable and conflicting with small sample sizes, referral bias, dissimilar study endpoints, differences in patient selection, methods and techniques of endoscopic intervention and the precise definition of rebleeding, specific and uniformly defined study endpoints are required. Unexplored research areas of quality of life and cost-effective issues are increasingly important concepts to consider in future trial design. As endoscopic failure to control variceal bleeding is encountered by even the most experienced endoscopists, the clear definition and early recognition of endoscopic failures and the implementation of local control methods including self-expanding oesophageal metal stents and improved quality PTFE-coated TIPS stenting are anticipated to improve bleeding control and survival in this high-risk cohort.

Several important and unresolved issues relating to the specific role of sTIPS in the management of patients with actively bleeding uncontrolled oesophageal varices remain. Published results are variable and conflicting and an important future goal will be to define and

identify the specific target population who would benefit or not from sTIPS. Another objective which requires further investigative research is accurately identifying stable but recurrent variceal bleeders who would benefit from pre-emptive or early-TIPS.

The literature review in this thesis has shown considerable variation in the quality of randomised trials evaluated, especially regarding generation of allocation sequences and allocation concealment adversely affecting patient selection, assessment and attrition bias. Despite the number of concluded studies, there remain unresolved questions. Understanding the problems inherent in the design, execution and interpretation of clinical trials in portal hypertension is critical to eliminating quality variations by addressing these deficiencies and answering these questions when planning future studies. In addition, the statistical power of trials remains a major problem in portal hypertension trials, where modest survival advantages are unlikely to be detected unless large-scale, multicentre randomised trials are undertaken incorporating sufficient patient numbers.

A further limitation is that only a modest number of published trials have performed blinded outcome assessment. The implications for future research into variceal bleeding are that adequately powered, meticulously conducted, properly reported multicentre trials need to continue to address unresolved issues. As patient recruitment becomes an increasing impediment, future studies require internationally accepted standard protocols to facilitate aggregated analyses and future meta-analyses. In addition, the increasing demand for medical fiscal discipline and logistic efficiency require the issue of cost to be adequately addressed in prospective studies, as illustrated by concerns raised at the recent Baveno Consensus Conferences on future improvements and research requirements in portal hypertension (de Franchis, 2024).

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“It is better to drink from the fountain than from the water jug”

Leonardo da Vinci, Italian polymath 1503

“Why think? Why not do the experiment?”

John Hunter, surgeon and anatomist 1783

This MD thesis is a natural extension of my 2009 MSc thesis that evaluated the role and efficacy of endoscopic injection sclerotherapy in the treatment of bleeding oesophageal varices in patients with alcohol-induced cirrhosis. The specific focus of the MSc thesis was the endoscopic control of acute variceal bleeding, the prevention of recurrent bleeding and the evaluation of prognostic factors which could predict early variceal rebleeding and death. These three clinical studies were subsequently published in *Annals of Surgery*, *Archives of Surgery* and the *World Journal of Surgery*.

Several fundamental and unresolved questions related to variceal bleeding remained unanswered after this prior work and form the basis of the current thesis. These included strategies to improve clinical prognostic scoring by eliminating intrinsic flaws in the existing Child-Pugh score, the accurate comparison of the relative efficacies of endoscopic variceal ligation versus injection sclerotherapy in achieving durable bleeding control in patients with active variceal bleeding, and an assessment of the technical limitations of endoscopic ligation in achieving variceal eradication and eliminating bleeding. In addition, the selection criteria of patients likely to benefit from the placement of a salvage transjugular intrahepatic portosystemic shunt (sTIPS), and the identification of clinical and laboratory risk factors and proposed prognostic models of mortality after sTIPS required detailed analysis and suggestions for improvement.

These important unanswered questions were examined in six novel clinical studies that assessed:

- (i) The development of a new recalibrated four-category Child-Pugh score which was compared to the original Child-Pugh and Model for End-stage Liver Disease (MELD) scores in predicting in-hospital mortality in decompensated alcoholic cirrhotic patients with acute variceal bleeding,
- (ii) A comparative cohort analysis of the haemostatic efficacy of endoscopic variceal ligation versus injection sclerotherapy in decompensated cirrhotic patients with actively bleeding oesophageal varices,
- (iii) A prospective clinical analysis defining the advantages and limitations of endoscopic variceal ligation in controlling acute variceal bleeding and achieving complete variceal eradication, thereby preventing variceal recurrence and rebleeding,
- (iv) The analysis of factors influencing in-hospital mortality after sTIPS placement in cirrhotic patients with recalcitrant variceal bleeding following failed endoscopic intervention,
- (v) The intermediate and long-term outcomes after sTIPS for uncontrolled variceal bleeding in a Strengthening the Reporting of Observational Studies Epidemiology (STROBE) compliant observational study, and
- (vi) The development of a novel CABIN prognostic score which was compared to other existing prognostic models in predicting in-hospital mortality after sTIPS.

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**THE DATA IN THE LITERATURE REVIEW OF THIS THESIS ARE BASED
IN PART ON THE FOLLOWING PUBLICATIONS BY THE AUTHOR:**

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Abbreviations used in this thesis

ACLD	Advanced chronic liver disease
AE	Adverse event
AIMS65	Albumin <3.0 mg/dL, INR >1.5, altered Mental status, Systolic blood pressure $\leq$ 90 mm Hg, age >65 years
APACHE II	Acute Physiology And Chronic Health Evaluation II score
AVB	Acute variceal bleeding
BOV	Bleeding oesophageal varices
BCS	Budd–Chiari syndrome
CABIN	Creatinine, Albumin, Bilirubin, INR, Na.
CTP	Child–Turcotte–Pugh classification
C-P	Child–Pugh classification
DSRS	Distal splenorenal shunt
ET	Endoscopic treatment
EVL	Endoscopic variceal ligation
FRS	Full Rockall score
GAVE	Gastric antral vascular ectasia
GOV	Gastro-oesophageal varices
GBS	Glasgow-Blatchford score
HE	Hepatic encephalopathy
HVPG	Hepatic venous pressure gradient
HRS	Hepatorenal syndrome
HBV	Hepatitis B virus
HVC	Hepatitis C virus
HCC	Hepatocellular carcinoma
IHPCS	Intrahepatic portocaval shunt
IST	Injection sclerotherapy
IGV	Isolated gastric varices
MELD	Model for End-stage Liver Disease
NSBB	Nonselective beta-blocker
OR	Odds ratio
OV	Oesophageal varices
PTFE	Polytetrafluoroethylene

PH	Portal hypertension
PV	Portal vein
PVT	Portal vein thrombosis
PCG	Portocaval gradient
RCT	Randomised controlled trial
SEMS	Self-expanding metal stent
SOFA	Sequential organ failure assessment score
SOS	Sinusoidal obstruction syndrome
STROBE	Strengthening the Reporting of Observational Studies Epidemiology
TS	Total shunt
sTIPS	Salvage transjugular intrahepatic portosystemic shunt
TIPS	Transjugular intrahepatic portosystemic shunt
UNOS	United Network for Organ Sharing

CHAPTER 1

INTRODUCTION

Cirrhosis is the leading cause of portal hypertension and oesophageal varices in the developed world which imposes a substantial global health burden with significant health care costs that have increased inexorably worldwide since 1990, due in part to exponential population growth and ageing (Devarbhavi, 2023). Outcomes and survival in patients with portal hypertension due to cirrhosis depend on the degree of liver decompensation, the presence of complications such as variceal bleeding, ascites or spontaneous bacterial peritonitis as well as the efficacy of the applied therapy (Sonderup, 2024). Progressive liver decompensation occurs more rapidly in patients with alcoholic cirrhosis than in those with cirrhosis due to viral hepatitis B or C and is aggravated by superadded alcoholic hepatitis. Once decompensation occurs in cirrhotic patients, mortality, without organ replacement, is as high as 85% over 5 years (Ferrarese, 2023). The importance of portal hypertension is defined by the frequency and severity of its complications including variceal bleeding, spontaneous bacterial peritonitis, and hepatorenal syndrome, which represent the leading causes of death and of liver transplantation in patients with cirrhosis (Ginès, 2021).

The natural history of cirrhosis is arbitrarily divided into a preclinical phase and a subsequent clinical phase (de Franchis, 2022). The preclinical phase is usually prolonged over several years. However, once clinical events such as the onset of ascites, encephalopathy and variceal bleeding occur, the remaining course of the disease is shorter and often fatal unless effective treatment is instituted (D'Amico, 2023). The development and progression of portal hypertension is a crucial determinant in the transition from the preclinical to the clinical phase of cirrhosis and is a contributing mechanism leading to the

onset of clinical ascites and hepatic encephalopathy and is a direct cause of variceal bleeding and bleeding-related death (Kaplan, 2023).

Portal hypertension due to cirrhosis is the pathophysiological consequence of an increase in both intrahepatic portal vascular resistance and portal venous inflow. Intrahepatic portal vascular resistance is caused by increased sinusoidal tone and intrinsic distortion of liver lobular architecture due to fibrosis interspersed with regenerative nodules, while greater portal venous inflow results from a combination of a hyperdynamic circulation and increased plasma volume (Jagdish, 2023). In response to increased portal venous pressure, a prominent portosystemic collateral circulation develops with progressive dilatation of pre-existing and vestigial venous channels and vessel neoformation. Variceal bleeding is the final stage in the sequence of events initiated by the onset and progressive increase in portal venous pressure in patients with clinically significant portal hypertension (Jothimani, 2023). These haemodynamic consequences result in the development and subsequent enlargement of oesophageal and gastric varices until, finally, beyond a critical point when intravascular venous pressure exceeds the elastic capacity of the vessel wall, the varix ruptures and acute bleeding ensues at several possible sites, the most significant of which is in the lower oesophagus (Ginès, 2021).

Oesophageal varices which are present in 50–60% of patients with compensated cirrhosis at the time of diagnosis, and in up to 85% of decompensated cirrhotic patients, have become an increasingly important public health issue and are a principal cause of death in the portal hypertensive population (Diaz-Soto, 2022; Abrales, 2023). The onset of acute variceal bleeding is the most serious and life-threatening complication of portal hypertension which has profound implications on the natural history and prognosis of patients with compensated cirrhosis (Magaz, 2020). Up to 30% of initial bleeding episodes

in patients with hepatic decompensation are fatal, while the 20% of portal hypertensive patients who rebleed within six weeks of the index variceal bleed are at increased risk of death (de Franchis, 2022). Endoscopic intervention is established as the emergency treatment of choice to control active variceal bleeding, but ultimately as many as 60% of patients will rebleed despite initial control unless effective follow-up treatment is provided (Garcia-Tsao, 2016). Secondary prophylaxis to prevent further variceal bleeding is thus crucial and a clinical imperative. There is universal consensus that patients surviving an initial bleeding episode should undergo long-term endoscopic variceal eradication, followed by entry into a surveillance programme (Tripathi, 2015).

Three inter-related and intersecting areas of information and intervention in portal hypertension are crucial for the optimal treatment and best possible outcome for patients with variceal bleeding. Knowledge and understanding of the natural history of portal hypertension in the context of compensated and decompensated cirrhosis is fundamental to the important clinical decisions that underpin the management of patients who present with acute variceal bleeding (Tranah, 2023). Improving survival also relies on an appreciation and awareness of the substantial portal hypertensive changes that occur in portal venous anatomy and functional hepatic reserve and which influence outcome as well as the limitations of targeted endoscopic intervention (Krige, 2023). The single most critical factor influencing outcome, however, is the ability of the endoscopist to provide effective, rapid and durable control of variceal bleeding when required to intervene. Failure to effectively control acute bleeding and the consequences of refractory bleeding have profoundly negative outcomes and substantially increase mortality rates (Balcar, 2024). The successful integration and application of these three elements to effectively achieve variceal bleeding control is the underlying thrust of this thesis.

The treatment of variceal bleeding has evolved and improved considerably over the past four decades (Zanetto, 2019; de Franchis, 2022). Mortality has decreased substantially, from an initial 42% reported in the seminal Graham and Smith study in 1981 to current overall mortality rates ranging from 15 to 20% at six weeks after the index variceal bleed (Abrales, 2023). In the Graham and Smith study, which has become a milestone reference in the history and treatment of portal hypertension, 60% of early deaths and 40% of late deaths were attributable to either the index bleed or to refractory variceal bleeding (Graham, 1981). Approximately one-third of patients experienced rebleeding within 6 weeks, and one-third of survivors had later variceal bleeds. Most deaths associated with variceal bleeding occurred soon after the initial bleeding episode. Graham and Smith demonstrated that statistically significantly different survival curves could be obtained from the same population by changing the zero time for calculating survival (Graham, 1981). For example, a 1-yr survival rate of 34% for all treated patients could be increased to 52% by eliminating from consideration those who failed to survive 2 weeks. The long-term survival of those surviving longer than 2 weeks was not statistically significantly different from published series of unselected cirrhotic patients without bleeding. Graham and Smith stressed that any substantial improvement in long-term survival must improve survival during the early period, immediately after hospital admission and thus control of the index bleed and prevention of subsequent variceal bleeding is the *sine qua non* of endoscopic intervention (Graham, 1981).

Significant advances have since included new vasoactive drug combinations with optimised dosage and duration of administration of intravenous *terlipressin* or *octreotide* during acute bleeding, and subsequent β -blockade with propranolol or carvedilol (de Franchis, 2022). In addition, improved endoscopic techniques and refinements of variceal ligation equipment

using multi-band devices and transparent ligator caps have improved luminal vision (Baron, 2009; Krige, 2019). Further developments have included the pre-emptive and selective use of radiologically inserted TIPS (Garcia-Pagan, 2020), recognition of the diminishing and now infrequent need for shunt surgery (Rosemurgy, 2016) and the exponentially increasing role of liver transplantation in cirrhotic patients, who progress with further hepatic decompensation despite endoscopic and medical therapy (Jagdish, 2023).

There is general consensus that the management of patients with portal hypertension must be individualized. The ideal treatment of portal hypertension necessary to prevent the consequences and the complications of variceal bleeding should be universally accessible, effective, safe, easy to administer and inexpensive. As no such treatment currently exists, the surgeon or gastroenterologist is obliged to select the most appropriate intervention from a list of currently available therapeutic options, none of which is universally effective or applicable to all patients (Krige, 2024).

The rational treatment of oesophageal varices therefore depends on a clear understanding and awareness of the risks of rebleeding and the response to each specific intervention. The selection of the correct and appropriate intervention is critical and requires a comprehensive understanding of the relative efficacy and safety of each treatment compared to other competing options (Krige, 2023). In addition, the use of the chosen intervention necessitates detailed knowledge of the criteria underpinning the correct selection of patients for treatment to maximize the therapeutic benefits of the appropriate choice while minimising the side effects of the treatment. The optimal management of bleeding oesophageal varices therefore requires a full appreciation of portal, gastric and oesophageal venous collateral anatomy, the pathogenesis and haemodynamic

consequences of variceal bleeding and the utility of each available therapy at specific stages in the natural history of portal hypertension (Jothimani, 2023).

The spectrum of prerequisite interventions necessary to control variceal bleeding and achieve effective and successful treatment of the severe and potentially life-threatening complications of portal hypertension are invasive, complex and may require advanced skills available only in referral centres, preferably with an interest and an established track record and expertise in managing portal hypertension (Treiber, 2005). No single intervention is appropriate or applicable to all patients and knowledge of the alternatives allows the well-informed surgeon, gastroenterologist or intensivist to choose the correct therapy for each clinical situation. A co-ordinated and integrated multidisciplinary team approach incorporating all the clinical specialities is essential as each of these therapies may be required at different stages in different patients (Krige, 2023).

Endoscopic treatment occupies a pivotal role in the management of patients with bleeding oesophageal varices and is established as the key first-line intervention, both during the acute event and subsequently to eradicate residual varices and thus prevent recurrent bleeding (Krige, 2005). Endoscopy provides direct visualization of varices and is the cornerstone of the diagnostic approach to confirm the presence of variceal haemorrhage (Kapoor, 2015). After control of the index bleed, there is a significant risk of rebleeding which is greatest during the first few days after the initial variceal bleed (Sharara, 2001). Survival after a major variceal bleed in a patient with minimal hepatic reserve depends largely on the rapidity and efficacy of the initial control of bleeding, as well as the presence and severity of underlying liver disease and the ability to support and avoid deterioration of the existing hepatic functional reserve (Krige, 2009b). Early rebleeding has been shown to

be a strong predictor of mortality and recurrent variceal bleeding substantially increases the risk of complications which further contribute to increasing mortality (Krige, 2009b), emphasizing that rapid and sustained control of variceal bleeding remains the principal imperative of endoscopic intervention (Triantos, 2006). Several important clinical considerations influence the choice of therapy as well as the prognosis in individual patients (Krige, 2009). These include the natural history of the disease causing the portal hypertension, the anatomic location of the bleeding varices, residual hepatic function, the presence of associated systemic disease, continuing drug or alcohol abuse, patency of major splanchnic veins and the response to each specific treatment (Henderson, 1998; Krige, 2024).

The most important determinants of an adverse outcome in variceal bleeding are the stage of hepatic decompensation in cirrhotic patients, hypovolaemic shock, HVPG >20 mmHg, active variceal bleeding at endoscopy despite vasoactive drug therapy and the presence of associated organ failure, especially renal dysfunction (Abraldes, 2023). Thus, the management of patients with variceal bleeding must include both treatment and control of active bleeding and the prevention of rebleeding, hepatic encephalopathy, renal failure and infection, in particular secondary bacterial peritonitis (Satapathy, 2014).

Although medical and endoscopic technical advances in treatment have reduced overall patient mortality (Garcia-Tsao, 2023; Abraldes, 2023), uncontrolled, recurrent and persistent refractory bleeding from recalcitrant varices and the consequences of progressive liver failure remain the commonest causes of early death in portal hypertensive patients (de Franchis, 2022). Despite receiving “gold-standard” pharmacological and endoscopic treatment, failure to control the index bleeding episode or early rebleeding

occurs in 15 to 20% of patients with acute variceal bleeding within the initial 5 days, and although survival has improved in the past three decades, approximately 80% of these high-risk patients will have variceal bleeding-related deaths, despite use of rescue therapies such as (TIPS) (Hernandez-Gea, 2017; Zhao 2023; Zhu, 2023). Variceal bleeding refractory to standard endoscopic and medical therapy occurs in up to 20% of acute variceal bleeding episodes and is associated with increased mortality which rises exponentially when liver reserve is limited and bleeding is persistent (Diaz-Soto, 2022).

Up to 20% of acute variceal bleeding episodes recur after endoscopic intervention of which a proportion are refractory to standard therapy and are associated with a high mortality. Refractory variceal bleeding presents as either (i) profuse bleeding that precludes clear visualization and thus endoscopic therapy, (ii) bleeding that persists despite the application of multiple bands, and (iii) variceal re-bleeding after apparent adequate banding. A high mortality rate of 30% to 50% is associated with uncontrolled refractory bleeding. Bridge therapy includes balloon tamponade, oesophageal stent placement, or TIPS (Songtanin 2024). The Baveno consensus meetings have defined failure to control variceal bleeding as the inability to control bleeding within the first 5 days that requires a change in intervention (de Franchis, 2015). If the acute bleeding persists despite the initial treatment and the patient is haemodynamically stable, a second endoscopic attempt may be useful, especially if the visibility during the initial endoscopy was suboptimal or if the initial procedure was undertaken by an inexperienced endoscopist. If the bleeding is severe or the patient is haemodynamically unstable, rescue therapies including oesophageal balloon tamponade, self-expanding oesophageal metal stents (SEMS) placement, or a sTIPS should be initiated (de Franchis, 2022; Zhao, 2023; Berengy, 2024; Songtanin, 2024).

The key clinical objectives of the initial evaluation of a patient with suspected AVB therefore include assessment of the severity of bleeding, identification of the source of bleeding and a risk assessment of prognosis, including the presence of infection and complications. Once therapy is initiated, careful assessment of the adequacy of bleeding control is necessary to determine the need for second line interventions. Endoscopy plays a critical role and is central to the management of active variceal bleeding (Kapoor, 2015). We have previously reported that despite initial endoscopic control of variceal bleeding, one in six patients (17%) rebled during the first hospital admission (Krige, 2012). In our analysis of 448 alcoholic cirrhotic patients (349 men, 99 women; median age 50 years) with variceal bleeding who underwent 805 endoscopic interventions (556 emergency, 249 elective) during the index hospital admission between January 1984 and August 2011, endoscopic intervention alone controlled variceal bleeding in 394 patients (87.9%), while 54 (12%) also required balloon tamponade. Within 24 hours 15 (3.3%) patients rebled; after 24 hours another 61 (17%, n=76) rebled and 93 (20.8%) died in hospital. Mortality increased exponentially as C-P score increased, reaching 80% when C-P score exceeded 13 (Krige, 2012).

While several previous studies have attempted to develop a classification system that both characterises the degree of liver dysfunction and predicts the prognosis of patients with cirrhosis based on clinical and laboratory values, there is currently no consensus which specific risk factors have the best prognostic value for early rebleeding and mortality after initial variceal bleeding in cirrhotic patients (Ferrarese, 2023). We have previously investigated predictors of mortality using stepwise multivariate logistic regression analysis in 310 prospectively documented alcoholic cirrhotic patients with acute variceal bleeding, who underwent 786 endoscopic variceal injection treatments between January 1984 and

December 2006 (Krige, 2009). Seventy-five (24.2%) of the 310 patients experienced rebleeding, 38 within 5 days of the initial treatment and a further 37 within 6 weeks of their initial treatment. Of the 15 variables studied and included in a multivariate analysis using a logistic regression model, a bilirubin level >51 mmol/l and transfusion of >6 units of blood during the initial hospital admission were predictors of variceal rebleeding within the first 6 weeks. Seventy-seven (24.8%) patients died, 29 (9.3%) within 5 days and 48 (15.4%) between 6 and 42 days after the initial treatment. Survival was influenced by the severity of liver failure, with most deaths occurring in Child-Pugh grade C patients. We found that six variables, encephalopathy, ascites, bilirubin level >51 mmol/l, international normalized ratio (INR) >2.3 , albumin <25 g/l, and the need for balloon tube tamponade were predictors of death within the first 6 weeks. Bilirubin levels >51 mmol/l and a transfusion of >6 units of blood were also predictors of variceal rebleeding (Krige, 2009).

Determining prognosis is an essential component of the initial assessment of cirrhotic patients with portal hypertension and bleeding varices as it provides the basis for critical treatment decisions (Gülcicegi, 2023). Several patient features, characteristics and variables are related to, and influence the course and outcome of cirrhosis and are relevant in formulating the prognosis (Rowe, 2024). Various prognostic variables can be combined into a prognostic model to improve the prediction of outcome. While in theory the concept of prognostic modelling in cirrhotic patients may appear elementary, in practice the analysis is complex because a wide spectrum of clinical differences exist between individual patients (Gülcicegi, 2023). Patients may present at various stages of progression in the evolution of cirrhosis, ranging from well-compensated, through the initial stages of decompensation to established decompensation, and with different combinations of clinical features, different laboratory liver function values and different responses to the treatment of the complications

of cirrhosis (Christensen, 1997). These variables and differences among patients with cirrhosis make formulation of a prognostic model multifaceted and complex (Christensen, 1997). This is an additional area where further investigations and analysis would benefit patient management.

Research Objectives

As outlined above, several major clinical issues in the management of acute variceal bleeding remain unanswered and the responses to these unresolved questions form the basis of the six clinical studies of this thesis which are outlined below.

1. Improvement of prognostic scoring: The ideal prognostic score should be accurate, objective, functional on a continuous scale, validated worldwide, be able to guide treatment and be easy to calculate. The C-P and MELD scores are currently widely used to assess severity of liver dysfunction and predict patient risk for in-hospital rebleeding and death. The original classification created by Child and Turcotte to predict mortality in portocaval shunt patients was subsequently modified by Pugh et al. to assess outcome in patients who underwent an oesophageal transection to control bleeding varices. The MELD score was subsequently developed to assess outcome after a radiologically placed TIPS. Neither score is ideal and both have intrinsic limitations related to their deployment and inclusion of biochemical and clinical components. Study 1 in this thesis addresses these issues and proposes and validates a new 4-category recalibrated C-P score.

2. Endoscopic control of acute variceal bleeding. Immediate and durable endoscopic control of BOV is the immediate objective of intervention and is crucial to survival. After endoscopic control of an index bleeding episode, most rebleeding events occur in the first 6 weeks, of which over half occur within 5 days of initial bleeding. Early rebleeding is the most consistently reported prognostic risk indicator of death at 6 weeks. This has led the Baveno

consensus conferences to propose the concept of achieving “5-day control of bleeding”, a period with no further bleeding and haemodynamic stability for 5 days after the initial admission. Study 2 in this thesis evaluated the relative efficacies of EVL and IST in arresting acute variceal bleeding in a matched controlled cohort study.

3. Determining the benefits and limitations of endoscopic banding in variceal bleeding.

Although the utility of endoscopic therapy in controlling acute variceal bleeding has been extensively reported, the long-term efficacy and safety of EVL in a high-risk cohort of patients with active variceal bleeding is poorly defined and documented. Since endoscopic treatment of varices must be performed repeatedly until varices are eradicated and then followed by life-long surveillance endoscopy to identify recurrent varices, a long-term follow-up study would be important to determine the rebleeding and recurrence rates as well as the cumulative survival rates in portal hypertensive patients who have received EVL. Such a study would clarify the benefits of a long-term surveillance programme and would define the incidence of endoscopic complications related to long-term EVL. Study 3 in this thesis assessed acute bleeding control, rebleeding, variceal eradication and recurrence after EVL treatment in a prospective longitudinal observational study.

4. Identifying factors influencing in-hospital mortality for salvage TIPS in cirrhotic patients with recalcitrant variceal bleeding after failed endoscopic intervention.

Technical advances in interventional radiology have led to the evolution and use of a transjugular intrahepatic portosystemic shunt (TIPS) as a minimally invasive salvage alternative to surgery in patients with uncontrolled variceal bleeding. TIPS is a percutaneous radiologically-created shunt between portal and hepatic veins which reduces portal vein pressure by diverting blood from the portal to the hepatic and systemic venous systems through a low-resistance intrahepatic stent. TIPS is now established as the preferred rescue or salvage procedure for patients who have either uncontrolled or severe recurrent variceal bleeding unresponsive to medical and

endoscopic treatment. Study 4 in this thesis investigated the outcome of salvage TIPS in patients who had life-threatening variceal bleeding resistant to standard treatments to identify clinical and laboratory risk factors predicting in-hospital death during the index admission.

5. Intermediate and long-term outcomes after salvage TIPS for uncontrolled variceal bleeding.

The reported long-term survival data after salvage TIPS placement are widely divergent due to differing inclusion criteria, population selection, timing of TIPS, severity of underlying liver disease and the experience of the facility in the management of critically ill patients with end-stage liver disease. Some reports combine the results of patients with active bleeding during TIPS with those who were haemodynamically stable during the procedure or undergoing an elective TIPS placement. To identify high-risk patients after TIPS insertion, previous studies have evaluated independent clinical and biochemical predictors of index admission mortality. Clinical factors identified include age over 60 years, the presence of encephalopathy and ascites, haemodynamic instability at the time of the TIPS procedure, use of inotropes, mechanical ventilation, balloon tamponade, comorbidities and sepsis. The commonest cause of late death after a TIPS procedure, in most series, is progressive liver failure. Accurate patient selection is the most important aspect of the TIPS procedure and post-TIPS outcome can reasonably be expected to be predicted after detailed assessment of the patient's overall status and hepatic function. Study 5 in this thesis assessed intermediate and long-term survival after sTIPS to identify possible prognostic factors influencing survival.

6. Development of a novel CABIN prognostic score to predict in-hospital mortality after salvage TIPS and to test the efficacy of this new score against other established prognostic models.

Several prognostic and risk scores have been developed to distinguish patients at risk for a poor clinical outcome after sTIPS insertion. These include the Acute Physiology and Chronic Health Evaluation (APACHE) II, Bonn TIPS early mortality (BOTEM), Child-Pugh (C-P), Emory, Freiburg index of post-TIPS survival (FIPS), Model for End-Stage Liver Disease

(MELD), and Model for End-Stage Liver Disease sodium (MELD-Na) scores. Although each of these individual models has been correlated with TIPS outcome, their relative performances have not been assessed in a detailed analysis. Study 6 in this thesis assessed the accuracy of a newly developed and novel CABIN score and compared the CABIN score to existing established risk scores to predict in-hospital mortality after sTIPS placement.

Relevance and motivation for the six research studies

Study 1

The natural history of cirrhosis is dependent on the degree of liver decompensation, the presence of complications such as variceal bleeding, renal compromise, ascites or spontaneous bacterial peritonitis and the efficacy of the applied therapy. Progressive liver decompensation occurs more rapidly in patients with alcoholic cirrhosis than in those with cirrhosis due to viral hepatitis B or C and is aggravated by superadded alcoholic hepatitis. Once decompensation occurs in cirrhotic patients, mortality without organ replacement is as high as 85% over 5 years. Assessment in this group of patients is complex and prognostic prediction is hence of crucial importance to clinicians. In a previous study we have shown using multivariate analysis in a logistic regression model that a bilirubin level >51 mmol/l and a transfusion of >6 units of blood during the initial hospital admission were predictors of variceal rebleeding within the first 6 weeks (Krige, 2009). In the same study, using stepwise multivariate logistic regression analysis, encephalopathy, ascites, bilirubin level >51 mmol/l, INR >2.3 , albumin <25 g/l and the need for balloon tube tamponade were predictors of death within 6 weeks (Krige, 2009).

Although several quantitative tests based on clinical and laboratory values have been proposed to evaluate liver reserve in chronic liver disease and to predict survival in patients

with decompensated cirrhosis, the C-P and MELD scores have remained the most consistent and widely used scoring systems both in clinical practice and research and are superior to other predictive systems in determining mortality within the first six weeks after a major variceal bleed. The advantages of the C-P score are its simplicity, use of easily obtained variables, its convenience as a prognostic tool and that it can be calculated at the bedside using mental arithmetic compared to the elaborate computations necessary for the MELD score which requires an online calculator (Krige, 2020).

However, for the C-P scoring system the subjective assessment of the degree of ascites and encephalopathy, arbitrary cut-off values for bilirubin, albumin and INR and suboptimal differentiation between mild and severe disease of patients in grade C limit the clinical application. Also, assigning equal weights to all variables in the C-P score may not be appropriate. The Child-Pugh scores may vary significantly between patients if single variables are modified or affected by medical treatment such as overzealous diuretic therapy, albumin infusion or ascitic paracentesis (Huo, 2008).

In contrast, the MELD score that was initially developed for predicting survival in patients undergoing TIPS shunts, is a prospectively developed and validated indicator of the severity of end-stage liver disease. The MELD score calculation utilises quantitative, objective measures based on three simple and objective laboratory variables, serum bilirubin, serum creatinine, and INR but requires logarithmic transformations and multiplication by several factors making it substantially more complex than the C-P score. Variables are weighted to account for relative importance in reflecting the severity of liver disease. The MELD scoring system therefore provides a more refined, granular grading system with a score ranging from 6 to 40 and, as such, has replaced the C-P score for prioritization for liver transplantation. Caveats of the MELD score include a cap at an overall maximum value of 40 points and the maximum assigned value of serum creatinine that is capped at 4 [units] even when the measured serum

level is higher. In addition, the MELD score does not include independent prognostic indicators that correlate with severity of portal hypertension such as the degree of ascites and hepatic encephalopathy (Krige, 2020).

To overcome the limitations of the arbitrary cut-off grading points in the existing C-P classification, a new 4-category recalibrated rC-P with revised cut-off levels of the original C-P classification and with the addition of a D category (A=5,6,7; B=8,9,10; C=11,12,13; D=14,15) is proposed. The objective of this study was to compare the relative abilities of the original C-P, MELD and the proposed new recalibrated rC-P to predict in-hospital rebleeding and death in patients with alcoholic cirrhosis and endoscopically proven acute oesophageal variceal bleeding. The C-P grade was categorized according to the Pugh modification and the revised cut-off levels of the rC-P score (A=5,6,7; B=8,9,10; C=11,12,13; D=14,15) and the MELD score was calculated by United Network of Organ Sharing (UNOS) adjustments. Receiver operating characteristic (ROC) curve analysis was performed to compare the ability of the C-P, rC-P and MELD scores to predict the risk of in-hospital rebleeding and death in 225 alcohol-induced cirrhotic patients with bleeding oesophageal varices.

Study 2

There is consensus that endoscopic control of bleeding is the emergency treatment of choice if actively bleeding oesophageal varices are present during diagnostic endoscopy (D'Amico, 2006; Burroughs 2008). However, data on the endoscopic control of major variceal bleeding and immediate mortality from uncontrolled bleeding in portal hypertensive patients is not sufficiently robust for an accurate or reliable estimate of efficacy to be made from the existing literature. Endoscopic variceal ligation has replaced IST as the endoscopic treatment of choice, supported by data from RCT's which show more rapid eradication of varices with lower rates of rebleeding and fewer oesophageal complications with EVL (Aggeletopoulou, 2018). However, detailed data on the relative success of each method in controlling AVB with *actively*

bleeding (“*spurting*”) varices are limited. The cohorts analysed in previous RCT’s comparing EVL with IST included only small numbers of patients with active variceal bleeding and provided conflicting results (Dai, 2015).

The objective of the second study was to compare the efficacy of emergency IST with EVL in achieving control of actively bleeding “*spurting*” oesophageal varices and the frequency of acute variceal rebleeding and death within six weeks in the largest comparative case-matched patient cohort to date. The study design and process followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies (von Elm, 2008). To reduce bias, investigators were blinded throughout the selection and matching process to the primary and secondary end points. The primary clinical endpoints of the study were: (i) primary endoscopic failure of the initial endoscopic intervention defined as failure to control AVB; (ii) secondary endoscopic failure defined as rebleeding within 5 days after initial endoscopic control; (iii) mortality during the initial hospital admission; (iv) 6-week mortality and (v) overall survival. The secondary endpoints were: (i) procedure-related complications and (ii) success in achieving variceal eradication as defined in the analysis criteria. Baveno criteria were used to define secondary endoscopic 5-day failure to control bleeding (de Franchis, 2022).

Study 3

Endoscopic variceal ligation has replaced IST in most centres as the endoscopic interventional procedure of choice for bleeding oesophageal varices, supported by RCT data that show more rapid eradication of varices with lower rates of recurrent bleeding and fewer endoscopic-related complications (Dai, 2015). However, few studies have specifically evaluated detailed outcome in relation to the technical constraints imposed by the design of the ligating device which influences the effectiveness of EVL in controlling acute bleeding and achieving

complete eradication of varices, a problem conceptually more applicable to endoscopic banding than sclerotherapy.

Present knowledge suggests that the risk of rebleeding is higher in C-P grade C patients. Although the utility of endoscopic therapy in controlling acute variceal bleeding has been extensively reported, the long-term efficacy and safety of EVL in a high-risk cohort of patients with AVB is poorly defined and documented. Since endoscopic treatment of varices must be performed repeatedly until varices are eradicated and then followed by life-long surveillance endoscopy to identify recurrent varices, a long-term follow-up study would be important to determine the rebleeding and recurrence rates as well as the cumulative survival rates in portal hypertensive patients who have received EVL.

To answer this question, the third study in this thesis tested the validity of the hypothesis that eradication of oesophageal varices by repeated EVL would reduce recurrent variceal bleeding and death from bleeding varices. The primary endpoints of the study were (i) effective endoscopic control of the index variceal bleeding event, (ii) success in achieving complete variceal eradication as defined in the analysis criteria, (iii) variceal recurrence, (iv) variceal rebleeding, (v) overall all sources rebleeding, and (vi) survival. Secondary endpoints were (i) time to eradication calculated from the first EVL session, (ii) number of banding sessions and (iii) endoscopic-related complications.

Study 4

Technical advances in interventional radiology have led to the evolution and implementation of transjugular intrahepatic portosystemic shunting (TIPS) as a less invasive salvage alternative to surgery in patients with uncontrolled variceal bleeding. TIPS provides a percutaneous radiologically-created stent shunt between portal and hepatic veins which reduces portal vein pressure by diverting blood from the portal to the hepatic and systemic venous system through a low-resistance intrahepatic stent. TIPS is now established as the preferred rescue for

salvage procedure for patients who have either uncontrolled or severe recurrent variceal bleeding unresponsive to medical and endoscopic treatment. Study 4 in this thesis investigated the outcome of salvage TIPS in patients who had life-threatening variceal bleeding resistant to standard treatments to identify clinical and laboratory risk factors that could predict in-hospital death during the index admission.

Study 5

The reported long-term survival data after salvage TIPS placement are widely divergent due to differing inclusion criteria, population selection, timing of TIPS, severity of underlying liver disease and the experience of the facility in the management of critically ill patients with end-stage liver disease. Some reports combine the results of patients with active bleeding during TIPS with those who were haemodynamically stable during the procedure or undergoing an elective TIPS placement. To identify high-risk patients after TIPS insertion, previous studies have evaluated independent clinical and biochemical predictors of index admission mortality. Clinical factors identified include age over 60 years, the presence of encephalopathy and ascites, haemodynamic instability at the time of the TIPS procedure, use of inotropes, mechanical ventilation, balloon tamponade, comorbidities and sepsis. The commonest cause of late death after a TIPS procedure in most series is progressive liver failure. Accurate patient selection is the most important aspect of the TIPS procedure and post-TIPS outcome can reasonably be predicted after detailed assessment of the patient's overall status and hepatic function. Study 5 in this thesis assessed intermediate and long-term survival after sTIPS to identify possible prognostic factors influencing survival.

Study 6

Several prognostic and risk scores have been developed to distinguish patients at risk for a poor clinical outcome after sTIPS insertion. These include the Acute Physiology and Chronic Health Evaluation (APACHE) II, Bonn TIPS early mortality (BOTEM), Child-Pugh (C-P),

Emory, Freiburg index of post-TIPS survival (FIPS), Model for End-Stage Liver Disease (MELD), and Model for End-Stage Liver Disease sodium (MELD-Na) scores. Although each of these individual models has been correlated with TIPS outcome, their relative performances have not been assessed in a detailed analysis. Study 6 in this thesis assessed the accuracy of a newly developed and novel CABIN score and compared the CABIN score to existing established risk scores to predict in-hospital mortality after sTIPS placement.

Conclusions and recommendations for future research

In the concluding chapter, the synopsis summarises the main findings and implications of the six clinical studies and makes recommendations for future directions of research in portal hypertension.

The studies reported in this thesis are novel, relevant and important and make a substantial contribution to the existing body of knowledge. As the six studies are clinically based and involve portal hypertensive patients with acute and life-threatening variceal bleeding which has a substantial mortality rate, any improvement in outcome will have a beneficial impact on existing patient care. The new proposed 4-category recalibrated Child-Pugh score is easy to calculate and can assist guiding treatment and predicting the risk of in-hospital variceal rebleeding and death. In the matched controlled cohort study, endoscopic ligation has been shown to be the optimal method of controlling acute variceal bleeding while the long-term study defined the benefits and exposed the limitations of variceal ligation. The three salvage TIPS studies identified factors influencing in-hospital mortality in cirrhotic patients with recalcitrant variceal bleeding after failed endoscopic intervention, as well as intermediate and long-term outcomes and predictive risk factors. The development of a novel CABIN prognostic score designed to predict in-hospital mortality after salvage TIPS was shown to be an

improvement over other established prognostic models and should be beneficial in future accurate patient selection for salvage TIPS.

Because portal hypertension is a complex haemodynamic disorder characterized by increased pressure within the portal venous system, an understanding of the underlying pathophysiological mechanisms is crucial for early detection, risk stratification, and targeted management strategies. Continued research into the molecular and cellular mechanisms driving portal hypertension will be required for the development of novel therapeutic approaches and improved clinical outcomes for affected patients.

Since the efficacy and success of endoscopic therapy may be compromised by recurrent bleeding and serious procedure-related complications, recommendations regarding the technical aspects of variceal ligation are addressed, as well as the need to supervise trainees when critical decisions are required. A prerequisite in demanding cases is early and close multidisciplinary consultation to facilitate appropriate therapy and optimal management. As the treatment of acute bleeding and prevention of recurrent variceal bleeding is best accomplished by a skilled, knowledgeable and well-equipped team using a multidisciplinary integrated approach, modern management requires the provision of the full spectrum of treatment options, including pharmacological therapy, endoscopic treatment, interventional radiological procedures, surgical shunts and liver transplantation.

There is a need to stimulate further research and analysis to define robust and objective endpoints when reporting the results of endoscopic ligation and adverse events which are likely to differ from the sometimes superficial and inadequate historical outcomes reported in

previous studies. The elusive goal of effective and safe endoscopic variceal banding remains long-term bleed-free survival with a minimum of procedure-related adverse events.

On the horizon is the prospect of integrating artificial intelligence, machine learning algorithms and neural network models in patient assessment to enhance scoring systems and predictive analysis. An unexplored research area is the combination of these three elements offering a potentially promising avenue for accurate non-invasive prediction, theoretically surpassing traditional methods. Artificial intelligence harnesses advanced algorithms to deliver accurate assessment of liver reserve, precise evaluation of portal dynamics, standardised scoring and outcome prediction. Utilizing data from electronic health records, machine learning algorithms could efficiently identify high-risk patients, triggering risk prediction tools to support clinicians. Furthermore, the emerging applications of artificial intelligence and neural network models offer the potential for a future towards precision medicine and personalised medicine by providing patient stratification for the most beneficial therapy with minimal risk. Although artificial intelligence has limitless potential, concerns remain, including data quality, standardisation, reproducibility, clinical implementation, ethical fears, legal liability, and regulatory issues.

In this thesis the complexity of oesophageal variceal management is emphasised, necessitating an integrated multidisciplinary approach and when refractory bleeding ensues, rescue treatment with radiologically placed intrahepatic stenting, and in some cases, salvage surgical options tailored to individual patient profiles. The thesis advocates a patient-centred approach in healthcare, balancing the incorporation of innovative technologies with ethical principles and the diverse needs of patients to optimize treatment efficacy and enhance healthcare accessibility.

CHAPTER 2

PROGNOSTIC SCORING IN CIRRHOSIS AND VARICEAL BLEEDING

Historical background

In 1964, two University of Michigan surgeons, Gardner Child, and Jeremiah Turcotte, developed and published a classification system designed to assess hepatic functional reserve in cirrhotic patients undergoing portosystemic shunt surgery for variceal bleeding (Child, 1964; Weichselbaum, 2022). Five variables, three clinical and two biochemical, were selected empirically and constituted the components of the classification. The variables, ascites, encephalopathy, nutritional status and serum levels of bilirubin and albumin were each divided into three classes, A, B or C in relation to minimal “A”, moderate “B”, or advanced “C” hepatic decompensation. In their publication reporting 128 patients who underwent an end-to-side portocaval shunt, postoperative mortality was 0% in class A, 9% in class B and 53% in class C patients, with an overall mortality of 17%.

The initial Child-Turcotte classification was subsequently modified in 1973 by Pugh and colleagues from Kings College, London to improve the existing score for prognostic use in cirrhotic portal hypertensive patients who underwent an oesophageal transection for bleeding oesophageal varices (Pugh, 1973). Nutritional status was replaced with INR and a numerical score ranging from 1 to 3 was assigned to each of the five variables, depending on the level and extent of deviation from normality. A composite total score ranging from 5 to 15 placed the patient into one of three possible categories, designated as grades A, B or C, with escalating mortality. In their publication which documented 38 patients who underwent an oesophageal transection for bleeding oesophageal varices, mortality for Child–Turcotte-Pugh grade A was 29%, grade B 38% and grade C 88% (Pugh, 1973). This modified Child–Turcotte-Pugh classification became widely used to predict outcome of

surgery in cirrhotic patients in general, and more recently, to stratify patients on the waiting list for liver transplantation. However, as with the original Child-Turcotte grading, neither the division into three arbitrary grades nor the scoring system which ranged from 5 to 15 had been validated statistically. Despite these shortcomings, the Child-Turcotte-Pugh score became established as the global reference scoring system and has endured for more than 50 years as a score to assess the severity of liver dysfunction and prognosis in cirrhotic patients. With the passage of time, the cumbersome eponymous title was shortened for convenience to the present Child–Pugh (C-P) score.

Over time the routine use of the C-P classification has exposed several limitations. Firstly, the score includes variables that are subjective because both the degree of ascites and the extent of hepatic encephalopathy (HE) are evaluated clinically and are liable to interobserver differences. In addition, both ascites and HE can be influenced or manipulated by medication including diuretics, albumin infusion or lactulose intake. In addition, there is no consistency as to when ascites and HE should be scored, at their best, or worst, or when independent of specific therapy. Also, the widespread use of ultrasonography has led to the more sensitive and accurate detection of ascites, but there is no uniformity or consistency in how different ascitic volumes identified by ultrasonography are categorized by various authors. Hepatic encephalopathy can be assessed either clinically or by psychometric testing or by using electroencephalography and it is not clear how subtle subclinical abnormalities are scored in the C-P classification. Secondly, all variables were selected empirically and the cut-off values for continuous variables such as bilirubin, albumin and INR were arbitrarily chosen. Thus, a patient with a bilirubin level of 55 $\mu\text{mol/L}$ who has a substantially better prognosis than a patient with a bilirubin level of $>250 \mu\text{mol/L}$ is awarded the same score of severity (“3”) for bilirubin concentration (‘the ceiling

effect') in the C-P classification. A similar problem exists for serum albumin in that the C-P classification does not differentiate between a patient with an albumin of 17 g/L compared to a patient with an albumin of 25 g/L ('the floor effect') although the lower level reflects significantly more severe and impaired hepatic synthetic function. Thirdly, the C-P score does not take into account the cause of cirrhosis or the possible coexistence of several causal factors such as persistent alcohol abuse, ongoing hepatitis B or hepatitis C virus replication, or the level of inflammatory activity in patients who have autoimmune hepatitis. Finally, the C-P score does not include a measure of renal function, which is a well-established and important prognostic marker in cirrhosis.

In the past decades efforts have been made to better understand and describe the natural history of end-stage liver disease, to stratify the risk of decompensation and to predict prognosis at any disease stage (Ferrarese, 2023). Given the complexity of liver decompensation, the prediction of short- and long-term survival cannot be assessed by a single parameter (Rowe, 2024). The ideal prognostic score to assess the extent of liver impairment in patients with cirrhosis and portal hypertension should be accurate, objective, useable on a continuous scale, validated worldwide, able to guide treatment and easy to calculate (Krige, 2020). During the last three decades, several other prognostic classifications have been designed to predict survival in patients with decompensated cirrhosis, but none gained wide acceptance until the development of the Model for End-stage Liver Disease (MELD) score (Ferrarese, 2023).

In view of the intrinsic limitations of the C-P score, the MELD score was developed by Patrick Kamath and colleagues at the Mayo Clinic as an alternative score to predict survival in patients after TIPS (Malinchoc, 2000). The initial version of the MELD score included the

aetiology of liver cirrhosis (alcohol or cholestatic vs other), but this variable was later found to be unnecessary and was discarded. The current version of the MELD score incorporates only three objective biochemical variables, total bilirubin, creatinine and INR and is currently primarily used to assign priority and justice ranking in liver transplantation candidates (Kamath, 2007). The score was initially named the Mayo End-stage Liver Disease score reflecting the institution where the score was developed. With the acceptance by UNOS as an instrument for organ allocation, the score was renamed as the Model for End-stage Liver Disease (MELD) which allowed wider acceptability while keeping the same abbreviation. After modification by UNOS, the currently used MELD equation to calculate the severity score is as follows: $\text{MELD score} = 0.957 \times \log_e (\text{creatinine mg/dL}) + 0.378 \times \log_e (\text{bilirubin mg/dL}) + 1.120 \times \log_e (\text{INR}) + 6.43$. Minimal values are set to 1.0 for calculation purposes. The maximal serum creatinine level considered within the MELD score equation is 4.0 mg/dl to avoid higher MELD scores in patients with concomitant intrinsic renal disease. Because donor livers are allocated to the recipients according to the severity of underlying disease (the 'sickest first' policy), UNOS suggested using the MELD system to prioritize adult patients on the transplantation waiting list. The MELD score has gained wide acceptance for predicting survival in patients undergoing liver transplantation. The strength of this score lies in the mathematical formula derived from a multivariate Cox regression analysis and uses a continuous scale and lacks a ceiling or a floor effect with a wide range of discrimination. MELD is based on objective, reproducible, and readily available laboratory data and the wide range of samples which have been validated (Gülcicegi, 2023).

An additional major advantage of the MELD score over the C-P classification is that renal function is included in outcome prediction. Renal dysfunction is a common occurrence in up to 75% of cirrhotic patients during the course of the disease, and the severity of liver

cirrhosis has been identified as a contributory factor to renal insufficiency. In addition, several studies have emphasized the prognostic impact of worsening renal function in cirrhosis. These lines of evidence highlight the need to take renal function into consideration for prognostic evaluation. An initial disadvantage, however, is that while it is possible to calculate the C-P score easily at the bedside by mental arithmetic, a calculator or an Internet connection to the UNOS web site (<http://www.unos.org>) is necessary to determine the MELD score. With the availability of smart phones with Internet access, this is no longer a factor. In addition, recent studies have shown that the predictive ability of MELD score can be increased by adding clinical (HE, ascites) and laboratory (Na) parameters. The incorporation of serum Na to the MELD formula improved prediction of mortality by 5%, over and above the risk corresponding to the MELD score for each unit decrease in serum Na. Consequently, the MELD-Na formula was incorporated into the US liver allocation program in 2006, and then in several other liver transplant programs worldwide.

To further improve the prognostication of the MELD score, attempts to overcome the pitfalls arising from the inaccurate measurement of renal dysfunction as provided by serum creatinine alone have been proposed. Recently, MELD 3.0 has been proposed to capture dynamic changes occurring in liver transplant candidates over time (Ferrarese, 2023). Other variants of the MELD score including MELD-lactate, MELD-plus and MELD-XI, the latter in patients receiving warfarin, have been proposed, aiming at improving prognostic accuracy in specific groups of patients. Interestingly, HE, ascites and hyponatraemia (as an indicator of ascites) are components of the C-P score or modifications thereof, but are not included in the MELD score (Kamath, 2013; Ferrase, 2023).

Comparative Child-Pugh and MELD scoring studies

Prognostic prediction is of crucial importance to clinicians. In order to find the optimal predictive scoring system in cirrhotic patients with portal hypertension and bleeding oesophageal varices, studies have evaluated the relative discriminative and prognostic abilities of C-P and MELD score in three categories:

- (i) Cirrhotic patients undergoing surgery but without variceal bleeding
- (ii) Patients with AVB, together with comparative assessments of the AIMS65, Glasgow-Blatchford (GBS), full Rockall (FRS) and MELD-Na model scores,
- (iii) Comparisons using modified or recalibrated MELD and C-P scores.

In the first category, Hoteit and colleagues from Emory University Hospital in Atlanta, Georgia compared the capability of C-P and MELD scores in predicting outcomes in 195 cirrhotic patients undergoing a variety of surgical procedures at two teaching hospitals over a five-year period (Hoteit, 2008). The primary endpoints were death or hepatic decompensation. The study included patients of whom 57.4% had a MELD score ≥ 12 and 79% were Child class B or C. Operative mortality overall was 8.7%. Patients who reached the endpoint had a higher MELD score, a higher C-P score and were more likely to have undergone an urgent procedure. Among patients undergoing elective surgical procedures, no statistically significant differences were noted in the mean MELD (12.8 ± 3.9 vs 12.6 ± 4.7 , $p=0.9$) or in the mean C-P (7.6 ± 1.2 vs $7.7 \pm .7$, $P = 0.8$) between patients who reached the endpoint and those who did not. Both mean scores were higher in the patients reaching the endpoint in the case of urgent procedures (MELD: 22.4 ± 8.7 vs 15.2 ± 6.4 , $p=0.0007$; C-P: 9.9 ± 1.8 vs 8.5 ± 1.8 , $p=0.008$). The performances of the MELD and C-P scores in predicting the outcome of urgent surgery were only fair, without significant differences between them ($AUC = 0.755 \pm 0.066$ for MELD vs $AUC = 0.696 \pm 0.070$ for C-P, $p=0.3$). The authors

concluded that the C-P and MELD scores performed equally, but only fairly well in predicting the outcome of urgent surgical procedures (Hoteit, 2008).

In the second category the optimal scoring system to predict 6-week bleeding-related mortality in cirrhotic patients with acute variceal bleeding, six scoring systems, the AIMS65, Glasgow-Blatchford (GBS), full Rockall (FRS), MELD, MELD-Na model and C-P scores were evaluated in four studies.

Mohammad and colleagues from Sohag University Hospital calculated the C-P, MELD, APACHE II, SOFA and AIMS65 scores in 120 cirrhotic patients with AVB to find the most accurate scoring system in predicting outcome in cirrhotic patients with BOV (Mohammad, 2016). Univariate and multivariate analyses were performed for all the measured parameters and scores. Eight patients (6.67%) died in the hospital. Advanced age, the presence of encephalopathy, rebleeding, and higher serum bilirubin were independent factors associated with higher hospital mortality. The largest area under the receiver operator curve (AUROC) was obtained for the AIMS65 score and SOFA score, followed by the MELD score and APACHEII score, then CTP score, all of which achieved very good performance (AUROC>0.8). AIMS65 score showed the best sensitivity, specificity, and negative and positive predictive values. Although the AIMS65 score was not significantly different from the MELD, SOFA, and APACHEII scores, the AIMS65 score was the optimal among them in prediction of mortality (Mohammad, 2016).

This contrasts with the publication by Budimir and colleagues who found that the Glasgow Blatchford, pre-endoscopic Rockall and AIMS65 scores showed no difference in predicting rebleeding rates and mortality in variceal bleeding (Budimir, 2016). A total of 225 patients,

mostly with alcoholic cirrhosis (86%) presented with endoscopically confirmed variceal bleeding during the study period. Rebleeding occurred in 22 (9.8%) patients and 30-day mortality was 39 (17.3%). Most patients died from the underlying disease, while 12 (30.8%) died from bleeding. There was no statistically significant difference among AIMS65, GBS and PRS scores in predicting mortality (AUROC 0.70 vs. 0.64 vs. 0.66) or rebleeding rates (AUROC 0.74 vs. 0.60 vs. 0.67). The GBS was superior in predicting the need for blood transfusion compared with the AIMS65 score (AUROC 0.75 vs. 0.61, $p = 0.01$) and PRS (AUROC 0.75 vs. 0.58, $p = 0.009$) (Budimir, 2016).

Ilioa and colleagues evaluated the usefulness of the Glasgow–Blatchford score (GBS), MELD score, and the C-P score for predicting short-term and hospital mortality in patients with AVB. A total of 47 patients were studied and GBS, MELD and C-P scores were assessed for their ability to predict 1- and 6-week mortality rates using a ROC curve. The 1- and 6-week mortality rates were 17.0 and 31.9% respectively. The median GBS, MELD, and C-P scores were 13 (range: 4–19), 10 (range: 0–34), and 9 (range: 5–13) respectively. The GBS was superior to both the MELD and the C-P scores for prediction of 1-week mortality [area under the curve = 0.82 (95% confidence interval: 0.66–0.98) vs. 0.71(0.47–0.96) and 0.72 (0.53–0.91)]. The MELD score was superior to both the C-P score and the GBS for prediction of 6-week mortality [area under the curve = 0.83 (95% confidence interval: 0.69–0.97) vs. 0.69 (0.52–0.85) and 0.67 (0.50–0.83)]. The authors concluded that for 1-week mortality, the GBS was superior to the C-P and the MELD scores in patients with OVB. However, for 6-week mortality, the MELD score was superior in patients with OVB (Ilioa, 2017).

Wang and colleagues evaluated the six scoring systems to determine the optimal scoring method to predict 6-week bleeding-related mortality in 202 cirrhotic patients with AVB (Wang, 2018). The prediction effect was compared by ROC curve and the AUC. The scores of non-survival groups evaluated by the AIMS65, GBS, FRS, MELD, MELD-Na and CTP (2.6 ± 1.1 , 12.9 ± 2.7 , 6.6 ± 1.8 , 26.9 ± 6.5 , 31.6 ± 9.3 , 9.6 ± 2.2) were higher than the survival group (1.2 ± 1.1 , 10.2 ± 3.4 , 5.1 ± 1.6 , 21.0 ± 6.4 , 22.8 ± 8.2 , 7.7 ± 2.0) ($p < 0.01$). The values of AUC and Youden index of AIMS65 and MELD-Na scoring systems [(0.808, 0.453) and (0.781, 0.516)] were superior to those of MELD (0.761, 0.454), CTP (0.748, 0.399), FRS (0.738, 0.358) and GBS scoring systems (0.726, 0.370). The authors concluded that the AIMS65 and MELD-Na scoring systems are recommended for evaluation of 6-week bleeding-related mortality in liver cirrhosis patients with AVB (Wang, 2018).

Six studies have compared the prognostic capabilities of Child-Pugh and MELD scores in cirrhotic patients with acute variceal bleeding. In a prospective 15-centre study in the USA, Fortune and colleagues from Yale University compared the prognostic value of C-P and MELD scores with a recently recalibrated MELD score in 70 patients with endoscopically proven acute bleeding (Fortune, 2017). All patients received antibiotics, vaptotide infusion and endoscopic band ligation. Primary outcome was 6-week mortality. Secondary outcome was 5-day treatment failure. Of the 70 eligible patients, 18 (26%) died within 6-weeks of the index bleed. Multivariate models showed that both admission C-P and MELD scores were independent predictors of survival. The discriminative values of C-P (AUROC: 0.75) and MELD (AUROC: 0.79) were good and not significantly different ($p = 0.27$). However, the calibration (correlation between observed and predicted mortality) test was significantly better for C-P than for MELD, with the recalibrated MELD model having the worst agreement. Predicted mortality for C-P A was $<10\%$, C-P B 10% to 30% and C-P C was

>33%. The authors concluded that the C-P score had the best overall performance in predicting 6-week mortality and was best at stratifying risk. The major limiting factor of this study is the relatively small number of patients entered, considering that this was a USA multicentre prospective study. Five-day treatment failure occurred in 16 (23%) of the 70 patients. Among the 16, 12 (17%) had uncontrolled bleeding within the first 48 hours of the index bleed and 4 (6%) had early rebleeding between days 2 and 5 (Fortune, 2017).

In a multicentre cohort study from Indianapolis, New York, Kansas City and Atlanta, Chalasani and colleagues compared the ability of MELD and C-P scores to predict mortality in 239 consecutive cirrhotic patients with acute variceal bleeding (Chalasani, 2002). The mean C-P and MELD scores were 8.8 ± 2.2 and 11 ± 8 and the in-hospital and 1-year mortality rates were 14.2% and 27%. The MELD score was predictive of in-hospital mortality (c-index: 0.82; 95% CI: 0.72–0.92). However, its prognostication was no different from the C-P (c-index: 0.85; 95% CI: 0.76–0.94). For 1-year mortality rates, MELD had a c-statistic of 0.75 (95% CI: 0.67–0.82) similar to the C-P score (c-statistic: 0.78; 95% CI: 0.70–0.86). The authors concluded that the discriminative ability of the MELD score to predict survival in cirrhotic patients with variceal bleeding was no better than the C-P score (Chalasani, 2002).

Laura Sempere and colleagues from Alicante in Spain investigated the prognostic indicators of short- and long-term survival in 201 cirrhotic patients with acute variceal bleeding (Sempere, 2009). Survival rate of the cohort was 77.1% at 6 weeks, 75.1% at 3 months, 65.7% at 12 months and 60.2% at 36 months. During follow-up, 96 patients (47.8%) died, 12 patients (6%) underwent liver transplantation, and 7 patients (3.5%) were lost to follow-up after discharge. Of the 96 deaths, 46 (47.9%) patients died of variceal

bleeding. The bleeding mortality rate was highest in patients with HCC 14/23 (60.8%) compared to patients without HCC 32/178 (17.2%). Age >65 years, HCC, C-P score >10, and MELD score >18 were associated with increased mortality in the multivariate analysis. The MELD score had a better discriminatory power than the C-P score in predicting mortality after VB at 6 weeks, 3 months, 12 months, and 36 months. The difference in accuracy between both models decreased in the prediction of long-term survival. The authors found that MELD and C-P scores together with age >65 and a diagnosis of HCC were useful indicators to assess the short- and long-term prognosis of patients with acute variceal bleeding (Sempere, 2009).

Amitrano and colleagues from Naples evaluated MELD score and the presence of HCC in predicting mortality in 172 cirrhotic patients admitted for the first episode of VB. Patient survival was evaluated at 6 weeks and 3 months (Amitrano, 2005). Fifty-four patients (31.4%) had HCC. Overall mortality was 21.5% at 6 weeks and 30.2% at 3 months. Mortality was 7.6% in patients with MELD scores <15 and 43.3% in patients with MELD scores >15 ($p < 0.0001$) at 6 weeks, and 14.3% in patients with MELD scores <15 and 55.2% in patients with MELD scores >15 ($p < 0.0001$) at 3 months, respectively. Mortality was increased in HCC patients compared to non-HCC patients at 6 weeks (31.5 vs. 17%; $p < 0.03$) or 3 months (51.8 vs. 20.3%; $p < 0.001$). Failure to control bleeding and early rebleeding were significantly more frequent as causes of death in patients with HCC than in patients without HCC at 6 weeks. Liver decompensation was the main cause of death and occurred more frequently in patients with HCC. The cut-off value of 15 points for the MELD score had the best sensitivity and specificity in distinguishing survivors from non-survivors, particularly if the MELD score was >15 with advanced HCC, the latter having independent prognostic significance for 3-month survival (Amitrano, 2005).

In a further study Amitrano and colleagues evaluated the risk factors affecting 5-day failure in 185 patients with liver cirrhosis and AVB. Hepatocellular carcinoma was present in 28.1% and portal vein thrombosis in 17.3% of patients (Amitrano, 2012). Five-day failure occurred in 16.8%; 12 patients (6.5%) had failure to control bleeding or early rebleeding, and 66.7% of patients died within 5 days. Overall 5-day mortality rate was 14.6%. Variables associated with mortality at 5 days were increased C-P and MELD scores, elevated WCC and advanced HCC. Using multivariate analysis, C-P grade C, WCC $>10^9/l$, and PVT were independent predictors of 5-day failure (Amitrano, 2012).

Bambha and colleagues from the Mayo Clinic investigated risk factors for 6-week mortality, and rebleeding within 5 days in 256 patients with cirrhosis and acute variceal bleeding (Bambha, 2008). Thirty-five patients (14%) died within 6 weeks. MELD score and units of packed red blood cells (PRBC's) transfused in the first 24 h were associated with 6-week mortality univariately (HR 1.11, $p<0.001$; HR 1.22, $p<0.001$) and bivariately (HR MELD = 1.10, $p<0.001$; HR per unit of PRBCs transfused = 1.15, $p = 0.005$). Patients with a MELD score >18 (HR = 7.4, $p<0.001$), both MELD score >18 and >4 units of PRBCs transfused (HR 11.3, $p<0.001$), both MELD score >18 and active bleeding at index endoscopy, and variceal rebleeding had increased risk of death 6 weeks post-acute variceal bleeding (HR 9.9, $p<0.001$; HR 10.2, $p<0.001$) (Bambha, 2008).

Despite widespread acceptance, several flaws of the C-P score as a prognostic indicator have been identified due to reliance on two subjective assessments (ascites and encephalopathy) which create inter-observer variations and hamper application in large datasets. In addition, the cut-points for the objective laboratory variables have never been validated and the C-P range with only 11 points (5 to 15) and three classes reduces C-P

utility for prioritization in organ allocation. In order to improve the discriminative ability of the C-P score for assessment of prognosis in cirrhotic patients with acute variceal bleeding three studies have created modifications to the Child-Pugh score to overcome existing limitations and are evaluated below.

Kaplan and colleagues identified new evidence-based cut-points for C-P laboratory values (INR, bilirubin, albumin) to improve predictive capacity for transplant-free survival in US military veterans (Kaplan, 2016). Using a cohort of over 9,000 cirrhotic US Veteran patients entered in the Veterans Outcomes and Costs Associated with Liver Disease (VOCAL) Study Group with 5-year follow-up, Cox proportional hazard survival model iterations were performed varying the upper and lower cut-points for INR, total bilirubin and albumin C-P scores. Cut-points yielding the highest Harrell's C-statistics for concordance with transplant-free survival were incorporated into a modified C-P (mC-P) score. Validation of the mC-P was performed at multiple time frames within the follow-up period of the cohort and within subsets defined by disease aetiology. The authors found that modification of the new C-P cut-points increased the Harrell's C-statistic for age- and gender-adjusted Cox proportional hazard models from 0.701 ± 0.002 to 0.709 ± 0.002 and the risk ratio per unit change from 1.49 (1.48–1.50) to 1.53 (1.52–1.54). The modified cut-points showed superiority in predicting 5-year transplant-free survival in various disease aetiology subgroups. A mC-P substituting serum creatinine for INR performed superiorly in predicting 5-year transplant-free survival. The authors concluded that the existing C-P cut-points do not optimally predict transplant-free survival, and defined new cut-points that provide better concordance with survival models. Compared to MELD, the current scoring system used for liver transplant allocation, both original and mCTP are superior predictors of intermediate- and long-term survival in their large cohort of cirrhotic patients (Kaplan, 2016).

Heuman and colleagues statistically re-examined the traditional cut-off points of C-P classification (A, B and C). The authors found that the A, B and C divisions were suboptimal for short-term prognosis in 599 cirrhotic patients referred for liver transplantation and proposed new C-P subclasses: A (5–6), B1 (7–8), B2/C1 (9–11), C2 (12 –13) and C3 (14–15). In the same study traditional C-P and MELD scores had similar discriminative ability for short- and long-term survival (Heuman, 2015).

In order to overcome the ceiling effect that may compromise the predictive power of C-P scores, Huo and colleagues from Taipei, Taiwan investigated the predictive ability of a refined CTP scoring method by awarding an additional point to cirrhotic patients who had serum albumin levels <2.3 g/dL, bilirubin levels >8 mg/dL and a prothrombin time prolongation >11 seconds (Huo, 2006). Using this score extension, a modified C-P score defined as class: A, 5–6 points; B: 7–9 points; C, 10–15 points; D, 16–18 points was used. The modified C-P system, containing class D, was compared to the MELD and original C-P system. Of the 436 study patients, 56 (12.8%) and 93 (21.3%) patients died at 3- and 6-month respectively. Using the c-statistic and mortality taken as the end point, the AUC for modified CTP was 0.895, compared with 0.872 for the MELD ($p=0.450$), and 0.809 for original CTP score ($p<0.001$) at 3 months. At 6 months, the AUC for modified CTP was 0.890, compared with 0.837 for the MELD score ($p=0.051$) and 0.756 for CTP score ($p<0.001$). The predictive ability of the modified C-P was always significantly better than original CTP system and was at least equal to or better than the MELD system at different time periods by comparing the AUC. The results showed that 23% of patients would have an increase of the C-P score for 1-3 points after modification; the vast majority (94%) of whom had an original score of 9 or higher. This strategy is useful to identify a subgroup of patients with severe hepatic decompensation who may have a dismal outcome, as reflected

by the significant trend of the shift of the scores from the original to modified model. The results suggest that this simplified approach may help refine the predictive ability of the C-P system without sacrificing the basic architecture or compromising the long-standing popularity. By extending the score range according to the influence of the laboratory-derived variables, the modified C-P system had a better performance than the original system and was as efficient as the MELD for outcome prediction in patients who are assessed for liver transplantation. A distinct feature of this study, however, is that most patients had chronic HBV infection which is prevalent in many Asian countries. A major limitation of this study is that the findings are not necessarily readily applicable to countries where alcohol is a common cause of end-stage liver disease (Huo, 2006).

Further proposals to improve the C-P score are the addition of creatinine and nutritional status, the latter a factor in the original Child score, and both of which are well-known parameters in deciding the prognosis in cirrhotic patients. Another factor to consider in the future is the addition of indicators of portal hypertension (presence or size of varices, previous bleeding, hepatic venous pressure gradient), which might improve the prognostic capacity of C-P score without losing any advantages. On the contrary, the MELD score may be best suited as a verifiable system in prioritizing candidates for liver transplantation, but factors affecting measurement of creatinine, such as different assays, gender and race, as well as different INR measurements must be accounted for in what is a justice system rather than utility system.

CHAPTER 3

THE PATHOPHYSIOLOGY OF VARICEAL BLEEDING

The contemporary management of bleeding oesophageal varices is based on a comprehensive understanding of the natural history of oesophageal varices, coupled with a detailed knowledge of the pathophysiology of portal hypertension and the consequences of cirrhosis and the resultant disruption of intrahepatic vascular architecture. The natural history of cirrhosis has a progressive and dynamic course, transitioning from a relatively stable state of compensated cirrhosis to an advanced stage of decompensated cirrhosis. Central to the dynamics of the transition is the degree of portal hypertension which serves as the primary driver of complications such as the development of varices, ascites, renal dysfunction, hepatic encephalopathy, hyperdynamic circulation and cardiomyopathy (Jagdish, 2023).

Varices are evident in one-third of compensated cirrhotic patients at diagnosis and in two-thirds of decompensated patients (Felli, 2023). The adaptative capacity of the portal circulation is individual-specific and is primarily dependent on the magnitude and extent of the intra- and extrahepatic collateral vascular connections between the portal and systemic circulations (Kaplan, 2023). From a pathophysiological and haemodynamic perspective, the most important clinically relevant collateral veins form at the gastro-oesophageal level, resulting in oesophageal varices in 60 to 70% of patients with varices (Ginès, 2021). The critical factor determining the clinical significance of portal hypertension and the development of complications is an increase in portal pressure above a threshold value (Figure 3.1). Variceal bleeding represents the final stage in a sequence of events initiated by a gradual increase in portal pressure, leading to the development and progressive

dilation of varices until finally rupture and bleeding occur (Krige, 2023). The threshold pressure for the development of varices in alcoholic cirrhosis is 12 mmHg (Garcia–Tsao, 2008), while variceal bleeding occurs at a threshold pressure of approximately 22 mmHg (Kaplan, 2023).

Significant advances in the understanding of the pathophysiology of portal hypertension have occurred in recent decades driven by the availability of new clinical evaluation methods, reliable experimental models and the application of recent progress in the understanding of cellular, molecular and systems biology (Bosch, 2015). Knowledge of the molecular mechanisms regulating both splanchnic and hepatic circulation has led to the development of emerging treatments based on evidence suggesting that both structural and vasoactive components, as well as angiogenesis contribute to an increase in hepatic vascular resistance (Cichoz-Lach, 2008; Bosch, 2015). Observations indicate that the formation of collateral veins, in response to portal hypertension, does not always result in sufficient decompression of the portal venous system and fails to adequately decrease portal pressure. This suggests that factors beyond anatomical mechanical resistance are involved in the development and persistence of portal hypertension (Tsai, 2007; Cichoz-Lach, 2008; Guixé-Muntet, 2024). In the portal hypertension model, pressure increases are due to elevated vascular resistance and a larger blood volume in the portal vascular bed. A further significant factor influencing portal pressure is increased blood flow in the portal circulation, resulting from hyperkinetic circulation, manifested as increased cardiac output and generalized vasodilation of the vascular bed (Felli, 2023). Increased portal flow further induces changes within blood vessels, enhancing vascular resistance (Guixé-Muntet, 2024).

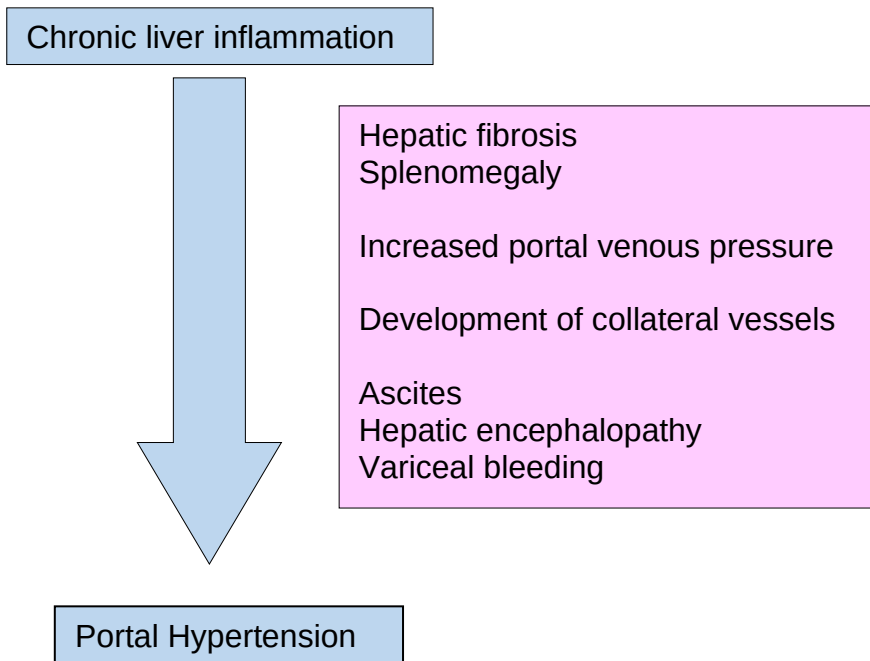


Figure 3.1 Sequence of clinical manifestations which occur as a consequence of chronic liver inflammation leading to a progressive increase in portal hypertension.

Prolonged liver damage triggers a cascade of structural and dynamic alterations that disrupt the hepatic microcirculation and are the primary instigators of portal hypertension during the progression of chronic liver disease (Guixé-Muntet, 2024). Overall, portal hypertension involves a complex interplay of factors including increased vascular resistance, altered blood flow dynamics and the intricate balance between intrahepatic vasoconstrictors and vasodilators. These mechanisms contribute to the development of increased vascular tone in the liver, emphasizing the importance of understanding these processes for effective treatment strategies. An elevated portal pressure which exceeds the normal threshold leads to portal hypertension and the compensatory development of an extensive peri-oesophageal and other collateral circulation which connects portal and systemic circulations (Felli, 2023).

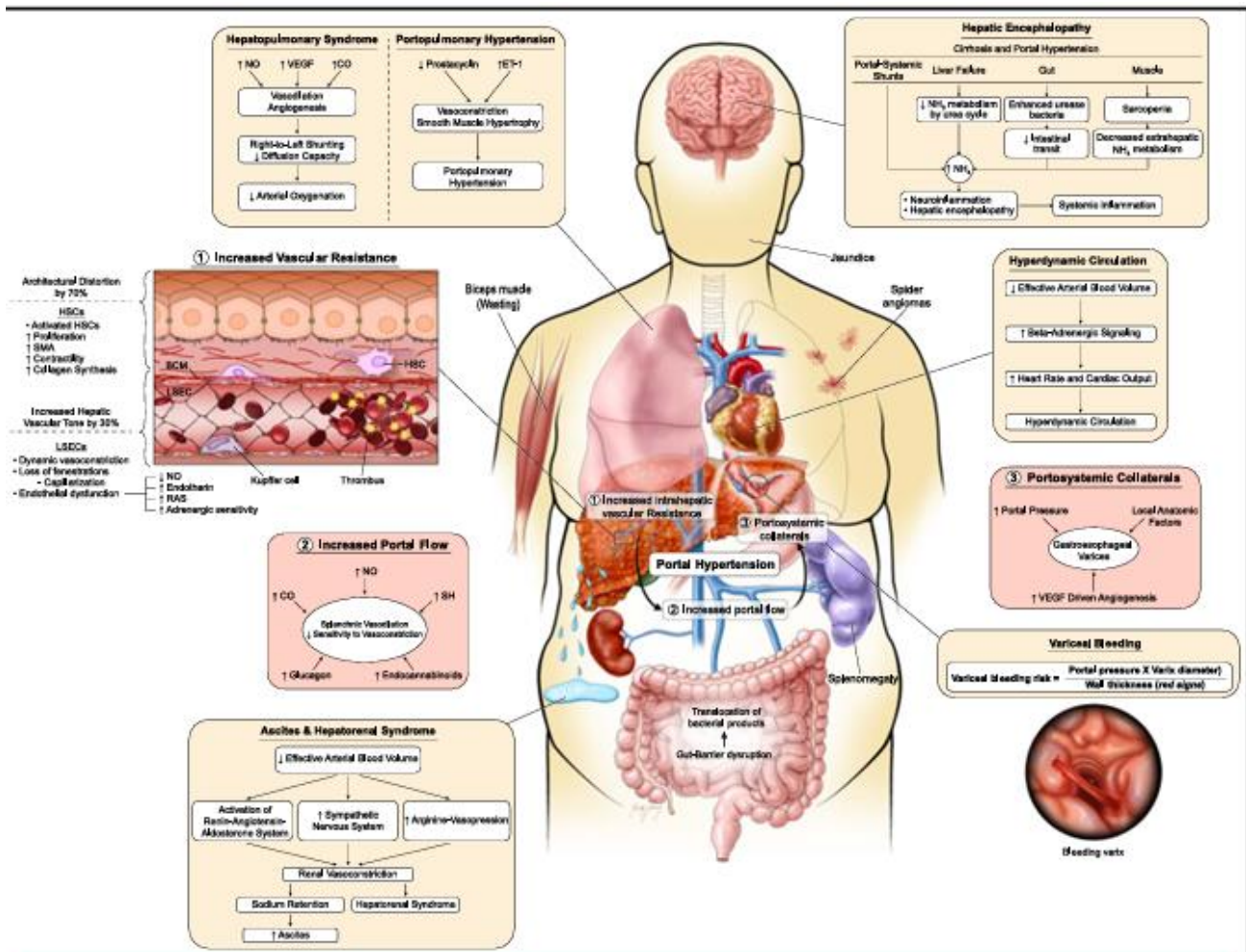


Figure 3.2 Pathophysiology of portal hypertension and related complications. Gastroesophageal varices represent the most clinically relevant collaterals because of the increased risk of bleeding which is directly dependent on increased variceal wall tension, determined by portal pressure, variceal diameter and wall thickness. (Kaplan D E. AASLD Practice Guidance on risk stratification and management of portal hypertension and varices in cirrhosis. *Hepatology* 2024;79:1180–1211).

Portal hypertension is the primary driver of the major complications encountered in cirrhosis and develops because of increased intrahepatic vascular resistance due to the impaired sinusoidal circulation and structural anatomical changes which occur in chronic liver disease (Figure 3.2). These morphological alterations follow increased extracellular matrix accumulation and fibrogenesis and cellular phenotype changes associated with liver sinusoidal endothelial cell dysfunction, hepatic stellate cell activation and inflammatory resident and infiltrating macrophages (Jagdish, 2023). The dysregulation of sinusoidal

endothelial and hepatic stellate cells is the principal element leading to increased vascular resistance, although hepatic microvascular thrombosis also plays a significant role in the development of portal hypertension (Turco, 2019). As a secondary event, portal hypertension induces splanchnic and systemic arterial vasodilation, leading to the development of a hyperdynamic circulatory syndrome and thereby aggravating clinically detrimental complications (Iwakiri, 2021). Splanchnic hyperperfusion is the result of severe changes in the extrahepatic vasculature including neoangiogenesis and hypocontractility of the splanchnic arteries. Although the gut-liver-axis also plays an important role in the development of complications of portal hypertension, the mechanical increase of portal pressure does not directly impair the gut barrier (Iwakiri, 2021).

The development of portosystemic collateral vessels prone to bleeding (i.e. varices) is one of the major causes of complications in portal hypertension. The understanding of the mechanisms underlying the formation of collateral vessels has evolved over the last decades. Early studies proposed that collateral vessels arose from passive dilatation of pre-existing venous channels due to increased intrahepatic resistance and portal venous inflow. More recent investigations suggest that collateral formation is not only induced by haemodynamic changes but also by vascular remodeling and structural adaptation in blood vessels induced by proangiogenic factors (Morales-Ruiz, 2020). These findings suggest the role of active molecular signalling in the formation of collaterals to counteract the increased intrahepatic resistance (Rudic, 1999).

Central to the development of portal hypertension is the occurrence of resistance at any point in the portal venous system, leading to a pressure gradient. Research has identified additional factors influencing portal blood flow and resulting in increased portal pressure.

Hepatic stellate cells found in liver perisinusoidal spaces and regulated by endothelial factors such as endothelin and NO, significantly modulate blood flow through hepatic sinusoids (Chen, 2008; Rockey, 2006; Reynaert, 2002). This process further exacerbates intrahepatic resistance to blood flow, thereby aggravating portal hypertension (Reeves, 2002; Ginès, 2021). Hepatic stellate cells are activated in response to chronic injury, leading to deposition of extracellular matrix protein and fibrogenesis, while liver sinusoidal endothelial cells undergo phenotypic remodelling resulting in capillarization of the sinusoids with decreased fenestrations and increased basement membrane thickness., thereby increasing intrahepatic resistance. This structural alteration impairs the exchange of substances between the sinusoidal lumen and hepatocytes, ultimately reducing hepatic perfusion (Figure 3.2).

Neurohumoral mechanisms triggered by portal hypertension promote splanchnic vasodilation, resulting in increased blood flow to the splanchnic organs. This redistribution of blood further exacerbates portal venous congestion and contributes to the progression of portal hypertension (Tsai, 2007; Cichoz-Lach, 2008; Krige 2009). Coupled with this, a dynamic component due to myofibroblast contraction and decreased vasodilators like nitric oxide further accentuate the resistance pathway. These two fundamental mechanisms lead to the progressive development of portal hypertension, leading to splanchnic vasodilation, neurohormonal disturbances, systemic vasodilatation, decreased mean arterial pressures, and an overall hyperdynamic state (Figure 3.1). In combination with these, gut microbial alterations, increased intestinal permeability, and systemic inflammation act as both precipitants and perpetrators of worsening portal hypertension and further downstream complications (Jagdish, 2023)

Persistent liver damage as occurs in chronic hepatitis B or C and continued excessive alcohol ingestion leads to cytokine and growth factors release and ultimately to fibrogenesis and pathological angiogenesis. Damaged hepatocytes release inflammatory mediators, recruiting leukocytes to the injury site with the release of pro-inflammatory mediators such as cytokines (tumour necrosis factor, interleukin IL-6 and IL-1 β), metalloproteinases, platelet-derived growth factor, connective tissue growth factor, transforming growth factor- β , fibroblast growth factor, and vascular endothelial growth factor (Lesmana, 2024). Hepatic stellate cells which differentiate into myofibroblasts, mediated by cytokines and growth factors, produce tissue fibrosis high in type I collagen which protects hepatocytes against further injury (Lesmana, 2024). Accumulation of inflammatory cells and tissue fibrosis increases resistance of the damaged cells to blood flow and oxygen supply, hence contributing to hypoxia. As a response to hypoxia, hepatic stellate cells release vascular endothelial growth factor and angiopoietin-1 which induce angiogenesis. Hypoxia also stimulates further inflammation leading to further fibrosis (Lesmana, 2024).

In conclusion, portal hypertension is a complex haemodynamic disorder characterized by increased pressure within the portal venous system. Understanding the underlying pathophysiological mechanisms is crucial for early detection, risk stratification, and targeted management strategies. Continued research into the molecular and cellular mechanisms driving portal hypertension holds promise for the development of novel therapeutic approaches and improved clinical outcomes for affected patients.

CHAPTER 4

THE IMPLICATIONS OF ALTERED OESOPHAGEAL VENOUS ANATOMY ON THE PERFORMANCE OF ENDOSCOPIC TREATMENT OF VARICES

A clear understanding of the altered gastro-oesophageal variceal anatomy due to the underlying pathophysiological changes in portal hypertension plays a key role in fully appreciating the rationale underpinning the application, efficacy and limitations of endoscopic therapy (Krige, 2009). The adaptations and changes that occur in oesophageal venous anatomy in patients with portal hypertension have significant acute, intermediate and long-term implications when endoscopic therapy, which deals directly with varices in the lower oesophagus, is used (Krige, 2009). Initial investigators faced logistical and technical complexities in accurately studying the venous anatomy of the lower oesophagus in patients with portal hypertension (Arakawa, 1983). The original anatomical studies involved injections of silicone rubber, resin and barium gelatin into cadaver and fresh post-mortem specimens to demonstrate oesophageal angioarchitecture (Arakawa, 1985; Butler, 1951; De Carvalho, 1966; Kegaries, 1934; Kitano, 1986; Noda, 1984; Vianna, 1987). Modern advances have led to better imaging techniques which, together with innovative and sophisticated investigations over four decades, have produced images that have provided a better insight and understanding of the venous anatomy of the lower oesophagus in portal hypertension (Spence, 1991, Spence 2000). These advances include percutaneous transhepatic portography and cineangiography, Doppler ultrasound (McCormack, 1983), histology using image analysis (Spence 1984a, 1984b) anatomical studies (Kitano, 1986), morphometry (Vianna, 1987) corrosion casting, multidetector computed tomographic techniques utilising three-dimensional image software, endoscopic ultrasound (Irisawa, 2001) and subsequently ultrasound microprobes (Obara, 2006).

Despite these advances, several clinically fundamental questions regarding the altered venous anatomy in portal hypertensive patients remained. These relate to (i) the reason the largest varices occur in the lower third of the oesophagus and why this site bleeds most frequently, (ii) why varices have a propensity to recur after apparently effective initial endoscopic eradication, and (iii) the significance of the endoscopically visible cherry spots and red “wale” markings present on varices. Elegant studies by Vianna and colleagues from the Liver Unit at King’s College Hospital in London, by Kitano and colleagues from Cape Town and by Spence and colleagues from Belfast have addressed these relevant questions by demonstrating and defining the morphology and histology of the oesophageal venous levels and the intrinsic oesophageal anatomical layers in portal hypertensive patients.

In a seminal study of the normal anatomy of the distal oesophagus, Vianna used a combination of radiographic techniques, corrosion casting, and morphometry to describe four zones of venous drainage, (i) a 2-3 cm gastric zone below the gastro-oesophageal junction draining into the short and left gastric veins, (ii) a 2-3 cm palisade zone superior to the gastric zone, acting as a watershed between portal and systemic circulations, (iii) a perforating zone 2 cm above the palisade zone, with perforating veins connecting intrinsic and extrinsic venous systems by joining submucosal to para-oesophageal venous plexuses, (iv) a 8-10 cm long truncal zone with perforating veins joining submucosal to extra-oesophageal veins. These investigators suggested that this anatomic pattern implied that venous flow was bidirectional in the palisade zone which acted as a high-resistance watershed between the portal and azygos systems (Vianna, 1987). In patients with portal hypertension the normal vascular system has to accommodate substantially increased venous flow and the alterations in anatomy as demonstrated have offered an insight into variceal development (Kriger, 2009). The palisade and perforating zones are important in

the context of oesophageal variceal ligation in which the objective is obliteration of the submucosal veins in the palisade zone followed by thrombosis of the perforating veins which connect the submucosal varices to extra-oesophageal collaterals (Kapoor, 2015)

In an innovative investigation of oesophageal and upper gastric portal hypertensive venous anatomy by Kitano et al, a refined resin-casting technique was used in fresh cadavers with portal hypertension and oesophageal varices to provide a three-dimensional image and a high-level resolution view of the angioarchitecture of the oesophageal microvasculature (Figures 4.1, 4.2) (Kitano, 1986). Four layers of veins were identified: (i) intra-epithelial channels, (ii) a superficial mucosal venous plexus, (iii) deep intrinsic veins and (iv) adventitial veins (Figure 4.3). The study confirmed the presence of perforating veins in the distal oesophagus. The superficial venous plexus communicated with the deep venous plexus, the peri-oesophageal collateral veins and the para-oesophageal collateral veins through the perforating veins (Kitano, 1986). In light of the anatomical findings in this study, Kitano and colleagues postulated that major variceal bleeding occurred as a result of rupture of large deep intrinsic variceal channels adjacent to the epithelial surface, or from a major branch of the superficial venous plexus near a direct connection to a large varix (Kitano, 1986). This study clarified the anatomy of oesophageal varices and the authors suggested that the venous communications were probably partly responsible for the recurrence of varices after sclerotherapy (Kitano, 1986). The detailed anatomy of the critical zone of bleeding provides a clue to the pathogenesis of variceal rupture (Spence, 1987). The constant perforating veins of the distal oesophagus and interconnections between layers of veins may explain the re-appearance of varices after eradication (Terblanche, 1983; McCormack, 1983; Spence, 1987).



Figure 4.1 A cross-section resin cast of the lower oesophagus and upper stomach showing two large tortuous deep intrinsic variceal channels with an overlying superficial venous plexus (Kitano, British Journal Surgery, 1986)

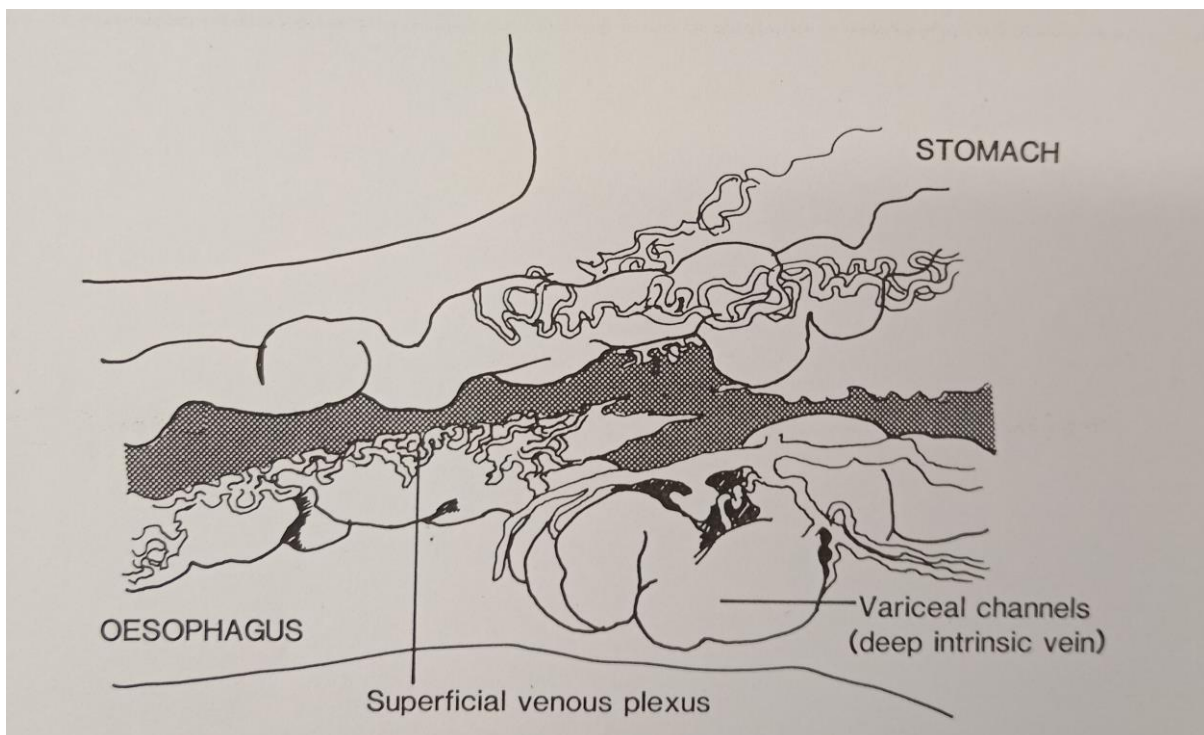


Figure 4.2 Diagram of the above resin cast (Kitano, British Journal Surgery, 1986)

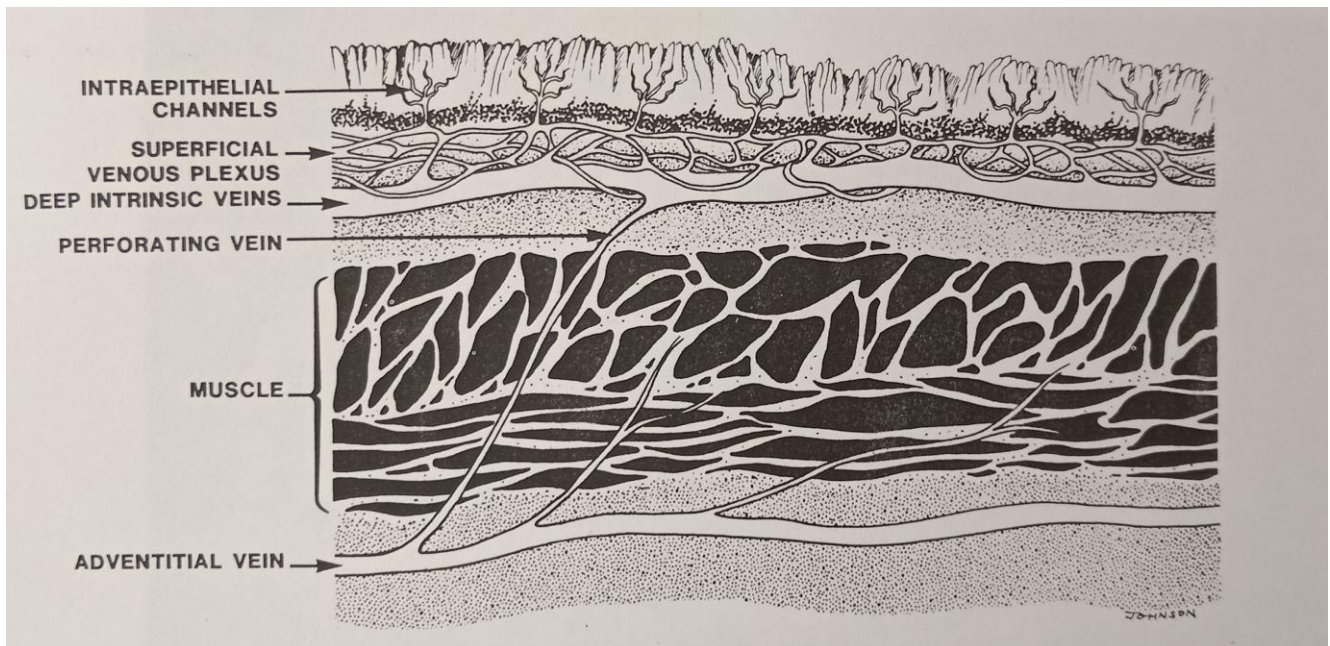


Figure 4.3 Diagrammatic representation of the four layers comprising the oesophageal venous drainage (Kitano, British Journal Surgery, 1986).

In an original histological study, Spence examined oesophageal rings after transection for varices and demonstrated dilated intraepithelial blood-filled channels which were present in all the specimens. In a comparison between rings removed from variceal patients and those removed during resections for oesophageal and gastric tumours, intra-epithelial channels were significantly larger and more numerous in varices patients ($p < 0.01$). Similarly, the area and number of dilated subepithelial channels beneath the epithelium and the area of lamina propria channels were significantly greater in the varices patients ($p < 0.05$). Depth of papillae and thickness of the squamous epithelium were also significantly greater in the varices group ($p < 0.05$, $p < 0.01$ respectively). Under electron microscopy the channels were lined with flattened cells which were not typical of endothelial cells but stained positively for Factor VIII-related antigen using indirect immunofluorescence. The authors proposed that these channels may correspond to the cherry-red spots seen on endoscopy and may have a role in the pathogenesis of variceal bleeding (Spence, 1983).

In a subsequent investigation Spence and colleagues used a quantitative computer assisted image analysis system to study the microvasculature of the lower oesophagus in 20 normal and seven specimens from patients with varices. Three zones were identified, zone 1 in the upper stomach, zone 2 from the oesophagogastric junction to 2-5 cm proximally into the lower oesophagus, and zone 3 which represented the remainder of the oesophagus. The mean relative area of veins in the lamina propria in each zone was measured. In zone 1 the mean relative area was 2.6% in normal specimens and 3.7% in variceal patients. In zone 2 the mean area of lamina propria veins increased to 19.8% in normal and 32.8% in variceal specimens and in zone 3 was 4.9% and 6.1% in normal and variceal specimens respectively (Table 4.1).

Table 4.1 Microvasculature analysis of lower oesophagus (Spence, 1984a, 1984b)

Zone 1-3	Normal specimens	Variceal specimens
Zone 1	2.6%	3.7%
Zone 2	19.8%	32.8%
Zone 3	4.9%	6.1%

The increase in area in the distal oesophageal veins was due to an increase in both the number and size of vessels in the lamina propria of Zone 2. The authors suggested that this observation may explain the tendency for oesophageal varices to bleed principally in the distal oesophagus (Spence, 1984a, 1984b).

Refinements in the understanding of lower oesophageal venous anatomy and the significance of persistent patent perforating veins in the lower oesophagus in patients with varices undergoing endoscopic treatment has been the subject of further investigations.

The development of EUS and other imaging systems has made it possible to observe collateral vascular structures and evaluate the vascular networks connected to variceal columns. Endoscopic ultrasonography with a mini-probe (EUM) has evolved as an important tool to identify and map oesophageal varices, para-oesophageal collateral veins as well as perforating veins in and around the oesophageal wall. EUM enables accurate measurements of para-OCV and OV sizes and the location of the perforating veins. The collateral deep veins seen on EUM are related to recurrence of OV. Several studies have evaluated the role of EUS in predicting OV recurrence after EVL. Leung et al. and Lo et al. reported that OV recurrence and bleeding increased significantly in patients with the severe-grade para-OCV's (Leung, 2023; Lo, 2024). Konishi et al. showed that patients who had OV recurrence after EVL were more likely to have severe-grade PV before treatment than those without recurrence ($p<0.01$). Furthermore, early recurrence (≤ 3 months) of OV after EVL was closely related to the presence of severe-grade gastric cardiac PV's, compared to mild PVs ($p<0.01$) (Konishi, 2022).

Although EVL is less invasive than sclerotherapy, variceal recurrence after EVL remains a significant problem and is higher in patients undergoing EVL which obliterates only mucosal and submucosal varices compared to sclerotherapy which thromboses deeper oesophageal veins, including perforating veins and para-oesophageal collaterals (Hou, 1995). Usually many of these perforating veins have valves that direct the flow away from the oesophageal lumen. Venous dilatation, occurring with increased pressure, causes these valves to become incompetent, allowing retrograde flow (Toyoda, 2001). Recurrence of oesophageal varices after endoscopic therapy depends on several factors, including the presence of perforating veins, the endoscopic technique used, the difference of anatomical features of

para-oesophageal collaterals and the development of the extravariceal collateral channels (Obara, 2006). The hypothesis that flow into the varices through perforators may be

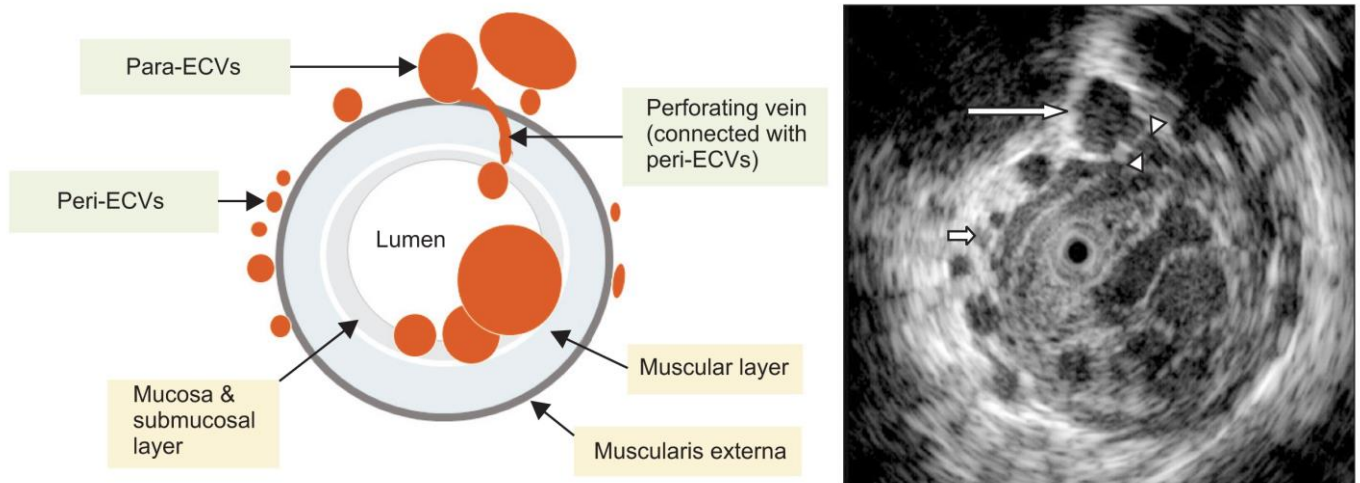


Figure 4.4. A schematic diagram showing oesophageal varices and vascular structures around the oesophageal wall using endoscopic ultrasonography with a mini-probe. Long arrow, para-oesophageal collateral veins (ECV's); short arrow, peri-ECV's; arrow head, perforating veins. From: Soung Won Jeong et al. Useful Endoscopic Ultrasonography Parameters and a Predictive Model for the Recurrence of Esophageal Varices and Bleeding after Variceal Ligation. Gut and Liver 2017;11:843-851

<https://doi.org/10.5009/gnl16458>

involved in oesophageal variceal dilatation and bleeding is supported by recent endoscopic ultrasound evaluation in which the number and diameter of perforating veins positively correlates with the size of oesophageal varices (Irisawa, 2001).

In a study from Seoul, Korea, Soung Won Jeong and colleagues assessed the usefulness of EUS to create a predictive model for oesophageal variceal recurrence and bleeding following EVL (Figure 4.4). Oesophageal variceal recurrence occurred in 42 of 144 patients (29.2%) after EVL, 10 of whom had variceal bleeding. Large diameter para-oesophageal

veins and the presence of perforating veins were significant predictive factors for variceal recurrence and bleeding after EVL (Jeong, 2017).

In a subsequent prospective cohort study which included 206 cirrhotic portal hypertension patients who underwent endoscopic variceal intervention (EVL or IST or EVL plus IST), Zheng and colleagues evaluated endoscopic ultrasound probe (EUP) findings to predict recurrence after oesophageal variceal eradication (Zheng, 2019). EUP was performed to evaluate peri-oesophageal collateral veins (peri-OCVs), perforating veins (PV) and para-oesophageal collateral veins (para-OCVs) every 6 months for up to 3 years. In addition, computed tomography (CT) was done to determine portal vein diameter, portal vein embolus, and major portosystemic collateral shunts. The relationship between oesophageal variceal recurrence and EUP findings was analysed. As many as 93.5% of patients developed recurrent oesophageal varices after 13.4 months (13.4 ± 9.2 months) during the 3-year follow-up. The median time to recurrence after EVL, IST and EVL plus IST was 10, 13 and 12 months, respectively. The risk factors, EVL ($p < 0.01$), Child-Pugh score ($p < 0.05$), large peri-OCVs ($p < 0.0001$) and PV ($p < 0.001$) were significantly associated with the recurrence of oesophageal varices (Zheng, 2019).

These findings were further substantiated by a study by Qi and colleagues who systematically evaluated the prevalence and association of oesophageal collateral veins (OCV's) with recurrence or rebleeding from oesophageal varices after endoscopic treatment (Qi, 2015). The authors searched PubMed, EMBASE, and Cochrane Library databases to determine and pool the prevalence of para-oesophageal veins (para-OVs), peri-oesophageal veins (peri-OVs) and perforating veins (PVs). The pooled prevalence of para-OVs, peri-OVs, and PVs in 28 identified papers was 73%, 88%, and 54%, respectively. The pooled prevalence of para-OVs and PVs in patients with recurrence of oesophageal varices

was 87% and 62%, respectively. The risk for recurrence of oesophageal varices was significantly increased in patients with PVs but not in those with para-OVs. Patients with para-OVs had a significantly higher incidence of rebleeding from oesophageal varices.

CHAPTER 5

ENDOSCOPIC METHODS USED IN ACUTE VARICEAL BLEEDING

5.1 The evolution of endoscopic variceal intervention

The treatment of variceal bleeding was dominated initially by operative intervention, first with portocaval shunt surgery and followed by operative modifications, in particular, selective splenorenal shunting pioneered by Dean Warren, designed to mitigate the problems of symptomatic post-shunt encephalopathy. Shunt surgery was followed by a quadruple paradigm shift into the modern era management of variceal bleeding and liver decompensation with the introduction of β -blockers, the development of liver transplantation, advances in transjugular portosystemic stent shunting and the evolution of endoscopic variceal intervention, initially with sclerotherapy and rigid oesophagoscopy, followed by fibre-optic and video endoscopy and then single and later multiband variceal ligation. (Figure 5.1).

The first report of endoscopic sclerosant injection into oesophageal varices to control variceal bleeding was in 1939 by two Swedish surgeons, Clarence Crafoord and Paul Frenckner after the latter had designed a modified needle which could be advanced down a rigid Jackson oesophagoscope to inject 6ml of quinine into bleeding oesophageal varices. This was followed by the pioneering work of Herman Moersch, a thoracic surgeon at the Mayo Clinic in Rochester, Minnesota and Cecil Patterson and Milford Rouse from Baylor University Hospital who presented their long-term results of injection sclerotherapy at the American Gastroenterological Association Meeting in Atlantic City, New Jersey in 1947 and

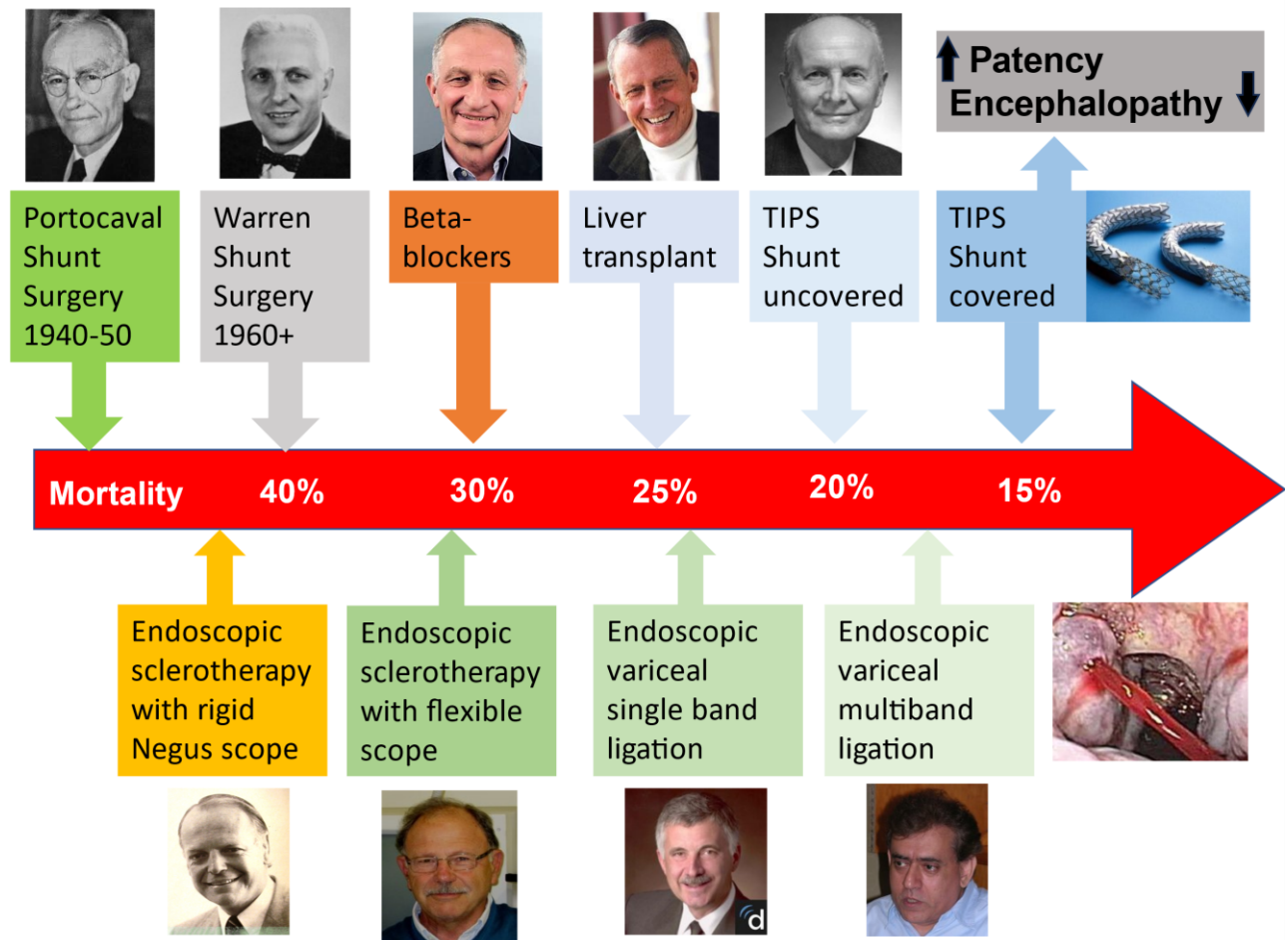


Figure 5.1 Historic variceal timeline showing the treatment development and the improvement in overall mortality over six decades from 40% in 1960 to 15% in 2020.

TOP panels: Left to right. Introduction of portocaval shunt surgery by Alan Whipple; the Dean Warren selective shunt; beta-blockers by Didier le Brech; liver transplantation by Tom Starzl; TIPS by Joseph Rosch.

BOTTOM panels: Left to right. The modern trial era of endoscopic variceal intervention was pioneered in Cape Town in 1978 by John Terblanche using the rigid Negus oesophagoscope for sclerotherapy; Flip Bornman introduced flexible fibre-optic sclerotherapy in a randomized controlled trial which compared fibre-optic to rigid oesophagoscopy; Greg Stiegmann pioneered single shot variceal banding in Denver; Zahid Saaed introduced the disposable multishot bander.

published their data in the same year in JAMA and Gastroenterology. Despite the initial enthusiasm and reported successes of endoscopic injection sclerotherapy, the introduction and increasing popularity of portocaval shunt operations by Blakemore and Whipple in 1946 overshadowed injection sclerotherapy which was used infrequently during the following two

decades (Krige, 2009). The next major clinical series in which injection sclerotherapy was used to control variceal bleeding was by Ronald Macbeth from Oxford who reported his experience in 30 patients in the British Medical Journal in 1955. Two important points highlighted in his report were that no serious complications occurred after injection sclerotherapy and, secondly, Macbeth stressed the need for further follow-up oesophagoscopy at six-month intervals following initial obliteration to identify and treat recurrent varices. Renewed interest in sclerotherapy was stimulated by a publication in 1973 by George Johnson and Harold Rodgers from Belfast and in Europe, Wodak and subsequently Pacquet introduced a successful paravariceal injection technique. In 1975 Bailey and Dawson described their modification of the rigid 50 cm Negus oesophagoscope in which a narrow 4cm slot was cut in the distal end opposite the beak as in a Gabriel proctoscope (Bailey, 1975). This modification was a major technical advance and facilitated the injection of varices as the slot allowed a varix to prolapse into the lumen of the oesophagoscope which gave improved visibility and allowed accurate and controlled intravariceal injection of sclerosant through the long offset angled needle (Krige, 2009).

However, by 1975, almost 40 years after the first use of injection sclerotherapy to control variceal bleeding, there still were no controlled data to confirm the efficacy of sclerotherapy and, in particular, whether survival was increased in treated patients (Westaby, 1983). To provide this important information, Terblanche in Cape Town initiated the first prospective controlled trial in August 1975 and published the results in 1979. In the 25-month study which included 64 patients with oesophageal varices, 24 patients were actively bleeding from varices and were treated with a Sengstaken-Blakemore balloon tube, and in 22 this was followed by emergency injection sclerotherapy using a rigid esophagoscope and general anaesthesia. These 22 patients were followed prospectively and had 51 episodes of endoscopically proven active bleeding from oesophageal varices which required

Sengstaken-Blakemore balloon tube control of bleeding during 36 separate admissions. Definitive control of variceal bleeding was achieved in 33 hospital admissions (92%), usually with a single injection (27 hospital admissions: 75%). The results were satisfactory in 26 (72%) hospital admissions. There were nine deaths (41% overall patient mortality rate), but no patient died primarily of variceal bleeding. The mortality rate per hospital admission was 25%. Injection sclerotherapy was proposed as the emergency treatment of choice for patients with proven bleeding oesophageal varices who do not stop bleeding on initial conservative treatment (Terblanche, 1979a). In a later analysis 31 patients were randomized, 15 to chronic injection group and 16 to a control medical management group. Varices were eradicated in the chronic injection group and once eradicated, no patient had recurrence of variceal bleeding (Terblanche, 1979b). The results of this trial, together with subsequent reports on the use of sclerotherapy in the management of acute variceal bleeding, led to a resurgence of interest in sclerotherapy. This was followed by the Kings College group in London who reported their initial experience using sclerotherapy and subsequently in two further papers with larger numbers (Macdougall, 1982; Westaby, 1985).

The next phase in the evolution of endoscopic intervention and haemostatic control of variceal bleeding was by Williams and Dawson from Kings College Hospital who reported that a flexible fibre-optic endoscope passed through an outer sheath was able to provide effective control of acute variceal bleeding (Williams, 1979). A subsequent and important prospective randomised trial from Cape Town compared rigid with fibre-optic endoscopy and demonstrated that flexible endoscopy was as effective as rigid endoscopy in both controlling acute variceal bleeding and achieving variceal eradication. In addition, the trial resulted in fewer oesophageal complications, including oesophageal perforation and

strictures (Bornman, 1988). The results of these trials established sclerotherapy as the pre-eminent endoscopic intervention for the treatment of variceal bleeding (Terblanche, 1989).

As the endoscopic technique evolved, experience showed that the overtube was not necessary during injection sclerotherapy, even for acute variceal injection sclerotherapy, and the use of the overtube became redundant (Krige, 2009). In a benchmark randomised controlled trial from Cape Town, elective injection sclerotherapy using flexible fiberoptic endoscopy as an outpatient procedure under conscious sedation was shown to be safer and as effective as rigid oesophagoscopy (Bornman, 1988). In this study undertaken during a 3-year period from June 1981 to July 1984, 70 patients who had endoscopically proven variceal bleeding were randomised to receive either fiberoptic injection sclerotherapy (IST, 36 patients) or a rigid scope technique (RIS, 34 patients), using ethanolamine oleate as the sclerosing agent. Control of the acute bleeding episode (IST 91%, RIS 95%) and the first hospital admission mortality (IST 34%, RIS 44%) were similar. Eradication of varices was achieved in 16/19 and 13/16 patients in the two respective groups of patients who survived longer than 3 months, and only 2 patients (both in the RIS group) had further major variceal bleeding. The overall complication rate per injection was significantly lower in the IST group ($p < 0.005$). Twenty-six patients (14 IST, 12 RIS) were alive at the end of the 4-year trial period. Of the total of 44 deaths, only 3 were not associated with a bleeding episode. Only five of the 29 patients who had their varices eradicated died during the trial period (median follow-up: 16 months). This study also stressed the importance of achieving eradication of all varices to prevent rebleeding and its attendant high mortality (Bornman, 1988).

The next landmark in the evolution of endoscopic variceal treatment was the development of variceal banding by Stiegmann from Denver, Colorado (Stiegmann, 1992; Stiegmann, 1996). Stiegman and Goff developed the first endoscopic ligation prototype which used an

elastic band stretched over a barrel attached to the tip of an endoscope to provide a single band delivery system. This required the placement of an overtube in the oesophagus for ease of passage of the banding equipment (Stiegmann, 1986). Subsequent technical progress and endoscopic engineering development led to a disposable multiband delivery system which could load and apply as many as six bands sequentially to varices without the need to reload or to use an overtube (Stiegmann, 1992; Stiegmann, 1996; Saeed, 1996). Commercially available multiband devices have replaced injection sclerotherapy and single shot banding in most centres world-wide. Further advances in endoscope development have led to video endoscopy and narrow diameter endoscopes which are easier to pass and are better tolerated by the patient (Krige, 2024).

5.2 INJECTION SCLEROTHERAPY OF OESOPHAGEAL VARICES

Control of the acute bleeding episode is the single most important predictor of outcome and survival in the management of variceal bleeding. To achieve this, the correct endoscopic variceal injection or banding technique is crucial. To standardize globally accepted endoscopic techniques for both injection sclerotherapy and variceal band ligation to achieve optimal outcomes and minimize procedure-related complications, the Cape Town group have provided detailed step-by-step instruction monographs and technical guidelines for both injection sclerotherapy and variceal band ligation methods which are summarised below (Krige, 2015; Krige, 2019; Krige, 2024).

Endoscopic injection sclerotherapy was developed (i) to control the initial acute variceal bleeding episode and then (ii) to eradicate residual varices and prevent rebleeding. Unlike specific standardised operations developed for the treatment of varices, sclerotherapy has been performed worldwide with varying protocols using irregular frequencies of injection

intervals and duration of variceal follow-up and endoscopic review (Krige 2009). A number of clinical and technical variables influence the success of endoscopic intervention of bleeding oesophageal varices (Krige 2024). Several relevant patient-dependent variables influence and increase the complexity of variceal management. These variables include the aetiology of portal hypertension and underlying hepatic reserve as the outcome in patients with either alcohol- or hepatitis-induced cirrhosis have different natural histories, especially when liver decompensation is evident, compared to varices secondary to portal vein thrombosis where liver reserve and parenchyma are preserved and normal (Krige, 2009).

Technical variables, including injection method and site, sclerosant type and solution concentration, cumulative sclerosant volume and frequency of subsequent injections may all affect the outcome of any individual sclerotherapy session or clinical trial assessment (Krige, 1999). The above variables demonstrate that sclerotherapy techniques have, to a large extent, been empiric and individualized (Krige, 2000b). As several fundamental sclerotherapy concerns regarding implementation and methodology remained indeterminate and imprecise, it is thus not surprising that the outcome of a number of controlled trials that have compared sclerotherapy with other interventions, including variceal ligation, have yielded conflicting and differing results (Krige, 2005; Krige, 2009a).

5.2.1 Injection sclerotherapy techniques

Three basic but different endoscopic techniques have been developed and used for injection sclerotherapy (Figure 5.2.1). Bleeding from oesophageal varices can be controlled by injecting sclerosant directly into the variceal channel (“intravariceal method”), or into the submucosa overlying the variceal column (“paravariceal method”) or a combination of both methods. In the intravariceal technique, 1 to 5 ml of sclerosant is injected directly into the

variceal lumen above the gastro-oesophageal junction and a further sclerosant injection given into the same variceal column more proximally. The volume of sclerosant injected will depend on the size and grade of the varix, smaller volumes, 1-2 ml for grade 1 or 2 varices while up to 5 ml can be used in grade 4 or 5 varices (Krige, 2009). The objective of the intravariceal injection technique is to produce thrombosis of the variceal column and, after

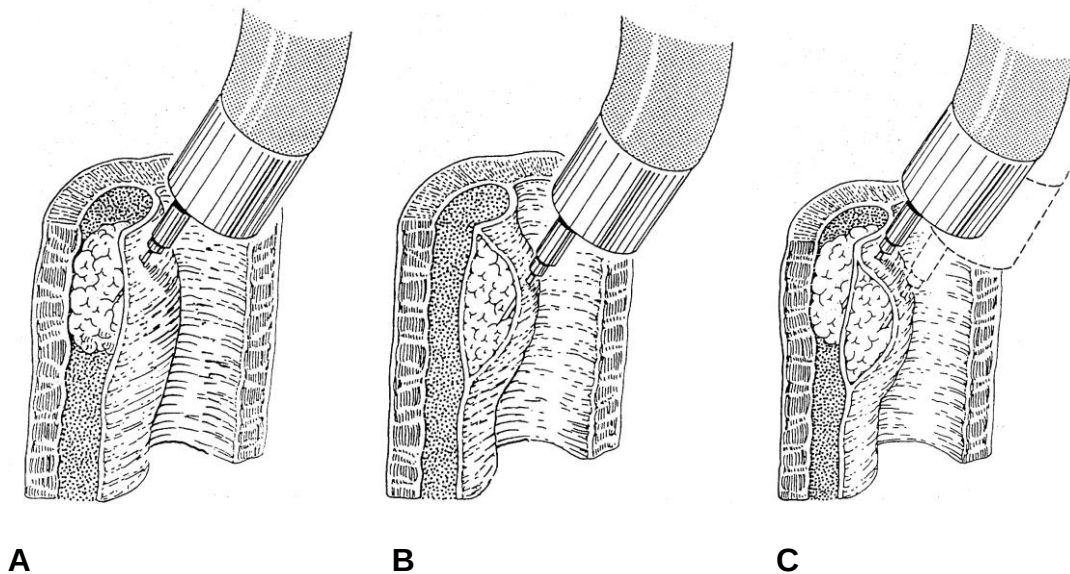


Figure 5.2.1 Technical variants of injection sclerotherapy. **A:** Intravariceal injection **B:** Paravariceal or submucosal injection. **C:** Combined intravariceal and paravariceal injections (Krige, Mastery of Surgery, 8th Ed. 2024)

repeated injections, to result in eventual eradication of the variceal channels in the lower oesophagus where the propensity for bleeding is greatest (Krige, 2023). The paravariceal or submucosal injection, when applied during an acute variceal bleeding episode, causes oedema of the submucosa overlying the varix which will result in a tamponading effect over the bleeding site and thus control acute variceal bleeding (Krige, 2007a; Krige, 2009; Krige, 2024).

5.2.2 Emergency sclerotherapy technique

5.2.2.1 Intravariceal Injection

Effective control of active variceal bleeding requires technical skill and precise positioning of the sclerotherapy needle and careful and accurate delivery of sclerosant into the correct location to safely staunch bleeding (Krige, 2009). Urgent control of bleeding with exact placement of the needle and sclerosant injection into the varix is undertaken promptly while there is adequate visibility and it is safe to proceed (Figure. 5.2.2). After bleeding has been

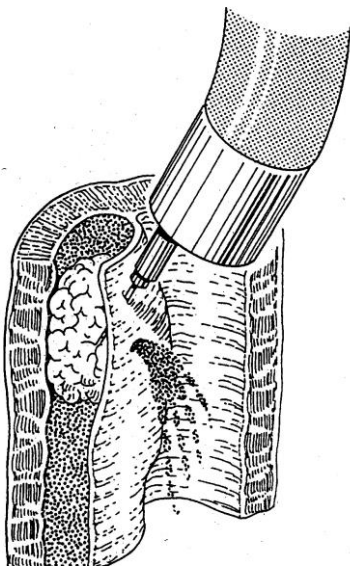


Figure 5.2.2 Emergency sclerotherapy: intravariceal injection technique (Krige, 2024).

controlled, the remaining variceal channels are sclerosed. A second series of injections is then performed at a higher level (Krige, 1996; Krige, 2009; Krige, 2024).

5.2.2.2 Combined paravariceal and intravariceal injection technique

This is the injection technique recommended by the Cape Town endoscopy unit to control active variceal bleeding. A small volume of sclerosant (1-2 ml 5% ethanolamine oleate) is first injected submucosally (“paravariceal”) 1 cm proximal to the bleeding site to tamponade the bleeding point. The procedure is then completed by injecting sclerosant into the variceal

lumen using the intravariceal technique (Figure.5.2.3). The remaining variceal channels are then sclerosed. (Krige, 1996; Krige, 2007b; Krige, 2009; Krige, 2024).

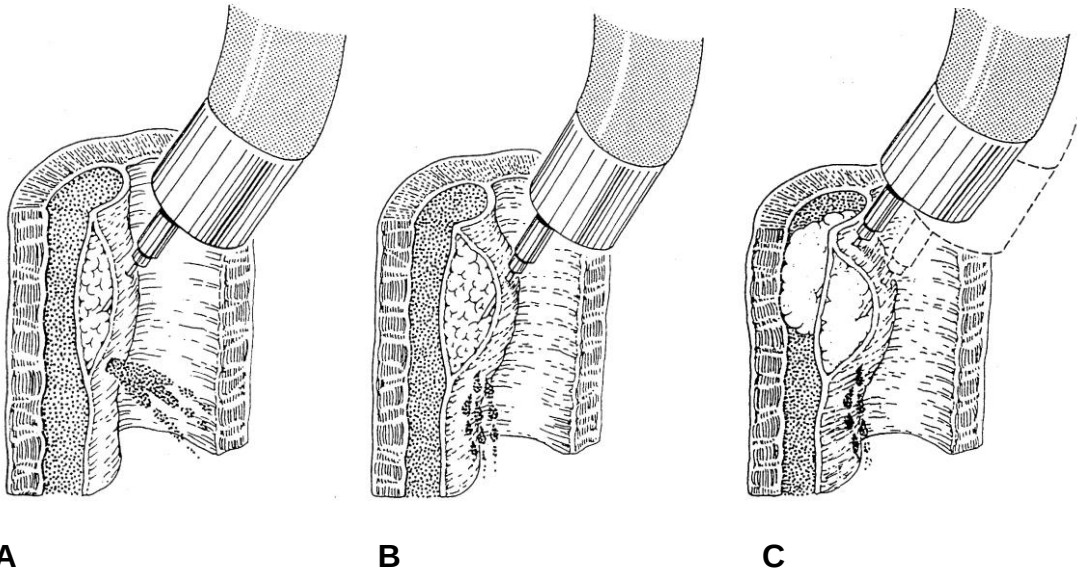


Figure 5.2.3 Emergency sclerotherapy: combined paravariceal and intravariceal injection technique. **A:** The initial paravariceal injection proximal to the bleeding point. **B:** Bleeding is controlled by the paravariceal submucosal injection. **C:** An intravariceal injection completes the procedure (Krige, Mastery of Surgery, 8th Ed. 2024).

5.3 ENDOSCOPIC VARICEAL BAND LIGATION

The concept and subsequent development of endoscopic variceal band ligation represented a seminal advance in the endoscopic treatment of varices and evolved to become an essential therapeutic keystone in managing acute variceal bleeding. The principles of band ligation are based on the fundamental understanding of the pathophysiological and anatomical changes in the intricate venous drainage of the oesophagus in portal hypertensive patients. The objective of banding is to obliterate the enlarged submucosal veins in the palisade zone, which is followed by thrombosis and obliteration of the perforating veins that connect the submucosal varices to extra-oesophageal collateral veins (Stiegmann, 1990).

The prototype equipment and technique of variceal ligation was developed by Stiegmann and colleagues from Denver, Colorado, as an alternative endoscopic method to treat oesophageal varices. The expectation was that ligation would be as effective as sclerotherapy but with fewer local procedure-related complications (Stiegmann, 1986). Ingenious medical engineering led to the system that uses small elastic “O” bands which are stretched and loaded onto a cylinder which is then attached to the tip of an end-viewing endoscope. During deployment the varix is sucked into the cylinder and is ensnared at its base when the band is dislodged, resulting in strangulation, necrosis and sloughing of the thrombosed varix and band about a week later. Six to eight elastic bands can be applied to the variceal columns during each endoscopy session.

During the initial experimental development and testing, canine model varices were treated by endoscopic band ligation using a flexible gastroscope and the recently developed elastic band ligating device attached to the tip of the gastroscope (Stiegmann, 1986). In the study, 37 oesophageal variceal sites in the dog model underwent endoscopic variceal ligation with successful ligation on the first attempt at 34 (92%) sites. Gross and microscopic examination of the treated sites 1-60 days later showed ischaemic necrosis of mucosa and submucosa after 24 hours, with an acute local inflammatory response, demarcation of viable and necrotic tissue and the appearance of granulation tissue after 3 to 7 days. Full thickness replacement of mucosa and submucosa with maturing scar tissue and near complete re-epithelialization occurred after 14 to 21 days and complete healing occurred after 50 to 60 days. Inflammation and scar tissue deposition consistently obliterated submucosal venous channels but left the muscularis propria intact. No perforations or other adverse clinical or histological effects occurred. Stiegmann concluded that endoscopic ligation of canine oesophageal varices was safe and resulted in effective obliteration of

vascular channels in the submucosa by a process of inflammation and scar formation (Stiegmann, 1986).

Encouraged by the success in the canine model, Stiegmann undertook a pilot study in humans. One hundred consecutive patients with bleeding oesophageal varices were treated with the newly developed endoscopic ligating device by applying the elastic "O" rings. As in the canine model, haemostasis was achieved by physical constriction at the base of the varix by the deployed rubber band, resulting in ischaemic necrosis of the strangulated mucosa and submucosa trapped within the band, followed by sloughing of the banded varix. The resulting shallow mucosal ulcer re-epithelialized over the following 14 to 21 days with scarring and shrinkage of the residual varix due to maturing fibrous tissue. Further banding of residual varices was continued after initial hospitalization to achieve variceal eradication. Follow-up ranged from 6 to 26 (mean:15) months. Bleeding was controlled until discharge from hospital or death in 18 of 21 patients who were actively bleeding at the index endoscopy. Overall, 26 patients died during the study, 12 during the index hospitalization. Forty-one of 88 initial survivors experienced 72 episodes of recurrent bleeding (1 to 4 per patient). All but five rebleeds occurred before eradication. Sixty of 88 patients (68%) who survived index hospitalization had their varices eradicated. A median of 5 (1-12) treatments were required. Only three non-bleeding complications resulted from 462 endoscopic treatment sessions. Stiegmann concluded that endoscopic ligation controlled active variceal bleeding and eradicated varices with efficacy rates similar to that of sclerotherapy and with minimal risk of complications (Stiegmann, 1990).

As the development of banding equipment progressed, the initial single-band delivery system which was the original prototype was subsequently replaced by the newer and

disposable multiband ligator. The original Stiegmann single-band apparatus allowed the deployment of only one variceal band at a time and required the placement of an oesophageal overtube to allow multiple withdrawals and safe re-insertions of the endoscope and the attached ligating cap. The difficulty of inserting and rail-roading the rigid plastic overtube over the endoscope and the prolonged banding procedure necessary as the cap could only carry a single band at a time requiring repeated reloading with a fresh band after firing led to the development of the more efficient and safer modern banding instrument. The attachment of the new multiband apparatus onto the end of the endoscope allowed the sequential delivery and serial placement of eight to ten individual bands during a single insertion of the endoscope, obviating the need for the cumbersome and uncomfortable overtube. The band ligation procedure was repeated at 2 to 3 weekly intervals until all the varices were obliterated or were too small to be safely sucked into the cap and banded (Krige, 2024).

5.3.1 Technique of endoscopic band ligation

(i) Single-shot banding

The banding technique is similar whether performed for an acute variceal bleed or for elective banding (Krige, 2024). Diagnostic panendoscopy is performed first and after confirming the need for variceal banding, the endoscope is removed and an overtube is backloaded by railroading the tube over the endoscope. The oesophageal overtube facilitates repeated re-introduction and removal of the endoscope and banding cap but increases patient discomfort and the potential for complications during insertion. Reloading the single-band ligator prolonged the banding procedure which was problematic, especially

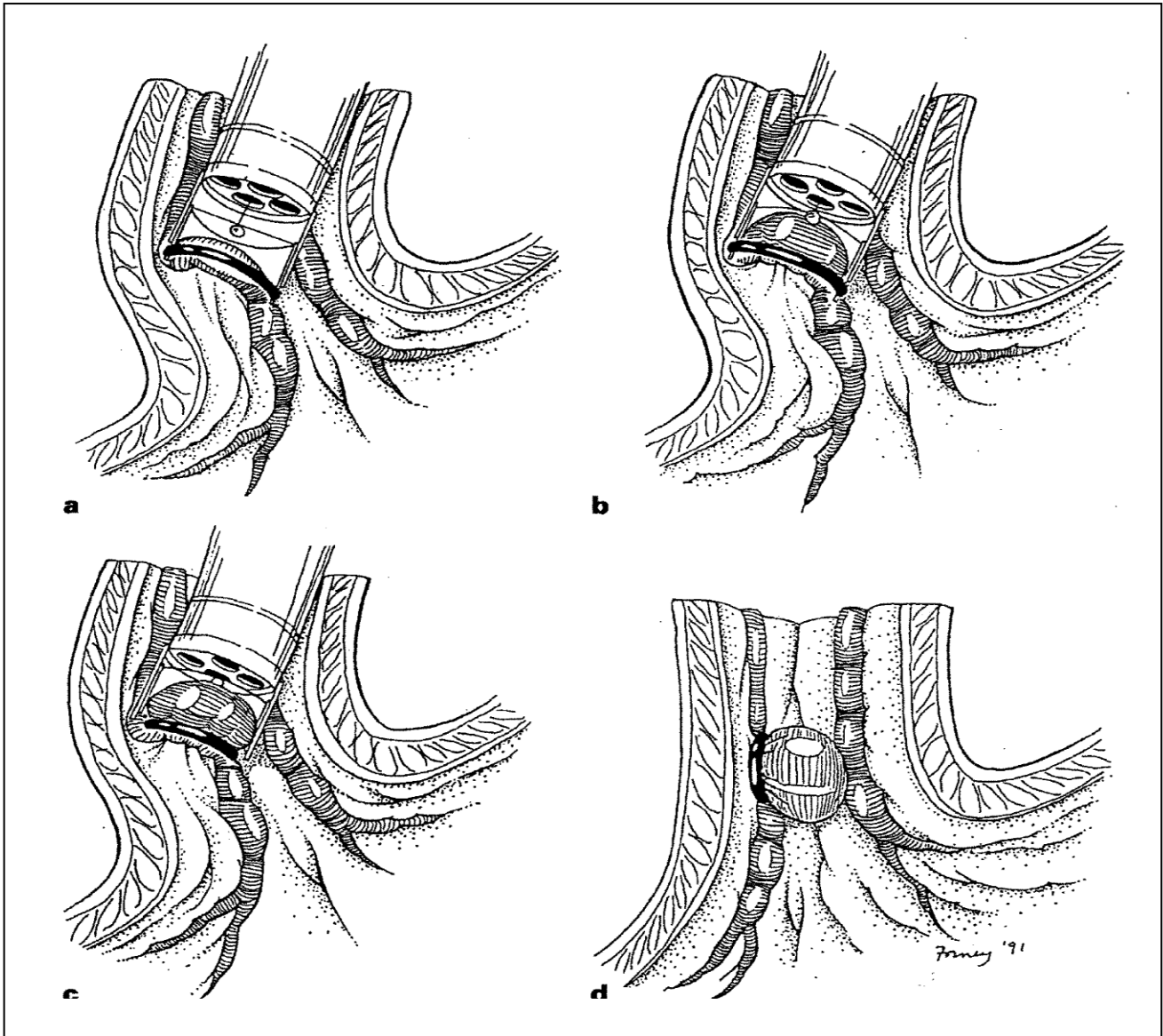


Figure 5.3.1 Endoscopic band ligation A-D. Endoscopic ligation of oesophageal varices using the flexible endoscope. **A.** Varix is approached under direct vision by the endoscopist. Full contact is made between the end of the ligating device and the tissue to be ligated. **B.** Endoscopist activates the endoscopic suction, which results in aspiration of oesophageal mucosa, submucosa, and the varix into the ligating device. **C.** A trip wire (which runs through the biopsy channel of the endoscope) is pulled, which moves the inner cylinder (over which the elastic **O** ring is stretched) toward the endoscope, displacing the small elastic band. **D.** The elastic band encircles the neck of the now ligated tissue, resulting in strangulation and thrombosis (Krige, Mastery of Surgery, 8th Ed. 2024).

during active bleeding or with poor patient tolerance. The endoscope is passed into the stomach and the lubricated overtube is advanced over the scope into the oesophagus using a corkscrew technique to facilitate easy passage through the cricopharyngeus sphincter. The endoscope is withdrawn and the banding cap is attached to the end of the endoscope. The nylon trip wire is passed through the vacuum lock of the biopsy channel entry port and exits via the distal biopsy channel opening and is attached to the clasp on the inside of the loaded inner cylinder. The endoscope is passed into the lower oesophagus and the target varix is identified and with manipulation the endoscope tip is positioned under direct vision so that the banding cylinder is in full 360-degree contact with the varix (Figure 5.3.1A). Once full contact is made, suction is applied which draws the varix and the surrounding mucosa into the banding chamber (Figure 5.3.1B). Once the chamber is completely filled with the varix, a "red-out" view occurs indicating that the band can be fired and released. In the single shot banding technique the trip wire is pulled to dislodge the latex **O** ring from the inner cylinder allowing the **O** ring to become securely attached around the base of the target varix (Figure 5.3.1C+D). With the availability of multishot ligators which are safer and more convenient, single shot banders are now seldom used (Krige, 2024).

(ii) Multiband application:

To overcome the cumbersome limitations of the original single band device which involved sequential reloading and reinsertion of the endoscope into the oesophagus, multiple band ligating devices, which include the Saeed Multiple Ligator (Wilson-Cook Medical, Inc, Winston-Salem, NC, USA) and the Speedband Superview Super 7 Multiple Band Ligator (Boston Scientific Corporation, Natick, MA, USA) have been developed. There are some design variations in the various banding devices available, including the availability of up to 10 bands depending on the commercial model chosen (Figure 5.3.5). However, the same

banding principles apply. The band ligator is attached onto the tip of the endoscope and the trigger cord is passed up the endoscope channel and anchored in the slot on the rotating

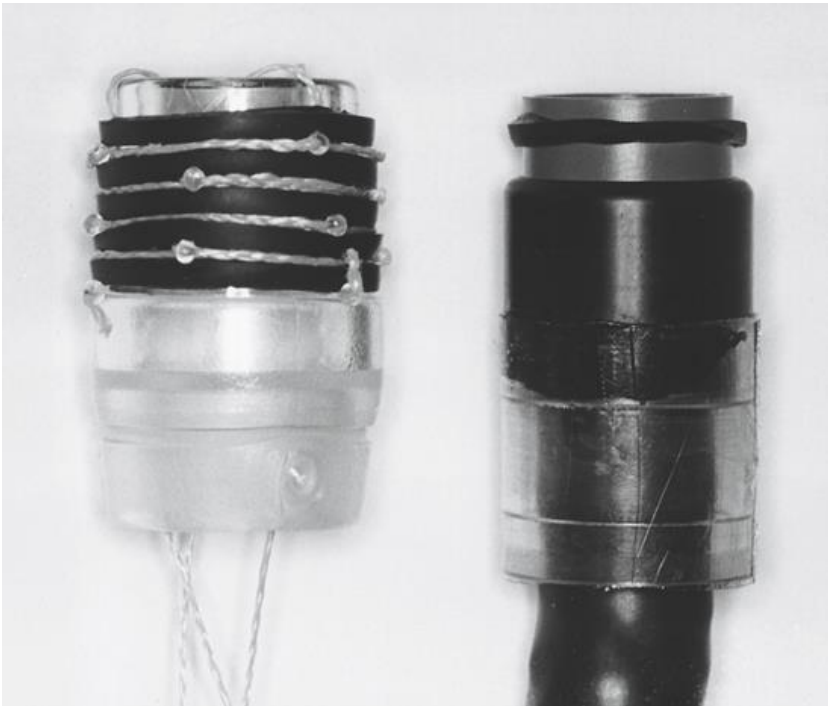


Figure 5.3.2 Loaded multiband (L) and single variceal banding (R) caps (Krige,2024).



Figure 5.3.3 Loaded single variceal banding cap with nylon trigger cord attached to an inner clasp.

spindle mounted at the biopsy channel port. After advancing the endoscope towards the target varix, suction is applied until “red out” occurs due to filling the cap by the varix and surrounding mucosa. The preloaded bands on the cap barrel are deployed one by one by rotation of the spindle which shortens the trigger cord and releases the stretched band which constricts the neck of the suctioned varix. Further tightening of the trigger cord allows repeated individual firing of the bands as the drawstring is shortened (Krige, 2024).



Figure 5.3.4 Speedband ® Multiple Band Ligator (Boston Scientific ®) loaded multiband cap with 6 bands and trigger cord displayed



Figure 5.3.5 Wilson-Cook ® banding device demonstrating the vacuum-assisted cap and delivery mechanism designed to deploy 6 elastic bands during a single oesophagoscopy session.

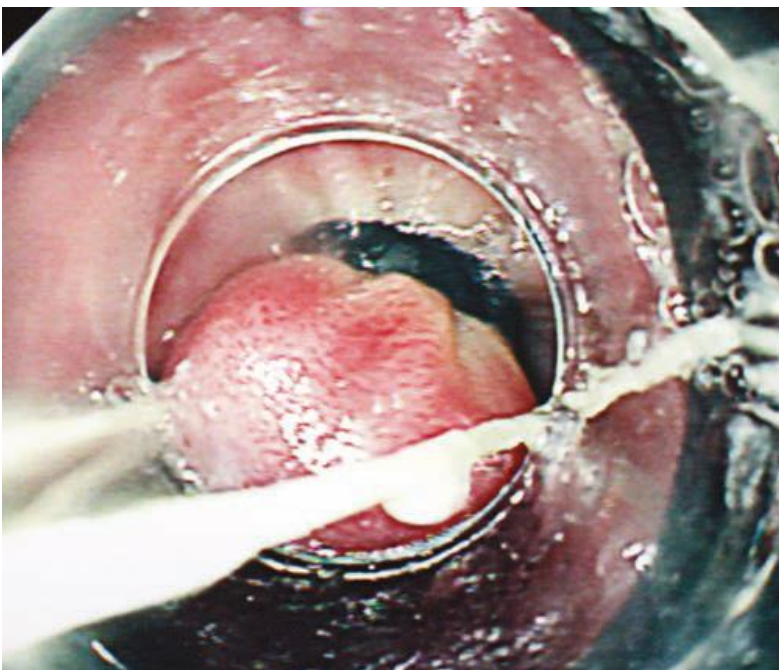


Figure 5.3.6 Endoscopic view of ligated varix with deployed band at variceal base.

As with single-shot banding, treatment begins with ligation of the culprit bleeding varix or alternatively, in the absence of bleeding, ligation of the most inferior part of the target variceal column (Figure 5.3.6). A single band is placed at its lower end and the next band applied to the adjacent variceal column at a slighter higher level in a spiral pattern. Large varices have additional bands placed more proximally, 2 to 5 cm higher up the oesophagus. On average, a total of six bands are applied during the initial session, although in the case of extensive grade 5 varices, up to 10 bands can be placed. Progressively fewer bands are required at subsequent sessions as the varices decrease in size and extent.

Three technical tips are useful when using the multiband ligator. The endoscopist should ensure that the silastic friction mount of the banding chamber is snugly attached to the end of the endoscope and that no air leaks are present. A loose fit may result in dislodgement of the cap on withdrawal. As the ligating cap and attached bands are larger than the end of the endoscope, the endoscopist may have difficulty passing the tip of the endoscope through the cricopharyngeus and the patient may experience discomfort at the back of the throat and gag while trying to swallow the cap on the tip of the endoscope. Liberal lubrication with KY jelly on the outside of the cap and flexing the patient's neck and the scope as the tip passes over the back of the patient's tongue will usually resolve any difficulty in passing the endoscope and allow smoother passage. The nursing staff should confirm that the wall suction is set at maximum to ensure that the varix will be sucked fully into the ligating chamber to allow the band to be deployed correctly at the base of the varix and encompass the entire varix. Technical difficulties with band deployment may occur during major variceal bleeding if blood clot fills the chamber while the endoscopist attempts to suck the bleeding varix into the chamber before releasing the band. In this situation, elevation of the head of the table and vigorous irrigation through the endoscopy channel will

usually dislodge the clot from the chamber and improve visibility. Once the bleeding varix is banded and bleeding is controlled, further bands can then be applied to the remaining varices. An important technical point is not to release suction until a band has been securely applied. This is necessary to avoid partial or incomplete banding where insufficient variceal tissue volume has been incorporated and captured by the band, which increases the risk of the band slipping or becoming dislodged with resultant and possibly major iatrogenic recurrent variceal bleeding (Krige, 2024).

Reduced visibility due to blood accumulating within the device chamber (or due to the ligating device itself) can make EVL challenging. If visualization is limited due to active bleeding, bands can be placed on the variceal columns at the gastroesophageal junction without identifying a specific varix. This approach may reduce variceal blood flow and result in less bleeding, and directed and precise band placement can then be accomplished once the field of vision improves. The suction cap on the tip of the endoscope reduces the operator's field of vision by 30%, which is a disadvantage when treating actively bleeding varices because blood clot may pool in the suction cap and further reduce visibility. The new transparent caps have improved visibility (Krige, 2024).

CHAPTER 6

COMPARATIVE STUDIES EVALUATING THE RELATIVE EFFICACIES OF ENDOSCOPIC VARICEAL LIGATION AND INJECTION SCLEROTHERAPY IN THE TREATMENT OF ACUTE VARICEAL BLEEDING

Five meta-analyses have evaluated the relative efficacies of EVL and IST for the treatment of patients with bleeding oesophageal varices. The first meta-analysis by D'Amico et al. included three RCT's and 309 patients in which pooled odds ratios (POR, 0.49; CI 0.31-0.78) showed a significant benefit from EVL (D'Amico, 2002).

A subsequent meta-analysis by Laine included seven randomized trials which showed that EVL reduced rebleeding (OR, 0.52 [95% CI, 0.37 to 0.74]), mortality (OR, 0.67 [CI, 0.46 to 0.98]), and death due to bleeding (OR, 0.49 [CI, 0.24 to 0.996]) compared with sclerotherapy (Laine, 1995).

The third meta-analysis assessed 12 trials involving 1309 patients. Seven of the trials included only patients with cirrhosis and in eight trials, a ligating device with an overtube was used. The median haemostatic efficacy of IST was 95% (76%-100%) compared with a median of 97% (86%-100%) for EVL ($p=0.4$) with a 2.5% difference favouring ligation (95% CI 0.4% to 4.6%) ($P=0.018$). The mortality percentage difference was 1.3%, favouring ligation (95% CI -2.3% to 4.9%) ($p=0.46$) (Triantos 2006).

A fourth meta-analysis which included 13 trials and 1,091 patients showed that the risk of variceal rebleeding was significantly reduced by EVL (POR 0.46, 95% CI 0.35-0.60) and while there were no significant differences in mortality, complications were significantly less frequent and less severe with EVL and the number of endoscopic sessions needed to achieve eradication was significantly lower than with sclerotherapy (de Franchis 2007).

The fifth and most recent meta-analysis by Dai et al. comprised 14 studies and 1236 patients and showed that EVL was significantly superior to IST with lower rebleeding and complication rates and higher rates of variceal eradication (Dai, 2015). In patients with actively bleeding varices undergoing EVL, rebleeding was significantly lower (RR=0.68, 95% CI: 0.57-0.81) and variceal eradication higher (RR=1.06, 95% CI: 1.01–1.12) in comparison to IST. The complication rate was significantly lower with EVL compared to IST (RR=0.28, 95% CI: 0.13-0.58) (Dai, 2015).

All these published meta-analyses however, have limitations that may influence the validity of the data and conclusions. Early studies included single band ligation devices which required repeated loading and passage through an oesophageal overtube, a cumbersome technique now outdated and replaced with modern multiband ligators. Sclerotherapy techniques in these studies were also not standardised and varied widely in sclerosant type, strength and volume used. In addition to variable needle size, the injection techniques also differed, with either intravariceal, paravariceal or combined methods applied. Treatment intervals and schedules also varied. Furthermore, included in the meta-analyses were studies from diverse countries with substantial differences in patient ethnicities, portal hypertension aetiologies, severity of hepatic decompensation and extent of oesophageal varices. The trials included in the meta-analyses also showed conflicting results due to inconsistencies in design which included short patient follow-up of less than 6 weeks, heterogenous populations, some with a predominance of patients with schistosomiasis, hepatitis B or C, or only extrahepatic portal vein occlusion or only children. In one trial in the meta-analysis more than half the patients had no history of variceal bleeding and received endoscopic intervention as primary prophylaxis, while in another trial patients were

randomized to either EVL or combined EVL and IST, factors that should have excluded these studies from the meta-analysis (Krige, 2020).

In a corrected updated evaluation of the 17 published randomized trials (Table 11.1, page 238) which compare EVL with IST, EVL performed significantly better than IST in controlling bleeding (2 trials), with less rebleeding (5 trials), less endoscopy-related complications (13 trials), achieving variceal eradication in fewer endoscopy sessions (11 trials) and improved survival (2 trials). However, varices recurred significantly more commonly after EVL than IST in 3 trials (Krige, 2020). These 17 published peer-reviewed prospective randomised trials comparing the efficacy of EVL versus IST are presented below.

EVL compared with IST in controlling and preventing variceal rebleeding; an analysis of 17 RCTs

In the first prospective randomised controlled trial comparing EVL to IST and published in the *New England Journal of Medicine* in 1992, Stiegmann and colleagues from the Department of Surgery at the University of Colorado in Denver conducted a multicentre study which entered 129 patients of whom 64 were randomly assigned to EVL and 65 to IST (Stiegmann, 1992). Four centres participated in the study, the University of Colorado in Denver, Baylor College of Medicine in Houston, Texas, the University of Southern California in Los Angeles and the Oregon Health Sciences University in Portland. Sclerotherapy used 3% STS diluted with saline to a 1% solution. Endoscopic ligation was performed using a Bard EVL single band device and an overtube. Active bleeding at the first treatment was controlled by sclerotherapy in 10 of 13 patients (77%) and by ligation in 12 of 14 patients (86%). More sclerotherapy-treated patients had recurrent bleeding during the study (48% vs. 36% for the ligation-treated patients, $p=0.072$). The eradication of varices required a

lower mean ($\pm$ SD) number of treatments with ligation (4 ± 2 vs. 5 ± 2 , $p=0.056$) than with sclerotherapy. The mortality rate was significantly higher in the sclerotherapy group (45% vs. 28%, $p=0.041$), as was the rate of complications (22% vs. 2%, $p<0.001$). The complications of sclerotherapy were predominantly oesophageal strictures, pneumonias, and other infections. The authors concluded that patients with cirrhosis who have bleeding oesophageal varices have fewer treatment-related complications and better survival rates when treated by EVL than by IST (Stiegmann, 1992).

Laine and colleagues conducted the second RCT which compared the safety and efficacy of IST and EVL in patients with BOV at the University of Southern California. Seventy-seven patients were randomised and treatment repeated weekly until variceal obliteration was achieved. After eradication, patients had endoscopic examinations every 3 months or for any episode of rebleeding. Recurrent varices were treated with the originally assigned form of endoscopic therapy. In the study patients were assessed for further bleeding, transfusion requirements, time in hospital, variceal eradication, number of treatment sessions required, complications, treatment failure and for risk of death. Rebleeding tended to be less frequent with EVL than with IST: 10 of 38 (26%) compared with 17 of 39 (44%) (difference, 17% [95 CI, -4% to 38%]), but the results in the two groups were comparable for blood transfusions, for length of hospital stay, and for risk of death. Comparison of Kaplan-Meier estimates of time to rebleeding and death showed no statistical differences between treatments. Complications were less common in the EVL group: fewer patients in the ligation group had oesophageal strictures (0 of 38 compared with 13 of 39 [33%]; $p<0.001$) and had fewer complicated oesophageal ulcers (1 of 38 [2.6%] compared with 6 of 39 [15%]; $p=0.11$). In addition, fewer ligation treatments were required to achieve variceal eradication (4.1 ± 0.3 compared with 6.2 ± 0.4 ; $p<0.001$). The authors concluded that EVL causes fewer local

complications than IST and achieves variceal eradication more rapidly and that ligation is a viable alternative to IST and may have some advantages as a treatment for bleeding oesophageal varices (Laine 1993).

In a study from King's College, London, Gimson and colleagues randomised 103 patients to either EVL or IST. Fifty-four patients were assigned to EVL and 49 to IST of whom 21 (39%) and 23 (47%), respectively, had active bleeding at index endoscopy. EVL used a Bard ligation device with an overtube and IST was performed using intravariceal 5% ethanolamine oleate. Both treatments were highly effective in controlling active bleeding (91% and 92% respectively). Variceal obliteration was not achieved for 22 patients in each group, but among those whose varices were eradicated, banding ligation achieved obliteration more quickly than did sclerotherapy (mean 39 [SD 4] vs 72 [7] days, $p=0.004$) and in fewer endoscopy sessions (3.4 [2.2] vs 4.9 [3.5], $p=0.006$). Rebleeding was less common in the banding ligation group than in the sclerotherapy group (16 [30%] vs 26 [53%], $p<0.05$). There was no difference in outcome between the groups, but 14 sclerotherapy patients were withdrawn from the trial (seven for orthotopic liver transplantation) compared with only five (one for liver transplantation) in the ligation group ($p<0.05$). Complication rates were similar in the two groups. The authors concluded that EVL is a safe and effective technique which obliterates varices more quickly and with a lower rebleeding rate than IST (Gimson, 1993).

In the fourth RCT Lo and colleagues from the Department of Medicine, Veterans General Hospital-Kaohsiung, National Yang-Ming University in Taipei, Taiwan, randomised 120 patients with bleeding oesophageal varices to either EVL or IST. All the patients were cirrhotic, 59 received IST and 61 received EVL. Treatment was repeated regularly until the

varices were obliterated. The mean follow-up period was 295 $\pm$ 120 days and 310 $\pm$ 105 days for the IST and EVL groups, respectively. Control of active bleeding was 12/15 (80%) in the IST group and 18/19 (94%) in the EVL group ($p=0.23$). The numbers of treatment sessions required to achieve variceal obliteration were 6.5 $\pm$ 1.2 in the IST group and 3.8 $\pm$ 0.4 in the EVL group ($p<0.001$). Recurrent bleeding from the gastrointestinal tract was 51% in the IST group compared with 33% in the EVL group ($p<0.05$). Recurrent bleeding from oesophageal varices was 36% in the IST group and 11% in the EVL group ($p<0.01$). However, bleeding from ectopic varices and congestive gastropathy was less common in the IST group (7%) than in the EVL group (18%) ($p=0.05$). Significant complications were encountered in 19% of the IST group and in 3.3% of the EVL group ($p<0.01$). Comparison of Kaplan-Meier estimates of time to death of both groups showed a significantly lower mortality in the EVL group ($p=0.011$). The authors concluded that both IST and EVL effectively arrest active bleeding from OV but that EVL was more effective than IST in decreasing the risk of rebleeding from OV with fewer complications and that EVL achieves obliteration of OV more rapidly than IST (Lo, 1995).

In the fifth RCT Hou and colleagues from the Department of Medicine, Veterans General Hospital-Taipei in Taiwan, randomised 134 cirrhotic patients to either EVL or IST. The clinical and endoscopic characteristics were similar in both groups. Active bleeding was controlled with EVL (20 of 20) as efficiently as with IST (14 of 16). Elective IST was quicker than ligation (7.9 $\pm$ 1.8 minutes vs. 11.5 $\pm$ 2.7 minutes, $p<0.001$), but there was no difference between emergent sclerotherapy (14.5 $\pm$ 5.8 minutes) and ligation (14.9 $\pm$ 4.1 minutes). Ligation reduced one grade of variceal size more quickly than sclerotherapy (1.1 $\pm$ 0.4 vs. 2.0 $\pm$ 1.7 session, $p<0.001$). The rebleeding rate was lower with ligation (13 of 67 vs. 28 of 67, $p<0.01$). Oesophageal ulceration was the most common source of

rebleeding. Recurrence of varices was more likely with ligation ($p=0.079$). The complication rate was higher with IST (15 of 67 vs. 3 of 67, $p<0.01$), with oesophageal strictures the most common cause. Survival rate was the same in both groups even after stratifying patients into good and poor hepatic reserve groups. Hepatic failure was the major cause of death, followed by exsanguination. The authors concluded that EVL was superior to IST with regard to rebleeding and complications but not in other aspects such as time to complete an elective procedure and recurrence of varices (Hou, 1995).

In the sixth RCT Sarin and colleagues from the G.B. Pant Hospital in New Delhi, India randomised 95 patients with variceal bleeding to receive weekly endoscopic sclerotherapy using alcohol ($n=48$) or endoscopic variceal ligation ($n=47$). The IST and EVL groups were comparable in aetiology, severity of liver disease and grade of varices. Endoscopic sclerotherapy and EVL were comparable in controlling acute variceal bleeding, (86% vs. 80%, $p=ns$). Endoscopic variceal ligation obliterated oesophageal varices in fewer sessions (4.1 ± 1.2 vs. 5.2 ± 1.8 , $p<0.01$) and a shorter time (4.4 ± 1.3 vs. 6.9 ± 3.4 weeks, $p<0.01$) than IST. Three (6.4%) patients rebled after EVL and 10 (20.8%) after IST ($p<0.05$). The actuarial percentage of variceal recurrence during a follow-up of 8.5 ± 4.4 months, was higher after EVL than IST (28.7% vs 7.5%, $p<0.05$). Oesophageal stricture formation after IST occurred in five (10.4%) patients, but in none after EVL. Significantly more patients developed gastropathy after IST than EVL (20.5% vs. 2.3%; $p=0.02$). Endoscopic sclerotherapy (52%) and EVL (59%) were equally effective in obliterating lesser curve gastric varices. Six patients died: three in each group. The authors concluded that (i) IST and EVL were equally effective in controlling acute bleeding; (ii) EVL achieved variceal obliteration faster and in fewer treatment sessions; (iii) EVL had a significantly lower rate of development of portal gastropathy and rebleeding, (iv) while both techniques influenced

gastric varices equally, there was significantly higher oesophageal variceal recurrence after EVL than IST (Sarin, 1997).

In the seventh RCT Baroncini and colleagues from the Department of Gastroenterology and Gastrointestinal Endoscopy at Bellaria Hospital, Bologna, Italy, determined the relative frequency of rebleeding, recurrence of varices and survival after treatment with the two techniques. A total of 111 patients without bleeding at the index endoscopy were randomly assigned to either EVL (n=57) or IST (n=54). After eradication of varices, patients received endoscopic examinations every three months and for each episode of rebleeding. The mean follow-up periods were 534 ± 42 days in the IST group and 496 ± 40 days in the EVL group. The two techniques were equally effective in eradicating varices (93% in EVL group and 92.5% in IST group). The mean number of sessions required to obtain eradication was slightly lower (mean $\pm$ SE) in the EVL group (3.5 ± 0.1 vs. 4.0 ± 0.1 , $p=0.004$), while the time required for eradication was longer (33.8 ± 2.1 vs. 27.3 ± 1.4 , $p=0.01$). Comparison of the Kaplan-Meier estimates of survival and time to first rebleeding did not show any statistically significant differences between the two groups. The rate of complications was significantly higher in the IST group than in the EVL group (31% vs. 11%, $p=0.001$), while the rate of recurrent varices during follow-up was higher in the EVL group (30% vs. 13%, $p=0.03$). The authors concluded that while both techniques were equally effective, EVL showed greater advantages in the short-term follow-up, but was associated with more frequent recurrent varices in the longer term (Baroncini, 1997).

In the eighth RCT Avgerinos and colleagues from the 2nd Department of Gastroenterology, Evangelismas Hospital in Athens, Greece, randomised 77 patients with cirrhosis with proven oesophageal variceal bleeding. After initial control of bleeding using sclerotherapy,

40 patients were randomly assigned to IST and 37 to EVL. Both procedures were performed under midazolam sedation at intervals of 7-14 days until all varices in the distal oesophagus were eradicated or were too small to receive further treatment. Eradication of varices required a fewer mean number of sessions with ligation (3.7 ± 1.9) than with IST (5.8 ± 2.7 , $p=0.002$). The mean duration of follow-up was similar in both groups (15.6 months ± 7.3 and 15 ± 7.4 , respectively). The proportion of patients remaining free from recurrent bleeding was significantly higher in the EVL group compared to the IST group ($\chi^2=3.86$, $p=0.05$). Only 13 patients (35%) developed complications in the EVL group compared to 24 (60%, $p=0.05$) in the IST group. The mortality rate was similar in both groups (20% and 21%, respectively). The authors concluded that EVL was better than IST in the long-term management of patients with cirrhosis after variceal bleeding which was initially controlled with sclerotherapy (Avgerinos, 2004).

In the ninth RCT, Lo and colleagues from Department of Medicine, Veterans General Hospital-Kaohsiung, National Yang-Ming University in Taipei, Taiwan, randomised 71 cirrhotic patients with active variceal bleeding to receive either EVL (37 patients) or IST (34 patients) immediately after endoscopic examinations (Lo, 1997). Primary success rate (bleeding stopped for 72 hours) was 97% in the EVL group and 76% in the IST group ($p=0.009$). The efficacy of ligation was similar to sclerotherapy in the control of oozing varices (100% vs. 89%, $p=0.23$), whereas ligation was superior to sclerotherapy in the control of spurting varices (94% vs. 62%, $p=0.012$). The requirement of vasoconstrictors after emergency endoscopic treatment was lower in the ligation group than in the sclerotherapy group (11% vs. 41%, $p=0.007$). Treatment failure within 1 month was 8% in the ligation group vs. 30% in the sclerotherapy group ($p=0.02$). Blood transfusion requirements were significantly lower in the ligation group than in the sclerotherapy group

(3.2+/-1.2 vs. 4.5+/-1.8 units, $p<0.01$). Rebleeding rate within 1 month was 17% in the ligation group and 33% in the sclerotherapy group ($p=0.19$). Significant complications were encountered in 5% of the ligation group and 29% of the sclerotherapy group ($p=0.007$). Mortality rates within 1 month were 19% in the ligation group and 35% in the sclerotherapy group ($p=0.19$). The authors concluded that EVL and IST were comparable in arresting bleeding in oozing varices, whereas EVL was superior to IST in the control of spurting varices. Patients treated with EVL required fewer vasoconstrictors and fewer transfusion units than patients treated with IST. Furthermore, EVL was associated with a lower complication rate than IST (Lo, 1997).

In the tenth RCT Sequeira and colleagues from the Division of Gastroenterology, Universidade Federal de São Paulo, randomised 40 patients to compare the efficacy of both treatments in eradicating oesophageal varices, and complications secondary to both treatments. Both IST and EVL were performed until variceal eradication. There were no severe complications. Variceal eradication was faster with EVL than IST although there was no statistical difference (mean number of sessions 3.05 vs 3.72, $p=0.053$). Benign complications were equal in both groups, although additional sedation was more commonly required in the IST group. The authors concluded that both treatments were equally effective in the eradication of oesophageal varices, although banding ligation was better tolerated and probably faster (Sequeira, 1998).

In the eleventh RCT De la Pena and colleagues from the Gastroenterology Unit, Faculty of Medicine, University Hospital "Marques de Valdecilla," in Santander, Spain, evaluated the safety and efficiency of EVL compared with IST in 88 patients with cirrhosis and recent variceal bleeding. Sclerotherapy was performed using ethanolamine and polidocanol

injection at 1, 2, and 3 weeks and every 3 weeks thereafter. The Stiegmann-Goff device was used for EVL at the same intervals. The rate of variceal eradication was the same for both groups, but eradication was accomplished sooner in patients undergoing EVL (5.3 ± 1.6 vs. 6.6 ± 2.4 endoscopic sessions, $p < 0.05$) and with fewer complications (19 vs. 6, $p < 0.005$). The rate of recurrent bleeding was lower in patients treated with EVL (31% vs. 50%, $p < 0.05$). After eradication, variceal recurrence was more frequent in patients treated with variceal ligation at 1 and 3 years (47% and 92% vs. 23% and 55%, $p < 0.01$). Portal hypertensive gastropathy was significantly worse in the patients who had EVL (17 patients vs. 6, $p < 0.01$). Survival and treatment failure were similar in both groups. The authors concluded that EVL was superior to IST in terms of the rate of recurrent bleeding and the occurrence of complications but worse with respect to recurrence of varices and the evolution of portal hypertensive gastropathy (de la Peña, 1999).

In the twelfth RCT, Masci and colleagues from the San Raffaele Hospital, University of Milano, in Milan, Italy, compared EVL with IST in patients with previous oesophageal bleeding proved by endoscopy (Masci, 1999). End points were rebleeding rate and death during a short (eradication period) or long-term follow-up (>1 year). One hundred patients (50 EVL, 50 IST) were enrolled and eradication rate, number of treatments needed to achieve eradication, recurrence of varices, rebleeding and complications were recorded and analysed. No differences were observed between the two groups regarding age, sex and Child class. One patient dropped out in the EVL group and 6 in the IST group. Eradication was obtained in 44 (88%) with EVL and 41 (82%) with IST with a mean of 3.41 and 5.29 treatments ($p < 0.001$), respectively. Rebleeding occurred during eradication in 6 patients (12%) in the EVL group and 21 (42%) in the IST group ($p = 0.001$). After eradication, 7 patients (14%) rebled in the EVL group and 4 (8%) in the IST group (not significant). Non-

variceal bleeding was observed in 5 patients (2 EVL and 3 IST) during follow-up. Two patients in the EVL group died after variceal rebleeding; 3 died of gastric bleeding; and 15 from non-haemorrhagic events (8 EVL and 7 IST). In the EVL group 14 patients had recurrent varices and 7 rebled; in the IST group 11 recurred, with rebleeding in 5. Major complications were fewer in the EVL group (1 stenosis, 4 chronic ulcers) compared to 18 patients in the IST group (9 stenosis and 9 chronic ulcers) ($p<0.005$). The authors concluded that EVL was preferable to IST for faster reduction and obliteration of varices, with a lower rate of complications and rebleeding before eradication (Maschi, 1999).

In the thirteenth RCT Fakhry and colleagues from the Theodor Bilharz Research Institute in Giza and the Faculty of Medicine, Cairo University, randomised 84 patients with BOV to compare the efficacy and safety of both treatments in eradicating oesophageal varices and the complications of both treatments (Fakhry, 1997). Both IST and EVL were repeated weekly until variceal eradication. Forty-one patients were randomised to IST and 43 to EVL. The two groups were well matched with regard to age, sex and Child-Pugh score. All 84 patients had schistosomiasis, of whom 77 also had hepatitis B or C. Patients in the EVL group needed fewer sessions for eradication of varices (2.8 ± 0.5) compared to IST (4.8 ± 0.9). Complications and side effects were less common in the EVL group (2.3%) compared to the IST group (65%). Other parameters such as effective control of active bleeding, long-term eradication of varices, recurrence of bleeding and death due to bleeding related complications were comparable in both treatment groups. The authors concluded that EVL was as effective as IST in the management of BOV both for active bleeding and the eradication of OV. However, the number of treatment sessions needed, and the complications were significantly lower in the EVL group (Fakhry, 1997).

In the fourteenth RCT Zargar and colleagues from the Department of Gastroenterology and General Surgery, Sher-i-Kashmir Institute of Medical Sciences, in Srinagar, Kashmir, India randomised 73 patients to determine whether EVL was safer and more effective than IST in adults with bleeding oesophageal varices due to extrahepatic portal venous obstruction (Zargar, 2005). Thirty-six patients underwent IST and 37 had EVL. Ligation and sclerotherapy were equally effective for achieving variceal eradication (94.6% vs. 91.7%, respectively; $p=0.67$). However, ligation achieved eradication with fewer endoscopic sessions (3.7 [1.2] vs. 7.7 [3.3]; $p<0.0001$) and within a shorter time interval (50.1 [17.7] days vs. 99 [54.8] days; $p<0.0001$). In the ligation group, recurrent bleeding was less frequent (2.7% vs. 19.4%; $p=0.028$; however, Bonferroni correction for multiple testing removed this significance) and the rate of major complications was lower (2.7% vs. 22.2%; $p=0.014$). Total cost per patient was significantly higher in the IST vs. the EVL group (\$216.6 [71.8] vs. \$182.6 [63.4]; $p=0.035$). During the follow-up period after variceal eradication, no significant differences were found between the IST and the EVL groups with respect to recurrent bleeding (3% vs. 2.9%; $p=1.0$), oesophageal variceal recurrence (9.1% vs. 11.4%; $p=1.0$), and formation of new gastric varices (9.1% vs. 14.3%; $p=0.51$). The authors concluded that EVL was superior to IST as EVL was less costly and achieved variceal eradication more quickly, with lower relative frequencies of recurrent variceal bleeding and complications (Zargar, 2005).

In the fifteenth RCT Villaneuva and colleagues from the Gastrointestinal Bleeding Unit, Department of Gastroenterology, Hospital de la Santa Creu Sant Pau, Barcelona, randomised 179 patients with cirrhosis and bleeding oesophageal varices to receive either sclerotherapy ($n=89$) or ligation ($n=90$). Therapeutic failure occurred in 21 patients treated with IST (24%) and in nine treated with EVL (10%) ($RR=2.4$, 95% $CI=1.1-4.9$). Failure to

control bleeding occurred in 15% vs 4%, respectively ($p=0.02$). Treatment group, shock and HVPG >16 mmHg were independent predictors of failure. Side-effects occurred in 28% of patients receiving IST vs 14% with EVL (RR=1.9, 95% CI=1.1-3.5), being serious in 13% vs 4% ($p=0.04$). Six-week survival probability without therapeutic failure was better with EVL ($p=0.01$). The authors concluded that the use of EVL instead of IST as emergency endoscopic therapy added to somatostatin for the treatment of acute variceal bleeding significantly improves the efficacy and safety (Villanueva, 2006).

In the sixteenth RCT, Luz and colleagues from the Gastrointestinal Endoscopy Unit, Hospital das Clínicas, São Paulo University Medical School, in São Paulo, Brazil, randomised 100 patients with variceal bleeding to receive either IST or EVL (Luz 2011). Sclerotherapy was performed using ethanolamine oleate intravariceal injection both above and below the bleeding site, with a maximum volume of 20 ml. In patients receiving EVL, banding was applied first at the bleeding site, followed by ligation of remaining varices in the distal oesophagus. Primary outcomes for both groups were initial failure of bleeding control (5 d), early re-bleeding (5 days to 6 weeks) and complications, including mortality. Fifty patients had IST and 50 EVL. No differences between groups were observed across gender, age, Child-Pugh status, presence of shock at admission, mean haemoglobin levels, and variceal size. No differences were found between groups for bleeding control, early re-bleeding rates, complications, or mortality. After 6 weeks, 36 (80%) IST and 33 (77%) EVL patients were alive and free of bleeding. A statistically significant association between Child-Pugh status and mortality was found, with a 16% mortality in combined Child A and B patients and 84% mortality in Child C patients ($p<0.001$). The authors concluded that despite the limited number of patients included in their study, their results suggested that IST and EVL were equally effective in the control of acute variceal bleeding (Luz, 2011).

In the seventeenth RCT Ali and colleagues from the Department of Gastroenterology, Shandong Provincial Hospital and Shandong University in Jinan, China compared the IST and EVL in 124 patients with endoscopically proven BOV (Ali 2017). Sixty-four patients were treated with IST and 60 with EVL. Patients were followed for a mean of 2 years, during which the incidence of complications, recurrence of bleeding and the number of treatment sessions needed to eradicate varices, mortality and survival were determined. Active bleeding during the first treatment was controlled by IST in 19 of 19 patients and by EVL in 16 of 16 patients. The likelihood of early rebleeding was slightly smaller in the patients treated with IST (7.8% versus 11.7%, $p=0.47$). However, late rebleeding rate was slightly more in IST patients (28.1% versus 23.3%, $p=0.54$) without statistical significance. The rate of eradication of varices in the IST group was slightly lower than in the EVL group (79.7% versus 86.7%, $p=0.30$). There were also no statistically significant differences in mortality (1.6% versus 3.3%, $p=0.61$) or survival rate (71.9% versus 78.3%, $p=0.41$) (all $p>0.05$) after IST and EVL. However, fever in the IST group was significantly higher compared to that of in the EVL group ($n=17$, 26.6% versus $n=6$, 10.0%, $p=0.02$). The authors concluded that both IST and EVL produced excellent results, were safe, effective, feasible and acceptable for EVB with minimum complications and obviate the need for subsequent procedures in the short term (Ali, 2017). (Table 11.1, page 238)

EVL for Control of Active Bleeding.

There is a perception that EVL is more difficult and less effective during active variceal bleeding because the banding cylinder decreases the field of view and blood clot which may enter the banding cylinder during aspiration of the varix can further obscure visibility. The prospective studies summarized above have not specifically addressed the efficacy of EVL in the presence of active bleeding but collectively included a subgroup of patients who

were actively bleeding when treated with EVL. In this cohort active bleeding was stopped with EVL in 80%–100% of patients. Stiegmann et al. achieved control of acute bleeding in 12 of 14 patients (86%) with EVL compared with 10 of 13 patients (77%) with IST (Stiegmann, 1992). Gimson et al. reported control of acute bleeding in 19 of 21 patients (91%) with EVL, and 21 of 23 patients (92%) with IST (Gimson, 1993). Laine et al., Lo et al., Hou et al. and Sarin et al. reported similar results with control of acute bleeding in 80%–100% of patients with EVL and in 77%–86% of patients with IST (Laine, 1995; Lo, 1995; Hou, 1997; Sarin, 1997). Stiegmann et al. reported encouraging early results with EVL in active variceal bleeding. This small-cohort study reported immediate control of bleeding in 22 of 23 (95%) patients. However, the 30-day mortality rate was 39% (9 of 23 patients), with four of the nine early deaths (44%) the result of continued or recurrent bleeding. Recurrent variceal bleeding occurred in 6 of the 14 survivors (43%) during a mean follow-up of nine months. These results are comparable to those of Fleig et al. who reported a 92% success rate with IST for control of active bleeding, a hospital mortality rate of 40%, and procedure-related complications of 12%. These data suggest that EVL is as effective as IST for control of acute variceal haemorrhage.

This was validated in another prospective study of EVL in acute variceal bleeding. Seventy-one patients with active variceal bleeding were randomized to either EVL ($n = 37$ patients) or IST ($n = 34$ patients). Cessation of bleeding was defined as no further bleeding within 72 hours and was achieved in 97% with EVL and 76% with IST ($p=0.009$). EVL and IST were equally effective for control of oozing varices ($p=0.23$), but EVL was better for controlling spurting varices (94% vs. 62%; $p=0.012$). At one month follow-up rebleeding occurred in 17% with EVL and 33% with IST ($p=0.19$), and survival at one month was similar in the two groups (mortality rate was 19% with EVL and 35% mortality with IST; $p=0.19$). However,

morbidity was significantly lower with EVL (5% vs. 29%; $p=0.007$). Thus, EVL is effective in the presence of acute bleeding and dispels the notion that the addition of the suction cap and the restricted view reduces the efficacy of EVL in active bleeding.

In a seminal meta-analysis by Laine and Cook, EVL was shown to be superior to sclerotherapy in reducing both rebleeding (OR 0.47, 95 %CI 0.29 to 0.78) and mortality (OR 0.67, 95 %CI 0.46 to 0.98) (Laine, 1995). Furthermore, EVL resulted in fewer adverse events (AEs) (oesophageal strictures, OR 0.10, 95 %CI 0.03 to 0.29) and required fewer endoscopic sessions to achieve variceal obliteration. In an updated meta-analysis that included 36 RCT's with 3593 patients, de Quados Onofrio et al. reported that EVL was associated with a significant improvement in bleeding control (RR 1.08, 95 %CI 1.02 to 1.15), mortality (RR 0.72, 95 %CI 0.54 to 0.97), and AEs (RR 0.29, 95 %CI 0.20 to 0.44) when compared with sclerotherapy. Furthermore, the risk of rebleeding was greater with sclerotherapy (RR 1.41, 95 %CI 1.03 to 1.94) (de Quados Onofrio, 2019).

CHAPTER 7

AN ANALYSIS OF ADVERSE EVENTS AFTER ENDOSCOPIC VARICEAL LIGATION FOR OESOPHAGEAL VARICES

Successful endoscopic control of acute oesophageal variceal bleeding is a critical element in determining ultimate patient outcome. Survival after an acute variceal bleeding episode depends on three fundamental elements: (i) the speed and efficacy of control of the initial bleeding event, (ii) the severity of the underlying liver disease and (iii) hepatic functional reserve. Endoscopic variceal ligation is established as the principal first-line intervention in patients with bleeding oesophageal varices, both during the acute event and for long-term prevention of recurrent bleeding. Despite an improved safety profile, emergency endoscopic intervention for actively bleeding varices has an inherent potential for procedure-related complications (Krige, 2005). In an updated analysis of the 17 published prospective randomized controlled trials comparing EVL with sclerotherapy, the reported incidence of endoscopic complications varies widely and ranges from an improbable low of 2% to a high of 69%, the divergent results likely due to arbitrary and inconsistent definitions of procedure-related adverse events (Table 11.1, page 238) (Krige, 2023). Since no formal reporting requirements exist, true complication rates may be underestimated due to inconsistencies in the type and severity of adverse events reported.

The accurate documentation and reporting of endoscopic adverse events (AEs) remain an Achilles' heel in gastrointestinal endoscopic research (Krige, 2023). Proposals for a uniform anatomical classification of AEs after EVL have neither gained traction nor been applied consistently, thus perpetuating the difficulty of accurately evaluating or comparing outcomes in equivalent EVL studies. Ideally, a practical reporting format for EVL AEs, composed of

both consequential and non-consequential adverse events is necessary, the former further subdivided into four distinct levels based on the principle of therapy required to correct the event (Krige, 2023a). The new AGREE grading system of endoscopic complications is a major advance and, if consistently applied, will remove the existing divergence and ambivalence found in data analysis when interrogating the granular detail required after EVL AEs (Nass, 2022).

Surprisingly, despite the global adoption of EVL as the endoscopic intervention of choice in bleeding varices, there is no published systematic review detailing the spectrum of complications that may occur after endoscopic band ligation. The Cape Town group has previously published a detailed analysis of the endoscopic complications after injection sclerotherapy, initially as a book chapter (Krige, 1999) and subsequently updated as a peer-reviewed journal article (Krige, 2005). The deficiency of publications on EVL-induced complications is addressed below.

Methods

Literature search and study selection

In this review and analysis, peer-reviewed publications were assessed to evaluate the incidence, spectrum, consequences and prevention of complications after EVL for bleeding oesophageal varices. Eligibility criteria included all publications documenting endoscopic variceal ligation outcomes, as well as case reports or series describing complications after endoscopic ligation. Conference abstracts and editorials were excluded. A predetermined systematic search strategy was implemented with initial results imported and merged into reference management software, ENDNOTE® (version X7, Clarivate Analytics, Philadelphia, PA, USA). The electronic search strategy comprising keywords and MeSH (see Supplementary material, Appendix S1), accessed PubMed Central National Center for

Biotechnology Information (NCBI) at the U.S. National Library of Medicine (NLM), the National Institutes of Health (NIH), Ovid MEDLINE (Ovid Technologies, Inc., New York), Ovid EMBASE (Elsevier, Amsterdam, Netherlands), ISI Web of Science (Thomson Scientific Technical Support, New York) and the Cochrane library databases. Searches were limited to studies involving humans and published in English from 1986 to 2023. The final search was performed in December 2023. Reference lists of relevant articles were also searched. After removal of duplicates articles and abstracts were assessed for inclusion. Full texts of relevant articles were retrieved and assessed. Individual patient data were extracted from selected studies using a standardized extraction form. All data collected were uploaded to an Excel (Microsoft) database and crosschecked for accuracy.

Incidence of complications after endoscopic therapy

There is no consensus regarding the definition or the classification of procedure-related complications that occur after the endoscopic treatment of oesophageal and gastric varices, and consequently the incidence varies widely in reported studies. A further weakness in the current variceal endoscopy literature is the absence of a validated, relevant and comprehensive grading system for complications related to endoscopic banding for acute variceal bleeding (Kramer, 2016). Much of the published data are flawed because the reporting process is often biased with subjective and retrospective information, and complication rates are generally operator dependent. Comparative analyses of complication rates are also hampered by variations in patient population, type and severity of liver disease and endoscopic technique used. In addition, differences in study design introduce a covert selection bias which may influence results. These biases include sampling and selection bias (specialist centres, expert endoscopists, differing patient populations)

confounding bias (emergency versus elective procedures) and measurement bias (incomplete reporting, delayed complications).

Many patients undergoing endoscopic variceal intervention have a limited prognosis, and therefore complications may not be identified or treated aggressively. The debilitated state of many patients undergoing endoscopic therapy also contributes to the medical difficulties they encounter, often making differentiation of a true complication of the procedure difficult. Complication rates are also higher when carefully documented in prospective studies, while some studies express complication rates in terms of incidence per patient treated or per procedure performed. In long-term studies, repeated intervention also increases the cumulative risk of endoscopic-related complications in the individual patient. The most reliable data indicate that 10-15% of patients undergoing endoscopic variceal intervention will develop a complication, but fewer than 1% of patients die as a direct result of the procedure.

Classification of type of EVL complications:

Endoscopic-related complications after variceal banding have been categorised as either (i) local effects involving the oesophagus which include ulceration, bleeding, stricture or perforation; (ii) regional respiratory and cardiovascular effects; and (iii) distant or systemic consequences. The magnitude or extent have been defined as either (i) minor events that are self-limiting and do not require specific treatment and do not interfere with the regular endoscopic programme or as (ii) major complications which are serious or life-threatening events that prolong hospitalisation. There is no existing unified classification which incorporates all the elements involved, i.e. anatomical location of the complication, the type of complication, or the severity or grade of the complication and the influence on patient

outcome. In the absence of a prevailing taxonomy, the description of banding-related complications in this thesis uses a narrative anatomical classification.

A: Oesophagus:

1. EVL-induced ulceration

Post-ligation ulcers occur because of mechanical strangulation of varices after EVL, rather than due to chemical phlebothrombosis induced by sclerosant after injection sclerotherapy and therefore behave differently. While the histological effects of endoscopic sclerotherapy in humans have been extensively described, the effects of endoscopic ligation have been sparsely reported. In an autopsy series the sequences of histological changes after EVL showed varying degrees of necrosis and superficial ulceration limited to the mucosa and submucosa with no involvement of the muscularis propria on days 1-5 (Stiegmann, 1985). Mechanical entrapment and strangulation with variceal thrombosis after ligation is usually limited to the superficial oesophageal mucosa and is followed by ischaemic necrosis, later sloughing of the bands and ligated variceal tissue, subsequent shallow mucosal ulceration with granulation tissue formation and then complete re-epithelialization of the mucosa with maturing scar tissue that heals over time (Polski, 2001). This contrasts with the findings after sclerotherapy, where a wide variation in the depth of tissue injury occurs and deep necrosis may be present. Variceal thrombosis was seen on day 2 after EVL. Differences in the depth of the tissue injury caused by ligation and sclerotherapy relate to the difference in consequences between mechanical and chemical intervention. While the maximum volume of variceal tissue that can be ligated is consistent and is limited by the volume of the banding chamber of the ligation device, many and often unpredictable procedural and technical variables influence the outcome of sclerotherapy. These include the type and volume of sclerosing solution injected, the length and size of the needle used for the injection, the method and technique of injection and patient tolerance and co-operation so

that coughing or gagging during the injection may result in inadvertent needle damage to the oesophagus.

Table 7.1 Complications related to EVL

A. Oesophagus

- (i) ligation-induced mucosal ulceration
- (ii) ulcer bleeding
- (iii) variceal recurrence
- (iv) variceal rebleeding
- (v) oesophageal obstruction
- (vi) oesophageal stricture
- (vii) dysphagia
- (viii) dysmotility
- (ix) perforation

B. Systemic

- (i) haemodynamic changes
- (ii) increased portal pressure
- (iii) portal hypertensive gastropathy
- (iv) duodenopathy
- (v) mesenteric thrombosis
- (vi) aspiration pneumonia
- (vii) bacteraemia
- (viii) meningitis
- (ix) brain abscess
- (x) spinal cord infarction
- (xi) paraplegia

C. Technical

- (i) overtube insertion complications
- (ii) difficult intubation related to cap friction
- (iii) barrel/cap dislodgement

D. Other local complications

- (i) tracheal obstruction
- (ii) pharyngeal mucosal injury
- (iii) laryngeal injury

In a comparative study the mean depth and resolution of ulcerations were significantly less in the EVL group than IST ($p < 0.0001$). Mean surface area of ulcerations in the EVL group was significantly greater ($p < 0.0001$). The oesophagitis grade was also less in the EVL group ($p < 0.001$). EVL patients also required fewer sessions to achieve obliteration

($p < 0.0001$) (Young, 1993). Mucosal sloughing and ulceration are regarded as a necessary accompaniment after EVL rather than a side-effect or adverse event and will heal by the end of 3 weeks. (Nijhawan, 1994; Arasu 2019; Karki, 2019). In a randomized controlled trial patients receiving 40 mg pantoprazole intravenously after EVL followed by 40 mg oral pantoprazole for 9 days had significantly smaller post-banding ulcers on follow-up endoscopy than subjects receiving placebo. However, the total ulcer number and patient symptoms were not different between the groups (Shaheen, 2005).

2. EVL-induced ulcer bleeding

Post-banding ulcer bleeding is an uncommon but serious complication of variceal banding with a substantial mortality rate and occurs if sloughing of a band occurs prematurely before the varix is thrombosed. This may happen if the varix has not been completely sucked into the banding cylinder of the ligating device or if the varix is small, but still patent or the oesophageal wall is scarred due to previous endoscopic treatment and the band cannot be properly placed. In addition, in the emergency setting, when blood obscures the endoscopist's vision, misplacement of the band occurs more frequently (Tosetti, 2021). Post-banding ulcer bleeding is defined as endoscopically confirmed (i) active bleeding from an ulcer base with a patent underlying varix or (ii) bleeding from ulcer/slough due to slippage or dislodgement of the rubber band. If band detachment occurs before variceal thrombosis, the patent underlying vessels in the ulcer base are exposed and can lead to severe and fatal bleeding. Significant post-banding ulcer bleeding occurs in 3.6% to 15% of cases, and the mortality is reported to be as high as 52%. (Vanbiervliet, 2010).

There are inherent shortcomings in most studies describing early rebleeding and mortality in view of the limited reports of this serious complication and the poorly established risk

factors and treatment methods. Studies have proposed that PBUB may be caused by reflux of gastric acid into the lower oesophagus, leading to exposure to acid of ulcer(s) and underlying vein(s). Alternate explanations include slippage of bands, infection of ulcers, and coagulopathy that lead to increased bleeding. Other studies have indicated increased risks associated with the number of deployed bands, size of varices, severity of liver failure, or if endoscopy and banding was performed as an emergency. Tierney et al. identified Child-Pugh class C status, high platelet ratio index, low prothrombin index, and EBL for acute variceal bleeding as risk factors for PBUB, while Vanbiervliet et al. suggested that previous variceal bleeding, peptic oesophagitis, high AST to platelet ratio index score, and low prothrombin time were risk factors for EVL-induced ulcer bleeding (Tierney, 2013; (Vanbiervliet, 2010). In the Cho study, MELD score >10, concomitant GV F3, and detachment of O-ring bands were independent risk factors for the EVL-induced ulcer bleeding (Cho 2017). In the Duenas study independent risk factors for post-banding ulcer bleeding were MELD score, hepatocellular carcinoma and total beta-blocker dose. Active bleeding or adherent clots at the time of endoscopy were associated with treatment failure or death (Duenas, 2020).

Classification of PBUB's based on their endoscopic appearance as either type A (ulcer with spurting), B (ulcer with oozing), C (ulcer with clot or pigmented base), and D (ulcer with clean base) may be useful in deciding treatment strategies. In the retrospective study by Jamwal et al. of 3854 EVL procedures, 3.6% patients developed PEBU and 32.6% died. Type A and B ulcers were responsible for 70% of the mortalities associated with PEBUs (Jamwal, 2017). In a case control study from Nice, France which included 605 patients, 21 patients had 23 spontaneous band slippages with endoscopy-confirmed bleeding from a

post-banding ulcer occurring ± 13 days following ligation. Eleven patients (52%) died following the bleeding complication. (Vanbiervliet, 2010).

Several traditional treatment methods, including cyanoacrylate injection, repeat EVL, and transjugular intrahepatic portosystemic shunts (TIPS), oesophageal self-expandable metal stent (SEMS), glue and sclerosant injection, Sengstaken-Blakemore tube placement or novel treatment such as haemospray have been suggested in past studies. (Tierney, 2013), (Sinclair, 2015). In a retrospective analysis of 28 patients with bleeding due to post-band ulcers. control of bleeding by SEMS was achieved in 23 (82.1%) patients, and overall, 6-week survival was 75% suggesting that SEMS is effective method to control oesophageal post-banding ulcer bleeding and a definite treatment bridge (Elbahr, 2020). There are also reports of either over-the-scope clipping or haemoclips as rescue therapy for post-EVL ulcer bleeding (Toyoda, 2001; Polski 2001; Mansilla-Viva, 2020). In a study that evaluated effect of PPI's on post-EVL ulcer bleeding, the bleeding-free survival rate during 8 weeks after EVL was significantly better in patients who received PPI therapy. It is assumed that acid suppression contributed to early healing of the post-banding ulceration by reducing gastroesophageal acid reflux in cirrhotic patients (Kang, 2016).

3. Variceal recurrence:

Current AASLD/ACG guidelines emphasize complete eradication of varices as the desired endpoint of EVL to prevent rebleeding (Garcia-Tsao, 2017). However, this endpoint is seldom achieved, with the reported incidence of variceal eradication ranging from a high of 95% to a low of 55% in RCTs (Table 5). A plausible explanation for this discrepancy and the wide reported range is that inconsistent definitions were used. In some reports the definition of variceal eradication included residual varices too small to be ligated effectively.

The wide variation in eradication rates may also be related to different treatment elements including treatment intervals, number of bands applied per session and selective banding of varices such as in some centres where only grade 3 to 4 oesophageal varices are banded. Ultimately, the results of any long-term banding study are influenced by the diligence and regularity of follow-up endoscopy and the meticulousness and reproducibility of observer and assessment methodology as well as the accuracy with which residual variceal size is recorded. The definition of variceal recurrence presupposes that varices have been proven endoscopically to have been eradicated and have since re-appeared and should therefore be distinguished technically from varices which have been persistent and never completely eradicated during treatment.

There is also increasing recognition that two major limitations of long-term EVL are the number of varices that are resistant to complete eradication and the substantial variceal recurrence rate after eradication. Both limitations are influenced by the design and mechanism of ligation. Experienced endoscopists know that EVL becomes increasingly difficult as varices decrease in size. Small varices are difficult to ligate effectively for two technical reasons. Grade 1 and 2 varices do not have sufficient variceal volume and tissue substance to provide purchase and grip for the constricting elastic band. In addition, mucosal fibrosis due to prior banding episodes further limits mucosal pliability and the ability to suck enough tissue into the cap, thus preventing successful band application. Of note are the number of RCTs reporting higher variceal recurrence rates in patients undergoing EVL (Table 11.1, page 238). Variceal recurrence may occur more frequently in patients undergoing EVL compared to IST due to persistence of small perforating transmural veins that connect the intrinsic intraluminal oesophageal varices with extrinsic extramural peri-oesophageal collateral veins. These perforating veins are not affected by banding and

remain patent, leading ultimately to recurrence. (Nagamine, 1999; Jeong, 2017; Zheng, 2019)

4. Variceal rebleeding:

Variceal rebleeding is classified by the Baveno VII criteria as (i) failure to control bleeding, i.e. rebleeding occurring within 5 days after the initial or index endoscopic intervention, and (ii) early rebleeding, i.e. bleeding occurring within 6 weeks after control of the initial variceal bleed (de Franchis, 2022). Variceal rebleeding occurs in 10 to 20% of patients and is associated with a mortality risk as high as 40%. However, available data may be flawed or inaccurate as rebleeding within 6 weeks after EVL encompasses a variety of causes. These include (i) initial technical failure to band all at-risk varices due to impeded or suboptimal visibility during the procedure because of active bleeding or clot within the cap or (ii) failure to effectively suction and incorporate all mucosal and submucosal variceal tissue into the cap before band release and deployment, or (iii) bleeding from adjacent “virgin” or endoscopic-naïve varices overlooked and not banded during the initial procedure, or (iv) bleeding from dislodged bands, or (v) bleeding from oesophageal mucosal ulceration as a consequence of banding (Krige, 2022). In addition, non-variceal bleeding may also occur in portal hypertension due to portal hypertensive gastropathy, gastric antral vascular ectasia, ectopic varices, or causes related to peptic ulceration and Dieulafoy’s lesions.

Most publications do not make a clear distinction between these different causes of early rebleeding nor do they separate failure to control the initial bleed from subsequent early rebleeding. In addition, there is no consensus on the most relevant clinical or technical predictors of early bleeding after EVL, nor are there clear guidelines on how to prevent or minimize rebleeding (Salman 2020).

There is significant heterogeneity in published studies with a wide spectrum of clinical, laboratory, ultrasonographic and endoscopic risk factors causing early rebleeding after EVL. These include decompensated cirrhosis, especially in Child-Pugh group C patients, the severity of bleeding, the presence of splenomegaly, spontaneous bacterial peritonitis, the volume of ascites, a low albumin, anaemia, high blood urea nitrogen, a prolonged PTT, the presence of portosystemic venous collaterals, a hepatic vein pressure gradient (HVPG) greater than 16 mmHg, active bleeding on endoscopy, large oesophageal varices (F3) and the presence of red colour signs (Lee, 2009). Early slippage of bands from treated sites is of further technical concern regarding the risk for rebleeding. In-vitro bench studies have shown differences in the resting inner diameters and radial retraction forces of bands on different ligation devices. The larger resting inner diameter and significantly lower retraction force in neoprene bands compared to rubber bands, predispose neoprene bands to early slippage (Polski, 2001).

In a meta-analysis of seven studies by Dai et al., risk factors for early rebleeding after EVL were severe grade of oesophageal varices, Child-Pugh classification C, presence of a moderate to large amount of ascites, thrombus in the portal vein, and a history of diabetes (Dai, 2013). In a subsequent systematic review and meta-analysis of 16 studies with data on 13,378 patients, the incidence, predictors, and outcome of post-EVL bleeding were evaluated by Giri et al. who found 14 significant predictors of early bleeding after EVL. Seven elements were significant on multivariate analysis in 2 or more studies (use of proton pump inhibitor after EVL, peptic oesophagitis, presence of gastric varices, greater number of bands used, presence of hepatocellular carcinoma, lower haemoglobin at admission, higher MELD score) and 7 factors were significant on univariate analysis in 3 or more studies (age, emergency EVL, large oesophageal varices, presence of high-risk stigmata,

higher serum bilirubin, lower serum albumin, Child-Pugh C status). In a subgroup analysis of 12 studies involving 753 patients, the pooled mortality incidence after early post-EVL bleeding was 25.2%. Mortality of all-cause bleeding was 27.2% while mortality with post-EVL ulcer bleeding was 24.5% (Giri, 2022). The analysis showed a pooled incidence of 7.7% for early post-EVL bleeding and 5.7% for bleeding due to ulcer development at the EVL site after a mean duration of 11.2 ± 3.2 days. (Giri, 2022).

In a study by Kim et al. of 454 patients who underwent emergency EVL, control of acute variceal bleeding failed in 47 (10.4%) patients. Initial hypovolaemic shock, active bleeding on endoscopy, and a history of previous EVL were independent risk factors for failure to control bleeding in the multivariate analysis. Common technical causes of EVL failure include unsuctionable varices due to previous EVL-induced scars, followed by insufficient ligation of the stigmata and inability to ligate the varix due to poor endoscopic visual field. Endoscopic variceal injection using cyanoacrylate (49%) was the most used on-site rescue treatment method, followed by insertion of Sengstaken Blakemore tube (15%), and repeat EVL (13%). The rescue treatments successfully achieved haemostasis in 91.7% of those in the EVL failure group (Kim, 2018).

5. Dysmotility

Oesophageal motility abnormalities in patients treated endoscopically for variceal bleeding have not been studied in detail, therefore accurate and robust data are lacking. Available data reveal that oesophageal varices reduce the mean amplitude and increase the mean duration of peristaltic waves but have little effect on overall lower oesophageal sphincter function. Transit time is however delayed and gastroesophageal reflux disease is common in up to 64% of the patients (Fass, 1997). Whereas band ligation appears to have little

impact on oesophageal motility, data are limited and are hampered by lack of standardisation, rendering conclusions about safety premature. Injection sclerotherapy spares the lower oesophageal sphincter but significantly reduces the mean amplitude of contractions, mainly in the lower one-third to one-half of the oesophagus. In addition, normal peristalsis may be occasionally or completely replaced by non-propagating simultaneous contractions that may result in chest pain or dysphagia in the absence of a stricture. Transient prolongation of acid clearance usually resolves within a week, except in patients who have developed a stricture (Fass, 1997). As with sclerotherapy, band ligation has no effect on LOS resting pressure and has minimal effect on oesophageal motility. The amplitude, duration and speed of peristaltic waves are generally unchanged after banding. Seventy-five percent of patients report transient dysphagia, usually lasting 24-72 hours and thought to be related to the presence of engorged varices after banding (Fass, 1997).

Three further clinical studies have assessed the effect of endoscopic intervention on oesophageal motility. In the first study 24 patients (mean age 49.5 years, 19 males, 5 females) underwent oesophageal manometry before and after EVL. Variceal ligation was performed at intervals of 2 to 4 (average 3.4 ± 2.1) weeks. Oesophageal manometry was repeated 4 weeks after variceal eradication and the amplitude, duration, propagation speed of the contractile waves and peristalsis were studied. Analysis of the lower sphincter pressure did not show differences before and after variceal ligation. In 10 patients dysmotility was recorded, and the amplitude of the contractile waves rose from 70.7 mmHg before variceal ligation to 89.7 mmHg after the procedure ($p < 0.05$), and duration increased from 3.55 seg. to 3.90 seg. ($p < 0.05$). The final analysis showed alterations of oesophageal motility characterized by increase in the amplitude and duration of the contractile waves (Fontenele Soares, 2006).

In the second comparative study 46 patients underwent oesophageal manometry 24 hours before IST or EVL and within 24 hours of two subsequent sessions. Lower oesophageal sphincter pressure was similar in the study group (mean 20.1 mmHg) and controls (17.6 mmHg) and the pressure did not change following IST or EVL. Amplitude of contractions in the lower 5 cm of the oesophageal body was similar in the two groups and decreased after two sessions of variceal therapy. There was no difference in the changes between the IST and EVL groups and these changes do not cause significant oesophageal symptoms (Narawane 1999).

In a third comparative study from Greece 60 patients had oesophageal manometry and 24-h intra-oesophageal pH monitoring after variceal eradication with either sclerotherapy or banding. After sclerotherapy, peristaltic wave amplitude decreased from 76.2 mmHg to 61.6 mmHg ($p=0.0001$), simultaneous contractions increased from 0% to 37.9% ($p=0.0008$), and the percentage of time with pH <4 increased from 1.60 to 4.91 in channel 1 ($p=0.0002$) and from 1.82 to 5.69 in channel 2 ($p=0.0006$). By contrast, the above parameters were not disturbed by ligation. The authors concluded that their data define the advantages of ligation over sclerotherapy for post-treatment oesophageal dysmotility and associated gastro-oesophageal reflux (Viazis, 2002).

6. Dysphagia

Whereas band ligation is reported to have little impact on oesophageal motility, data are limited and hampered by a lack of standardisation rendering conclusions about safety premature. Transient dysphagia after variceal banding is most commonly due to dysmotility and oesophageal spasm and typically lasts about 24 to 48 hours. Three pathophysiologic mechanisms have been proposed to explain the occurrence of dysphagia following EVL. In

a study from Temple University School of Medicine, Philadelphia, Arasu and colleagues assessed the incidence of dysphagia following endoscopic variceal band ligation (Arasu, 2019). Patients completed a modified version of the Mayo Clinic Dysphagia Questionnaire ≥ 90 days after their last EVL session. The 39 patients had a mean age of 61.7 ± 8.6 years and included 23 males. The median number of banding sessions was 2 with a median of 9 bands placed overall. Twelve patients (30.8%) developed new-onset dysphagia post-EVL. This is novel information as although it is common to have transient dysphagia immediately post-banding, the assumption has been that the dysphagia will resolve over time. While dysphagia prevalence was high, there was no evidence that EVL caused significant structural abnormalities of the oesophagus in those who had subsequent barium swallow or upper endoscopy. By contrast, Viazis et al. demonstrated that EVL had no impact on oesophageal motility unlike sclerotherapy that leads to a significant decrease of the amplitude of peristaltic waves, an increase of simultaneous contractions in the tubular oesophagus, and an increase in pathologically proven gastroesophageal reflux disease (Viazis, 2002). Similarly, in a case series published by Berner et al. the majority of EVL treatments did not result in worsening of motility or reflux scores and none with symptoms (Arasu, 2019).

7. Oesophageal obstruction:

Complete oesophageal obstruction after EVL can occur due to over-suctioning when, in addition to the target varix, mucosa from the opposite wall is also sucked into the cap thereby incorporating and trapping the oesophageal mucosa circumferentially into a single band. A literature search reveals a total of 12 case reports of complete oesophageal obstruction following endoscopic variceal ligation (Jalil, 2018). The most common site of obstruction is at the inferior oesophagus. Complete oesophageal obstruction has been

found to be more common in women, old people, those who have undergone repeated ligation, and in individuals with large varices (Zhang, 2019). A variety of endoscopic techniques can remove the obstructing band using a rat-tooth or hot biopsy forceps, an endoloop cutter or a 1.5-cm snare technique with blended cutting, or a clear cap fitted to a gastroscope with a “can opener” manoeuvre.

8. Oesophageal stricture

The exact pathogenesis of oesophageal strictures after treatment of oesophageal varices remains unclear. Tissue reaction to sclerosant is believed to be the major determinant after IST, whereas EVL-induced alterations in motility and acid reflux are presumed to be contributory. A meta-analysis by Laine and Cook that compared EVL vs IST found that the odds ratio for developing an oesophageal stricture was 0.10 (0.03 to 0.29) in patients who underwent EVL (Laine, 1995). The most commonly proposed mechanism is fibrosis, which typically presents as late dysphagia, allowing time for fibrosis progression and stricture formation (Nikoloff, 2011; Hilmi, 2011).

In a study from Spain, de la Pena et al. found oesophageal stenosis in seven of 105 (6.7%) patients treated with sclerotherapy and in 10 of 148 (6.7%) after EVL. Four of seven IST patients developed stenosis during the first eradication process (mean: 11 months, 1-60), but this early stenosis was observed in only one of 10 VL patients (mean: 20 months, 1-72). Stenosis was severe in three of seven IST patients (43%) but in only two of ten EVL patients (20%). The incidence of oesophageal stenosis was similar after treatment of oesophageal varices with IST and EVL, although EVL tended to produce later stenosis. Variceal treatment-induced strictures were dilated using a TTS balloon or Savory dilators

with endoscopic guidewire placement with a mean of 6.2 sessions and no endoscopic treatment failures (Weston, 2000).

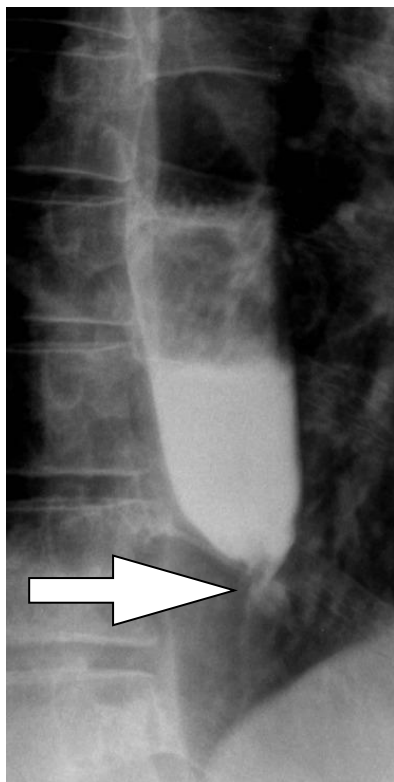


Figure 7.1. Gastrografin swallow showing complete distal oesophageal obstruction (arrow).

9. Oesophageal perforation

Major complications such as oesophageal perforation, occur up to 10 times more frequently with IST than EVL, with a range between 0.5% to 6%. The depth of ulceration, the length and angle that the sclerotherapy needle penetrates into the oesophageal wall, and the volume of sclerosant injected are risks for perforation. Young et al. determined the depth of ulceration and degree of esophagitis to be significantly greater with IST compared to EVL. Before development of the multiband ligator, EVL perforation was associated with direct trauma from passage of the overtube. (Weston, 2000). Although the rate of deep oesophageal injury after EVL is low, transmural oesophageal necrosis has been reported in patients on immunosuppression (Schoonbroodt, 1994).

10. Gastric mucosal consequences

It has been suggested that the entire GI tract, which drains into the portal venous system, might undergo PHT-related changes known as portal hypertensive intestinal vasculopathy (PHIV). This most often involves the stomach and can be a common source of occult or overt bleeding (Elwakil, 2016). Portal hypertensive gastropathy and duodenopathy include a wide spectrum of diffuse macroscopic mucosal lesions that correspond histologically to dilated vessels in the mucosa and submucosa in the absence of erosions or inflammation. In view of excellent results of band ligation in achieving eradication of oesophageal varices, the banding effect on the development or worsening of portal hypertensive gastropathy and duodenopathy has raised concerns among endoscopists. In a study to assess the effect that oesophageal variceal eradication either by endoscopic sclerotherapy or band ligation had on portal hypertensive gastropathy and duodenopathy, 60 patients were studied and classified into three groups: (i) Group I: 20 patients with no history of bleeding or endotherapy as a control group, (ii) Group II: 20 patients with complete oesophageal variceal eradication by endoscopic banding, Group III: 20 patients with complete oesophageal eradication by endoscopic sclerotherapy. Portal hypertensive gastropathy was present in 55% of controls, in 70% in EVL and 65% in IST groups. Portal hypertensive duodenopathy [PHD] was present in 20% of controls, 35% in EVL and 35% in IST patients. Portal hypertensive gastropathy and duodenopathy both increased after complete eradication of the varices by either EVL or IST, but without statistical significant differences (Elnaser, 2005).

In a study to determine the impact of oesophageal variceal eradication by EVL on PHG and PHD using endoscopic and histopathologic assessment, 50 patients had complete EVL variceal eradication. The degree of severity of PHG and PHD were recorded before and 4

weeks after variceal eradication. After obliteration, only 19 (38 %) patients had mild PHG versus 37 (74 %) before EVL, while severe PHG was found in 31 (62 %) patients versus 11 (22%) before EVL, with a highly significant difference. No significant changes were found for endoscopic PHD lesions before and after variceal eradication. Pathological changes including angiogenesis, ectasia and blood extravasation in stomach and duodenum significantly increased after EVL. Large oesophageal varices (III–IV) and Baveno scores at baseline endoscopy were independent risk factors for development of severe PHG after variceal obliteration ($p < 0.05$). PHG increased significantly, endoscopically and pathologically, after variceal obliteration by EVL. Although PHD did not significantly change on endoscopy, pathological examination documented statistically significant changes in the duodenum after EVL (Elwakil, 2016).

Other local complications

11. Technical complications related to device malfunction

Technical and manipulative skills and familiarity with banding equipment assembly and correct use are essential for safe and effective band deployment when used for bleeding varices. Device failures and patient adverse events may occur when using and firing the bands with the current commercially available multi-band ligators. Analysis of the Manufacturer and User Facility Device Experience (MAUDE) database which collects major adverse reports involving FDA-approved medical devices found 3531 reports describing 4720 device failures and 258 patient-related adverse events with multi-band ligators from January 2011 to September 2021. The most common device failures were failure to fire, premature activation when bands were fired too soon, device breakage involving the trip wire or trigger cords, entrapment of the device components with band entanglement during deployment, misfiring or detachment of the ligating unit from the tip of the endoscope (Liu

2015). The most common patient-related adverse events reported were variceal bleeding, device detachment in the oesophagus, dysphagia, oesophageal perforation, oesophageal laceration, haematoma and death (Tatro, 2023).

12. Barrel/ ligating cap dislodgement

Dislodgment of the ligator barrel/ banding cap in the oesophagus has been described in 6 cases. All occurred when upgraded slimmer model gastroscopes were used resulting in a mismatch between the outer diameters of the upgraded endoscopes and the fitting sizes of the band ligator caps (Syn, 2003). This emphasizes the need to check the multiband ligator carefully for compatibility with the endoscope and to ensure a firm fit between the attached barrel and the tip of the endoscope. An additional technical problem with the multiple-band ligator is detachment of the trigger cords attached to the transparent barrel when all six bands have been fired. During the removal of an endoscope, the now untethered Opti-Vu plastic barrel of the ligation set may become dislodged from the endoscope. Attention to ensure that the barrel is still attached to the tip of the endoscope is an important safety step on completion of the banding procedure (Leung, 2003). If the barrel becomes dislodged in the oesophagus thus creating an iatrogenic oesophageal foreign body, for which retrieval with either a basket or a grasping forceps or a controlled radial expansion (CRE) dilation balloon can be used (Tuncer, 2003; Pokharna, 2006). An uncommon but clinically relevant complication is dislodgement of previously placed endoscopic bands when oesophageal balloon tamponade is used for uncontrolled bleeding after banding (Mogrovejo, 2014).

13. Overtube complications

Several complications unique to EVL were directly related to placement of the overtube which was required when the original single-shot banding equipment was used and was

caused by pinching of oesophageal mucosa between the lip of the overtube and the scope. Pharyngeal and oesophageal lacerations as well as oesophageal perforation occurred while railroading the stiff plastic overtube over the endoscope. In addition the bite block at times also separated from the distal plastic sheath which then required endoscopic extraction from the stomach (Levy, 1997; Meirelles dos Santos, 1997). Fortunately, the advent of multiband equipment has made the use of an overtube redundant thus avoiding traumatic iatrogenic oesophageal injuries.

Systemic complications:

14. Bacteraemia

The incidence of bacterial infection in hospitalized cirrhotic patients is higher than in other patient populations, ranging from 33% to 61%. (Maulaz, 2003). Bacterial infections account for up to 38% of deaths in patients with chronic liver disease, both directly and indirectly. The frequent occurrence of bacterial infections in cirrhotic patients results in part from the patients' deficient defence mechanisms. Accordingly, systemic alterations that have been described include complement deficiency in immunoglobulin level activity as well as serum bactericidal activity, alterations, defects in opsonization, decreases in the phagocytic activity of the reticuloendothelial system, and neutrophilic dysfunction (Maulaz, 2003). Before the procedure, bacteraemia was present in 7/62 (11%) sessions. Significant bacteraemia during and 30 min post-procedure developed in 8/32 (25%) and 12/30 (40%) of EVL and IST sessions, respectively ($p=ns$), and in 1/14 (7%) upper gastrointestinal endoscopy sessions. There was more frequent bacteraemia with severe liver disease in the EVL but not in the IST group. The incidence was higher with emergency sclerotherapy compared to elective sclerotherapy (6/8 [75%] vs 6/22 [27%]; $p<0.01$). One patient in the IST group developed spontaneous bacterial peritonitis. The authors concluded that bacteraemia occurs

frequently following EVL and IST in patients with advanced liver disease and bacteraemia is more common after emergency sclerotherapy (Kulkarni, 1999).

15. Meningitis and brain abscess

A variety of serious remote infectious complications such as septicaemia, spontaneous bacterial peritonitis, pneumonia, bacterial endocarditis, perinephric abscess, and cerebral abscess after EIS have been reported in patients with liver cirrhosis and diabetes mellitus due to *α-haemolytic streptococcus*, *staphylococcus epidermidis*, and *diphtheroids*. EVL, by contrast, rarely induces serious bacteraemia or infectious sequelae. The bacteraemia and infections after EVL procedure are usually transient, self-limiting, and mild compared with those after IST. In patients who had undergone either IST or EVL, transient bacteraemia occurred within 24 hours after the onset of bleeding in 17.2% of the IST group and 3.3% of the EVL group ($p < 0.03$); infectious sequelae occurred in 18% of the IST group and 1.8% of the EVL group ($p < 0.03$). (Lo, 2020) Factors responsible for the higher frequency of transient bacteraemia after IST compared with EVL include (i) the mechanical strangulation of varices during EVL that obliterates the submucosal venous channel, thereby diminishing the entrance of bacteria into the bloodstream; (ii) the injector needle used during IST is easily contaminated (Nagamine, 1999; Laviv, 2009; Shih, 2006).

16. Cerebral air embolism (CAE)

In patients who develop sudden acute neurological symptoms, early diagnosis and appropriate intervention may prevent devastating neurological injury and death. The most accepted emergency treatment for CAE includes hyperbaric oxygen, consideration of lidocaine, and identification of the source of the air embolism. (Ghannam, 2019). In a case report a patient suddenly became unresponsive after uncomplicated EVL of two varices. His

GCS score dropped to 7 and a head CT showed pneumocephalus and a suspected air embolism of the right hemisphere. The mechanism of air embolism after EVL remains uncertain, but mucosal damage related to invasive endoscopic procedures is thought to be the major cause of air embolism (Kobari, 2018).

17. Haemodynamic/portal pressure changes after endoscopic variceal ligation:

In a study which measured the haemodynamic variations after EVL a "before" HVPG (pre) was performed and another HVPG 24 hours "after-ligation" (post) in 30 cirrhotic patients undergoing EVL. Pre- and post-HVPG median results were 16.5 mmHg (14-20) and 19.5 mmHg (17-21), respectively, with a significant increase after the procedure ($p < 0.001$). Percentage variations in portal pressure, based on the baseline gradient values (12, 16 and 20 mmHg), were higher for patients with a lower basal HVPG versus a higher HVPG for any of the categories compared ($p = 0.087$, $p = 0.016$ and $p < 0.001$, respectively). In the study, 36.7 % of patients showed a ≥ 20 % gradient increase after ligation. (Gonzalo Bada, 2020) supporting the need to maintain vasoconstrictor treatment after adequate haemostasis is achieved with EVL for bleeding oesophageal varices.

In a similar study the impact of endoscopic variceal ligation on the pressure of the portal venous system was investigated. Portal venograms were performed before ligation in 29 cirrhotic patients and again after variceal obliteration to assess venographic findings and pressure changes. Seventeen of 25 (68%) patients experienced elevated pressure and eight (32%) patients had reduced pressure after ligation. Five patients (20%) experienced rebleeding before variceal obliteration; all of them presented with elevated portal pressures after variceal obliteration. Among the eight patients with decreased portal pressure, seven (87%) had other major collaterals apart from oesophageal varices, compared to three of 17

(18%) patients with elevated portal pressure who had other major collaterals). The authors concluded that 68% of patients undergoing EVL experienced elevated portal pressure, while 32% had decreased portal pressure. Elevation of portal pressure after variceal ligation may be an important factor in variceal rebleeding. The presence of other major collaterals apart from oesophageal varices may be responsible for the decrease in portal pressure after obliteration of oesophageal varices (Io, 1996).

18. Vascular complications

Rare reported complications include isolated superior mesenteric venous thrombosis (Tachibana, 1995) and spinal cord venous infarction, both of which resolved on conservative treatment. It is speculated that the pathogenesis of the latter involved congestion of the abdominal–epidural–spinal cord venous network with increased thoracoabdominal cavity pressure after EVL (Tofuku 2008).

19. Pulmonary effects

In a study that compared the safety of injection sclerotherapy using ethanolamine oleate and band ligation in 28 patients with varices, 14 patients underwent IST and the other 14 underwent EVL. All patients underwent spirometry and ABG pre-, 2 days and 3 weeks after the procedures. Two days after the procedures the PEF and FEF 50 decreased significantly in IST patients when compared to EVL patients ($p < 0.001$), and FEV1, FVC, FEF25, FEF75, PaO₂ and O₂ saturation decreased significantly in the same group ($p < 0.05$). After 3 weeks from the procedures the VCin, VCex, FEV1, FVC and FEF25 decreased significantly in the IST group ($p < 0.001$), and the FEF 50, PEF, PACO₂, PAO₂ and O₂ SAT decreased significantly in the same group. Band ligation was found to be safe for the lung with no significant changes after EVL (Rezk, 2013).

Strategies to prevent endoscopic-related complications

Endoscopic therapy is a well-established and integral part of the management of acute variceal bleeding and the long-term treatment of patients after a variceal bleed. Although complications after endoscopic therapy for variceal bleeding are common, most are minor and do not interrupt the treatment programme. In a small group of patients, however, the success of therapy is compromised by recurrent bleeding and serious procedure-related complications. Most of the serious complications related to endoscopic therapy occur in patients with severe liver disease in whom control of bleeding is difficult. It is not the complication that is a breach of optimal care, but rather the failure to anticipate or recognise a complication and respond appropriately. Mature clinical judgement is necessary in acute problematic or complex cases, and careful supervision of trainees or assistance by an experienced endoscopist becomes essential when critical decisions are required. Early and close multidisciplinary consultation is useful in demanding cases to facilitate appropriate therapy and optimal management.

Several critical generic precautions are important to avoid both local and systemic complications, regardless of the type or technique of endoscopic intervention used to control acute bleeding. Effective resuscitation should precede endoscopy in patients with evidence of recent major bleeding. Diagnostic and therapeutic endoscopy should be performed in a well-equipped unit with competent assistance and careful monitoring. All endoscopic procedures performed with conscious sedation or general anaesthesia require peri-procedural vital signs. This monitoring may detect early signs of patient distress so the physician can respond adequately in time. The most widely available monitoring equipment used during endoscopic procedures are pulse oximetry, single-lead continuous electrocardiographic monitoring and automated blood pressure monitoring. Pulse oximetry

measures oxygenation more than ventilation, so the decreases in oxygenation saturation will be reflected later than hypoventilation. Pulse oximetry cannot detect hypercapnia, which is an early sign of hypoventilation. With the increased use of propofol, capnography which measures the levels of CO₂ in blood may become necessary equipment in endoscopy. Increased CO₂ levels denote hypoventilation and are an early warning sign for subsequent hypoxemia. Therefore, the American Society of Anesthesiologists recommends using capnography in moderate or deep sedation.

It is prudent to perform endoscopy with only the minimum sedation needed for a safe procedure. High-risk patients and those with significant cardiopulmonary disease need only topical oropharyngeal anaesthetic spray and the minimum intravenous sedation. In a frail patient, a benzodiazepine alone may be safer than the combination of a benzodiazepine and an opiate. Medications used for sedation should be titrated to the desired level of sedation using small, incremental doses. Flumazenil, a benzodiazepine antagonist, and naloxone, an opiate antagonist, must be available should a cardiopulmonary complication occur. Meticulous attention should be given to suctioning of the mouth and hypopharynx by a dedicated assistant to avoid aspiration. Early endotracheal intubation is crucial if major bleeding occurs.

If variceal bleeding continues or recurs during the index admission despite two adequate treatments, other definitive therapy should be instituted. Treatment with H₂-blockers or sucralfate does not prevent ulceration but may accelerate healing. Omeprazole has been effective in the treatment of chronic ulcers. Special care should be taken in patients with deep ulceration and persistent pain, fever, an increasing pleural effusion, and deterioration of liver function, which suggest transmural necrosis and impending perforation.

Variceal eradication with EVL requires fewer endoscopic treatment sessions and causes substantially fewer oesophageal complications. Although the incidence of early gastrointestinal rebleeding is reduced by EVL in most studies, this does not result in an overall survival benefit relative to IST. Simultaneous combination therapy (EVL+IST) of large varices confers no advantage over EVL alone. A staged approach with initial EVL followed by IST when varices are small requires further evaluation as this sequential combination may prove to be the optimal method of minimising variceal recurrence. Overall, current data demonstrate clear advantages for using EVL *ab initio* in preference to IST. EVL should therefore be regarded as the endoscopic technique of choice in the treatment of oesophageal varices (Aggeletopoulou, 2018).

Conclusion

The reported variability in the rates of adverse events can be ascribed to the methodology of data collection in which meticulous prospective contemporaneous documentation provides the most accurate information, the duration of follow-up, and the definition of an adverse event. Some authors include minor incidents, such as transient hypoxaemia or self-limited bleeding as adverse events, whereas others report only significant adverse events that prevent completion of the procedure or result in hospitalisation. Additionally, many publications rely on self-reporting, and as most reported data are collected only from the immediate peri-procedure period, the rate of late adverse events and mortality may be underestimated (Ben-Menachem, 2012).

Endoscopists should be aware of the different types and the expected frequencies of these complications, to use strategies to minimize their occurrence and to recognize and treat them appropriately should they occur. Furthermore, it is essential to recognize patients with a higher likelihood of developing complications. Attention must be paid to patients' pre-

existing or comorbid medical conditions and their ability to cope with potential complications. The proper understanding of monitoring equipment leads to procedure quality improvement and decreases the risk of complications (Leelasinjaroen, 2018). There is a need to stimulate further research and analysis to optimize robust and objective endpoints when reporting the results of EVL and AEs which are likely to differ from the sometimes superficial and inadequate historical outcomes reported in previous RCTs. The elusive goal of effective and safe endoscopic variceal banding remains the attainment of long-term bleed-free survival with a minimum of procedure-related adverse events (Krige, 2023b).

Prevention of endoscopic adverse events is based on knowledge of the relevant risk factors and their mechanisms of occurrence. Thus, suitable training of future gastroenterologists and endoscopists is required for these complex procedures. When facing a complication, appropriate management is generally provided by an early diagnosis followed by prompt therapeutic care tailored to the situation (Blero, 2012).

CHAPTER 8

THE ROLE AND APPLICATION OF SALVAGE TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (sTIPS) FOR UNCONTROLLED OESOPHAGEAL VARICEAL BLEEDING

Few, if any, developments over the past three decades have advanced the management of refractory oesophageal variceal bleeding more than the use of transjugular intrahepatic portosystemic shunt (TIPS). Initially discovered serendipitously and evaluated in animal studies over 50 years ago. TIPS was rapidly applied clinically. and the technique is now also used for several other portal hypertensive-related clinical indications, as well as bridging to future liver transplantation (Ferral, 2023). Several technical advancements have improved on the originally implemented short and long-term outcomes of the procedure (Lee, 2023). This section of the thesis reviews the historical background and evolution of TIPS and examines the concept of TIPS as a salvage procedure for uncontrolled or refractory variceal bleeding, including patient assessment and preparation, TIPS insertion technique, contra-indications to using sTIPS, complications of sTIPS insertion and the clinical results for sTIPS.

The clinical TIPS research component of the thesis in chapters 13, 14 and 15 focuses on three clinical studies which include (i) an analysis of risk factors predicting in-hospital mortality in patients undergoing a rescue or sTIPS for uncontrolled variceal bleeding, (ii) the intermediate and long-term consequences and survival of patients after sTIPS, and (iii) the development of a novel CABIN scoring model designed to identify high-risk category patients and improve prediction of outcome after sTIPS.

8.1 Evolution and TIPS development

Conventional methods of opacifying the portal system have in the past included direct portography via splenic parenchymal injection, or indirectly via intra-arterial contrast injection into the splenic or superior mesenteric arteries, with delayed digital subtraction angiography (DSA). More elaborate methods included translumbar portal vein puncture, umbilical vein catheterization, rectal vein cannulation under spinal anaesthesia or via laparotomy with cannulation of a mesenteric vein branch. All these methods produced fair-to-good opacification of the portal venous system but did not allow selective contrast injections or manipulative procedures in the portal venous system (Wang, 2021). The first method of transvenous portal vein access occurred by chance. To avoid the incidence of biliary peritonitis after percutaneous transhepatic biliary puncture, Hanafée et al. performed cholangiography by accessing and puncturing the biliary tract via the jugular, vena caval and hepatic veins in 1967. During the procedure the puncture needle inadvertently entered the portal vein and, with contrast injection, led to visualisation of the portal system. This fortuitous finding laid the foundation for transjugular portal vein access and the creation, application, and development of TIPS (Hanafée, 1967).

In 1969, Josef Rösch and colleagues were the first to describe an experimental interventional technique allowing creation of a transjugular intrahepatic portosystemic shunt in dogs by implanting a silicone-coated spring coil which achieved patency for as long as 2 weeks (Rösch, 1969). A subsequent report by Rösch from Portland, Oregon detailed the use of a modified Ross trans-septal needle-catheter system for creating a transjugular portacaval shunt in forty dogs and was used successfully in cadavers (Rösch, 1971). After this pioneering work, other investigators created intrahepatic shunts using other methods,

including resecting a cylindrical core of liver tissue with a rotating drill or a cryoprobe. Burgener and Gutierrez established temporary intrahepatic portocaval (IHPC) shunts by withdrawing an inflated latex balloon catheter through a parenchymal needle track. However, the problem of maintaining shunt patency persisted, as shown by the results of transjugular intrahepatic shunts performed between the left portal and left hepatic veins in 50 dogs using Dotter's coaxial catheter system that all occluded within two days and fibrosed after three weeks (Gutierrez, 1979).

Based on the initial experimental results of transjugular intrahepatic shunting, Gordon and Colapinto in 1982 successfully created the first transjugular portosystemic shunt in a human during which a balloon was used to dilate the shunt channel. Due to technical limitations, a stent was not placed in the channel and durable patency was not achieved through the tract created between the hepatic vein and the portal vein. However, a subsequent publication by the same authors reported technical success in 15 of 20 patients with life-threatening variceal bleeding using a transjugular Grüntzig balloon dilatation catheter. An average decrease of 5.9 mm Hg in portal vein pressure was measured in 11 patients for whom sequential pressures could be obtained. Two patients survived longer than 12 months without subsequent surgery and three other patients who later underwent an operation were found to have patent shunts. Nine patients with successful shunts died within 30 days of the procedure, comparing favourably with reported operative death rates of 40% to 80% in emergency shunt procedures. Follow-up portal venograms demonstrated shunt patency in six of nine patients, in one after 8 months. Tract patency was determined in four of seven patients on whom an autopsy was performed up to 6 months after the TIPS was created (Colapinto, 1983; Gordon, 1987).

Although most early investigators who worked with IHPC shunts succeeded in correctly placing a shunt, their efforts were frequently marred by early shunt closure as the Teflon

tubes used to stent the shunt usually migrated out of the track to the heart leading to early closure of the shunt (Palmaz, 1985).

The development and clinical deployment of an expandable metal stent to bridge the hepatic parenchyma between the two veins was the key to a more durable connection with longer patency. This marked the birth of the modern TIPS procedure (Fanelli, 2014). The first TIPS in humans using a metal Palmaz stent was reported in 1988 from the University of Freiburg in Germany. Via a right internal jugular vein approach, a modified Brockenbrough needle was used to puncture the right branch of the portal vein from the right hepatic vein. Two Palmaz stents were placed after balloon dilation of the shunt channel. The pressure gradient of the portal system decreased from 38 to 18 mmHg. This milestone event introduced this minimally invasive intervention for the bleeding complications of portal hypertension. The wider availability of self-expanding bare/uncovered metal Wallstents (*Schneider, Minnetonka, Minn., USA*), ushered in the greater use of TIPS. In 1992, Laberge et al. reported the preliminary clinical results of 25 patients who underwent TIPS and showed that TIPS was a safe and effective treatment for patients with variceal bleeding, especially in those with severe liver disease awaiting transplantation (Laberge, 1992).

The portal vein is often seen during attempted percutaneous transhepatic cholangiography (PTC), and led to direct percutaneous transhepatic portal vein access, embolisation and other interventions. Left gastric (coronary) vein embolization is now a standard option during the TIPS procedure in selected patients. The first description of a percutaneous radiological technique to occlude the left gastric vein in patients with oesophageal varices was by two Swedes from Lund. In 1974, Anders Lunderquist, a radiologist and Johannes Vang, a surgeon, using a method like PTC, percutaneously puncturing an intrahepatic

portal vein branch allowing fluoroscopic manipulation of a guidewire and a 5Fr catheter via the portal vein into the left gastric vein. Thirty ml of a 50% glucose and thrombin solution was injected to sclerose the left gastric vein. This was successful in four patients. (Lunderquist, 1974). This procedure became popular worldwide for a decade after the initial description and a variety of materials including gelatin sponge, autologous blood clot, steel coils, bucrylate and absolute alcohol were used to embolise and sclerose the varices. To overcome the bleeding risk of the procedure in patients with severe ascites or advanced cirrhosis or portal hypertension, other portal vein access methods were used, including transjugular and umbilical vein routes. However, in a subsequent publication reporting 22 patients with portal hypertension and bleeding varices in whom the feeding coronary vein was occluded with bucrylate, follow-up examination in eight patients 1-12 months later showed recanalization of previously obliterated veins in six, although these veins were substantially smaller than before the procedure. In patients in whom the veins remained occluded, new veins had opened elsewhere with reconstituted blood flow to the oesophageal varices (Lunderquist, 1974).

8.2 TIPS as a salvage procedure for uncontrolled oesophageal variceal bleeding

Until three decades ago, the only reliable method of creating a durable portosystemic shunt to reduce portal pressure was by major abdominal surgery usually by creation of a vascular anastomosis between the portal system and inferior vena cava by a side-to-side portocaval or mesocaval shunt or, alternatively, as a splenorenal shunt. The development and subsequent introduction into routine clinical practice of a percutaneous radiologically placed TIPS connecting a hepatic vein with a portal vein branch represented a paradigm shift in the multidisciplinary management of complicated portal hypertension (Vizzutti, 2020). The haemodynamic effects of TIPS result in a substantial reduction in the portocaval pressure

gradient by connecting the hypertensive portal venous system with the lower pressure systemic circulation via the intrahepatic shunt. The procedure can be achieved with significantly lower morbidity and mortality rates compared to operative surgical shunting (Kaplan, 2023). The patency of the newly created low-resistance conduit is typically maintained by deploying a 10mm self-expandable uncovered or covered metal stent across the length of the hepatic parenchymal track to counteract the natural recoil.

The indications for TIPS have dramatically expanded since its introduction in 1988 (Ferral, 2023). However, while there are a variety of clinical sequelae of PH that should improve with TIPS, there are few large, high-quality RCTs that demonstrate this efficacy (Carroll, 2023). The TIPS shunt is now a well-established interventional procedure of proven benefit in patients with variceal bleeding refractory to endoscopic and medical therapy, as well as for patients who have intractable diuretic-resistant ascites (Lee, 2023). As clinical experience with TIPS has grown, the procedure is no longer limited to salvage treatment of endoscopically uncontrolled variceal bleeding (Hung, 2019). The indications have expanded to include several conditions related to portal hypertension where substantial improvements in patients' prognosis have been achieved (Qi, 2015). These include TIPS for bleeding related to complicated ectopic varices, portal vein thrombosis, Budd-Chiari syndrome, and hepatic veno-occlusive disease (Posa, 2023). TIPS is also the ideal non-operative bridge to liver transplantation or shunt surgery in patients with liver decompensation compounded by acute variceal bleeding, as the intraportal position of a TIPS stent disturbs surgery less in the porta hepatis (Tripathi, 2020), although superior right atrial extension can interfere with a future liver transplant.

While TIPS is a life-saving procedure in high-risk patients, the important clinical implications, consequences, and disadvantages after stenting, include *inter alia* cost, stent dysfunction, impairment of liver function, hepatic encephalopathy and cardiac overload. Each stent costs in the region of R25,000 and more than one stent may be required, either during the initial insertion or subsequently. Regular post-insertion stent surveillance with duplex Doppler is necessary as metal stents are prone to stenosis and occlusion. In addition, as there is an inevitable deterioration in hepatic function due to the diversion of portal venous blood flow through the TIPS, the hepatic encephalopathy rate ultimately increases to levels of standard portocaval shunts and may become debilitating in some patients. Development of hepatic encephalopathy and shunt dysfunction are the most relevant complications of transjugular intrahepatic portosystemic shunt. However, the introduction of newer polytetrafluoroethylene (PTFE)-covered stents has resulted in less TIPS dysfunction. Covered TIPS stents such as the Viatorr models (W. L. Gore & Associates, Flagstaff, AZ, USA) offer improved patency but have other risks such as malposition or migration. Stent reduction or occlusion are options for intractable hepatic encephalopathy.

The number of complications related to the procedure itself is inversely proportional to experience. For that reason, TIPS should be performed in experienced referral centres with over 90% expected procedure success rates. Balloon-occluded retrograde transvenous obliteration (BRTO) and variants may be used to supplement TIPS by allowing occlusion of varices, typically gastric fundal varices.

8.3 Indications for TIPS

A TIPS shunt reduces the portosystemic pressure gradient in over 90% of cases (Clark, 2008). In patients with cirrhosis and variceal bleeding, TIPS is used in three clinical situations: (a) as rescue or salvage therapy in patients with uncontrolled or persistent life-threatening refractory variceal bleeding (salvage TIPS); (b) in patients in whom bleeding has been controlled after endoscopic, pharmacological and antibiotic treatment, but who are at high risk of rebleeding (early or pre-emptive TIPS [pTIPS]); and (c) in patients who have recurrent episodes of variceal bleeding after initial control despite optimal endoscopic and pharmacological secondary prophylaxis. (Horhat, 2021). The latter two situations have been studied and evaluated in several meta-analyses (Abuelazm, 2023; Boike, 2021; Carroll 2023; Guo, 2022)

8.3.1 Salvage TIPS

Salvage TIPS has proven effectiveness in cirrhosis and life-threatening or refractory VB unresponsive to the combination of vasoactive drugs, endoscopic treatment, and antibiotic therapy. The primary outcomes are control of bleeding and improvement in survival. Despite effective control of bleeding, in-hospital mortality remains as high as 30% in some series and is associated with hyper-bilirubinaemia, renal failure, hyponatraemia, sepsis, inotrope use and a high APACHE II score. No robust data are available to definitively select or exclude patients for the TIPS procedure, although in a French study a series of patients with Child–Pugh scores of C14 or C15 and refractory variceal bleeding had an in-hospital mortality of 100% despite control of bleeding. After the implementation of the MELD score for liver graft allocation in France in 2007, successful liver transplantation in five consecutive selected candidates after salvage TIPS in Child–Pugh C14-C15 patients was performed with 100% survival in this small cohort. Most centres now regard salvage TIPS

as a futile procedure in Child–Pugh C14 or C15 cirrhotic non-transplant candidates (Guo, 2022)

8.3.2 Pre-emptive or early TIPS

Risk factors for early rebleeding after successful medical and endoscopic variceal intervention are the severity of liver disease as evaluated by Child–Pugh or MELD scores and the severity of the bleeding episode. Pre-emptive (early) TIPS (pTIPS) is a strategy that anticipates treatment failure and death by pre-emptively placing TIPS, soon after therapeutic EVL in patients at high risk of failing standard therapy (Jakab 2020). The concept of pTIPS was first introduced by Monescillo et al in 2004. In their study, high-risk patients, defined by a hepatic venous pressure gradient (HVPG) >20 mm Hg were randomised into two groups, one group being allocated to TIPS placement within the first 24 hours after stabilisation and the other to standard treatment. Rebleeding and survival were significantly better in the pTIPS group. The main limitations of this study were the need for routine HVPG measurement to identify and select high-risk patients and their use of oesophageal injection sclerotherapy that is known to have failure rates of up to 30%. (Monescillo, 2004). Subsequent studies in high-risk patients have used simpler more clinically applicable definitions

In a pivotal study by García-Pagan et al in 2010, 63 patients with cirrhosis (Child–Pugh C10–C13) and VB or Child–Pugh B with active bleeding during endoscopy within 72 h after admission were randomly assigned to receive pTIPS (32 patients) or standard therapy using non-selective beta blockers (propranolol or nadolol) plus EVL (31 patients) (Garcia-Pagan, 2010). During a median follow-up of 16 months, rebleeding or failure to control bleeding occurred in 14 patients (45%) in the standard therapy group, compared with one patient (3%) in the pTIPS group. Survival at 1 year was significantly better in the pTIPS

group (87.5% vs. 61.3%) and hepatic encephalopathy was not more frequent (Garcia-Pagan, 2010). Subsequent studies have confirmed less rebleeding with pTIPS. However, survival benefit in Child–Pugh B cirrhotic patients with active VB remains unresolved and no universal recommendation has been formulated in patients with Child–Pugh C14–C15 cirrhosis.

8.3.3 Secondary prophylaxis of variceal bleeding

Secondary prophylaxis of variceal bleeding relies on non-selective β -blockers and endoscopic treatment. If recurrent bleeding occurs despite optimal secondary prophylaxis, TIPS placement should be considered. The strongest evidence of TIPS efficacy is for the secondary prevention of variceal bleeding and the treatment of refractory diuretic-resistant ascites, as shown by meta-analyses of RCTs (Fidelman, 2012). A further meta-analysis of 12 RCTs showed a significant decrease in rebleeding and death due to rebleeding after TIPS placement when compared to endoscopic treatment (Horhat, 2021). More recently, two RCTs compared TIPS and standard secondary prophylaxis after a first episode of VB in unselected Child–Pugh A to C patients. Lower rebleeding rates were observed in the two studies in patients treated by TIPS. However, there was no difference in survival in both studies (Horhat, 2021).

8.4 Comparative meta-analyses of TIPS and endoscopic intervention.

Six meta-analyses have evaluated RCTs comparing TIPS with endoscopic therapy. Two of the meta-analyses also included surgical shunts as comparators (Khan, 2006; Zhou, 2019). The first meta-analysis from Italy included 750 patients in 11 RCT's and assessed recurrent bleeding, encephalopathy, and mortality. Pooled risk differences were recurrent bleeding, -31% (95% CI, -39%, -23%); encephalopathy +16% (95% CI, +10%, +22%); death due to all

causes +2% (95% CI, -4%, +9%); and death due to bleeding -5% (95% CI, -11%, +6%). Clinically important complications occurred in 22% of patients with both treatments. TIPS dysfunction occurred in 55% of patients. The authors concluded that TIPS markedly reduced the risk of rebleeding but increased the risk of encephalopathy, without affecting survival and that TIPS was not a first-choice therapy for prevention of recurrent variceal bleeding (Luca, 1999).

In the second meta-analysis from the Liver Unit at The Royal Free Hospital in London, 11 RCT's involving 811 patients were analysed. Variceal rebleeding was significantly more frequent with ET (47%) when compared with TIPS (19%), but there was no difference in mortality. Post-treatment encephalopathy occurred significantly less often after ET (19%) than after TIPS (34%). In the studies showing resource use, TIPS was more expensive. The authors concluded that TIPS reduced rebleeding but did not improve survival and increased the incidence of encephalopathy (Papatheodoridis, 1999).

The third meta-analysis from Burroughs and Vangeli published in the Scandanavian Journal of Gastroenterology, in 2002, evaluated 13 RCTs which included 948 patients (Burroughs, 2002). Analysis showed that TIPS patients had a significant reduction in rebleeding OR 3.28 (95% CI 2.28–4.72), which meant that 4 patients (95% CI 3–6) needed to be treated with TIPS to prevent 1 rebleeding episode. In addition, TIPS resulted in a consistent increase in *de novo* or worsening hepatic encephalopathy. The OR was 0.48 (95% CI 0.34–0.67) so that TIPS would result in an episode of *de novo* or worsening encephalopathy in 1 of 8 patients. Thirdly, the meta-analysis confirmed that TIPS did not confer a survival advantage. In this cumulative meta-analysis there was a consistent but non-significant difference in survival between TIPS and ET (banding ligation in 4 trials and sclerotherapy in

9 trials) in favour of endoscopic treatment. Given that the evaluation comprised over 900 patients, this consistency in the survival equivalence provided good evidence that TIPS did not have a survival benefit (OR 0.875, 95% CI 0.65–1.17). Of note patients enrolled in the meta-analyses that underwent elective TIPS and ET and salvage TIPS patients were not included. In addition, patients in the endoscopy arm of the trials who were rescued by TIPS for rebleeding were also not considered, a percentage which ranged from 4.2% to 29.6% (Burroughs, 2002).

In the fourth meta-analysis, as a Cochrane review, Khan and colleagues from the Liver Unit at the Queen Elizabeth Hospital in Birmingham compared the effects of shunts (total surgical shunt (TS); distal splenorenal shunts (DSRS) or TIPS with endoscopic therapy (ET, sclerotherapy and/or banding) for prevention of variceal rebleeding in cirrhotic patients. Twenty-two trials evaluating 1409 patients were included. TIPS therapy compared with ET demonstrated significantly less rebleeding at the cost of significantly increased acute and chronic hepatic encephalopathy. There were no significant differences regarding mortality and duration of in-patient hospital stay. The proportion of patients with shunt occlusion or dysfunction was 3.1% following TS (two trials), 7.8% following DSRS (four trials), and 59% (range 18% to 72%) following TIPS (14 trials). The authors concluded that all shunts resulted in a significantly lower rebleeding rate at the expense of a higher incidence of encephalopathy and that TIPS was complicated by a high incidence of shunt dysfunction. No survival advantage was demonstrated with any shunt (Khan, 2006).

The fifth meta-analysis from Wenzhou in China which included 12 RCTs showed reduced variceal rebleeding and reduced deaths due to rebleeding after TIPS but increased post-treatment encephalopathy (Zheng, 2008).

In the sixth meta-analysis Zhou and colleagues from Beijing, China compared short-term and long-term survival after portosystemic shunts, including surgical portosystemic shunts and TIPS and endoscopic therapy (ET) in patients with variceal bleeding and cirrhotic portal hypertension (Zhou, 2019). Twenty-six publications comprising 28 RCTs were included in the analysis. These studies included a total of 2845 patients: 496 (4 RCTs) who underwent either surgical portosystemic shunts or TIPS, 1244 (9 RCTs) underwent either surgical portosystemic shunts or ET, and 1105 (15 RCTs) underwent either TIPS or ET. There was no significant difference in overall mortality and 30-day or 6-week survival among the three interventions. TIPS showed a trend toward lower variceal re-bleeding (RR=0.46, 95% CI=0.36-0.58, $p<0.001$), but a higher incidence of hepatic encephalopathy than ET (RR=1.78, 95% CI=1.34-2.36, $p<0.001$), (Zhou, 2019).

In the final analysis, a summation of these six meta-analyses which compared TIPS with endoscopic therapy showed lower variceal re-bleeding rates after TIPS, an increased incidence of hepatic encephalopathy, but ultimately no difference in survival.

8.5 Patient selection, assessment, and preparation

There is consensus that patients being considered for a TIPS procedure should be managed in a specialist liver unit with expertise in the treatment of portal hypertension and variceal bleeding (Lee, 2023). When pharmacological and endoscopic treatment fail to control life-threatening variceal bleeding, the decision whether a salvage or rescue TIPS is appropriate and technically feasible is made in consultation with an experienced interventional radiologist. Absolute and relative contraindications to TIPS insertion are listed in Table 8.1. Absolute contraindications include congestive heart failure, severe tricuspid incompetence, and severe pulmonary hypertension (mean pulmonary pressure >45 mm Hg). Relative contraindications include anatomic factors that may complicate placement of

the shunt or reduce the technical success, such as portal or hepatic vein thrombosis, previous liver surgery and multiple liver cysts. Patients with a history of hepatic encephalopathy are at increased risk for worsening of existing encephalopathy (Fidelman, 2012).

TABLE 8.1: Contraindications to placement of a Transjugular Intrahepatic Portosystemic Shunt

Absolute	Relative
Primary prevention of variceal bleeding	Hepatocellular carcinoma, especially central
Congestive heart failure	Obstruction of all hepatic veins
Severe tricuspid regurgitation	Portal vein thrombosis
Severe or moderate pulmonary hypertension	Severe coagulopathy (INR > 5)
Multiple hepatic cysts	Thrombocytopenia of < 20,000 cells/cm ³
Uncontrolled systemic infection or sepsis	Hepatic encephalopathy
Unrelieved biliary obstruction	

Because TIPS insertion is technically demanding and invasive, the procedure should only be performed by, or under the supervision of, an experienced interventional radiologist. While TIPS insertion can be performed using conscious sedation, most interventional radiologists prefer general anaesthesia, with endotracheal intubation for the procedure. Patency of the right internal jugular, hepatic and portal veins and favourable abdominal anatomy should first be confirmed by Duplex ultrasound or other cross-sectional imaging. After the TIPS procedure, patients should be admitted to a Hi-care unit for close monitoring. Laboratory blood tests including complete blood count and INR, electrolytes, urea and creatinine levels and liver function tests are checked daily and urine output and mental status monitored continuously. A liver ultrasound and duplex Doppler is performed 24 hours after the TIPS procedure to directly confirm shunt patency. Detection of hepatopetal flow in

the main portal vein and stent and hepatofugal flow in the branch portal veins indicate a functioning and patent TIPS stent.

8.6 Technical aspects of TIPS insertion

TIPS kits are available with the required needles, catheters, sheaths, balloons and guidewires. The metal stents are usually provided separately and were initially uncovered. Covered stents at first had limited availability and were more costly. Second generation covered stents are now more readily available, but the selection and placement technique are more exacting and ideally need specific training by a proctor (Lee, 2023).

Step 1: Venous Access

The right internal jugular vein is the preferred access for TIPS insertion as the vein is usually large and provides favourable straight access to the inferior vena cava and hepatic veins. This facilitates the placement of the stiff sheath and cannula required for the TIPS procedure. Ultrasound (US) examination of the neck is useful to identify the exact anatomic positions and to assess the patency of the right internal jugular vein (Figure 8.1), as well as to guide the puncture. When the right internal jugular vein is occluded or radiologically inaccessible, the right external jugular vein, the right subclavian vein or the left internal jugular vein can be used as alternative routes for venous access (Kalva, 2009). Once patency is confirmed, the patient is placed in a slightly head-down position to distend the vein and reduce the risk of air embolism. The vein is typically punctured with an 18-G needle under US guidance. The needle enters the neck just posterior to the sternocleidomastoid muscle midway between the mastoid and medial right clavicle providing space for manipulation of the catheters and avoiding the risk of a right pneumothorax. After confirming that the needle tip is correctly positioned within the internal jugular vein lumen by freely aspirating venous blood into a normal saline filled syringe, or by

injecting contrast to opacify the vein, usually a 0.035-inch guidewire is advanced well into the superior or inferior vena cava and the needle is then exchanged for a 5-Fr sheath over the guidewire. The guidewire is replaced with a stiffer 0.035-inch guidewire which is advanced into the inferior vena cava. The venotomy site is serially dilated to accommodate a 10-Fr working sheath that is railroaded into the internal jugular vein and IVC (Kalva, 2009).

Step 2: Hepatic venography

The next step involves selective catheterization of the right hepatic vein using an angled multipurpose catheter and a J-guidewire. Right hepatic vein access is preferred, although portal vein access can be obtained from any hepatic vein, if necessary. The catheter is initially advanced into the IVC, and the guidewire withdrawn into the catheter which is then gradually pulled back towards the cavo-atrial junction and rotated right laterally to gain access to and allow selective catheterization of the right hepatic vein (Figure. 8.2). Deep

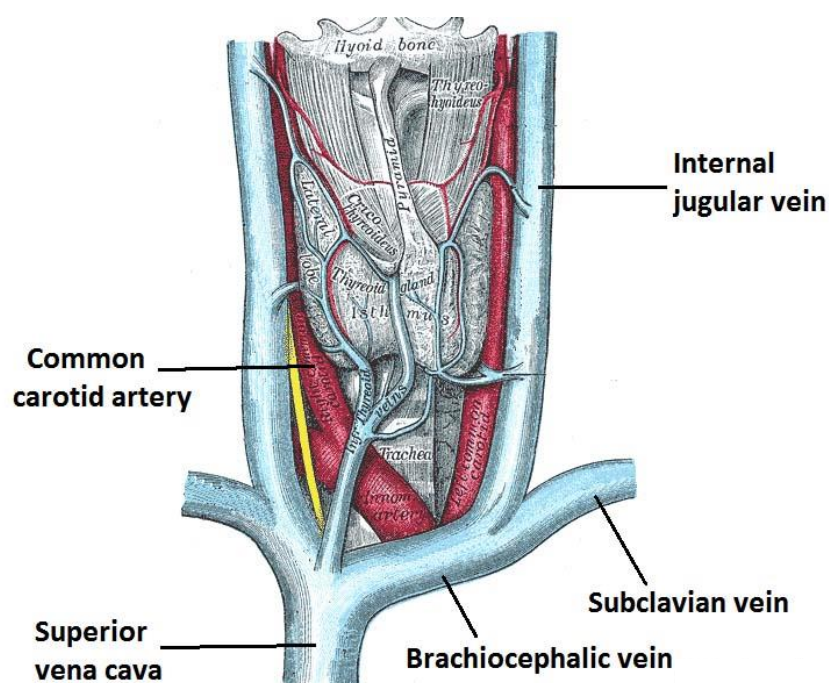


Figure 8.1 Anatomy of the right internal jugular vein

inspiration provided by the anaesthetist may favourably change the angle of the hepatic vein. The configuration of the angled portion of the catheter can be modified by advancing the guidewire. When the catheter selectively enters the right hepatic vein, the guidewire is advanced further into the vein. The use of a curved guidewire, such as the 3 mm J wire, usually permits easier access into the distal hepatic vein than does the use of an angled tipped hydrophilic wire, such as a Glide wire (*Terumo Corp, Tokyo, Japan*) that tends to readily enter side-branches.

If the multipurpose angled catheter does not enter the hepatic vein, a variety of other catheters and guidewires can be used. The catheter is advanced into the distal portion of the hepatic vein and contrast is injected with oblique views to determine whether the right or middle hepatic has been entered. (Figure 8.2) The right hepatic vein may have a superior capsular branch. Lateral or oblique views may help to distinguish right from the middle hepatic vein.

A 10-F sheath such as that in the Rösch-Uchida kit (*Cook, Bloomington, Ind., USA*) is then advanced into the hepatic vein over a stiff Amplatz guide wire (*Medi-tech Boston Scientific, Watertown, Mass., USA*). Once the stiff cannula is in the hepatic vein, the hub pointing to the 4 o'clock position suggests the right hepatic vein has been selected, whereas the 1 o'clock position favours the middle hepatic vein. (Kalva, 2009).

Step 3: Wedged Hepatic Venography and Measurement of Portosystemic Gradient

After confirming the location of the hepatic vein, a selective catheter is used to obtain a wedge pressure. After wedging the catheter into a small hepatic vein, the wedged hepatic vein pressure (WHVP) is measured but can be erratic. The free hepatic vein pressure is then measured. The difference between the WHVP and free hepatic vein pressure is the

corrected sinusoidal pressure (CSP) or the “hepatic vein pressure gradient” This is abnormal if over 6 mm Hg and suitable for TIPS if over 12 mm Hg. The WHVP may not reflect portal pressure in presinusoidal portal hypertension, main portal vein thrombosis, or with portosystemic shunting (Kalva 2009). These should be excluded on imaging. A wedged hepatic venogram may be performed to localise portal vein branches by injecting 30-40 ml of contrast or CO₂ through the end-hole of a wedged catheter while obtaining DSA images.

Step 4: Accessing the portal vein, portography, direct measurement of portal venous pressure.

Typically, the right portal vein branch would be anterior to the right hepatic vein, so the needle tip would need to be directed anteriorly. The right portal vein is posterior to the middle hepatic vein. This relationship should be confirmed on prior imaging. Through the catheter, a stiff 0.035-inch Amplatz guidewire is advanced distally into the hepatic vein and the 10-Fr sheath with a distally curved stiffening steel cannula is then advanced into the hepatic vein.

A Colapinto or Rösch-Uchida needle (Cook) is used to puncture the right portal vein. The needle with outer catheter or coaxial outer catheters is advanced under fluoroscopic guidance into the curved sheath and cannula. After positioning the needle approximately 25 mm within the hepatic vein, the needle tip is exposed by retracting the outer sheath. While twisting the curved cannula toward the target portal vein, the needle is advanced in the suspected direction of the portal vein as determined on the imaging. A firm thrust may be required to enter the fibrotic liver. After removing the inner needle, the catheter is slowly

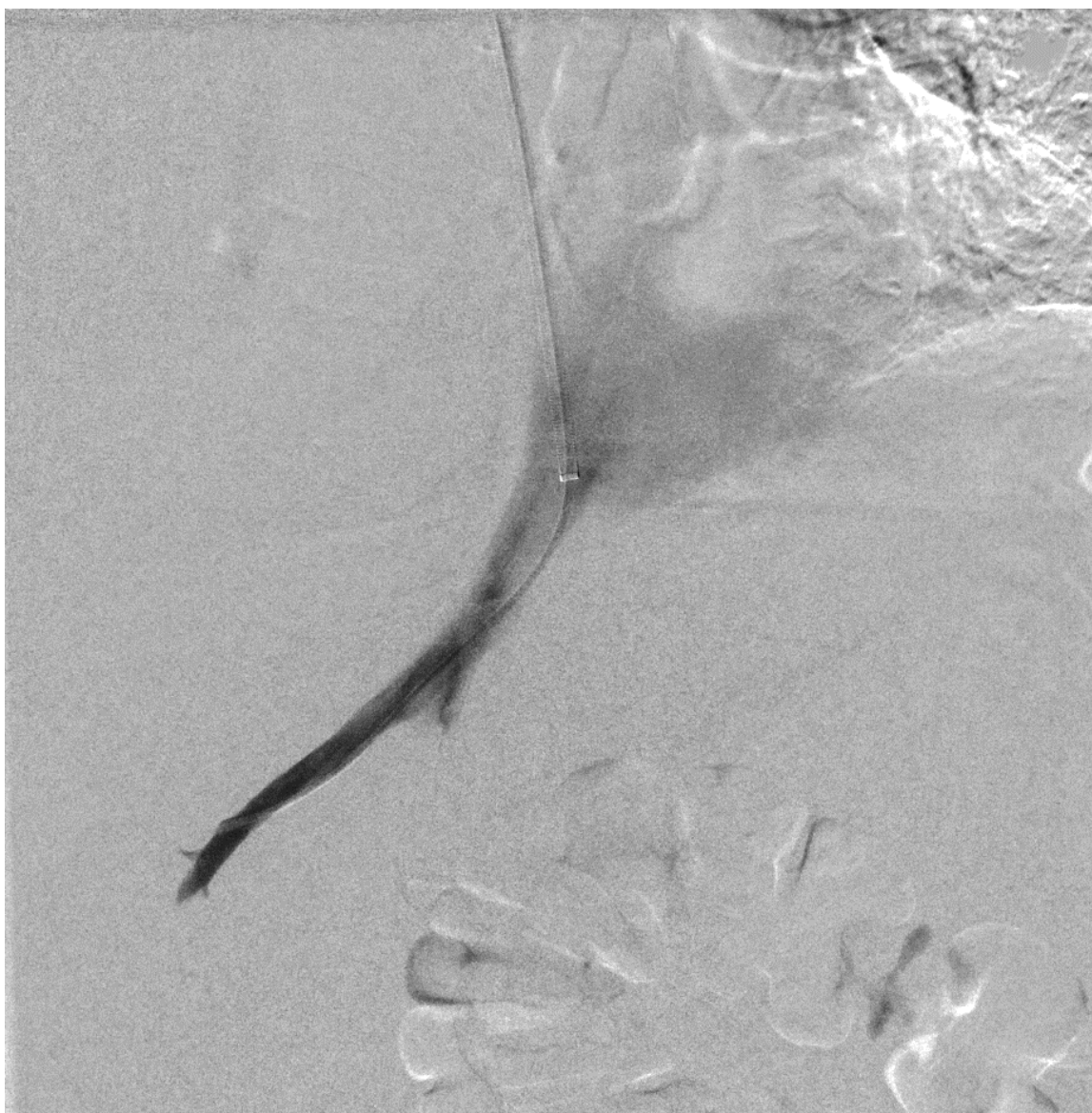


Figure 8.2 Right hepatic venogram

withdrawn with suction applied by a contrast-filled syringe attached to the needle hub. On aspiration of venous blood into the syringe, contrast is injected to confirm portal vein entry. (Figures 8.3, 8.4) Failing this, needle passes are repeated using different puncture directions, trying to avoid repeatedly entering prior needle tracks, until a portal venous branch is successfully accessed. Inadvertent puncture of the hepatic capsule is a risk in small and shrunken livers and may need embolisation of the tract if substantial.

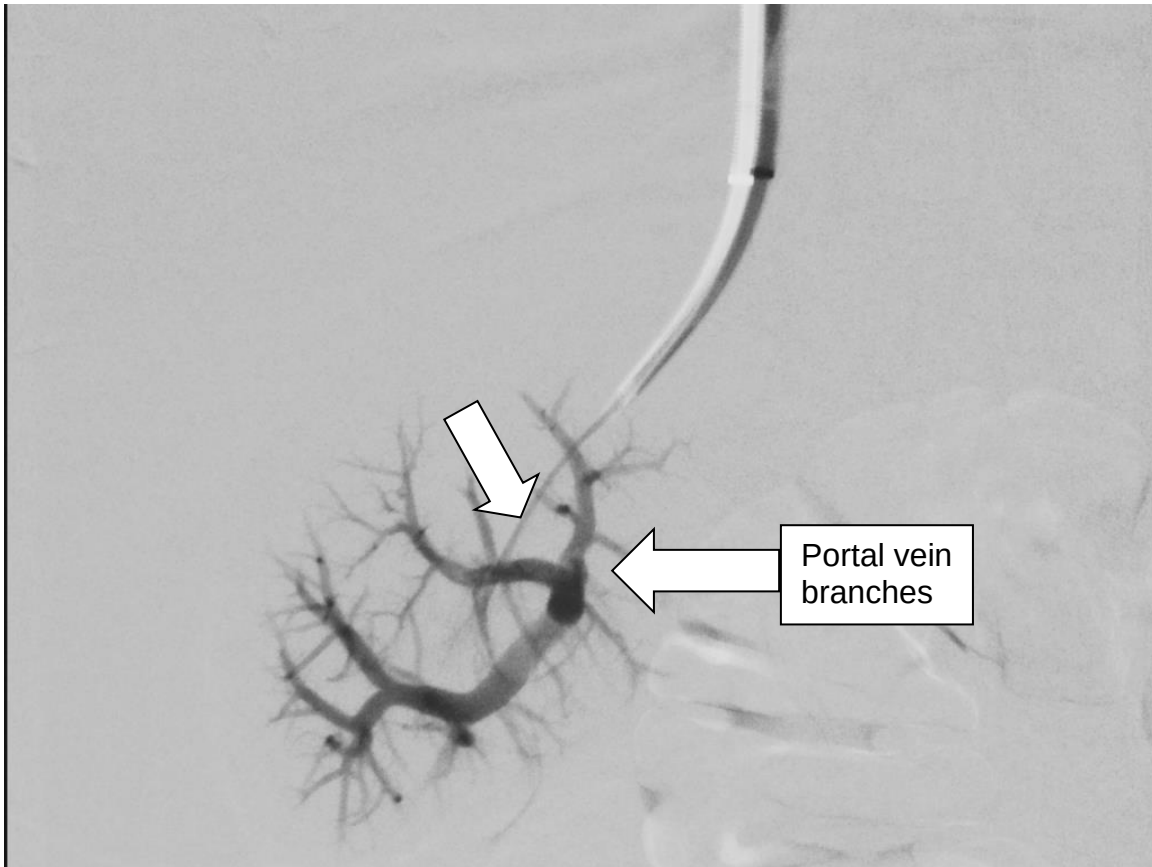


Figure 8.3 Right portal venogram [catheter unlabelled arrow]

After confirmation of portal vein entry, an Amplatz extra-stiff guidewire (Medi-tech Boston Scientific, Watertown, Mass., USA) or hydrophilic guidewire is introduced through the catheter and then into the portal vein. Excessive needle movement should be avoided to prevent loss of access (Abujedah, 2007). The guidewire should ideally pass into the main portal vein and then the splenic vein but may require catheter manipulation or feeding of the guidewire so that it prolapses into the main portal vein.

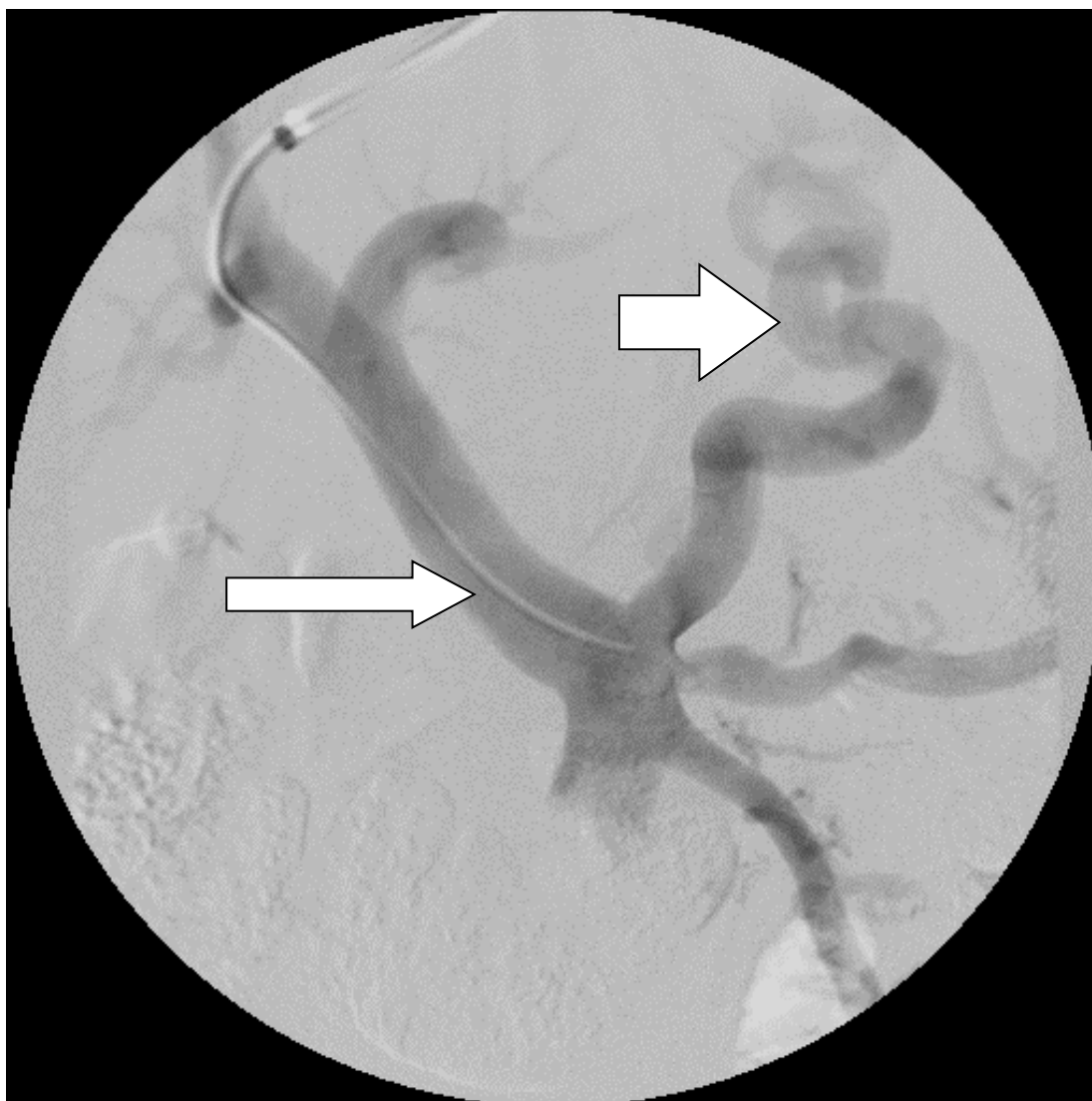


Figure 8.4 Catheter in the right portal vein (thin arrow). Large left gastric vein (wide arrow)

A 5F multipurpose or cobra catheter is positioned in either the superior mesenteric vein (SMV) or the splenic vein, for confirmation of portal vein entry by injection of contrast material (Figure 8.4). Entry into a recanalized umbilical vein can simulate SMV entry. Direct portal pressure is then measured. A formal portal venogram, ideally via a calibrated 5-Fr pigtail catheter (Figure 8.5) is used to confirm portal vein patency and flow direction and the presence of varices and/or other portosystemic shunts, as well as give an idea of the portal vein puncture site.



Figure 8.5 Calibrated catheter with markers (arrow) at 10 mm intervals in right and main portal vein

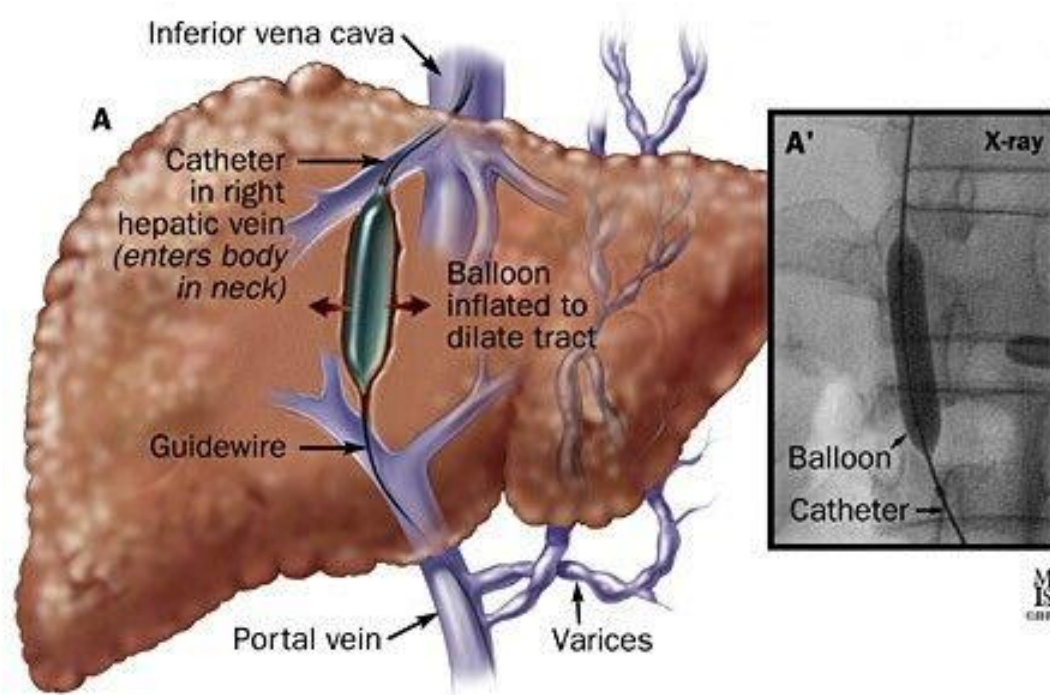


Figure 8.6 Balloon dilatation of intrahepatic parenchymal tract. *Adapted from Bhogal HK, Sanyal AJ. Using transjugular intrahepatic portosystemic shunts for complications of cirrhosis. Clin Gastroenterol Hepatol. 2011;9(11):936-46,*

Step 5: Dilatation of the Parenchymal Tract

A stiff guidewire (e.g., 0.035-inch Amplatz extra stiff guidewire) is then advanced into the splenic vein or SMV and the catheter is exchanged for a 6 mm diameter 40mm length low-profile angioplasty balloon. This is used to dilate a tract through the hepatic parenchyma interposed between the hepatic and portal veins (Figure 8.6). Waist-like narrowing of the balloon should be seen at the hepatic vein exit site and the portal vein entry site (Figure 8.7). These should be noted to guide later stent placement.

Once the tract has been dilated, the 10-Fr sheath is advanced over the guidewire into the main portal vein, possibly using a larger diameter balloon. The inner stiff cannula of the 10-Fr sheath may also aid in advancing the sheath into the portal vein. A repeat portogram

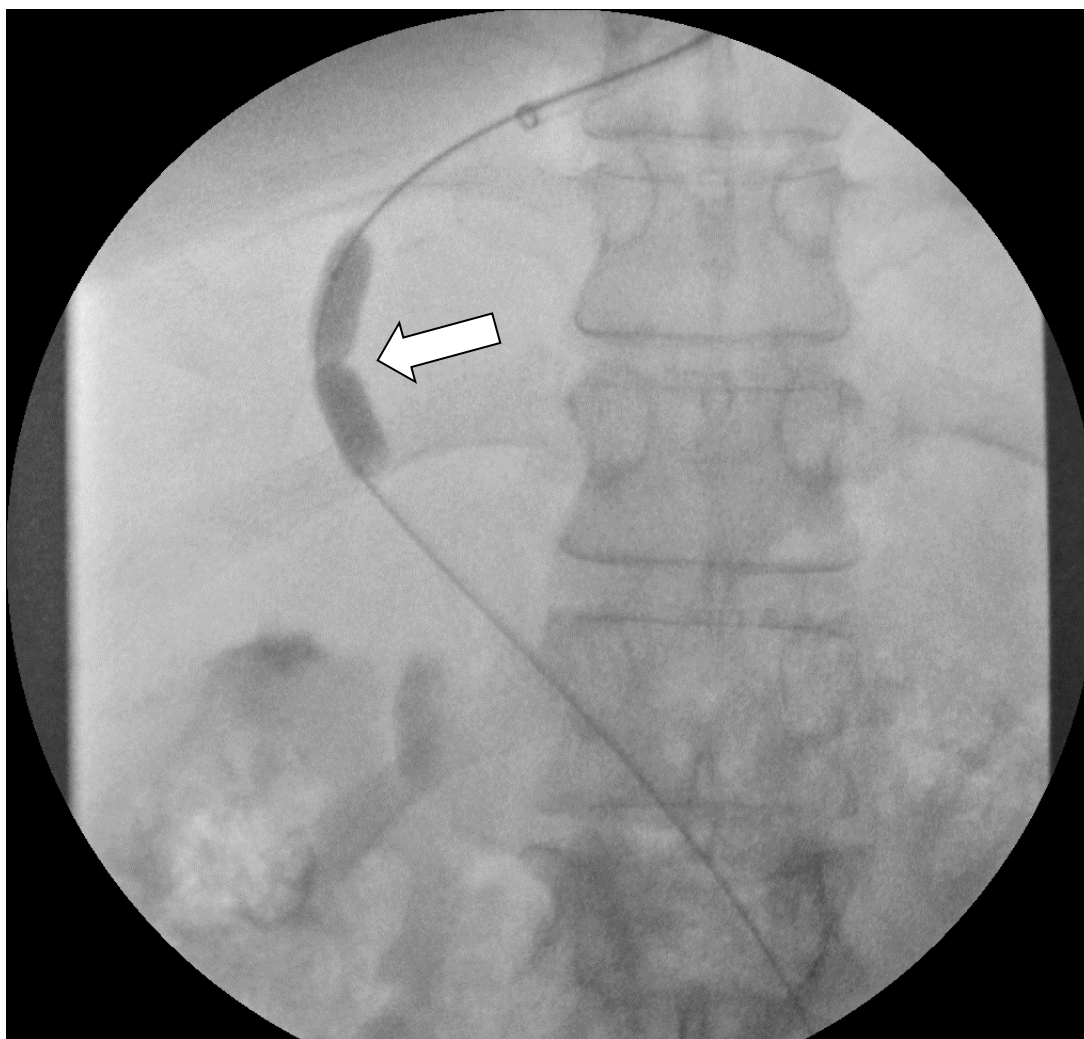


Figure 8.7 Balloon dilatation of intrahepatic parenchymal tract. Note the waist in the balloon indicating vein wall (arrow)

with the calibrated pigtail and optionally simultaneous injection via the 10-Fr sheath in the hepatic vein can clarify hepatic and portal vein wall locations. The length of the tract from the hepatic vein-IVC junction to the portal vein entry site can be measured using the radiopaque markers of the calibrated pigtail catheter as a reference. The measured length is the minimum length of the stent that will be required to cover the parenchymal tract.

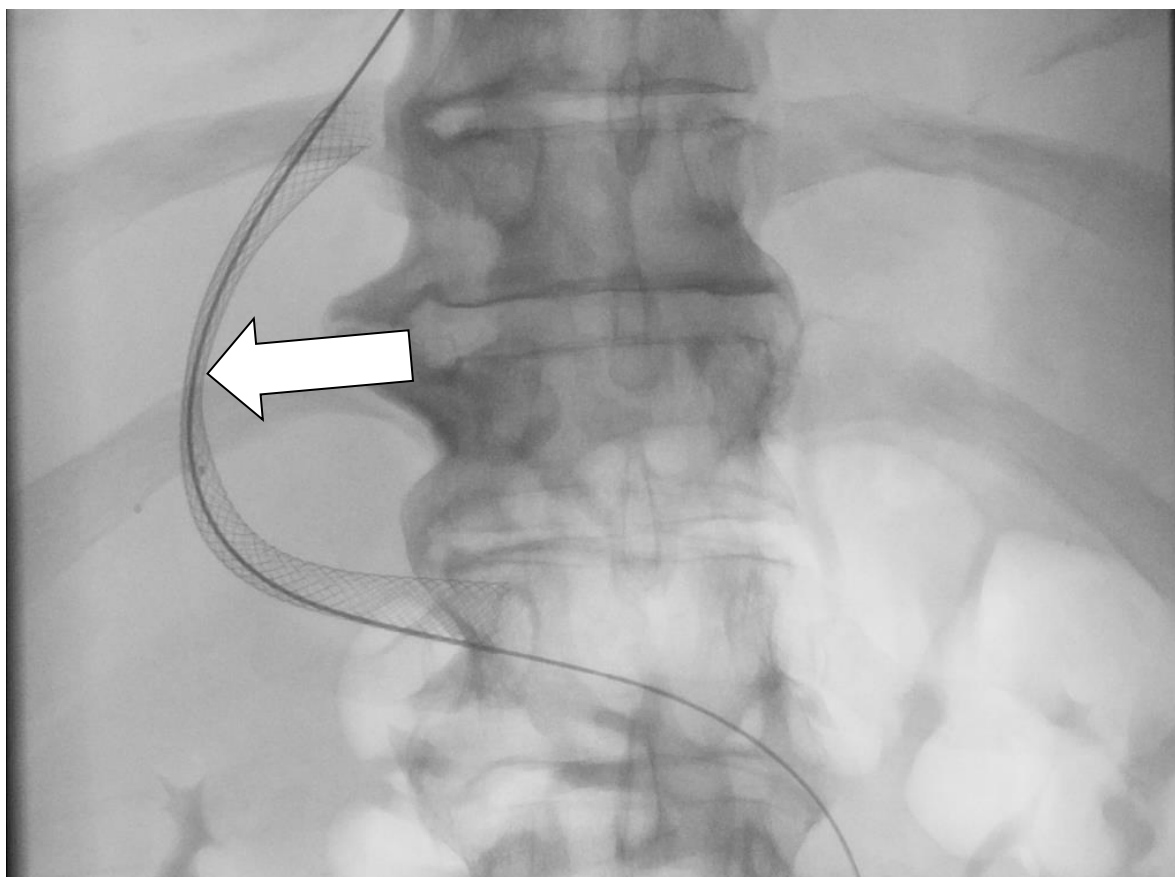


Figure 8.8 Deployment of intrahepatic stent that is still stenosed across the parenchymal track (arrows) before balloon dilatation.

Step 6: Deployment of a Stent Across the Parenchymal Tract

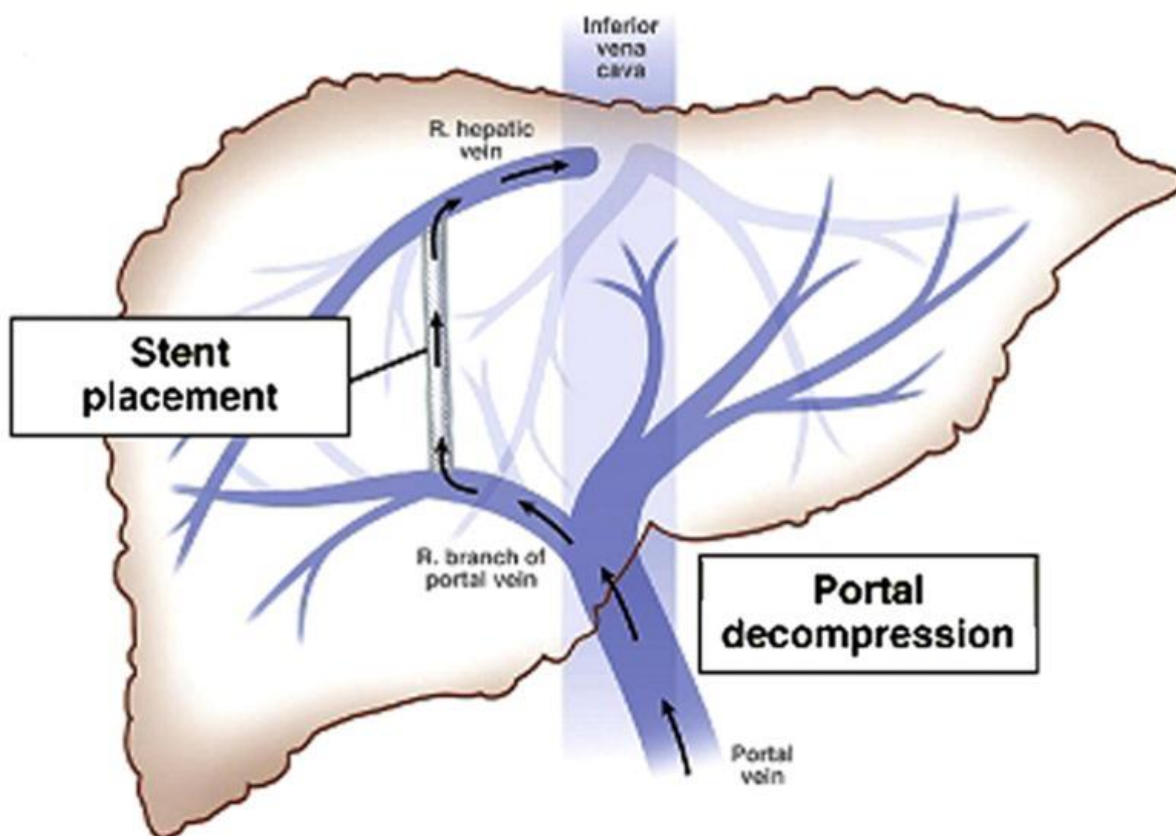
Typically, a 10-mm diameter metal stent such as a Wallstent (*Schneider, Minnetonka, Minn., USA*) or covered stent was used, with length as determined by the portogram and separation distance of hepatic and portal vein wall balloon waisting plus recommended extension distance. Deployment technique is as advised for the specific stent. The stent delivery catheter is introduced over the guidewire well into the 10-Fr sheath (Abujudeh, 2007) (Figure 8.8). Withdrawing the outer 10-Fr sheath precedes deployment of the metal stent within the portal vein. The entire system is slowly withdrawn over the guidewire so the radiopaque 10F sheath superior marker is in the upper hepatic vein. The superior end of

the stent should just extend to, or just through the hepatic vein ostium, as this is often an area of later stenosis, but this can be difficult to judge especially with stents that shorten on



Figure 8.9 Patent TIPS stent (between arrows) in right portal and hepatic veins

deployment. (Figure 8.8). The stent delivery system is then removed and the newly deployed endoprosthesis is dilated with an 8-mm or 10 mm-diameter angioplasty balloon (Figure. 8.9).



TIPS Procedure for Portal Decompression

Adapted from Bhogal HK, Sanyal AJ. Using transjugular intrahepatic portosystemic shunts for complications of cirrhosis. *Clin Gastroenterol Hepatol.* 2011;9(11):936-46,

Figure 8.10 Diagram of TIPS stent positioned between the right hepatic and right portal veins.

Step 7: Portography and Measurement of Portosystemic Gradient

Following TIPS placement, repeat portography should show TIPS flow with some intrahepatic flow into the portal vein branches. and minimal or no varices (Figures 8.9, 8.10, 8.11, 8.12). The target CSP gradient of 12 mm Hg may assist in deciding to further balloon dilate the stent.

Step 8: Additional Procedures

Additional procedures to maintain TIPS patency or lessen the risk of recurrent bleeding are as below.

(i) A kinked stent This can lead to shunt thrombosis and may be due to using too peripheral a portal venous branch during puncture. After other views confirm the kink, placing another stent may help.

(ii) Embolization of gastro-oesophageal varices

Persistently seen gastro-oesophageal varices on the post-TIPS venogram may benefit from embolisation (Hung and Lee 2019). After direct venography, embolic materials such as coils, Amplatzer plug occluders (*AGA Medical, Plymouth, MN.*), cyanoacrylate, as well as sclerosants can be used in left gastric and short gastric varices.

In a meta-analysis of 6 studies comparing outcomes in 662 patients with variceal bleeding who underwent TIPS with or without variceal embolisation, embolotherapy was associated with a lower rate of rebleeding, but with similar incidences of shunt dysfunction, encephalopathy and mortality when compared with TIPS alone (Patel, 2021; Qi, 2015).

8.7 Post-procedural care after TIPS placement

In the post-TIPS period, the patient is nursed in an ICU to monitor haemoglobin levels, nasogastric tube output, haemodynamic stability, and evidence of rebleeding, TIPS-related adverse events, and neurological signs of encephalopathy. Liver and renal function tests, full blood count and coagulation profiles are performed daily to assess response. TIPS patency is monitored with serial Doppler ultrasound evaluation 1 day, 1, 3, and 6-monthly after the procedure.

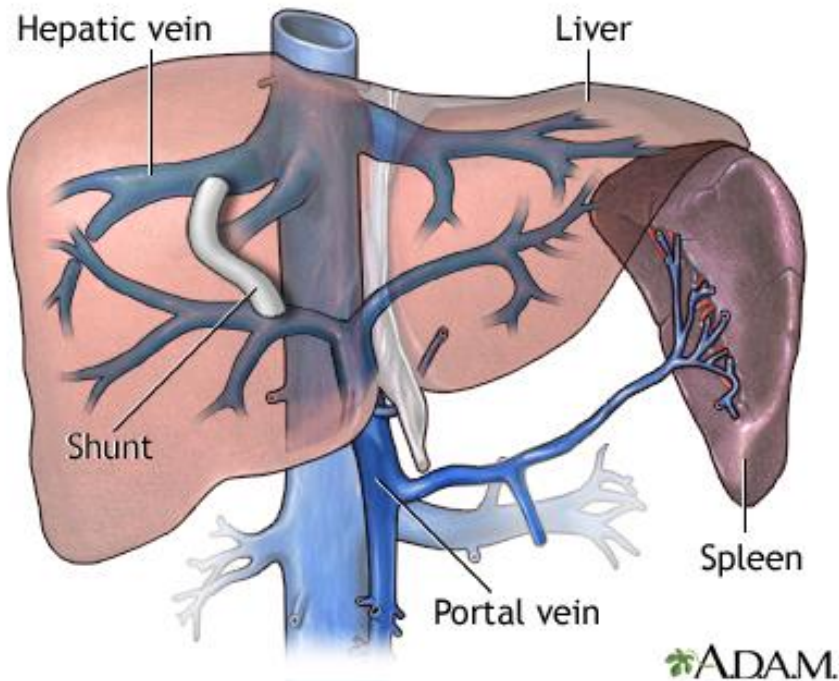


Figure 8.11 Diagram showing position of the TIPS stent between right portal and right hepatic veins (*Adapted from Bhogal HK, Sanyal AJ. Clin Gastroenterol Hepatol. 2011;9:936-46*)

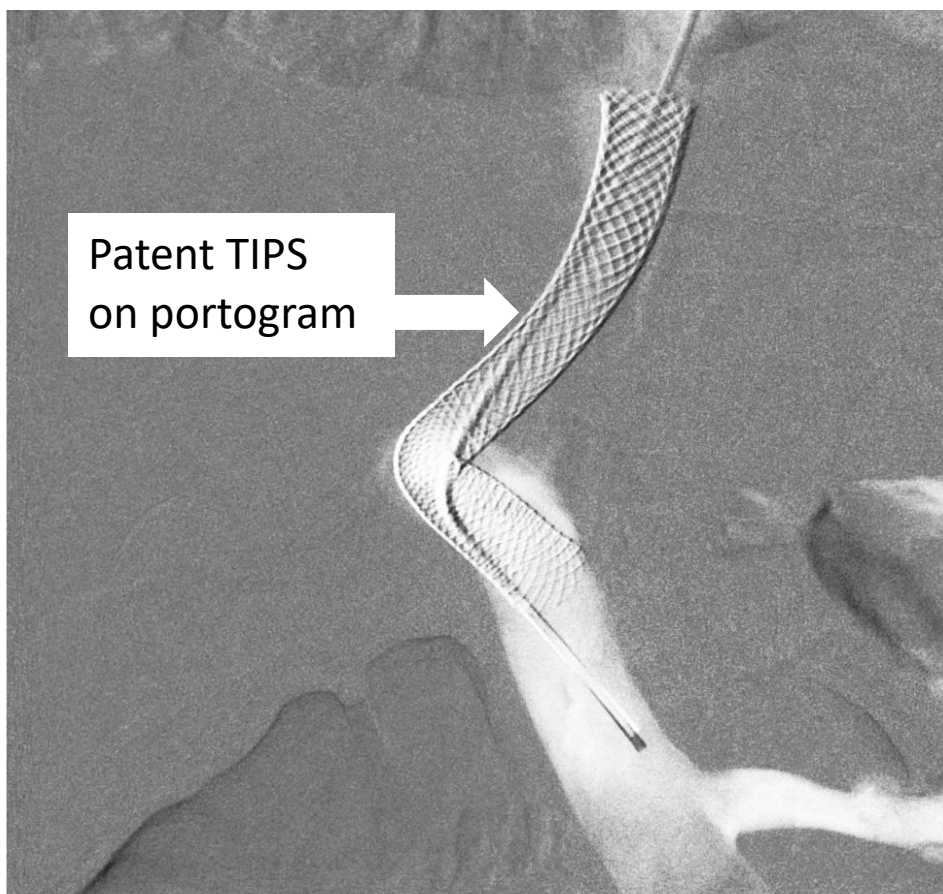


Figure 8.12 Patent TIPS stent between portal and hepatic veins

8.8 Complications of TIPS placement

Although TIPS placement is now available in most major tertiary institutions and in several of the large specialist hospital groups in South Africa, the technique of accurate stent insertion can be difficult and technically demanding and requires the manipulative skills of an experienced interventional radiologist. The overall procedural complication rate ranges from 10 to 20% (Lopera, 2023). The procedure-related mortality after TIPS insertion is <2%, while overall in-hospital mortality varies according to the indication for the index TIPS and patient co-morbidities (Kaplan, 2023). The 30-day mortality rate may be as high as 30% and is largely dependent on pre-existing patient factors, in particular the presence of serious co-morbidities, the degree of hepatic decompensation, the magnitude of the index variceal bleed and the urgency of TIPS placement (Freedma, 1993). Several of the TIPS complications that may occur during, or after placement, are due to haemodynamic consequences. Procedural complications include intra-abdominal bleeding and haemoperitoneum due to laceration of Glisson's capsule, accidental puncture of the perihepatic vessels, hepatic artery thrombosis, haemobilia, bile leaks, biliary peritonitis, and cholangitis (Patel, 2021). In addition, the procedure may cause bacteraemia, myocardial perforation, intra-abdominal bleeding, TIPS migration, arrhythmias, acute myocardial infarction, pulmonary thromboembolism, disseminated intravascular coagulation, pneumonia, and adult respiratory distress syndrome. The late complications are TIPS occlusion and hepatic encephalopathy (Saad, 2014).

Potential adverse events and procedure-related technical complications during and after TIPS placement can be categorized as those occurring with (i) internal jugular vein puncture, (ii) transhepatic needle puncture, (iii) transvenous access to the portal vein, (iv)

portal venous cannulation, (v) stent deployment, (vi) consequences of portosystemic shunting, and (vii) adverse reactions to the contrast material (Freedman, 1993)

8.8.1. Local puncture site complications:

During internal jugular vein access, puncture site haematoma may develop especially with uncorrected coagulopathy and multiple needle passes. However, these have reduced with use of ultrasound guided venous puncture. Inadvertent carotid puncture with pseudoaneurysm is uncommon.

Table 8.2 Complications of transjugular intrahepatic portosystemic shunt

<u>Related to Needle Puncture or Access</u>	<u>Stent-Related</u>	<u>Related to Portosystemic Shunting</u>
Liver capsule puncture	Thrombosis	Hepatic encephalopathy
Intraperitoneal bleeding	Migration	Hepatic ischaemia
Haemobilia	Occlusion	Hepatorenal
Biliary fistula	Haemolysis, “Endotipsitis”	

8.8.2. Complications during inferior vena cava or hepatic vein catheterization:

Guidewires and catheters crossing the right atrium to reach the hepatic veins may precipitate cardiac arrhythmias. Continuous real-time cardiac monitoring by the anaesthetist is essential to detect and treat arrhythmias promptly. Rare complications include cardiac injury and cardiac tamponade.

8.8.3. Complications during portal vein puncture:

The most critical and rate-limiting step in TIPS is the trans-parenchymal portal vein puncture and access (Patel, 2021). Depending on operator expertise, multiple passes may be required to puncture the portal vein and can cause potentially fatal bleeding. The biliary tree, hepatic artery, extrahepatic portal vein and hepatic capsule are all at risk (Patel 2021).

8.8.4. Extrahepatic portal vein puncture:

Puncture of the liver capsule occurs in up to a quarter of patients and can lead to substantial haemoperitoneum in 1–2% of cases (Patel, 2021). Small livers such as in those patients with advanced cirrhosis, or in children, are at higher risk of extracapsular punctures (Lopera, 2023). The most dangerous major complication during TIPS is intraperitoneal bleeding due to extrahepatic portal vein injury. Due to the lack of tamponade from the hepatic parenchyma, extrahepatic puncture with subsequent balloon dilation may cause substantial intraperitoneal bleeding, exacerbated by elevated portal pressure (Patel, 2021).

8.8.5 Hepatic arterial and venous injuries

8.8.5.1 Hepatic Artery Injuries

Accidental puncture of the hepatic artery or its branches during TIPS insertion is uncommon with a reported incidence of 6%, with less than 2% having clinical significance (Lopera, 2023). Entry into a branch of the hepatic artery may be recognized by sharp angulation of the wire to the left and then toward the midline when the wire reaches the aorta. In cases of a replaced right hepatic artery from the superior mesenteric artery, the course of the wire may closely simulate the course of the PV. Contrast injection should clarify the situation. Balloon dilation into the hepatic artery can be serious. (Patel, 2021). With cirrhosis and PV thrombosis, the hypertrophied hepatic artery can increase accidental arterial access. In

most cases, the unwanted arterial access can be exited, but occasional arteriovenous fistulae, bleeding, pseudoaneurysms, dissection, occlusion and arteriobiliary fistulas can occur. (Gaba, 2011). Arteriportal fistulas may also worsen pre-existing portal hypertension (Lopera, 2023).

8.8.5.2 Portal or mesenteric vein dissection is uncommon but may lead to pseudoaneurysms or thrombosis. Most dissections are self-limited if due to the guidewire only but larger devices can cause bleeding. Intravascular haemolysis occurs in 10% of patients with bare metal stents but this usually resolves after 3–4 weeks, once the stent becomes covered with a neo-intimal layer (Lopera, 2023).

8.8.6 Biliary puncture and fistula formation

Biliary fistula formation due to puncture during TIPS occurs in <5% of patients. Although bile duct or gallbladder puncture is usually well tolerated, a biliary-portal fistula may result in haemobilia, cholangitis, sepsis, and stent infection (Patel, 2021). If a biliary to TIPS fistula arises, marked pseudo-intimal hyperplasia and secondary stent occlusion may result (Lopera, 2023).

8.8.7 Non-target organ injury is an uncommon complication of transhepatic needle puncture during the TIPS procedure (Patel, 2021). Non-target organs at risk of injury include gallbladder, right kidney, duodenum and the hepatic flexure of the colon (Gaba 2011).

8.8.8 Post-procedural Complications

8.8.8.1 Post-TIPS liver ischaemia, infarction, and liver failure.

Hepatic ischaemia and infarction related to less sinusoidal flow due to over-shunting of blood from the portal to the systemic veins are rare after TIPS. Hepatic perfusion after TIPS depends on the arterial buffer reserve, which is negatively correlated with the Child-Pugh score. Stent compression of the hepatic artery may also cause hepatic ischaemia or infarction. Incipient or developing liver ischaemia should be suspected by persistent or worsening right upper quadrant pain, elevated and increasing liver enzymes including AST, ALT and bilirubin, prolonged INR and subclinical or overt hepatic encephalopathy. CT and MRI scans are useful to demonstrate the extent of ischaemic injury when the diagnosis is suspected (Gaba, 2011).

8.8.9 TIPS dysfunction

8.8.9.1 Early and late TIPS occlusion

TIPS stenosis and occlusion are the most frequent complications related to shunt placement. The causes of TIPS occlusion are categorized as due to (i) technical factors, (ii) bile-related and (iii) non-bile-related.

Technical factors such as stent shortening and migration account for early stent occlusion and dysfunction. Bile-related factors, such as traversing bile ducts during shunt creation resulting in biliary portal fistulas, have been associated with TIPS occlusion. Non-bile-related causes of dysfunction include tract stenosis related to pseudo-intimal hyperplasia. Duplex ultrasound evaluation of the TIPS will show velocity changes suggesting stenosis that can be confirmed using venography (Gaba, 2011). Hypercoagulable patients, particularly those with Budd-Chiari syndrome, are more likely to develop early acute shunt thrombosis (Patel, 2021). Given the thrombogenicity of bile, biliary-venous fistulas are the

most common cause of acute shunt blockage with bare metallic stents. However, in the contemporary era of covered stent grafts, this specific issue has been significantly reduced. With the presently available stent-grafts, a substantial number of acute shunt thromboses have been attributed to suboptimal TIPS position or configuration, causing shunt outflow obstruction (Patel, 2021).

Stent dysfunction is defined as loss of portal decompression due to occlusion or stenosis of the stent and has been reported in up to 71% before the introduction of covered stents. Shunt insufficiency is further defined as an increase in the PPG to >12 mmHg or an increase in the PPG of $>20\%$ from the post-TIPS value where the post-TIPS value is <12 mm Hg, or the recurrence of portal hypertensive complications. The reduction in shunt patency is because of thrombosis or intimal hyperplasia. Shunt patency should be monitored with duplex Doppler ultrasound every 6 months and venography with measurement of PPG if shunt dysfunction is suspected by ultrasound or clinically. Primary patency refers to shunt patency without intervention, and secondary patency is a measure of shunt performance with interventions. The introduction of covered stents in the late 1990's and early 2000's was based on data showing better patency in animal models. Several clinical studies have confirmed the advantage of PTFE-covered over bare stents at reducing shunt dysfunction. Covered stents have primary patency rates of 76–89% and 1 year shunt dysfunction of up to 15% (Horhat, 2021).]

8.8.10 Stent migration

Covered stent-grafts are however more prone to migration than bare metallic stents due to their slippery outer layer. Also, during placement the stent may also protrude too far into the inferior vena cava or right atrium or be too inferior into the main portal vein in up to 20% of

patients. Cephalad migration into the IVC and heart may result in cardiac arrhythmia, right atrial perforation, aorto-atrial fistula, or IVC thrombosis (Chalasani, 2000). Protrusion into the IVC may preclude safe cross-clamping during liver transplantation. Inferior protrusion into the portal vein may also complicate transplant surgery and require portal vein reconstruction. On occasion, stents may migrate during or shortly after placement because of catheter and balloon manipulation. To avoid newly placed stent migration, complete deflation of the balloon before changing its position is essential. Although challenging, migrated stents can be successfully retrieved using snares, but in some cases surgical removal may be necessary.

8.8.11 Hepatic Encephalopathy

The major clinical side-effect after TIPS insertion is the aggravation or development of hepatic encephalopathy (HE). Diversion of portal venous flow through the shunt leads to new or increased encephalopathy in 30–40% of patients with TIPS (Patel, 2021). The presence of HE before TIPS independently determines both the incidence of post-TIPS encephalopathy and long-term survival (Corbett, 2012). The introduction of PTFE-coated stents has improved outcomes and reduced encephalopathy rates compared to bare stents. A RCT by Bureau confirmed the effect of reduced encephalopathy after two years follow-up (Bureau, 2008). Fewer clinical events with covered stents, in particular variceal bleeding that can precipitate hepatic encephalopathy, are important observations. Reducing the degree of shunting by using a narrower covered stent (8mm vs. 10mm) or other flow-restricting techniques has the potential to reduce encephalopathy rates even further (Gaba, 2011). Independent factors that predict post-TIPS encephalopathy include increased age, prior hepatic encephalopathy, higher Child-Pugh score, high creatinine levels, and low serum sodium or albumin values (Hung, 2019).

8.8.12 Microbial Seeding and Infection

8.8.12.1 Endotipsitis and infection

TIPS infection (“tipsitis” or “endotipsitis”) is an uncommon complication that occurs in less than 1% of patients. Tipsitis is due to microbial seeding and is defined by the presence of persistent bacteraemia associated with vegetation or thrombus within the TIPS without any other identifiable source of infection (Hung, 2019). Fever may be present in some patients. The diagnosis of endotipsitis requires a high degree of clinical suspicion and detailed imaging and laboratory evaluation are required to rule out other potential sources of infection which include the biliary tree, gallbladder, the intestine, and ascitic fluid in cases of untreated bacterial peritonitis. Most reports are with the use of bare stents, but endotipsitis may also occur with covered stents. Treatment options include prolonged antibiotic therapy and rarely liver transplantation if eligible (Patel, 2021). Liver abscesses may occur due to infected bilomas, haematomas, or rarely as a complication of liver infarction and require percutaneous catheter drainage (Lopera, 2023).

8.8.14 Haemodynamic changes and consequences after TIPS insertion

The diversion of blood through the liver after TIPS results in increased right atrial pressure, pulmonary capillary wedge pressure and an adverse cardiac index. Several studies have assessed the consequences of these haemodynamic changes on mortality after TIPS. Ascha and colleagues from the Cleveland Clinic reviewed 418 patients who underwent TIPS and found that RA pressure increased by a mean 4.8 ± 3.9 mmHg ($p < 0.001$) and HVPG decreased by 6.8 ± 3.5 mmHg ($p < 0.001$). Multivariate linear regression analysis showed that a higher MELD score, lower platelet count, splenectomy and a higher portal vein pressure were independent predictors of higher RA pressure ($R = 0.55$). Three variables

predicted 3-month mortality after TIPS in a multivariate analysis: age, MELD score, and C-P grade C and an increase in the RA pressure after TIPS (Ascha, 2016).

Kovács et al. assessed the short term haemodynamic and cardiac magnetic resonance imaging (MRI) changes after TIPS in 11 patients with liver cirrhosis and intractable oesophageal varices or refractory ascites. These authors found that the amount of shunted blood after TIPS was more than the preload reserve of the right and left ventricles and this was manifested by a significant increase of the pulmonary capillary wedge pressure and persistent enlargement of the left and right atria (Kovács, 2019).

Van der Linden et al. studied the short and mid-term haemodynamic changes after TIPS in 16 sedated biopsy-proven cirrhotic patients and found an increase in the mean pulmonary artery pressure (PAP), cardiac index, and RA pressure after TIPS. After a transient balloon occlusion of the shunt, these haemodynamic variables were measured again. Interestingly, all haemodynamic determinations returned to baseline except for the mean PAP, which remained significantly elevated. This haemodynamic change persisted after one month, suggesting that the increase in pulmonary pressure after TIPS is not only due to volume overload but also due to neurohumoral changes. This is consistent with findings from previous studies that evaluated the haemodynamic changes after TIPS placement (Van der Linden, 1996).

In a study from France, Azoulay et al. investigated 12 cirrhotic patients who underwent a TIPS procedure for refractory ascites or refractory oesophageal variceal bleeding. Haemodynamics were measured before TIPS, at 30 min, and one month after TIPS. Significant changes recorded included the decrease in HVP from 15 ± 3 to 7 ± 3 mmHg at

30 min after TIPS, and the subsequent level of 8 ± 3 mmHg at one month. The cardiac index increased from 4.5 ± 1.3 to 5.7 ± 1.5 at 30 min after TIPS and subsequently to 7.4 ± 1.4 L/(min·m²) at one month (Azoulay, 1994).

The best strategies to prevent TIPS complications are to apply optimal patient selection, meticulous technique, operator experience, and immediate correction of identified adverse events (Lopera, 2023). The introduction of PTFE-covered stent grafts has led to improvement in long-term TIPS patency. An RCT published in 2007 supported PTFE-covered stents as the preferred type of stent for TIPS. In that study, 80 patients were randomized to receive either a covered (n=39) or a bare (n=41) metal stent and were followed for 2 years after TIPS placement. Patients with a PTFE-covered stent had a significantly lower rate of TIPS dysfunction (15% vs 44%), compared to patients treated with bare-metal stents, as well as higher rates of primary patency (76% vs 36%), lower rates of clinical relapse (10% vs 29%), and were less likely to develop encephalopathy (33% vs 49%). Based on these data, a PTFE-covered stent is recommended as the standard of care device for de novo TIPS.

8.9 TIPS Maintenance

Recurrence or worsening of symptoms of portal hypertension should prompt an ultrasound with duplex Doppler of the TIPS stent to exclude stenosis or occlusion. Shunt velocities of 250 cm/s or higher or 50 cm/s or lower are associated with a high (>90%) sensitivity and specificity for shunt dysfunction. In addition, most clinicians book routine TIPS surveillance tests at regular intervals using ultrasound with duplex Doppler in asymptomatic patients. Patients with ultrasound suspected TIPS dysfunction should undergo TIPS venography. If the original TIPS was created using a bare-metal stent, placement of a covered stent is

likely to improve long-term shunt patency. Other commonly used options include balloon angioplasty and the placement of additional stents to extend cranial or caudal lengths of the stent.

Hepatic encephalopathy refractory to medical management or progressive hepatic dysfunction after TIPS placement may require endovascular shunt occlusion or reduction. (Hung, 2019).

8.10 Results of salvage TIPS

The outcome of salvage TIPS for uncontrolled or refractory variceal bleeding have been reported in 24 studies since the first publication in 1994. The outcomes in these studies, especially rebleeding and mortality rates, vary widely due to differing institutional selection and inclusion criteria, the timing of TIPS placement, the spectrum and severity of the underlying liver disease and inclusion of a preponderance of C-P grade C patients in some studies. Other reports include only patients with recent or active variceal bleeding requiring balloon tamponade, inotropic support, intubation, and ventilation during the TIPS procedure and excluded stable patients who underwent elective TIPS. In studies reporting exclusively salvage or rescue TIPS in patients with uncontrolled life-threatening or endoscopically unmanageable variceal bleeding, in-hospital mortality rates range from 17% to 56% which are substantially higher than for elective TIPS. Mortality is also substantially greater in high-risk patients and the wide difference in the mortality rates reported from different units probably reflects variable and non-comparable patient selection and risk stratification. A significant observation in each of these 24 studies was that TIPS controlled bleeding in >90% of patients. An analysis of the salient details and results of each of the 24 studies is provided below. Only publications which reported patients who underwent sTIPS for uncontrolled bleeding have been included and analysed in the 24 studies presented below.

Other early studies include the 1992 publication by LaBerge, Ring and Gordon from the Department of Radiology at the University of California, San Francisco (UCSF) who reported their first 25 TIPS patients, less than half of whom were actively bleeding, and was therefore not included (LaBerge, 1992). Similarly, a further report from Ring and colleagues at UCSF, documents 13 patients referred for liver transplantation who had either active or recurrent variceal bleeding despite sclerotherapy. All 13 underwent TIPS using expandable, flexible metallic stents and bleeding was controlled in all 13, seven of whom subsequently underwent liver transplantation (Ring, 1992). In a subsequent publication the next year the same group from San Francisco reported their first 100 TIPS procedures which were completed in 96 patients, of whom 30 had acute variceal bleeding (LaBerge, 1993).

Helton, Belshaw and Johansen from Seattle, Washington, reported on 59 consecutive patients who underwent 80 TIPS procedures (Helton, 1993). TIPS was unsuccessful in 4 patients (7%) and initially succeeded in 55 (93%). Twenty-three patients (39%) were actively bleeding at the time of the procedure and in 6 (26%), bleeding was never controlled. In-hospital mortality (25%) was related to bleeding at the time of TIPS (56% for emergency versus 5.5% for non-emergency).

Le Moine, Devière and colleagues in Belgium from the departments of Gastroenterology and Radiology at the Hôpital Erasme, Université Libre de Bruxelles, reported the efficacy of sTIPS in 24 patients who had failed sclerotherapy for variceal bleeding (Le Moine, 1994). TIPS was successful in all patients with reduction of size or disappearance of varices in 96% of patients. Four patients (17%) developed encephalopathy and six (25%) rebled during the follow-up period (median 5 months; range 1-19). Thirty-day mortality was 17% and 29% during the follow-up period. Deaths were mainly due to liver failure, especially

after procedures performed as emergencies. Significant decrease in liver function was observed in the days following the procedure. Shunt revision was required in nine (38%) patients (Le Moine, 1994).

The first clinical report which included only sTIPS patients who underwent rescue treatment for variceal bleeding in 1994 was from the Liver Unit at the Royal Free Hospital in Hampstead, where Andrew Burroughs and Dame Sheila Sherlock had established a tertiary liver referral centre for patients from the greater London area and south-east England (McCormick, 1994). Over a 2-year period the unit managed 242 episodes of variceal bleeding of whom 20 patients (Child-Pugh grades A=1; B=7; C=12) with uncontrolled bleeding, required an emergency sTIPS. Although the procedure initially controlled bleeding in all patients, six had early rebleeding within 5 days, and further shunting was required in two patients. Two patients had late rebleeding related to shunt occlusion and had a further TIPS procedure followed by later portacaval shunting. Twelve patients died within 40 days from liver failure and sepsis, and two late deaths occurred after 2 and 6 months, unrelated to bleeding. The authors concluded that sTIPS was an effective therapeutic option in patients with acute variceal bleeding refractory to medical and endoscopic treatment, but despite achieving control of bleeding, the 60% in-hospital mortality rate after TIPS was high, reflecting the severity of the underlying liver disease and the consequences of a major variceal bleed (McCormick, 1994).

In a study by Encarnacion and Palmaz from the Department of Radiology, University of Texas Health Science Centre, San Antonio, USA, TIPS was performed in 64 patients (C-P A = 2, C-P B 32, and C in 31. Twelve patients died within 30 days of TIPS, and another 14 died thereafter. The cumulative survival rate was 67% at 6 months and 56% at 1 year.

Cumulative 30-day survival was 69% for unstable patients. Thirty-day survival was 91% for C-P A and B combined and 71% for C-P C patients (Encarnacion, 1995).

In the second reported sTIPS study which came from the Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, USA, 49 patients were treated with sTIPS, 46 of whom had refractory variceal bleeding. Shunt insertion was successful in 48 (98.0%) of 49 patients. Median portal-systemic gradient was reduced from 22.5 (range 9-36) to 12 (range 4-20) mm Hg. Thirty (61.2%) of 49 patients survived more than 30 days; four patients died more than 30 days (mean follow-up: 8.4 months) after sTIPS. Significant differences ($p<0.05$) were found between those who survived >30 days and those who did not, with respect to pre-procedural prothrombin time, bilirubin, albumin, alanine aminotransferase, and treatment with vasopressin and nitrates, balloon tamponade, or mechanical ventilation. The pre- and post-TIPS portal vein pressures were significantly lower in survivors. Survival was inversely proportional to Child-Pugh class ($p<0.01$) and to APACHE II score ($p<0.01$). The single determinant most closely associated with decreased survival in the month after TIPS was the APACHE II score, a score of 18 stratifying patients into those at low and high risk of mortality. Only 1 (7.7%) of 13 patients with Child-Pugh C cirrhosis and an APACHE II score >18 survived more than 30 days. The authors concluded that patients with advanced cirrhosis, especially those with high pre-TIPS APACHE II scores, were at high risk for reduced survival after TIPS, despite adequate portal decompression (Rubin, 1995).

Jalan and colleagues from the Centre for Liver and Digestive Diseases at the Edinburgh Royal Infirmary reported on 17 patients who underwent a TIPS (Palmaz stent $n=4$, Wallstent $n=13$). TIPS reduced the mean portal pressure gradient from 22.2 to 9.7 mmHg (p

<0.001). Mortality within 30 days of the initial bleed was 42% and rebleeding occurred in 16% of patients. Encephalopathy after TIPS developed in 25% and active infection in 20% of patients. The authors concluded that TIPS could be performed successfully in this group of patients, who are often not suitable for surgery, and that TIPS should be regarded as the preferred mode of treatment for uncontrolled variceal bleeding in patients with cirrhosis, but that overall mortality was high whatever treatment was used (Jalan, 1995).

Sanyal and colleagues from the Division of Gastroenterology, Medical College at Virginia Commonwealth University, Richmond, USA reported the results of sTIPS in 29 patients with control of bleeding in all. Thirty-day and 6-week survival rates were 63% and 60%, respectively; in those without aspiration, the 6-week survival rate was 90%. After a median follow-up period of 920 days, 46% of the original cohort was alive and 2 episodes of early rebleeding and 4 late rebleeds occurred. Eight patients developed encephalopathy. Stent stenosis requiring dilation occurred in 6 of 11 patients within 6 months. The authors concluded that TIPS was highly effective as salvage therapy in high-risk patients with active variceal bleeding despite endoscopic therapy (Sanyal, 1996).

In a 1997 study from the Department of Surgery at the Detroit University Health Centre in Michigan, Tyburski and colleagues evaluated 33 patients (n=5 Child B, n=28 Child C) who had sTIPS procedures. Mean portosystemic gradients before and after the initial TIPS procedure were 18 and 7 mm Hg respectively. By 18 months after the TIPS procedure, 16 patients (48%) died of rebleeding or hepatic failure. Subsequent upper gastrointestinal tract bleeding occurred in 14 patients (42%). All 8 patients in whom occlusion or stenosis of the TIPS was promptly corrected, survived, while 5 of the 6 patients (83%) in whom occlusion or stenosis of the TIPS was not corrected, died. A low initial albumin level (22 ± 4), increased

initial total bilirubin level ($68 \pm 75 \mu\text{mol/L}$) and an elevated prothrombin time (18.0 ± 3.4) were predictive of death before 18 months. (Tyburski, 1997).

In a subsequent report from the Liver Unit at the Royal Free Hospital, Patch, Burroughs, and colleagues evaluated 33 clinical and laboratory variables in 54 patients before sTIPS to establish predictors of mortality. Twenty-six patients died within 6 weeks. In a multivariate analysis, 6 factors had independent prognostic value: moderate/severe ascites, requirement for ventilation, WBC, PLT count, partial thromboplastin time with kaolin and creatinine, from which a prognostic index (PI) score was derived. Despite immediate control of bleeding by sTIPS, patients with uncontrolled variceal haemorrhage had a high mortality, particularly when associated with markers of advanced liver disease, sepsis and multi-organ failure, in whom TIPS is probably not justified (Patch, 1998).

Banares et al. from Department of Gastroenterology at the Hospital General Universitario Gregorio Marañón in Madrid reported the outcome with sTIPS in 56 patients with a Strecker stent after temporary control of bleeding with balloon tamponade. Eleven of 56 patients were Child-Pugh A, $n=22$ C-P B, and $n=23$ C-P C. The mean time between TIPS indication and insertion was 17 ± 10 h (range 4-24 h). Control of bleeding was achieved in 53 patients (95 %). Eight patients had recurrent bleeding at 1 month after TIPS, 7 during the first week after sTIPS. The 1-month actuarial probability of rebleeding was 22%. The main complications of the procedure were massive haemoperitoneum ($n=1$), cardiorespiratory arrest ($n=2$), cardiac failure ($n=1$), acute renal failure ($n=2$), and bacteraemia ($n=7$). Operative mortality (30 days) was 28%. The actuarial probability of survival at 30 days was significantly lower in C-P C patients than in C-P A or B (48% vs 90%; $p < 0.001$). The presence of ascites, hepatic encephalopathy, and serum albumin level before TIPS were

independent prognostic factors associated with the risk of operative mortality (Bañares, 1998).

An analysis of 11 patients undergoing a sTIPS in Germany was reported by Gerbes and colleagues from the Institute for Diagnostic Radiology, Klinikum Grosshadern at the University of Munich. Clinical examination, blood sampling, Doppler sonography of TIPS flow, and upper gastrointestinal endoscopy were performed at days 1, 7, and 30 and at three-month intervals after TIPS. Mean follow-up was 549 (1-987) days. Variceal bleeding was controlled by sTIPS in 10 of the 11 patients. Early rebleeding (<2 weeks) occurred in 3 of the 11 patients and 4 of the 11 developed TIPS stenoses. De novo or deterioration of pre-existing hepatic encephalopathy occurred in 2 (18%) patients (Gerbes, 1998).

A further publication from the Royal Free Liver Unit compared the efficacy of sTIPS in 112 patients who had either uncontrolled gastric fundal (n=28) or oesophageal variceal bleeding (n=84). Variceal bleeding was controlled in all patients after TIPS except for 1 in each group. During a median follow-up period of 7 months, 20 in the OV group (24%) and 8 in the GV group (29%) rebled (Chau, 1998).

In a study by Barange, Péron and colleagues from the Service d'Hépatogastro-Entérologie, Fédération Digestive, Toulouse in France 32 consecutive patients with refractory gastric variceal bleeding were evaluated and followed-up until death, transplantation, or at least 1 year (median: 509 days; range 4 to 2,230). Haemostasis was achieved in 18 out of 20 patients actively bleeding at the time of the procedure. In the 32 patients, rebleeding rates were 14%, 26%, and 31%, respectively at 1 month, 6 months, and 1 year. De novo encephalopathy occurred in 5 (16%) patients. Seven patients had

complications of whom 4 died. TIPS primary patency rates were 84%, 74%, and 51%, respectively, at 1 month, 6 months, and 1 year with survival rates of 75%, 62%, and 59% (Barange, 1999).

In a study from Sydney, 67 patients underwent sTIPS in whom 65 (97%) were successfully placed with a 30-day mortality of 21%. Predictive factors for mortality were transfer from another institution, urgency of procedure, sepsis, encephalopathy, higher mean serum bilirubin and low serum albumin. On regression analysis, mortality was predicted independently only by Child-Pugh C and older age. When stratified by Child-Pugh class, cumulative survival rates at 1 year for class A, B and C were 100, 90 and 34%, respectively. Although 3 of 25 patient deaths were due to variceal rebleeding, 30 (46%) patients had 41 rebleeding episodes (mean 4.8 months; range, 3 days-38 months). Cumulative rebleeding rate at 1 year was 25%. When investigated, shunt abnormalities (stenosis, occlusion) were identified in all cases of rebleeding (Williams, 1998).

In the Bizollon study from the Hepatology Unit in Lyon, France, 26 of 28 patients (C-P C n=17) had a successful sTIPS with control of bleeding in 25 patients. The two patients with failed sTIPS insertion died of persistent bleeding <48 h. The 40-day mortality was 25%. Five patients died (one from persistent bleeding from gastric varices and four from multi-organ failure). Total bilirubin was the only independent factor associated with early mortality on multivariate analysis. Fifteen surviving patients were listed for liver transplantation: four died and eight were transplanted <6 months after TIPS. Among the six patients who survived but were ineligible for transplantation, two died and four were alive. Two episodes of early rebleeding and eight of late rebleeding occurred. Actuarial survival was 75% at one year and 52% at two years (Bizollon, 2001).

Azoulay, Castaing, Bismuth and colleagues from the Department of Liver Surgery and Liver Transplantation, Centre Hépato-Biliaire, Hôpital Paul Brousse, Villejuif, Paris investigated factors associated with mortality after early sTIPS for uncontrolled variceal bleeding. Salvage TIPS was performed in 58 patients and 23 variables were assessed prospectively to identify predictors of mortality within 60 days of the procedure. Bleeding was controlled in 52 of 58 patients (90%), persisted in six (10%), and recurred in four (7%). Overall, 17 (29%) and 20 (35%) patients died within 30 days and 60 days of sTIPS. Five died of persistent bleeding, two of recurrent bleeding, and 13 patients died of terminal liver failure. Actuarial survival following sTIPS was 51.7% at 1 year. Independent predictors of early mortality were sepsis, the use of catecholamines and balloon tamponade. No single factor nor a combination of factors before sTIPS predicted mortality confidently in any given patient (Azoulay, 2001).

The study by Abujudeh and colleagues from the Department of Radiology, New Jersey Medical School, Newark, USA evaluated 16 patients who had a sTIPS for uncontrolled variceal bleeding. Technical success was 88% (14/16 patients), overall mortality was 36% (5/14 patients) with a reduction in the mean portal venous pressure gradient of 64% (Abujudeh, 2005).

In the Tzeng study from the Department of Radiology, Chi-Mei Foundation Medical Centre, Tainan, Taiwan, survival analyses were performed in 107 patients who underwent sTIPS to evaluate the ability of the various models to predict 30-day, 60-day and 360-day mortality. APACHE II, Child-Pugh and MELD scores were calculated. No patient died during the TIPS procedure, but 82 patients died during the follow-up period. Thirty patients died <30 days after TIPS; 37 patients died <60 days and 53 patients died <360 days. Univariate analysis

indicated that hepatorenal syndrome, use of inotropic agents and mechanical ventilation were associated with elevated 30-day mortality. Multivariate analysis showed that a C-P score >11 or a MELD score >20 predicted increased risk of death at 30, 60 and 360 days. APACHE II scores could only predict mortality at 360 days (Tzeng, 2009).

The study by Gazzera and colleagues from the Institute of Diagnostic Radiology in Torino, Italy, evaluated 82 patients who underwent sTIPS for refractory variceal bleeding to identify predictors of early mortality. The technical, haemodynamic, and clinical success rates were 91.6%, 78% and 86.6%, respectively. Complications occurred in 21 cases (25.6%): eight were major (two stent migrations, one pulmonary embolism, one haemoperitoneum, one haemobilia, three intrahepatic haematomas) and 13 were minor (encephalopathy responsive to medical therapy). Twenty-one patients (25.6%) died due to disseminated intravascular coagulation (DIC) (n=2), bleeding (n=8), cardiopulmonary failure (n=2) and liver failure (n=9). The predictors of mortality were C-P C, high serum creatinine and prolonged prothrombin time. The authors concluded that the technical success of TIPS may not lead to haemodynamic and clinical success. Complications were often due to impaired coagulation and inadequacy of the stent-graft and early mortality was influenced by pre-existing clinical and laboratory factors (Gazzera, 2012).

In an analysis from the Pierre et Marie Curie Hospital in Paris, 372 patients with cirrhosis and variceal bleeding were hospitalized between March 2007 and March 2011; 31 patients underwent salvage TIPS, 10 with Child-Pugh C 14-15 cirrhosis. Bleeding stopped after TIPS in 8/10 patients, but only 1 patient showed improvement of liver function. Five patients with Child-Pugh C 14-15 cirrhosis (MELD 29-40) underwent liver transplant with 100% 6-month survival (Rudler, 2013).

In the Casadaban study from the Division of Interventional Radiology at the University of Illinois College of Medicine, predictive factors for survival were investigated in 101 patients with acute life-threatening variceal bleeding who underwent sTIPS between 1998-2013. TIPS were inserted 119 ± 167 hours after initial bleeding events. Haemodynamic success was achieved in 90%. Median final portosystemic pressure gradient was 8 mmHg. Variceal rebleeding occurred in 21%. The four original MELD components showed significant correlation with mortality on multivariate Cox regression: baseline bilirubin, creatinine, INR and liver disease aetiology, validating the MELD system for emergency cases. No other significant predictive parameters were identified. The authors concluded that MELD was an excellent predictor of 90-day mortality after sTIPS (Casadaban, 2015).

In a cohort study by Hermie, Dhondt and colleagues at the University Hospital in Ghent, Belgium, 32 patients with C-P C score <14 or Child-Pugh B plus active bleeding at endoscopy, underwent TIPS with, or without, combined variceal embolization to control acute oesophageal variceal bleeding. TIPS failed to control bleeding in one (3.7%) patient. There was no rebleeding during 1-year follow-up. Ten (31.3%) patients died within 6 weeks after TIPS. Early mortality was associated with MELD score ≥ 19 and haemodynamic instability. If haemodynamic instability occurred with a MELD score ≥ 19 , 6-week mortality peaked at 77.8% (Hermie, 2018).

In the Zhu study from the Department of Gastroenterology and Hepatology, West China Hospital, Sichuan University in Chengdu, China, safety and outcome was assessed in 58 cirrhotic patients with uncontrolled VB who underwent sTIPS from March 2009 to November 2017 (Zhu et al. 2019). TIPS was successfully performed in 57 (98.3%) patients at 89.5 h (mean) after initial bleeding. After TIPS, bleeding ceased in 52 (91.2%) patients, and 51

(89.5%) patients had a portal pressure gradient below 12 mmHg. Only one (1.8%) major procedure-related complication occurred without any clinical consequences, and no procedure-related deaths occurred. During follow-up, 55 hepatic encephalopathy (HE) episodes occurred in 19 (33.3%) patients, and the median time of the first HE episode was 3.1 months. Seven (12.3%) patients experienced shunt dysfunction after 8.7 months (median). The 6-week, 1-year, and 2-year variceal rebleeding rates were 10.5%, 17.1%, and 20.0%, respectively. The LT-free survival rates at 6 weeks, 1 year, and 2 years were 87.7%, 81.8% and 73.6%, respectively (Zhu, 2019).

In a large multicentre study, predictors of rebleeding and mortality were assessed in 144 patients with refractory variceal bleeding who underwent a sTIPS. Maimone and colleagues used three logistic regression multivariate models to individualize prognostic factors for 6-week and 12-month mortality. Log-rank test was used to evaluate survival according to Child-Pugh classes and Bureau's criteria. TIPS failure occurred in 23 (16%) patients and was associated with pre-TIPS portal pressure gradient and pre-TIPS intensive care unit stay. Six-week and 12-month mortality were 36% and 42%, respectively. Pre-TIPS intensive care unit stay, MELD, and Child-Pugh score were independently associated with mortality at 6 weeks. Independent predictors of mortality at 12 months were pre-TIPS intensive care unit stay and Child-Pugh score. TIPS was considered futile in patients with Child-Pugh score of 14-15 (Maimone, 2019).

In the largest multicentre European study to date, survival and predictors of mortality were assessed in 164 patients with cirrhosis from five centres treated with sTIPS between 2007 and 2017 (Walter 2021). Patients were retrospectively divided into a derivation cohort (83 patients) and a validation cohort (81 patients). Comparisons were performed using the

Mann-Whitney and Fisher's exact test. Six-week overall survival (OS) was correlated with variables on the day of the TIPS using Kaplan-Meier curves with log-rank test and univariate/ multivariate analyses using the Cox model. Eighty-three patients were included in the derivation cohort (male, 78%; age, 55 years, alcohol-associated cirrhosis, 88%; MELD 19 (r15-27); arterial lactate, 3.7 mmol/L (r2.0-8.3). Six-week OS rate was 58%. At multivariate analysis, the MELD score and arterial lactate were associated with 6-week OS. Six-week OS rates were 100% in patients with arterial lactate ≤ 2.5 mmol/L and MELD score ≤ 15 and 5% in patients with lactate ≥ 12 mmol/L and/or MELD score ≥ 30 . The 81 patients of the validation cohort had similar MELD and arterial lactate level but lower creatinine level (94 vs 106 $\mu\text{mol/L}$, $P=0.008$); 6-week OS was 67%. Six-week OS rates were 86% in patients with arterial lactate ≤ 2.5 mmol/L and MELD score ≤ 15 and 10% for patients with lactate ≥ 12 mmol/L and/or MELD score ≥ 30 . In the overall cohort, rebleeding rate was 15.8% at 6 weeks, and the acute-on-chronic liver failure grade was independently associated with rebleeding. The authors concluded that after salvage TIPS, 6-week mortality remains high and can be predicted by MELD score and lactate. Survival rate at 6 weeks was $>85\%$ in patients with arterial lactate ≤ 2.5 mmol/L and MELD score ≤ 15 , while mortality was $>90\%$ for lactate ≥ 12 mmol/L and/or MELD score ≥ 30 . (Walter, 2021)

In a retrospective single centre study of 106 cirrhotic patients (males 82%, age 54 ± 9 years, alcoholic cirrhosis 70%, Child-Pugh score B/C 94%) who underwent sTIPS one-year transplant-free survival was 33.2% if secondary prophylaxis was inadequate vs 65.2% if it was adequate ($p=0.008$). Independent factors associated with survival were a lower Child-Pugh or MELD score, control of bleeding and no infection, or hepatic encephalopathy after TIPS (Bouzbib, 2021).

In a multicentre study, Kumar and colleagues from the Sheila Sherlock Liver Centre at the Royal Free Hospital, London evaluated TIPS in 78 patients (acute decompensation (AD) $n=21$ [38.2%]; acute-on-chronic liver failure (ACLF) $n=57$ [47.8%]; $p = 0.41$). In ACLF, rescue TIPS insertion was an independent favourable prognostic factor for 42-day mortality. In contrast, rescue TIPS did not impact on the outcome of patients with AD. This study showed that in patients with failure to control acute variceal bleeding, the presence and severity of ACLF determines the risk of 42-day and 1-year mortality. Rescue TIPS was associated with improved survival in patients with ACLF (Kumar, 2021).

In a study from the Institute of Liver and Biliary Sciences, New Delhi, India, 66 cirrhotic patients with refractory variceal bleed who underwent rescue TIPS within 24-h were analysed. The baseline MELD score was 22.3 ± 7.9 and active bleeding was present at endoscopy in 34.8%. Mortality at 6-week and 1-year was 20.6% and 38.2%, respectively; rebleeding rate was 1/34; 2.9%. Rescue TIPS placed within 8-h compared with 8-24 h had lower 6-week (48.6% vs. 12.9%; $p = 0.003$) and 1-year mortality (62.9% vs. 16.1%, $p = 0.001$) despite comparable rebleed rates (2/31; 6.5% vs. 2/35; 5.7%; $p = 0.90$). Active bleeding at endoscopy, presence of AKI, MELD-Na >24 and mean arterial pressure >64.5 mmHg independently predicted 6-week mortality in rescue TIPS-group (Mukund, 2023).

In a meta-analysis by Weichselbaum et al., the efficacy and safety of salvage TIPS was evaluated in 23 studies which included a total of 1430 patients with cirrhosis and refractory variceal bleeding. The percentage of Child-Pugh stage C patients in the individual studies in the meta-analysis ranged from 29% to 100%, 56% of whom had alcoholic cirrhosis. Follow-up duration of the studies ranged from 4 to 31 months. The meta-analysis found that one-third of patients undergoing sTIPS died within the first 6 weeks after TIPS insertion

which increased to 46% at 1 year. Of note however, is that only 15% of patients rebled during follow-up after TIPS placement and 9% died from uncontrolled rebleeding (Weichselbaum, 2022). These findings suggest that the recent improvements in the management of patients with acute variceal bleeding do not translate into survival benefits, once patients have refractory variceal bleeding. Additional studies are required to identify potential risk factors leading to a poor prognosis after salvage TIPS in patients with refractory variceal bleeding and to determine the impact of the degree of liver failure on the patients' prognosis.

4.11 Models of survival after salvage TIPS

Previous attempts to develop prognostic models for patients undergoing TIPS procedures have been hampered by heterogeneous indications, including expanded use of TIPS as an urgent salvage or rescue procedure, or as an elective procedure for the prevention of recurrent variceal bleeding or for diuretic-resistant ascites. Consequently, the prognostic markers and models vary widely, and are not applicable nor sensitive enough when specific single patient indications are evaluated. In addition, many proposed scoring systems have not undergone prospective evaluation to confirm absolute sensitivity in predicting death, and thus are of little clinical value (Patch, 1998).

Historically, studies have reported variable short-term mortality rates for salvage TIPS, ranging between 19% and 60% (Lopera, 2005). Tenuous outcomes continue to be reported for salvage TIPS in haemodynamically unstable patients. Active bleeding at the time of TIPS creation confers a 2.9-fold greater odds risk of death. A retrospective analysis reported 34% mortality at 30 days in patients with haemorrhagic shock undergoing salvage TIPS, in addition to overall unfavourable morbidity (Pandhi, 2020). Mortality is therefore

substantially greater in high-risk patients and the wide difference reported in the mortality rates from different units reflects variable and inconsistent patient selection and risk stratification (Table 8.3). Given this high mortality rate, it is prudent to identify predictors of short- and long-term mortality in patients considered for sTIPS. Several prognostic scores for predicting survival after sTIPS have been developed but there are few specific robust predictors of mortality (Fidelman, 2012).

The two most widely used prognostic models or risk scores for patients undergoing sTIPS are the Child-Pugh and MELD scores. A MELD score >18 predicts a significantly higher mortality 3 months after TIPS, compared with patients with MELD scores of <18 . Individual variables previously reported to adversely impact outcomes after TIPS include age, gender, need for emergency/salvage TIPS, encephalopathy, ascites, variceal bleeding, C-P class C, MELD score, bilirubin $>51\text{mmol/L}$, INR, creatinine, alanine aminotransferase $>100\text{ IU/L}$, sodium level, albumin and portosystemic gradient (Ascha, 2016).

Retrospective analyses have also shown that Child-Pugh grade C, acute variceal bleeding requiring emergency TIPS placement, serum bilirubin level $>51\text{mmol/L}$, alanine aminotransferase levels $>100\text{ IU/L}$, and pre-TIPS encephalopathy unrelated to bleeding are associated with an increased risk of post-TIPS mortality (Maimone 2019). Other models have been developed. Bureau and colleagues found that the combination of a bilirubin level $>50\mu\text{mol/L}$ ($>3\text{mg/dl}$) and a platelet count $<75 \times 10^9/\text{L}$ was a predictor of mortality within 1 year after sTIPS. The Freiburg index of post-TIPS survival (FIPS) using age and bilirubin, albumin, and creatinine levels was developed to improve the prognostic predictability for patients undergoing TIPS in which the median overall survival was significantly less in patients in the high-risk group compared to the low-risk group (Lee, 2022). In the Sanyal

study reported from the Medical College of Virginia in Richmond, Virginia, age >70 years, serum bilirubin level of >6 mg/dL, serum creatinine level of >3 mg/dL, hepatic encephalopathy, aspiration pneumonia, pO_2 level <60 mm Hg, and an alveolar to arterial oxygen gradient of >150 mm Hg due to ARDS, all correlated significantly with the likelihood of dying during the first 6 weeks (Sanyal, 1996). In the Tzeng study from the Chi-Mei Foundation Medical Centre in Yung Kang City in Taiwan univariate analysis showed that hepatorenal syndrome, use of inotropic agents and mechanical ventilation were associated with elevated 30-day mortality ($p<0.05$). (Tzeng, 2002).

Multivariate analysis showed that a Child-Pugh score >11 or a MELD score >20 predicted increased risk of death at 30, 60 and 360 days ($p<0.05$). APACHE II scores predicted mortality at 360 days ($p<0.05$). In the Patch and Burroughs study six factors had independent prognostic value: moderate to severe ascites, requirement for ventilation, white cell blood count, platelet count, partial thromboplastin time and creatinine (Patch, 1998). In a study from the Cleveland Clinic the independent predictors of mortality were an APACHE III score of >90, the use of pressors, and jaundice. Patients with all three risk factors had a 92% 1-month mortality rate compared to 11.2% for patients with no risk factors.

The above studies have demonstrated collectively that an APACHE III score >90, Child-Pugh score >11, MELD score >20, the use of pressors, aspiration pneumonia, pO_2 level <60 mm Hg, an alveolar to arterial oxygen gradient of >150 mm Hg, mechanical ventilation, age >70 years, serum bilirubin level of >6 mg/dL, serum creatinine level of >3 mg/dL, serum bilirubin level >51mmol/L, alanine aminotransferase levels >100 IU/L, and pre-TIPS hepatic encephalopathy were predictive of early death in hospital after sTIPS.

The high mortality rates of sTIPS reflect the results and consequence of performing the procedure in high-risk patients as a life-saving emergency when standard treatment has failed. To improve outcome in high-risk patients who, after initial endoscopic control of an acute variceal bleeding episode, are at risk for further bleeding, the role of early or pre-emptive TIPS has been investigated. In a systematic review and meta-analysis of four controlled trials, Deltenre and colleagues reported that early TIPS in cirrhotic patients with AVB was associated with lower rates of bleeding within 1 year (OR=0.08, 95% CI=0.04-0.17, $P<0.001$) both among Child-Pugh B patients, (OR=0.15, 95% CI=0.05-0.47, $P=0.001$) and among Child-Pugh C patients (OR=0.05, 95% CI=0.02-0.15, $P<0.001$) without higher rates of encephalopathy (OR=0.84, 95% CI=0.50-1.42, $P=0.5$), (Deltenre, 2015). A subsequent meta-analysis from the Cleveland Clinic, Ohio, evaluated the safety and efficacy of early TIPS within the first 5 days after a major oesophageal variceal bleed compared to endoscopic therapy for secondary prophylaxis. In nine RCT's involving 608 cirrhotic patients, early TIPS had a significant risk reduction in 1-year mortality and the 1-year incidence of variceal rebleeding, with no significant difference in the incidence of hepatic encephalopathy at 1 year (Halabi 2016).

A subsequent meta-analysis of 7 studies (3 RCT's and 4 observational studies) comprising 1327 patients (310 received pre-emptive TIPS and 1017 received drugs plus endoscopy) compared the effects of pre-emptive TIPS versus endoscopy plus nonselective beta-blockers in a specific population of high-risk patients with cirrhosis and acute variceal bleeding (Child-Pugh-B + active variceal bleeding (CP-B+AB) or Child-Pugh C <14 points). Overall, pre-emptive TIPS significantly increased the proportion of high-risk patients who survived for 1 year. This effect was observed in CP-B+AB patients and in patients with Child-Pugh C scores <14 points. Pre-emptive TIPS significantly improved control of

bleeding and ascites without increasing risk of hepatic encephalopathy in Child-Pugh C and CP-B+AB patients, compared to drugs plus endoscopy. Cox analysis of patients who received pre-emptive TIPS showed that patients could be classified into 3 categories for risk of death, based on age, serum level of creatinine, and Child-Pugh score. In each of these risk categories too, pre-emptive TIPS increased the proportion of patients who survived for 1 year, compared with drugs plus endoscopy. In this meta-analysis of data from 1327 patients with cirrhosis, acute variceal bleeding, and Child-Pugh score between 10 and 13 points or CP-B+AB, pre-emptive TIPS increased the proportion who survived for 1 year in both subgroups separately compared with drugs plus endoscopy (Nicoară-Farcău, 2021).

In a further systematic review, meta-analysis and sequential trial analysis of randomized trials, evaluated nine studies (four RCTs and five cohort studies) comprising 2861 patients. The overall pooled risks of mortality at 6 weeks and 1 year were 17.9% and 26.7% respectively. Although pTIPS was associated with lower 6-week rebleeding risk, data from pooled RCTs showed no significant difference in mortality at 6 weeks or at 1 year.

In a later updated two-stage individual patient data meta-analysis from 8 studies (4 RCTs and 4 observational) 1389 patients (342 pTIPS and 1047 drugs + endoscopy) were included. This confirmed the significant survival advantage of pTIPS in high-risk patients with cirrhosis and AVB. The authors recommend pTIPS as the preferred first-choice treatment in this category of patient (Nicoară-Farcău, 2023).

Bare/uncovered versus covered TIPS stents

In 2010, Qi and colleagues published the first meta-analysis that compared the patency and clinical outcomes of TIPS with covered versus bare expandable metal stents (Qi, 2010).

The statistical analyses showed that shunt patency, hepatic encephalopathy, and survival were significantly improved using covered stents. However, as only one RCT and five observational studies were included in the meta-analysis, the conclusions may not be valid. Subsequently in 2015 the authors published another meta-analysis that employed a fixed-effect model and included two RCTs (Qi, 2015). The statistical analysis showed only a borderline survival benefit. A third meta-analysis in 2017 included four RCT's. A random-effect model was employed. The authors found that covered-stents had significantly higher probabilities of overall survival (HR = 0.67, 95% CI = 0.50–0.90, $p = 0.008$) and shunt patency (HR = 0.42, 95% CI = 0.29–0.62, $p < 0.0001$) than bare-stents. Additionally, covered-stents had a lower risk of hepatic encephalopathy than bare-stents (HR = 0.70, 95% CI = 0.49 – 1.00, $p = 0.05$).

In the last three decades TIPS has emerged as an innovative and essential option for patients experiencing complications of portal hypertension. While bleeding oesophageal and gastric varices and ascites have been long-standing indications for TIPS placement, newer indications such as for hepatorenal syndrome, hepatopulmonary syndrome, use before abdominal surgery and re-canalization of the portal vein in chronic portal vein thrombosis are emerging. Overall, with newer stent technology and more research in this area, the clinical utility and potential of TIPS has rapidly expanded. A renewed focus on randomized-control trials and long-term outcomes will be a crucial element in selecting appropriate TIPS recipients and recommending appropriate use for this procedure (Carroll, 2023). Patient selection and expertise in TIPS placement remain paramount for a successful outcome (Carroll, 2023). The need for an accurate, practical, and utilitarian bedside prognostic score before sTIPS is evident, which led to the development of the novel CABIN score outlined in research component of this thesis.

CHAPTER 9:

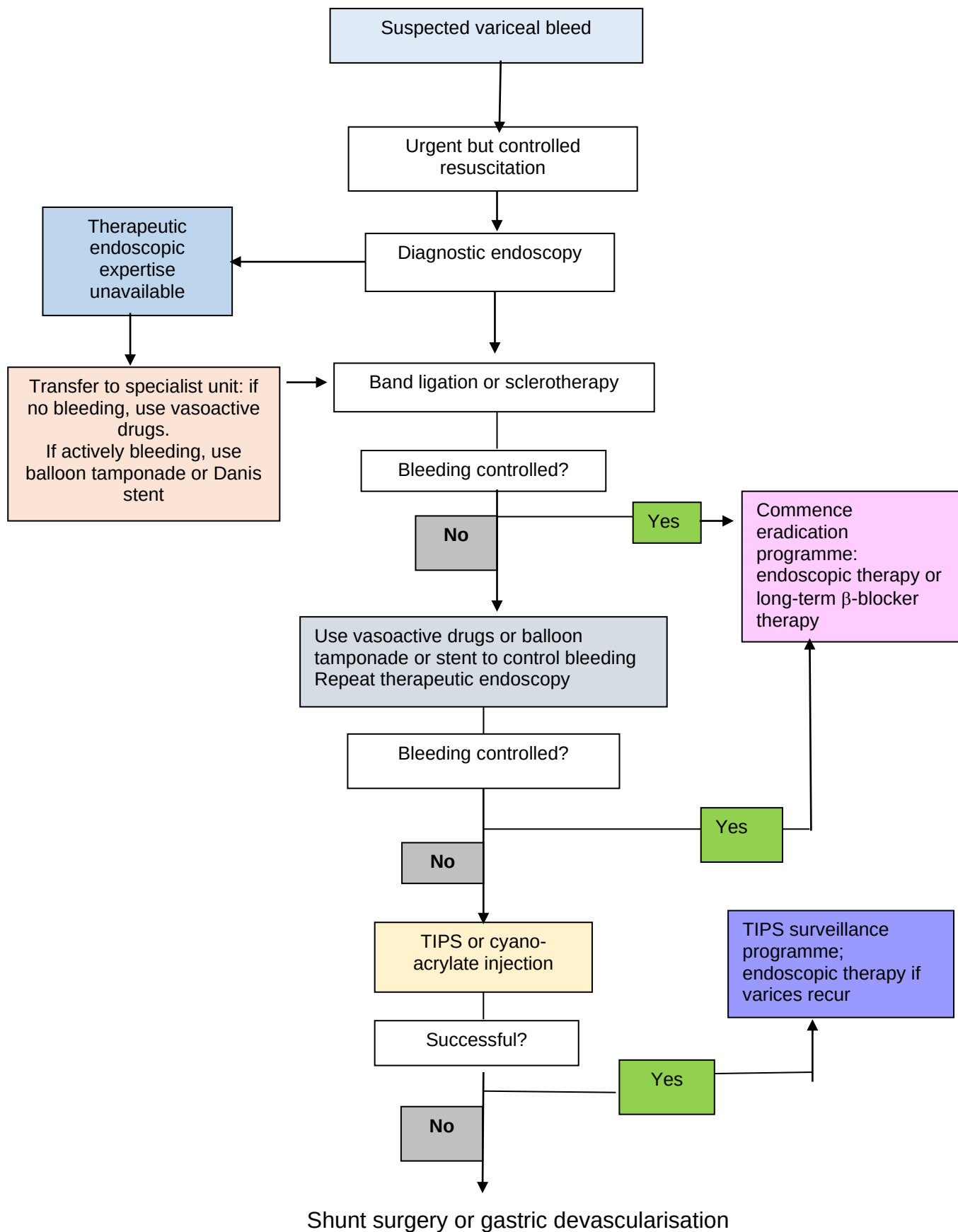
PATIENTS AND METHODS

General management strategy of patients admitted with variceal bleeding

Patients who present to Groote Schuur Hospital or the University of Cape Town Private Academic Hospital with a major variceal bleed are managed according to the specific upper gastrointestinal bleeding protocol used in the gastrointestinal clinic, details of which have been published previously. The initial management involves effective resuscitation, pharmacologic therapy with vasoconstrictors, antibiotic prophylaxis, and endoscopic therapy. Intravascular fluid management, timing of endoscopy and endoscopic control of bleeding are the key elements in the treatment. In summary, the protocol principles include urgent resuscitation and airway protection which takes precedence over other investigations. Rapid and secure large bore peripheral venous access is obtained, and intravenous fluid replacement initiated. Patients in whom oesophageal varices are suspected as the source of bleeding are rapidly resuscitated and undergo urgent endoscopy as soon as they are stable to identify the source of bleeding. Patients are nursed in an intensive or high-care unit. The specific details of further management have been published (Krige, 2005; Krige, 2007a; Krige, 2007b; Krige, 2009a; Krige, 2023; Krige, 2024). An outline of the management algorithm used is shown in Figure 9.1.

Initial measures

The extent and urgency of initial therapy depends on the severity of the gastrointestinal bleeding. Haemodynamically stable patients, who are not actively bleeding, or have stopped bleeding, undergo urgent endoscopy and intervention in the gastrointestinal clinic during office hours where the necessary endoscopic equipment required to control bleeding is available. Unstable patients who continue with major or uncontrolled variceal bleeding

Figure. 9.1 Algorithm for management of acute variceal bleeding (Krige 2024)

are actively resuscitated by the surgical, ICU and anaesthetic staff before further endoscopic intervention is performed in theatre where a fully equipped and prepared mobile endoscopy stack is available for emergency interventional endoscopy. Emergency endoscopy does not commence until venous access and central venous pressure lines are inserted and resuscitation procedures and volume replacement are initiated to correct hypovolaemia. If bleeding is profuse or if the patient is encephalopathic, an endotracheal tube is inserted and the endotracheal tube cuff inflated to protect the airway and avoid aspiration before endoscopy commences. Aggressive intravascular volume replacement and overzealous expansion of circulating blood volume is avoided to prevent a paradoxical increase in portal hypertension and precipitate further variceal bleeding. Central venous pressure is maintained at between 2-5 cm H₂O.

In haemodynamically stable patients without a history of cardiovascular disease, a restrictive red blood cell transfusion strategy is the standard of care, as recommended by all major guidelines, with a haemoglobin threshold of $\leq 7\text{g/L}$ before a RBC transfusion is initiated. The British Society of Gastroenterology variceal guidelines are applied and clotting factors, if deficient, are replaced with fresh blood, fresh frozen plasma, vitamin K₁ and platelet transfusions. A platelet transfusion is given to patients who are actively bleeding and have a platelet count of $<50 \times 10^9/\text{L}$ and fresh frozen plasma is administered to patients who have a fibrinogen level of $<1\text{ g/L}$ or an INR of 1.5 or activated partial thromboplastin time >1.5 times normal. In patients with overt bleeding, octreotide is administered as an initial intravenous bolus dose of 100 μg and then as a continuous intravenous infusion of 50 μg per hour for 72 hours after endoscopic intervention to minimize the risk of rebleeding. All patients receive oral lactulose to minimize the onset of encephalopathy and intravenous

antibiotics to prevent spontaneous bacterial peritonitis. In addition, patients receive 250 mg erythromycin intravenously 30-60 minutes before endoscopy to promote gastric emptying and improve endoscopic visibility. If erythromycin was not available, 10mg of intravenous metoclopramide was used as an alternative, if not contraindicated (Krige 2005, Krige 2007a, Krige 2007b, Krige 2009a, Krige 2024).

Therapeutic intervention for variceal bleeding

Standard endoscopic techniques were used throughout the duration of the study (Krige 1994, Krige 1996, Krige 2024). In the first decade of the study injection sclerotherapy was used and in the second decade endoscopic variceal ligation was standard practice. After intravenous sedation with midazolam, the diagnostic endoscopy and the variceal injection sclerotherapy was performed using a fiberoptic endoscope (*model GIF 1T20 or K10; Olympus Corp, Lake Success, NY*) during the first decade of the study and video-endoscopy during the last decade. The sclerosant, 5% ethanolamine oleate, was injected into, and adjacent to, the bleeding oesophageal varix using a combined intra- and paravariceal technique (Krige 1994). A maximum total volume of 25 ml of sclerosant was injected at any one endoscopy session for control of acute variceal bleeding or when large varices (grade 4 or 5) were encountered during elective sclerotherapy. An intravariceal technique alone with smaller total volumes of sclerosant was used for elective injection sclerotherapy when varices were grade 3 or less in size (Krige 1996). Endoscopic details including the location, size and extent of the varices, the site of active bleeding and the volume of sclerosant injected at each intervention were recorded. Endoscopic variceal ligation used multiple band shooters including the Saeed Multiple Ligator (Wilson-Cook Medical, Inc, Winston-Salem, NC, USA) and the Speedband Superview Super 7 Multiple Band Ligator (*Boston Scientific Corporation, Natick, MA, USA*) (Krige, 2009).

Refractory variceal bleeding due to failure of emergency endoscopic therapy

If major variceal bleeding recurred despite effective initial endoscopic and pharmacological therapy, the patient underwent an urgent repeat oesophagoscopy and gastroscopy and further ligation or injection of the bleeding site. If variceal bleeding was profuse and endoscopic intervention was not possible, or bleeding continued despite endoscopic intervention, mechanical control of the bleeding site by balloon tamponade or oesophageal stenting was used. Any patient who rebled after two successive emergency endoscopy treatments during a single hospital admission was recognized as having a prohibitively high mortality if further endoscopic therapy was pursued. These patients had a balloon tube or oesophageal stent inserted to control active bleeding, were resuscitated and then treated with a radiologically placed TIPS stent (Krige, 2009; Krige, 2019).

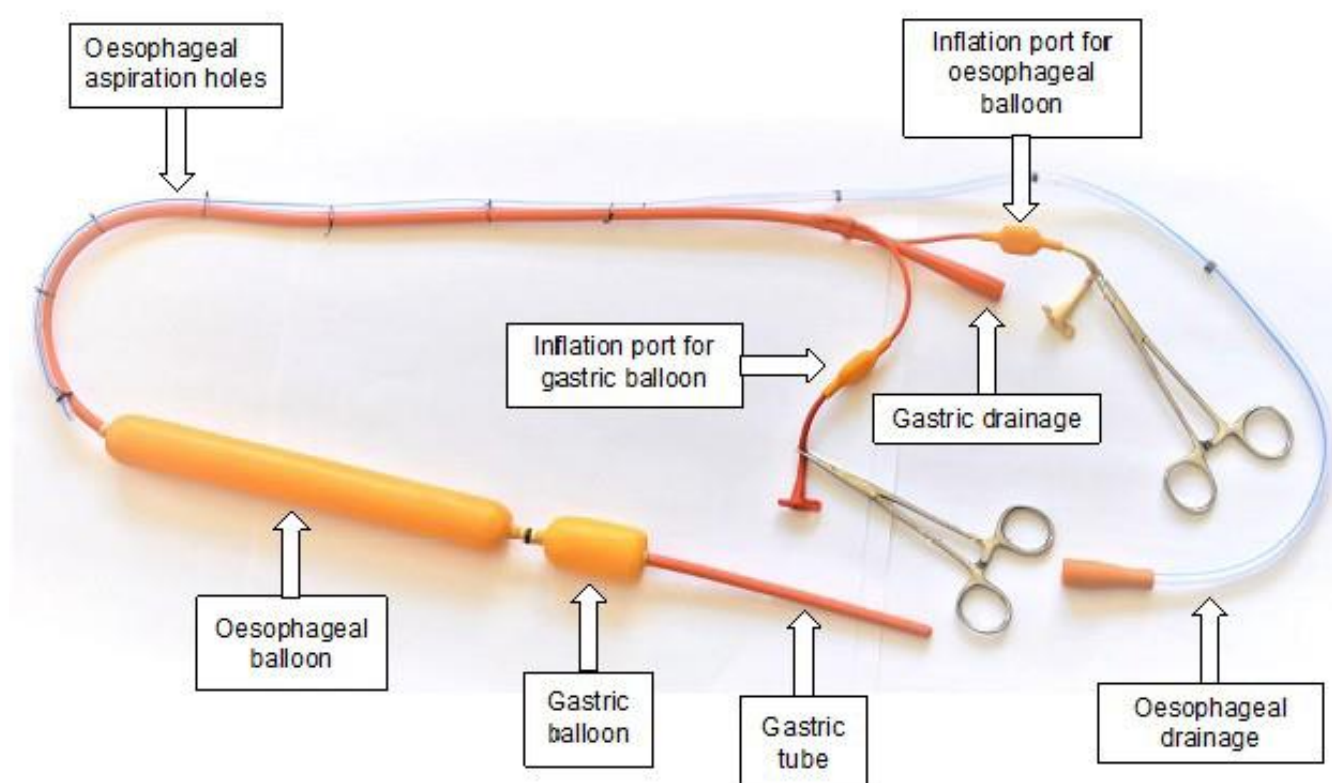


Figure 9.2 Four lumen Sengstaken balloon tube (Krige, 2019)

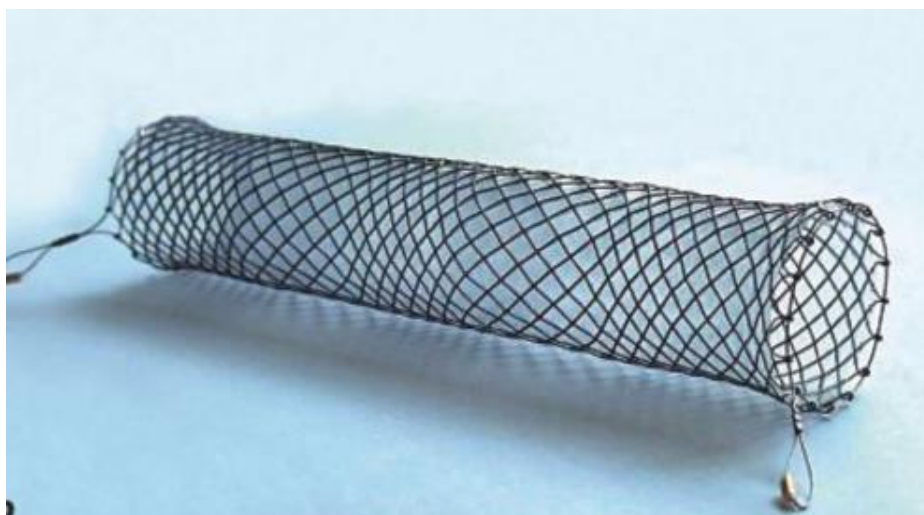


Figure 9.3 Danis oesophageal stent (ELLA-CS®)

The initial and the second endoscopic intervention a week later were performed during the index admission to hospital. Subsequent endoscopic intervention was undertaken at regular intervals at an outpatient clinic until the varices were eradicated. After variceal obliteration, surveillance endoscopy was performed at 3 and 6 months and then annually to identify patients in whom varices had recurred. Repeat endoscopic intervention was performed whenever residual or recurrent varices were identified during surveillance endoscopy (Krige, 2009).

Once the acute variceal bleeding had been controlled, all patients had a comprehensive and detailed medical assessment which included documentation of clinical, biochemical and endoscopic factors which might influence or contribute to variceal rebleeding and mortality. A detailed liver-specific history was obtained regarding the current or previous bleeding episodes, the duration and amount of alcohol intake, family history of liver disease or previous exposure to viral hepatitis. The physical examination documented the presence of stigmata of chronic liver disease including jaundice, peripheral and sacral oedema, spider angiomas, gynaecomastia, palmar erythema, testicular atrophy, white nails,

Dupuytren's contractures, hypertrophic osteo-arthropathy, clubbing, foetor hepaticus, flapping tremor and cutaneous purpura and petechiae. Abdominal examination documented the presence of a firm or nodular or enlarged liver, splenomegaly, ascites, caput medusa and Cruveilhier-Baumgarten syndrome with a para-xiphoid venous hum due to retrograde flow in a patent umbilical vein. The examination, in addition, sought to establish clinical evidence of encephalopathy, asterixis and cognitive dysfunction.

All patients had full laboratory studies including haematologic, biochemical and specific serologic testing. Patients' fluid and electrolyte status was evaluated by measuring serum electrolytes, urea, and creatinine. Standard biochemical tests of liver dysfunction were measured including serum albumin, bilirubin, GGT, alkaline phosphatase, AST, and ALT. All patients had hepatitis B surface antigen and anti-HBc core antigens tested. Hepatitis C was assessed by antibodies to HCV detected by enzyme linked immuno-absorbent assay. Positive results were confirmed by recombinant immunoblot assay. Patients with suspected primary biliary cirrhosis had their serum antimitochondrial antibody levels tested. Patients without an evident cause of cirrhosis were screened for haemochromatosis including serum ferritin and transferrin saturation levels, alpha-1-antitrypsin deficiency, and Wilson's disease. Autoimmune hepatitis was tested by antinuclear and smooth muscle antibodies and serum IgG levels. In selected patients in whom a definitive diagnosis was unclear, a plugged or transjugular liver biopsy was done if there was significant ascites, and transjugular portal wedge pressures were measured.

Transcutaneous abdominal ultrasound was done to assess liver size and appearance including the features of steatosis, cirrhosis or atrophy-hypertrophy complex, portal vein patency and diameter, direction of portal vein flow, spleen size and duplex Doppler

ultrasonography to identify surrogate features of portal hypertension and verify patency and direction of portal venous flow. If abdominal ultrasound identified an area of concern, a four-phase contrast-enhanced abdominal computerised tomogram was done to verify the ultrasound findings.

Data collection

All study data, including the initial baseline and all subsequent follow-up clinical, haematologic, biochemical and endoscopic findings were recorded prospectively on a standard proforma for each patient and the information was entered in a computer programme data base maintained by a dedicated research assistant. The diagnosis of cirrhosis was established by clinical evaluation, laboratory data, findings on radiological imaging including ultrasound and portal venous doppler assessment, and in selected patients, liver biopsy and hepatic vein wedge pressure measurements. Cirrhosis was considered to be alcohol related if patients gave a history of sustained heavy alcohol consumption over several years and exclusion of other causes.

All patients in the study received their first emergency and all subsequent endoscopic interventions in the unit. The study design and analysis of all six studies were approved by the appropriately convened Departmental and Institutional Ethics and Research Committees. Data validation and quality-control procedures followed accepted international Good Clinical Practice guidelines and the study was conducted in accordance with the Declaration of Helsinki.

CHAPTER 10

Study No 1

A NEW RECALIBRATED FOUR-CATEGORY CHILD-PUGH SCORE PERFORMS BETTER THAN THE ORIGINAL CHILD-PUGH AND MELD SCORES IN PREDICTING IN-HOSPITAL MORTALITY IN DECOMPENSATED ALCOHOLIC CIRRHOTIC PATIENTS WITH ACUTE VARICEAL BLEEDING. A COHORT ANALYSIS.

Introduction

Although advances in treatment have reduced overall mortality in patients with PHT and OV, uncontrolled or recurrent bleeding and hepatic decompensation remain the commonest causes of in-hospital mortality. The Child-Pugh and MELD scores are widely used to assess severity of liver dysfunction and predict patient risk for in-hospital rebleeding and death. However, the predictive abilities of both these scores in patients with variceal bleeding are variable with current evidence limited by small sample sizes, referral bias, dissimilar study endpoints, differences in patient selection and techniques of endoscopic intervention, and inconsistent definitions of rebleeding (Krige, 2020). Both the C-P and MELD scores have intrinsic limitations. The C-P design has arbitrary cut-off grading points, and the MELD score lacks clinical components which reflect underlying liver function and reserve.

To overcome the limitations of the arbitrary cut-off grading points in the existing C-P classification this research proposes a new 4-category recalibrated C-P score (rC-P) with revised cut-off levels (A=5,6,7; B=8,9,10; C=11,12,13; D=14,15). The objective of this investigation was to compare the relative ability of the original C-P, MELD and the new proposed rC-P score to predict in-hospital rebleeding and death following the index

admission for acute variceal bleeding in patients with portal hypertension secondary to alcoholic liver cirrhosis.

Methods

Patient population

The study included all adult patients admitted with endoscopically proven acute oesophageal variceal bleeding from January 1, 2000 to December 30, 2017. Patient records were de-identified for the purpose of the study. To assess risk factors in a defined population and to minimize possible confounding variables, only those patients with bleeding oesophageal varices due to alcohol-related cirrhosis and who were treated with endoscopic therapy were analysed. Patients with non-alcoholic cirrhosis or other causes of portal hypertension were excluded from the analysis to maintain a homogenous cohort. The diagnosis of cirrhosis was established by clinical evaluation, laboratory data, findings on radiological imaging including ultrasound and portal venous doppler assessment and, in selected patients, liver biopsy and hepatic vein wedge pressure measurements. Cirrhosis was alcohol related if patients gave a history of sustained heavy alcohol consumption over several years. C-P grade was categorized according to the Pugh modification and the revised cut-off levels of the rC-P score (A=5,6,7; B=8,9,10; C=11,12,13; D=14,15) and the MELD score was calculated by United Network of Organ Sharing (UNOS) adjustments.

Therapeutic intervention for variceal bleeding

The management of each episode of acute variceal bleeding, including the endoscopic haemostatic techniques employed, has been described in detail in chapter 9. Where initial endoscopy failed to control active bleeding, a Sengstaken–Blakemore or Minnesota balloon tube or a self-expanding oesophageal stent was placed for temporary control during resuscitation and endoscopy repeated when appropriate (Krige, 2021).

Definitions and outcomes

The primary endpoints of the study were variceal rebleeding and death during the index hospital admission. Time zero was defined as time of admission. Failure to control bleeding was defined as continued bleeding despite optimal medical management, endoscopic therapy, and balloon tamponade. Rebleeding was defined as any episode of upper gastrointestinal bleeding that occurred after the initial bleeding episode had been successfully controlled by endoscopic therapy, or bleeding that occurred subsequently between scheduled treatment sessions. Mortality was defined as death from any cause.

Statistical Analysis

Categorical variables were reported as frequency (percentage) and continuous variables as mean $\pm$ standard deviations. Receiver operating characteristic (ROC) curve analysis was performed to compare the ability of the C-P, rC-P and MELD scores to predict the risk of in-hospital rebleeding and death. Areas under the ROC curves (AUROC) with 95% confidence intervals (CIs) were reported. We compared the performance of the two scoring systems by using the DeLong tests. A p value <0.05 was considered statistically significant. Statistical analyses were performed using *Stata 14.0, StataCorp LP*.

Results

Patient characteristics

During the 288 month study period, 403 consecutive adult patients were treated for bleeding oesophageal varices. Patients with non-alcoholic causes of portal hypertension (n=168) or who had received endoscopy elsewhere and were referred for TIPS or liver transplantation (n= 12) were excluded from the study. Data in the remaining 225 patients with alcoholic cirrhosis and proven oesophageal variceal bleeding who received only

Table 10.1 Baseline characteristics of 225 patients with alcoholic cirrhosis and oesophageal variceal bleeding who had endoscopic therapy during the index admission to hospital.

Variables	n
Gender	
Male	175
Female	50
Age	
Median	50 years
Range	27-87 years
Total Bilirubin	
<34	108
34-51	34
>51	83
Albumin	
>35	35
28-35	191
<28	99
INR	
<1.7	146
1.7 – 2.2	55
>2.2	24
Ascites	
Nil	82
Mild	50
Moderate to severe	93
Hepatic encephalopathy	
Nil	132
Grade I-II	39
Grade III-IV	54
Varices	
Grade 1	6
Grade 2	38
Grade 3	114
Grade 4	56
Grade 5	7
Duration of admission (patients alive)	
Median	5 days
Range	1-129
Deaths	41 (18.2%)
Rebleeding	31 (13.7%)

Table 10.2 Rebleeding and death according to Child-Pugh score, original (C-P) and revised (rC-P) grades in 225 patients with alcoholic cirrhosis and bleeding varices.

Child-Pugh score	n	Rebleeding n	C-P grade Rebleeding	rC-P grade Rebleeding	Deaths n	C-P grade Deaths	rC-P grade Deaths
5	11	1	(A) 2/33 6.1%	(A) 5/55 9.09%	0	(A) 0/33	(A) 0/55
6	22	1			0		
7	22	3			0		
8	31	3	(B) 10/79 12.7%	(B) 12/87 13.8%	3	(B) 4/79 5.1%	(B) 7/87 8%
9	26	4			1		
10	30	5			3		
11	23	3	(C) 19/113 16.8%	(C) 10/61 16.4%	7	(C) 38/113 33.6%	(C) 12/61 32.8%
12	19	5			6		
13	19	2			7		
14	14	2			8		
15	8	2		(D) 4/22 18.2%	7		(D) 15/22 68.2%

Table 10.3 Rebleeding and death according to MELD scores in 225 patients

MELD	n	Rebleeding (%)	Deaths (%)
6 – 10	68	6 (8.8)	6 (8.8)
11 – 20	111	14 (12.6)	17 (15.3)
21 – 30	39	9 (23.1)	14 (35.9)
31 - 40	7	1(14.2)	4 (57.1)

endoscopic therapy for bleeding during their index admission to hospital form the basis of this study. Baseline characteristics are shown in Table 10.1. The 225 patients [175 (77.8%) male, 50 (22.2%) female] had a median age of 50 years (IQR 43-57) and underwent a total of 261 endoscopic treatments. Thirty-three (14.7%) patients were C-P grade A, 79 (35.1%) were grade B and 113 (50.2%) were grade C. MELD scores ranged from 3 to 40. Thirty-three (14.7%) patients were rC-P grade A, 109 (48.4%) were grade B, 61 (27.1%) were grade C and 22 (9.8%) were grade D.

Outcome

In-hospital rebleeding

One hundred and ninety-four (86.2%) patients had successful control of bleeding during first endoscopy and did not rebleed. Thirty-one (13.8%) underwent repeat endoscopy for recurrent bleeding (Table 10.2). Of these, 12 (5.3%) required balloon tamponade. Median length of hospital stay was 5 days (range 1-129 days).

Overall Mortality

Overall, 41 (18.2%) patients died. The mortality rate was higher in patients who rebled (4/31, 21.1%) and in those who required balloon tamponade (8/12, 66.7%). In terms of the C-P score, mortality in grades A-C were 0%, 7.5% and 32.7% respectively while, for the rC-P, mortality was 0%, 8%, 31.1% and 68.1% for grades A-D respectively (Table 7.3). Mortality was 8.8% for MELD 6-10, 15.3% for 11-20, 35.9% for 21-30 and 57.1% for 31-40. Liver failure (n=29, 70.7%) was the most common cause of death.

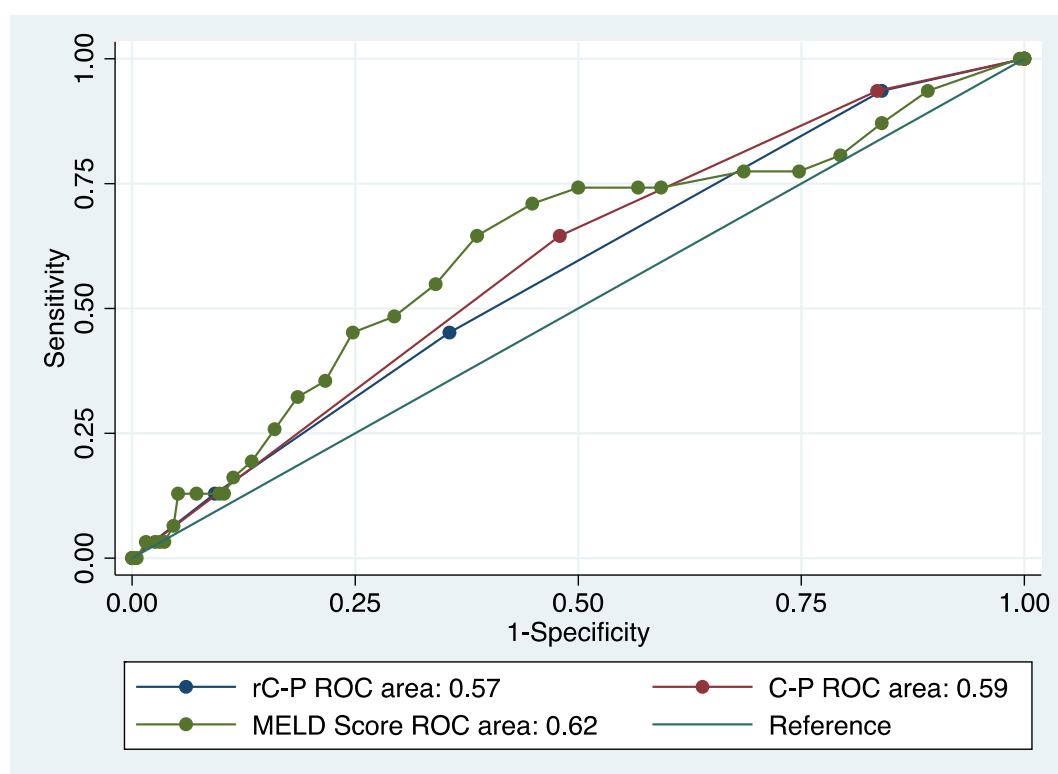
Predictive performance

In-hospital rebleeding

Overall, predictive ability for rebleeding was poor with no significant difference in performance between the 3 scoring systems (AUROC 0.59, 95%CI 0.50-0.67 for C-P,

AUROC 0.62, 95% CI 0.51-0.73 for MELD and AUROC 0.57, 95% CI 0.47-0.67 for rC-P, $P=0.72$ C-P (ROC Figure 10.1).

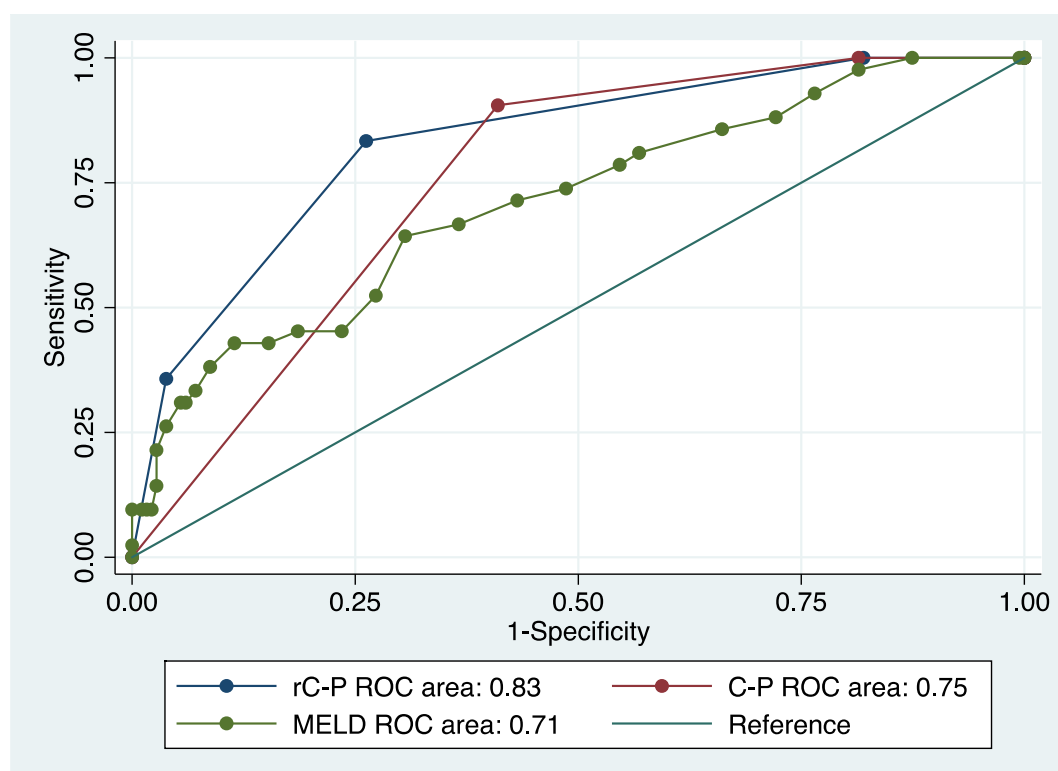
Figure 10.1: Comparison of Discriminatory Ability of C-P, rC-P and MELD to Predict Rebleeding



Mortality

There was no difference in the ability to predict death between the C-P and MELD scores C-P (AUROC 0.75, 95%CI 0.71-0.81) and 0.71, 95% 0.62-0.80 respectively, $P=0.35$). The rC-P had significantly improved discriminatory capacity (AUROC 0.83, 95% 0.77-0.89) compared to the C-P and MELD to predict death ($p=0.004$). (Figure 10.2).

Figure 10.2: Comparison of Discriminatory Ability of C-P, rC-P and MELD to Predict Death



Discussion

An accurate, objective, and reproducible scoring system that predicts outcome and identifies high risk patients who have portal hypertension and bleeding oesophageal varices is a key component for determining clinical strategy and underpins overall patient management (Al Sibae, 2011). In this study the ability of a new rC-P score to predict oesophageal variceal rebleeding and death was compared to the original C-P and MELD scores in an alcoholic cirrhotic population in whom the index variceal bleed was treated with emergency endoscopic intervention. The new rC-P score demonstrated a significantly improved ability to predict death, compared to both the C-P and MELD scores but ultimately was no better in predicting rebleeding. Importantly, although the initial endoscopic intervention was effective in controlling acute variceal bleeding from oesophageal varices in most patients, one in 20 patients had uncontrolled bleeding and one in 12 had recurrent

variceal bleeding during the index admission. The mortality rate in this cohort of decompensated alcohol-related cirrhotic patients was 18.2%, which is similar to the 23.6% reported by D'Amico et al (D'Amico, 2023) and the 18.4% documented by Thomopoulos et al (Thomopoulos, 2006), but higher than the 17.5% (Chalasani, 2003), 15.3% (Boix, 2007) and 14.5% (Carbonell, 2004) mortality rates reported by other authors, a difference which may reflect the alcoholic population in our study.

Although several prognostic models have been proposed to predict mortality in patients with cirrhosis, the C-P and MELD scores have remained the most consistent and widely used scoring systems, both in clinical practice and research, and are superior to other predictive systems in determining mortality within the first six weeks after a major variceal bleed (Reverter, 2014). The advantages of the C-P score are its simplicity and easily obtained variables and convenience as a prognostic tool and calculations can be done at the bedside using mental arithmetic compared to the elaborate computations necessary for the MELD score, which require an online or pocket calculator. However, subjective assessment of the degree of ascites and encephalopathy, arbitrary cut-off values for bilirubin, albumin and INR and suboptimal differentiation between mild and severe disease of patients in grade C may limit the clinical application of the C-P system (Augustin, 2009). Also, assigning equal weights to all variables in the C-P score may not be appropriate (Kaplan, 2016).

In contrast, the MELD score is a prospectively developed and validated indicator of the severity of end-stage liver disease that utilizes quantitative, objective measures, including bilirubin, creatinine, and INR values to predict mortality. Also, variables are weighted to account for relative importance in reflecting severity of liver disease. The MELD scoring

system therefore provides a more refined, granular grading system with a score ranging from 6 to 40 and as such has replaced the C-P score for prioritization of patients for liver transplantation (Trieu, 2018). Caveats of the MELD score include a cap at a maximum value of 40 points and the maximum assigned value of serum creatinine is capped at 4, even when the measured serum level is higher. In addition, the MELD score does not include independent clinical prognostic indicators that correlate with severity of portal hypertension such as the degree of ascites and hepatic encephalopathy (Ferrarese, 2023).

The new 4-category rC-P scoring system provides a refined stratification of patients in the C category of the original C-P, and allocates patients with scores of 14 and 15 to a category D. The results show that the rC-P may be better than the C-P and MELD scores at predicting in-hospital death, but not rebleeding, in patients who present with variceal bleeding secondary to alcoholic liver cirrhosis (Krige, 2020).

This study has the limitations of a retrospective analysis. The study duration is over a 26-year period during which improvements in supportive care, vasoactive drugs and antibiotic therapy will have occurred. A major strength of this study however is that it was conducted in a single centre in a well-defined population of consecutive patients using a standard endoscopic technique and was supervised by the same group of investigators during the study period. The robustness of this study is enhanced by the prospective data collection, restriction of subjects to alcoholic cirrhotic patients and the complete follow-up of the cohort. The use of rebleeding and death as the main outcomes provided consistent and objective end-points.

In this analysis the rC-P classification system used scores stratified into four categories with three-point cutoffs, which demonstrated an improved ability to predict in-hospital mortality, but not rebleeding, compared to existing scoring systems. Future prospective studies incorporating and evaluating the full spectrum of prognostic factors including clinical variables, renal function and liver biochemistry, endoscopic findings and portal pressures are necessary to devise a new validated variceal rebleeding risk score which will be a valuable addition to improving the effective management of patients with portal hypertension and bleeding oesophageal varices. This proposed modified and recalibrated C-P model will require validation in future prospective studies including a wider spectrum beyond alcoholic cirrhosis.

CHAPTER 11

Study No 2

ENDOSCOPIC VARICEAL LIGATION COMPARED TO INJECTION SCLEROTHERAPY IN DECOMPENSATED CIRRHOTIC PATIENTS WITH ACTIVELY BLEEDING OESOPHAGEAL VARICES: A COMPARATIVE COHORT ANALYSIS.

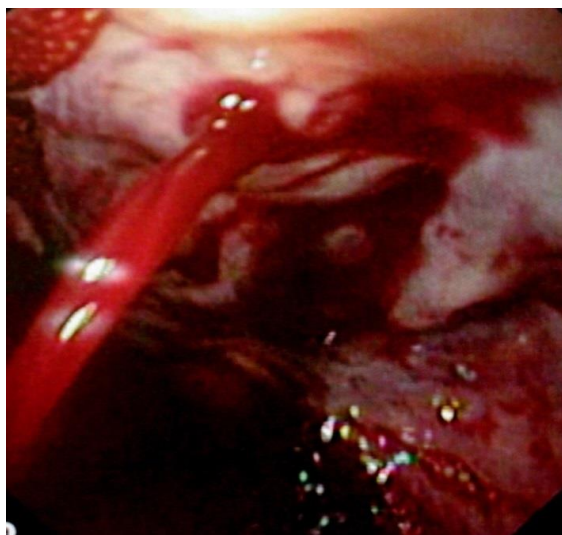
Acute variceal bleeding has a mortality rate of up to 20% for the index bleeding event and 10% for subsequent bleeding episodes. Endoscopic intervention is the first-line treatment to control active bleeding, but around 60% of patients will rebleed after successful initial control if effective follow-up treatment is not provided. Endoscopic variceal ligation is the endoscopic treatment of choice, supported by data from RCTs which show more rapid eradication of varices with lower rates of rebleeding, and fewer oesophageal complications compared to IST. However, detailed data on the relative success of each method in controlling AVB with *actively* bleeding (“*spurting*”) varices are limited. The cohorts analysed in previous RCTs comparing EVL with IST include only small numbers of patients who had active variceal bleeding with conflicting results (Dai, 2015). In this study the comparative efficacies of EVL and IST in controlling *actively* bleeding oesophageal varices are analysed in the largest matched patient cohort to date.

Patients and Methods

Adult patients admitted with variceal bleeding between January 2000 and December 2018 were assessed. Only patients with *actively* bleeding (“*spurting*”) oesophageal varices who received their first emergency and subsequent procedures in the unit were included in the study (Figure 11.1). The outcome of endoscopic interventions, both emergency and

subsequent elective, was analysed to assess the efficacy of EVL compared to IST in initial AVB control as well as long-term efficacy.

Figure 11.1 Actively bleeding “spurting” oesophageal varix



Study design.

The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for reporting observational studies. A comparative case-matched analysis was done of consecutive patients who received their first emergency endoscopic intervention for *actively* bleeding (“*spurting*”) oesophageal varices as well as subsequent procedures in the unit. Data were retrieved from a prospectively maintained faculty approved oesophageal varices registry and patients were manually matched one-to-one before outcome measures were reviewed. To reduce bias, investigators were blinded throughout the selection and matching process to the primary and secondary end points. Data were analysed on 28 February 2020 after a minimum 12-month follow-up period.

Study endpoints

The primary clinical endpoints of the study were: (i) primary endoscopic failure of the initial endoscopic intervention defined as failure to control AVB; (ii) secondary endoscopic failure

defined as rebleeding within 5 days after initial endoscopic control; (iii) mortality during the initial hospital admission; (iv) 6-week mortality and (v) overall survival. The secondary endpoints were: (i) procedure-related complications and (ii) success in achieving variceal eradication as defined in the analysis criteria.

Techniques of endoscopic intervention

Fibreoptic endoscopy (model GIF 1T20 or K10, Olympus Corp., Lake Success, NY) was used during the first decade of the study and video-endoscopy during the second decade. The techniques of both methods of endoscopic intervention used in this study have been published previously (Krige, 2013, 2017, 2023) and are described in detail in chapter 5. In patients treated with IST, eradication was defined as the absence of varices and for EVL eradication was defined as disappearance of varices or residual varices too small to be sucked and trapped in the banding device. After variceal eradication, surveillance endoscopy was performed at 3 and 6 months and then annually to identify patients in whom varices had recurred. All patients were given β -blockers during follow-up unless specifically contra-indicated.

Rebleeding

Baveno criteria were used to define secondary endoscopic 5-day failure to control bleeding (de Franchis, 2015, 2022). Any recurrent bleeding episode after the first variceal sclerotherapy or ligation session or subsequently between scheduled treatment sessions was investigated by emergency endoscopy and treated according to endoscopic findings. Additional variceal sclerotherapy or ligation was undertaken if bleeding was due to residual or recurrent varices.

Statistical analysis

Student's t test was used to compare differences between groups for continuous variables, and the chi-square test was employed for categorical data. Kaplan–Meier survival curves

were constructed and compared using the log-rank test. A p-value <0.05 was considered significant. SAS System Package version 9.2.1 software (SAS Systems International, Cary, North Carolina, USA) was used for statistical analysis. Data were censored at the time of the last clinic visit or endoscopy session, TIPS placement or death.

Table 11.1 Demographic and clinical data in IST and EVL cohorts

	Total n=80	IST n=40	EVL n=40
Male	56	28 (70%)	28 (70%)
Female	24	12 (30%)	12 (30%)
Age in years (range)	51 (r 22-86)	51 (r 25-86)	51 (r 22-82)
Cirrhosis - alcohol	56 (70%)	29 (72.5%)	27 (67.5%)
Cirrhosis - cryptogenic	8 (10%)	4 (10%)	4 (10%)
Cirrhosis - hepatitis B	5 (6.3%)	2 (5%)	3 (7.5%)
Cirrhosis - hepatitis B + alcohol	8 (10%)	4 (10%)	4 (10%)
Cirrhosis - NAFLD	2 (2.5%)	1 (2.5%)	1 (2.5%)
Cirrhosis - hepatitis C	1 (1.3%)	0	1 (2.5%)
Child-Pugh grade A	9 (11.3%)	3 (7.5%)	6 (15%)
Child-Pugh grade B	32 (40%)	19 (47.5%)	13 (32.5%)
Child-Pugh grade C	39 (48.8%)	18 (45%)	21 (52.5%)

Legends: IST: injection sclerotherapy, EVL: endoscopic variceal ligation

Results

Demographic data, cause of cirrhosis, C-P grade and hepatic reserve of both groups were similar (Table 11.1). Overall endoscopic control of active bleeding was successful in 75 of the 80 patients (Table 11.2). In the two groups bleeding control during the index endoscopic procedure was achieved after EVL in 39 of 40 patients (97.5%) and in 36 of 40 patients (90%) after IST (Table 11.2). In the five patients, one in the EVL group and four in the IST

Table 11.2. Outcome: index admission, at 6 weeks, and overall survival in IST and EVL cohorts

	Total n=80	IST n=40	EVL n=40
Uncontrolled variceal bleeding despite endoscopic intervention	5 (6.3%)	4 (10%)	1 (2.5%)
Rebleeding after initial control	18 (22.5%)	10 (25%)	8 (20%)
(i) due to varices	13	7	6
(ii) due to ulceration	5	3	2
Blood transfusion (number of patients)	65 (81.3%)	31 (77.5%)	34 (85%)
Blood units transfused	6 (r 2-14)	4 (r 2-10)	6 (r 2-14)
Varices eradicated	27/33 (82%)	14/16 (88%)	14/17 (82%)
Index admission deaths	23 (28.8%)	10 (25%)	13 (32.5%)
Child-Pugh grade A	0/9 (0%)	0/3 (0%)	0/6 (0%)
Child-Pugh grade B	4/32 (12.5%)	2/19 (11%)	2/13 (15%)
Child-Pugh grade C	19/39 (49%)	8/18 (44%)	11/21 (52%)
Surviving patients: number of days in hospital	6 (range 1-31)	7 (range 1-31)	5 (range 1-14)
Index admission deaths (days alive)	1 (range 1-37)	1 (range 1-37)	2 (range 1-16)
6 week mortality	26 (32.5%)	12 (30%)	14 (35%)
Child-Pugh grade A	0/9 (0%)	0/3 (0%)	0/6 (0%)
Child-Pugh grade B	5/32 (16%)	3/19 (16%)	2/13 (15%)
Child-Pugh grade C	21/39 (54%)	9/18 (50%)	12/21 (58%)
Overall mortality	39 (49%)	20 (50%)	19 (48%)
Child-Pugh grade A	1/9 (11%)	0/3 (0%)	1/6 (17%)
Child-Pugh grade B	12/32 (38%)	8/19 (50%)	4/13 (31%)
Child-Pugh grade C	26/39 (67%)	12/18 (67%)	14/21 (67%)

Legends: IST: injection sclerotherapy. EVL: endoscopic variceal ligation.

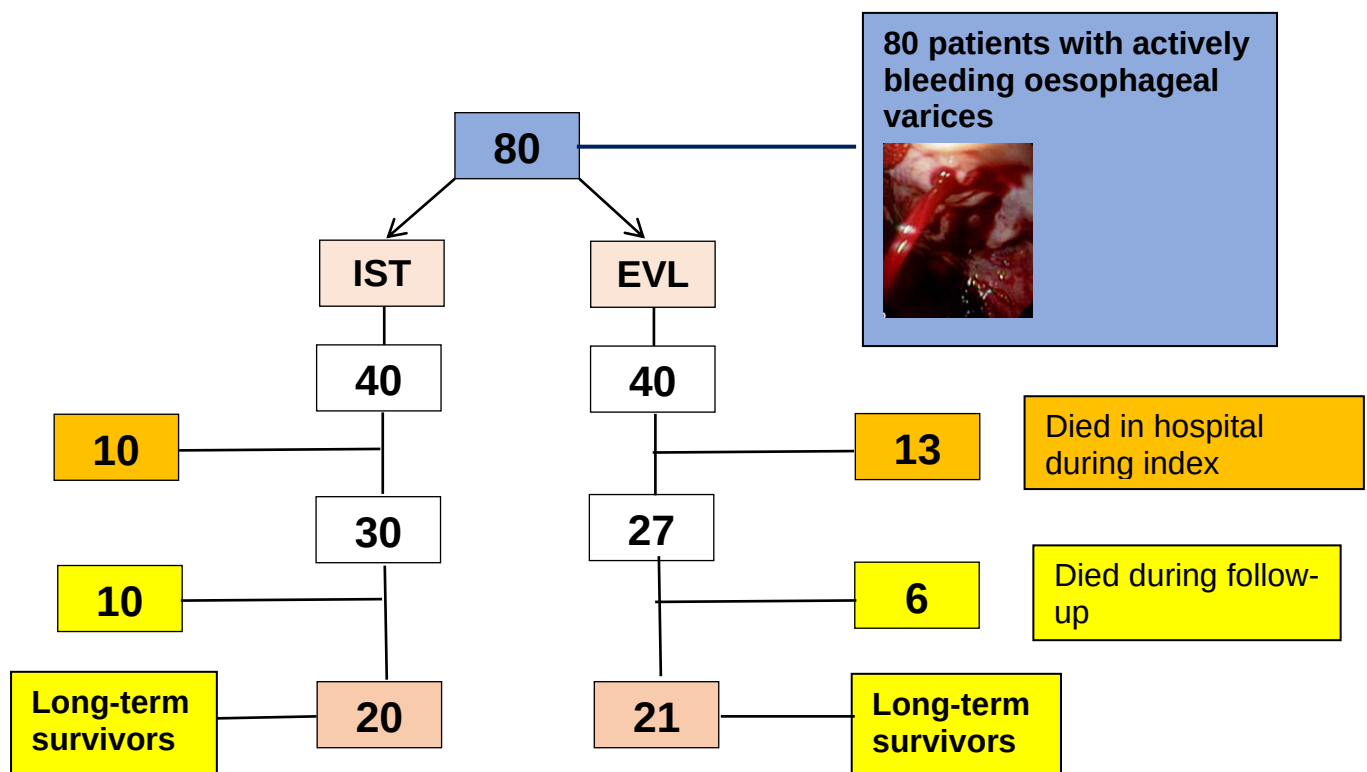
group in whom active bleeding could initially not be controlled due to torrential bleeding, a balloon tube was used. All five were C-P grade C and 4 of the 5 (EVL n=1, IST n=3) ultimately died of liver failure aggravated by major blood loss despite eventual control of bleeding during the index admission.

Overall 18 (22.5%) of the 80 patients rebled during the index admission, all within 120 hours of the index endoscopy, and required 22 additional endoscopic procedures to control bleeding (Table 11.2). Five-day failure of bleeding control was 20% in the EVL group and 25% in the IST group. Rebleeding from oesophageal varices during the index admission in the 2 groups was similar (EVL n=6 vs IST n=7). Overall eight patients (20%) in the EVL group rebled in hospital (varices=6, oesophageal ulceration=2) while ten patients (25%) in the IST group rebled in hospital (varices=7, oesophageal ulceration=3). Overall successful endoscopic control of variceal bleeding during the index admission was similar (EVL 82.5% vs IST 72.5%). Overall more complications occurred in the IST group (20%) compared to the EVL group (5%) ($p=0.08$). Endoscopy-induced oesophageal ulceration was less common in EVL than in IST (3 vs 9). In the EVL group complications included encephalopathy (n=1) and drip phlebitis (n=1) while in the IST group complications included encephalopathy (n=1) and SBP (n=1).

Oesophageal varices were eradicated after EVL in 14 of the 17 patients (82.4%) who survived longer than 3 months after a median of 3 banding procedures (range 2 to 8), during a median of 6 months, (range 2 to 11 months) (Table 2). Oesophageal varices were eradicated after IST in 14 of the 16 patients (87.5%) who survived longer than 3 months after a median of 4 sclerotherapy procedures (range: 3 to 6) during a median of 7 months, (range: 3 to 10 months) (Table 11.2).

The overall index in-hospital admission mortality for both cohorts was 28.7% (n=23) with no significant difference in mortality rates (EVL n=13, IST n=10) between the two groups during the index admission (Figure 11.2). The 13 deaths in the EVL group were due to multi-organ and liver failure, five of which were precipitated by rebleeding; mortality in C-P group A was 0%, C-P B 15% and C-P C 52%. The 10 deaths in the IST group were due to liver and renal failure, five of which were aggravated by rebleeding; mortality in C-P group A was 0%, C-P B 5% and C-P C 50% (Table 11.2).

Figure 11.2: Outcome in the 80 matched IST and EVL patients



Legend: IST injection sclerotherapy, EVL endoscopic variceal ligation

Median follow-up was 43.2 months (range 9-240 months). Six patients in the EVL group died of liver failure (n=4) or advanced HCC (n=2) at a median of 26 months, range: 1

month-6 years, none with further variceal bleeding. Ten patients in the IST group died of liver failure (n=4), advanced HCC (n=3), lung cancer (n=1) or due to variceal rebleeding (n=2) at a median of 26 months, range: 1 month-9 years (Figure 11.2). Overall mortality in the EVL group was 19 (47.5%) which included C-P group A 17%, C-P B 31% and C-P C 66.7%. Overall mortality in the IST group was 20 (50%) which included C-P group A 0%, C-P B 42% and C-P C 66.7%. Forty-one of the 80 patients in the study are alive at a median of 3.6 years (EVL n=21, range: 1-8 years; IST n=20, range: 3 months-12 years).

Discussion

The principal objectives of endoscopic variceal intervention are expeditious control of acute bleeding and safe and cost-effective eradication of residual varices to prevent rebleeding. However, despite applying optimal standards of care, up to 10% of patients have persistent or recalcitrant variceal bleeding and 15% to 20% die during the first 6 weeks, often due to progressive liver or multi-organ failure aggravated by recurrent bleeding (Garcia-Tsao, 2017, 2023). This matched observational comparative study in prospectively documented patients evaluated the best endoscopic method of controlling actively bleeding oesophageal varices at the index presentation. The study showed that EVL performed better than IST in controlling active bleeding during the first endoscopic intervention in patients with AVB and provided better bleeding control at 5 days with lower variceal rebleeding rates and less procedure-related complications, but ultimately had similar 6 week and overall survival rates compared to IST. While the superiority of EVL over IST did not achieve statistical significance, a numerical advantage was present in four of the five categories assessed with only recurrence of varices being worse. This study specifically used 5-day treatment failure and 6-week mortality as key bleeding outcomes as defined by Baveno criteria (de Franchis, 2022). Both these specific time intervals are acknowledged as important primary

endpoints and surrogate markers to provide global assessment of outcome of intervention in AVB and to establish international criteria and standards for interventional variceal endoscopic benchmarking.

No randomized study exists which specifically compares EVL with IST in patients who all had actively bleeding oesophageal varices encountered during the index endoscopy. In published trials and meta-analyses comparing EVL vs IST only a minority of patients recruited had active bleeding so the comparative efficacy of either endoscopic method has never fully been tested or subjected to rigorous scientific scrutiny in this specific situation. This is the first study to critically evaluate the relative efficacies of EVL and IST in two comparative cohorts of patients all of whom had active oesophageal variceal bleeding at the time of the first endoscopy. In the only other similar comparative study from Taiwan, 71 cirrhotic patients who had either *oozing* or *spurting* variceal bleeding were randomized to receive EVL (37 patients) or IST (34 patients). Primary success rate defined as bleeding control for 72 hours was 97% in the EVL group and 76% in the IST group ($P=.009$). The efficacy of ligation was similar to sclerotherapy in the control of oozing varices (100% vs. 89%, $P=.23$), whereas ligation was superior to sclerotherapy in the control of spurting varices (94% vs. 62%, $P=.012$) (Lo, 1997). The strength of the data in the Taiwanese study is diluted by the inclusion of oozing varices unlike our study which was designed to evaluate the comparative efficacies of EVL and IST exclusively in patients with actively bleeding or “spurting” varices.

Five meta-analyses have evaluated the relative efficacies of EVL and IST for the treatment of patients with bleeding oesophageal varices. The first meta-analysis by D’Amico et al. included three RCTs and 309 patients in which pooled odds ratios (POR, 0.49; CI 0.31-

0.78) showed a significant benefit from EVL (D'Amico, 1995). Subsequently a second meta-analysis by Laine included seven randomized trials which showed that ligation reduced rebleeding (OR, 0.52 [95% CI, 0.37 to 0.74]), mortality (OR, 0.67 [CI, 0.46 to 0.98]), and death due to bleeding (OR, 0.49 [CI, 0.24 to 0.996]) compared with sclerotherapy (Laine, 1995). The third meta-analysis assessed 12 trials involving 1309 patients. Seven of the trials included only patients with cirrhosis and a ligating device with an overtube was used in eight trials. The haemostatic efficacy of sclerotherapy was a median of 95% (76%-100%) compared with a median of 97% (86%-100%) for endoscopic ligation ($p=0.4$) with a 2.5% difference favouring ligation (95% CI 0.4% to 4.6%) ($p=0.018$). The mortality percentage difference was 1.3%, favouring ligation (95% CI -2.3% to 4.9%) ($p = 0.46$) (Triantos, 2006). A later fourth meta-analysis which included 13 trials and 1,091 patients showed that the risk of variceal rebleeding was significantly reduced by EVL (POR 0.46, 95% CI 0.35-0.60) and while there were no differences in mortality, complications were significantly less frequent and less severe with EVL and the number of endoscopic sessions needed to achieve eradication was significantly lower than with sclerotherapy (de Franchis, 2007). The fifth and most recent meta-analysis by Dai et al. comprising 14 studies and 1236 patients showed EVL to be superior to IST with lower rebleeding and complication rates and a higher rate of variceal eradication (Dai, 2015). In patients with actively bleeding varices undergoing EVL both rebleeding and variceal eradication were significantly lower (RR = 0.68, 95% CI: 0.57-0.81) and higher (RR = 1.06, 95% CI: 1.01–1.12) respectively in comparison to IST group. The complication rate was significantly lower in EVL group compared to the IST group (RR=0.28, 95% CI: 0.13-0.58) (Dai, 2015).

These published meta-analyses, however, have limitations which may influence the validity of the data and conclusions. Early studies included single band ligation devices which

require repeated loading and passage through an oesophageal overtube, a cumbersome technique now outdated and replaced with modern multiband ligators. Sclerotherapy techniques in these studies were not standardised and varied widely in terms of sclerosant type, strength and volume used. In addition to variable needle size, the injection techniques also differed with either intravariceal, paravariceal or combined methods, as did the treatment intervals and schedules used (Dai, 2015). Furthermore, included in the meta-analyses were studies from diverse countries with substantial differences in patient ethnicities, portal hypertension aetiologies, severity of hepatic decompensation and extent of oesophageal varices. The trials included in the meta-analyses also show conflicting results due to inconsistencies in design which included short patient follow-up of less than 6 weeks (Villanueva, 2006), heterogenous populations, some with a predominance of patients with schistosomiasis, hepatitis B or C (Siqueira, 1998; Fakhry, 1997) only extrahepatic portal vein occlusion or only children (Zargar, 2005). In one trial included in the meta-analysis more than half the patients had no history of variceal bleeding and received endoscopic intervention as primary prophylaxis (Ferrari, 2005) while in another trial included in the meta-analysis patients were randomized to either EVL or combined EVL and IST (Al Traif, 1999), factors which should have excluded the inclusion of these studies in the meta-analysis. In an accurate updated evaluation of the 17 randomized trials which compare EVL with IST (Table 11.3) EVL performed significantly better than IST in controlling bleeding (2 trials), with less rebleeding (5 trials), less endoscopy-related complications (13 trials), in fewer endoscopy sessions to achieve variceal eradication (11 trials) and improved survival (2 trials). However, varices recurred significantly more commonly after EVL than IST in 3 trials (Kriger, 2020).

Experts agree that endoscopic control of variceal bleeding, especially during profuse bleeding, requires a high level of manipulative skill, experience and mature judgement. Despite initial scepticism and concerns that EVL would prove less effective than sclerotherapy in achieving control of actively bleeding varices, EVL was superior to IST in arresting “spurting” varices in this study and there were very few failures of acute haemostasis. These findings are contradictory to the general belief in which some authorities claim that EVL may be more difficult to perform than IST during active variceal hemorrhage because the reduced field of view and the visual constraints imposed by blood or clot filling the cap during profuse bleeding may obscure vision and limit accurate deployment of bands (Lo, 1995). In addition, as banding has evolved, advances in equipment design and the advent of multiband ligating devices which avoid the need for a cumbersome overtube have provided better compliance and lessened the discomfort of EVL.

Endoscopic failure to control variceal bleeding is encountered by even the most experienced endoscopists (Cho, 2016). Up to 20% of variceal bleeding episodes can be refractory to standard therapy and are associated with increased mortality (Garcia-Tsao, 2017). This study emphasizes the critical importance of initial control of variceal bleeding during the first endoscopic intervention when active bleeding is present. In the five patients with torrential variceal bleeding and failed endoscopic control, mortality was 80% despite balloon tamponade. This patient subgroup has the highest mortality and invariably are C-P group C who do not tolerate major blood loss and prolonged hypotension. It is evident from this data and the observations of others that the efficacy of endoscopic intervention in controlling AVB and mortality from bleeding are closely related to the severity of the underlying liver disease. As anticipated, mortality in this study increased exponentially as

liver reserve diminished. The data demonstrated that C-P grade C patients, who have the least hepatic reserve, were more likely to require balloon tamponade in addition to endoscopic therapy to control acute bleeding. The study shows that in this high-risk group, even when endotherapy successfully controlled variceal bleeding, progressive liver failure resulted in high mortality rates during the first admission, especially in patients with a C-P score >13 (Krige, 2020).

While neither method of endoscopic intervention has any effect on portal flow or resistance, the mechanisms of action differ. EVL utilizes mechanical strangulation in which the dimensions and design of the banding device limit the volume of the ligated tissue with less collateral oesophageal wall damage and less local complications. In contrast, IST produces a chemical thrombosis after needle puncture and injection of sclerosant into or adjacent to the varix with substantially higher local oesophageal complication rates. Overall, our study demonstrated more complications in the IST group compared to the EVL group, findings similar to previous studies that demonstrate fewer side effects after ligation compared to sclerotherapy. The major drawback of EVL is a higher tendency to variceal recurrence. Accumulated evidence suggests that patency of variceal para-oesophageal and peri-oesophageal feeder vessels predisposes to variceal recurrence. These feeder vessels are occluded more efficiently by sclerotherapy than ligation, which is usually confined to the mucosal and submucosal collaterals. Furthermore, the recurrence of varices may become more frequent with time.

This study has several limitations. First, most of the patients had alcohol-induced cirrhosis, whereas non-alcoholic steatohepatitis, which has become an important cause of cirrhosis, is under-represented in this study. Second, half the included patients were C-P grade C

with hepatic decompensation which have the highest mortality and our results can therefore not be generalized to all other patient populations. Third, as the study was conducted in a single-centre academic tertiary referral centre with experienced on-call endoscopists and staff available around the clock, patient selection and treatment bias may occur as similar advanced interventions may not be available or replicated in smaller hospitals. Fourth, the number of patients with failure was small and insufficient to identify criteria influencing endoscopic failure. The use of “all-cause rebleeding” was applied as a strategy to minimize bias in the definition of rebleeding. Even with these limitations, this study provided robust data that corroborates previous evidence.

The strengths of this study derive from the implementation of modern protocol-driven standardized IST and EVL techniques in a single institution specialist endoscopy centre with a particular interest in portal hypertension which may have increased the treatment effect. Further, because patients included those at high risk for rebleeding, the data are likely representative of a real-world situation, improving the robustness of the findings. To provide the highest possible level of uniformity and to minimise differences in the zero-time entry, only patients who received their initial and subsequent treatment in our unit were studied. By including consecutive patients treated in a single institution, the study minimized possible biases that may arise from patient selection, referral practices and local variations in treatment strategies. The use of rebleeding and death as the main outcomes provided consistent and objective endpoints in the study. Unlike other studies which include non-consecutive patients, incomplete reporting of inclusion and exclusion criteria and have incomplete follow-up or inclusion of patients at differing disease stages without separate analyses, our study design avoided these pitfalls by excluding non-measurable biases.

In conclusion, this single centre comparative matched study showed that EVL outperformed IST with higher efficacy and lower complication rates and provides further confirmation of the safety of EVL. Endoscopic variceal ligation is established as the optimal endoscopic method for controlling active variceal bleeding and the long-term eradication treatment of oesophageal varices despite the higher tendency to recurrence. Recurrences did not impose a higher risk of rebleeding or require more sessions for further eradication if patients underwent regular endoscopic surveillance. The essential future requirements for improving survival in these high-risk patients are self-evident and include effective control of AVB, prevention of further rebleeding and minimising deterioration of liver function.

Table 11.3. Summary of published randomized controlled trials of EVL vs IST

Author	Year	Number of patients	Number in each group		Control of bleeding		Varices eradicated		Eradication sessions		Rebleeding		Major complications		Variceal recurrence		Survival	
			EVL	IST	EVL	IST	EVL	IST	EVL	IST	EVL	IST	EVL	IST	EVL	IST	EVL	IST
Stiegmann	1992	129	64	65	86%	77%	55%	56%	4	5	36%	48%	2%	22%	33%	50%	72%	55%
Laine	1993	77	38	39	89%	89%	59%	69%	4.1	6.2	24%	31%	24%	56%	-	-	89%	85%
Gimson	1993	103	54	49	91%	92%	82%	71%	3.4	4.9	30%	53%	69%	65%	-	-	52%	18%
Lo	1995	120	61	59	94%	80%	74%	63%	3.8	6.5	11%	36%	3.3%	19%	-	-	84%	68%
Hou	1995	134	67	67	100%	88%	87%	79%	3.5	4.6	18%	33%	4%	22%	48%	30%	79%	84%
Sarin	1997	95	47	48	86%	80%	94%	94%	4.1	5.2	6.4%	20.8%	45%	50%	28.7%	7.5%	93%	89%
Baroncini	1997	111	57	54	-	-	93%	93%	3.5	4.0	16%	19%	11%	31%	30%	13%	79%	78%
Avgerinos	1997	77	37	40	-	-	95%	98%	3.7	5.8	27%	48%	35%	60%	31%	44%	80%	79%
Lo	1997	71	37	34	97%	76%	-	-	-	-	17%	33%	5%	29%	-	-	81%	65%
Siqueira	1998	40	20	20	-	-	90%	100%	3.1	3.7	0%	5%	-	-	0%	0%	100%	95%
De la Pena	1999	88	42	46	-	-	79%	71%	5.3	6.6	31%	50%	14%	41%	47%	23%	81%	78%
Masci	1999	100	50	50	-	-	88%	82%	3.4	5.3	12%	42%	18%	38%	32%	27%	80%	78%
Fakhry	2000	84	43	41	94%	94%	-	-	2.8	4.8	16%	15%	2%	65%	21%	20%	93%	93%
Zargar	2005	73	37	36	100%	83%	95%	92%	3.7	7.7	3%	19%	3%	22%	11%	9%	-	-
Villanueva	2006	179	90	89	96%	85%	-	-	-	-	7%	12%	4%	13%	-	-	87%	79%
Luz	2011	100	50	50	92%	96%	-	-	-	-	22%	14%	-	-	-	-	77%	80%
Ali	2017	124	60	64	100%	100%	87%	80%	-	-	23%	28%	10%	27%	-	-	78%	72%

EVL endoscopic variceal ligation, IST injection sclerotherapy, Bold and colour highlighted comparisons are significant (**p<0.05**)

CHAPTER 12

Study No 3.

AN ANALYSIS OF THE BENEFITS AND THE LIMITATIONS OF ENDOSCOPIC LIGATION IN ACHIEVING COMPLETE VARICEAL ERADICATION AND PREVENTING VARICEAL RECURRENCE AND REBLEEDING IN A COHORT OF 140 ADULT PATIENTS WITH BLEEDING OESOPHAGEAL VARICES.

Introduction

Endoscopic variceal ligation has replaced IST in most centres as the endoscopic interventional procedure of choice for BOV, supported by RCT data that show more rapid eradication of varices with lower rates of recurrent bleeding and fewer endoscopic-related complications (Dai, 2015). However, few studies have specifically evaluated detailed outcome in relation to the technical constraints imposed by the design of the ligating device which influences the effectiveness of EVL in controlling acute variceal bleeding and, in particular, achieving *complete* eradication of varices, a problem conceptually more applicable to endoscopic banding than sclerotherapy. This prospective study, based on a protocol-driven standardized EVL technique, assessed the efficacy of EVL in controlling acute variceal bleeding, preventing variceal recurrence and rebleeding and achieving complete eradication of oesophageal varices in a cohort of patients who presented with their index variceal bleeding event.

PATIENTS AND METHODS

Consecutive adult patients with endoscopically proven BOV between January 2000 and December 2018 were assessed. Only patients who received their first emergency and all subsequent EVL procedures in the unit were included in the study. Patients who had received sclerotherapy or had endoscopic treatment initiated elsewhere were excluded from the study group and the analysis. The outcome of all endoscopic treatments, both emergency and subsequent elective therapy, was analysed to assess the efficacy of EVL in both acute variceal bleeding control and long-term efficacy.

Data extraction

All data were entered prospectively on a bespoke computer programme by a dedicated research and data manager. Outcome data included the efficacy of EVL in controlling acute bleeding, recurrent oesophageal or gastric variceal bleeding, variceal eradication success, the need for salvage TIPS placement and overall survival. Data were analysed on 28 February 2020.

Study endpoints

The primary endpoints of the study were (i) effective endoscopic control of the index variceal bleeding event, (ii) success in achieving complete variceal eradication as defined in the analysis criteria, (iii) variceal recurrence, (iv) variceal rebleeding, (v) overall all sources rebleeding, and (vi) survival. Secondary endpoints were (i) time to eradication calculated from the first EVL session (ii) number of banding sessions and (iii) endoscopic-related complications.

Acute bleeding management and technique of variceal ligation

Details of the acute bleeding management protocol have been presented in Chapters 5 and 9. Diagnostic endoscopy and EVL were performed urgently as soon as the patient was stable, using either fiberoptic endoscopy (model GIF 1T20 or K10; Olympus Corp, Lake Success, NY) during the first decade of the study or video-endoscopy during the last decade. Endoscopic banding devices used during the study period included the Saeed Multi-band Ligator (Cook Endoscopy, Winston-Salem, North Carolina), and the Speedband Superview Super 7 Multiple Band Ligator (Boston Scientific Corp, Natick, Mass). During endoscopy for the sentinel bleed and subsequent acute bleeds, a band was applied first to the bleeding varix and then proximally in a helical fashion for approximately 10 cm to the remaining varices, regardless of size.

Patients underwent regular EVL until complete variceal eradication which was defined as disappearance of varices. In a subcategory of patients, residual varices were either too small or insufficiently pliable to be suctioned into the banding device to allow secure deployment of a band to the varix. In this group further band ligation was not technically possible and safe and complete

eradication was therefore not pursued. Full details of the variceal ligation technique have been published previously. After the initial EVL session during the index admission to hospital, subsequent variceal ligation procedures were undertaken at two-week intervals as an outpatient until the varices were eradicated or unsuitable for continued ligation. Surveillance endoscopy was performed at 3 and 6 months and then annually to identify recurrence of varices and repeat EVL performed whenever technically feasible. All patients were given non-selective β -blockers (NSBB) during follow-up unless specifically contra-indicated.

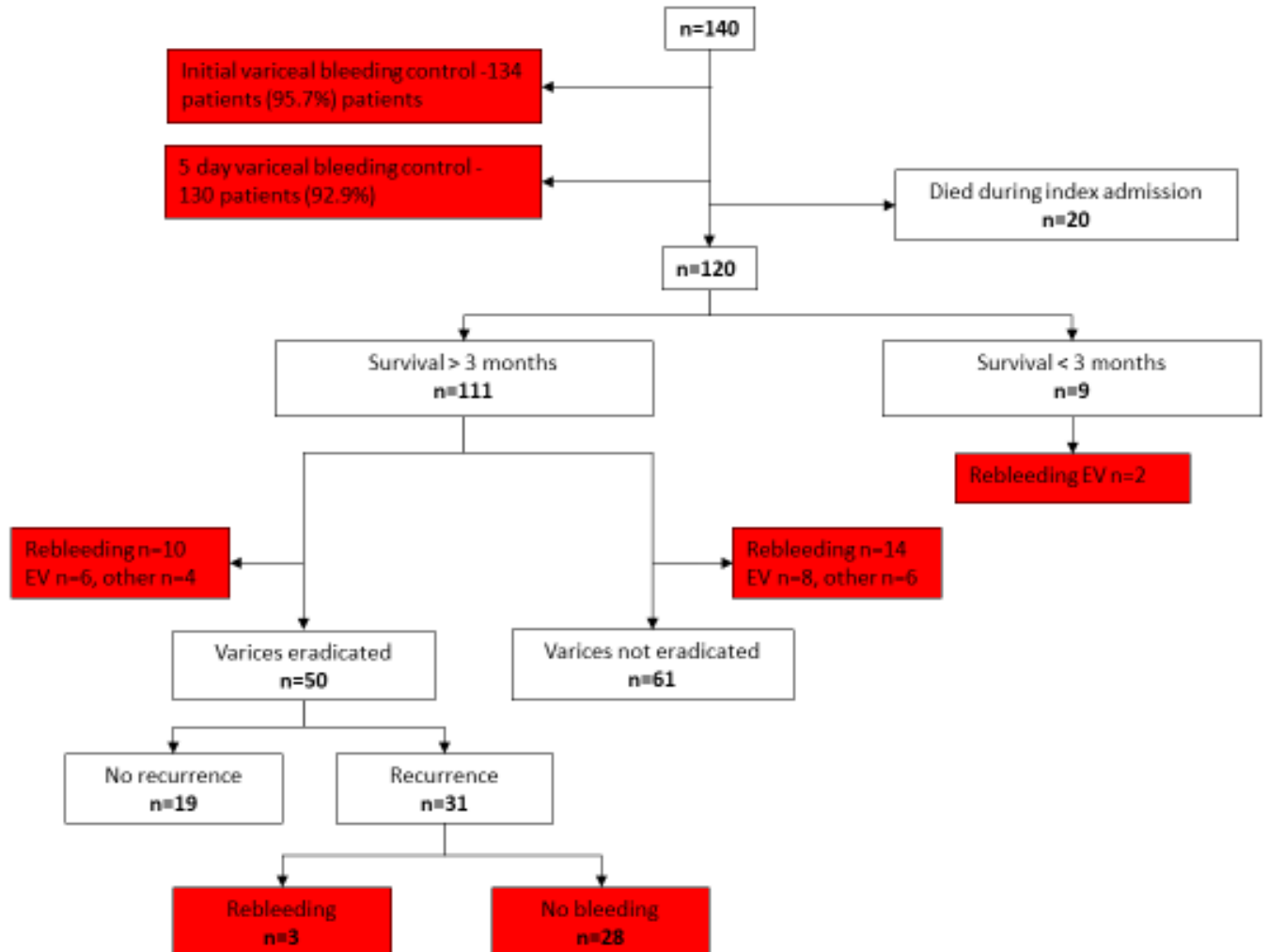
Rebleeding

Baveno criteria were used to define 5 day and 6-week failure to control bleeding (de Franchis, 2015). Any recurrent bleeding episode after the first variceal ligation session or subsequently between scheduled treatment sessions was investigated by emergency endoscopy and treated according to endoscopic findings. Additional variceal ligation was undertaken if bleeding was due to residual or recurrent varices. Other sources of bleeding, such as gastric varices, portal hypertensive gastropathy, peptic ulcers or erosive gastritis were included in the definition of rebleeding and treated on their merits. Eradication of varices was defined as the absence of oesophageal varices on repeat endoscopic examination during follow-up visits.

Data analysis

The Student t-test and χ^2 test were used when appropriate and the Kaplan–Meier method was used to estimate the cumulative incidence of re-bleeding and actuarial survival. Differences in survival in the three Child-Pugh grades were analysed using the log-rank test. A p value <0.05 was considered significant. SAS System Package version 9.2.1 software (SAS Systems International, Cary, North Carolina, USA) was used for statistical analysis. Data were censored at the time of the last clinic or endoscopy visit, TIPS placement or death. Ethical and institutional review board approval was obtained before study initiation and data analysis.

Figure 12.1. Flow diagram showing outcome after the first variceal bleed in 140 patients treated by emergency EVL



RESULTS

The 140 patients (100 men, 40 women, median age: 50 years; range: 21-84 years) included 32 Child-Pugh grade A, 48 grade B and 60 grade C patients when assessed on first admission to hospital (Table 12.1). The underlying diagnoses were alcoholic cirrhosis n=75, (53.6%), hepatitis B infection n=13, (9.9%), cryptogenic cirrhosis n=13, (9.9%), hepatitis and alcohol n=9 (6.4%), NAFLD n=8 (5.7%), schistosomiasis n=7 (5%), and portal vein thrombosis n=5 (3.6%). The remaining ten patients had autoimmune hepatitis (n=3), hepatitis C (n=2), and one each of

granulomatous hepatitis, myelofibrosis, Budd-Chiari, chronic active hepatitis and PSC. The 140 patients received 160 emergency and 298 elective EVL procedures during a total of 928 endoscopy sessions.

Control of bleeding during the index endoscopic procedure:

Acute bleeding was successfully controlled by EVL in 134 of 140 patients (95.7%) during the index endoscopic procedure. In six patients acute bleeding could not be controlled by EVL and a balloon tube was inserted for immediate control. A further four patients rebled from varices within 5 days after the index endoscopy. Cumulative 5-day failure to control bleeding was 7.1% (n=10; C-P grade A n=0, grade B n=1, grade C n=9). These ten patients required 11 additional endoscopic banding sessions and four patients with recalcitrant variceal bleeding required a salvage TIPS.

Index admission mortality:

The index in-hospital admission mortality was 14.2% (n=20) with a median survival of 8 days (range 1-44 days). Ten patients died of multi-organ failure (MOF) including two of the four patients who had a salvage TIPS. A further seven patients died of progressive liver failure, another as a result of advanced HCC and two elderly vasculopathic patients each died of a myocardial infarction. The index admission mortality for the 32 Child-Pugh A patients was 0, the 48 Child-Pugh B patients 2.1% and the 60 Child-Pugh C patients 31.7% (19 of 60 patients).

Rebleeding after the index admission

Overall, 26 (21.7%) of the 120 surviving patients had 31 subsequent rebleeding episodes after discharge from hospital. Two of these patients survived less than 3 months (Figure 12.1). Sixteen patients had 21 OV rebleeding episodes which were successfully treated with emergency EVL. The 6-month OV specific rebleeding incidence was 8.3% (n=10 patients), 12 months 12.5% (n=15), 2 years 12.5% (n=15) and beyond 2 years the total cumulative rebleeding rate after initial index control was 13.3% (n=16). The remaining ten patients had bleeding from other sources which included gastric varices (n=3), gastric ulcers (n=4), duodenal ulcer (n=1), oesophagitis (n=1), Mallory-Weiss tear (n=1). The 6-month overall all sources rebleeding incidence was 13.3%

Table 12.1 Number of banding procedures and time to eradication of varices

Child-Pugh grade	Number of patients	Survival > 90 days	Number eradicated	Number of banding procedures mean (range)	Months to eradicate mean (range)	Number recurred
A	n=32	32	15	3 (1-13)	15 (1-55)	9
B	n=48	44	18	2 (1-12)	4 (1-29)	12
C	n=60	35	17	2 (1-5)	3 (1-47)	10
Total	n=140	111	50	2 (1-13)	5 (1-55)	13

Table 12.2 Rebleeding after index admission in 120 surviving patients

	Overall bleeding from all sources		Bleeding from oesophageal varices	
	Patients	Bleeding events	Patients	Bleeding events
<6 months	16 (13.3%)	22	10 (8.3%)	16
6-12 months	21 (17.5%)	28	15 (12.5%)	20
1- 2 years	25 (20.8%)	30	15 (12.5%)	20
> 2 years	26 (21.7%)	31	16 (13.3%)	21
Overall	26 (21.7%)	31	16 (13.3%)	21

Table 12.3 Cumulative survival by Child-Pugh grade

Child-Pugh Grade	Number of patients	1 year survival	3 year survival	5 year survival	10 year survival
A	n=32	30 (93.7%)	29 (90.6%)	29(90.6%)	25 (78.1%)
B	n=48	40 (83.3%)	36 (75%)	34 (70.8%)	31 (64.5%)
C	n=60	30 (50%)	26 (43.3%)	21 (35%)	17 (28.3%)

(n=16 patients), 12 months 17.5% (n=21), 2 years 20.8% (n=25) and beyond 2 years the total cumulative rebleeding rate after initial index control was 21.7% (n=26) (Table 12.2).

Eradication of varices:

Eradication was achieved in 50 of 111 patients (45%) who survived longer than 3 months, after a median of 2 banding procedures (range 1 to 13), during a median of 6 months, (range 0.5 to 55 months) (Table 12.2). OV remained eradicated in 19 (C-P grade A n=6, grade B n=6, grade C n=7) patients with a median follow-up from eradication of 25 months (range 4 to 112 months). Seven of the 19 patients died after a median survival of 44 months (range 4-112 months).

Recurrent bleeding after variceal eradication:

Three of the 31 patients with recurrent OV after eradication presented with variceal rebleeding at 3, 4 and 25 months respectively and were successfully treated with EVL.

Varices not eradicated:

The 61 patients whose OV were not eradicated had a total of 224 banding procedures (median 5 banding procedures, range 1-11) during a mean of 25 months. Twenty three of the 61 patients died (18 due to progressive liver failure, 3 with MOF aggravated by recurrent BOV and 2 due to hepatorenal failure) at a median of 23 months (range 3-103 months). The remaining 38 patients were followed up for a median of 6 months (range 0.5-99 months). In 41 patients that had at least 4 banding sessions OV reduced in size to either grade 1 (n=25) or grade 2 (n=16) none of whom rebled despite no further EVL. This group in whom EVL was not technically possible were regarded as “functional eradication” as results were comparable to those with complete eradication.

Oesophageal complications:

Oesophageal stricturing at the banding site was noted in 16 patients during a follow-up endoscopy, none of which required oesophageal dilatation for relief of symptoms and resolved after passage of the endoscope.

Survival analysis:

During a median follow-up period of 42 months (range 9-220 months) 69 (49.3%) of the 140 patients died (mean: 6.7 months, range 0.03-141.7 months). Liver failure (n=46) was the most common cause of death followed by MOF in 14 patients. The cumulative survival of all 140 patients by life table analysis was 71.4% at 1 year, 65% at 3 years, 60% at 5 years and 52.1% at 10 years. Survival according to C-P grading is presented in Table 12.3.

DISCUSSION

In this study the efficacy of EVL was evaluated in a large cohort of consecutive portal hypertensive patients using specific and validated endpoints including control of initial bleeding event and subsequent variceal eradication, rebleeding and recurrence. Acute control of active variceal bleeding was highly successful, and haemostasis was achieved in 95.7% of patients with minimal banding morbidity. However, varices were *completely* eradicated in only 45% of patients who survived more than 3 months. Furthermore, recurrent varices developed in 62% of patients in whom varices had been eradicated and 9.7% of these had further variceal bleeding. Overall, 81% of patients in this study had bleeding that was effectively controlled during the index banding procedure and, after repeat banding, never bled again from oesophageal varices. However, the remaining 19% of the cohort had refractory and complicated variceal bleeding and required either balloon tamponade during the index endoscopy (4%) or rebled during the initial hospitalisation (3%) or rebled subsequently (12%) over the next 24 months from residual or recurrent oesophageal varices. As EVL is now universally regarded as the endoscopic method of choice for treating OV (Dai, 2015) the data in this study are relevant and pertinent to current endoscopic variceal management and emphasize several important and unresolved issues related to the role of EVL in achieving haemostasis in actively bleeding varices and achieving variceal eradication to prevent rebleeding (Tripathi, 2015; Fortune, 2017; Garcia-Tsao, 2017).

Experts agree that EVL requires a high level of manipulative skill and mature judgement, especially when applying the bands during active variceal bleeding (Baron, 2009). Despite initial scepticism and concerns that EVL would prove less effective than sclerotherapy in achieving control of actively bleeding varices because of the visual constraints imposed by blood or clot filling the cap during profuse bleeding thus obscuring vision and limiting accurate band deployment, there were very few failures of acute haemostasis in this study. In three small non-randomized studies (Saeed, 1997; Hou, 2000; El-Saify, 2005), active variceal bleeding control was reported in 100% of patients. Patient numbers in these studies, however, were small and there was no consistency in the definition of duration of control of active bleeding. In an updated analysis of 17 prospective RCTs comparing EVL with sclerotherapy, bleeding variceal control with EVL ranged from 86% to 100% and was significantly better than IST in 2 (Lo, 1997; Villanueva, 2006) of 17 RCTs (Table 12.4). However, the reported efficacy of EVL in these RCTs varied widely due to arbitrary and inconsistent definitions of bleeding control (Krige, 2020).

The incidence of variceal rebleeding after EVL in RCTs ranges from 0% to 36% (Table 12.4). In a meta-analysis (Dai, 2015) of 14 RCTs, the overall rebleeding rate for EVL patients was 21.7% compared to an earlier analysis of RCTs which showed a median rebleeding rate of 32% (D'Amico, 1995). However, the calculations and denominators in many papers are not clearly defined and lack adherence to uniform standard definitions of rebleeding including time periods, whether overall or confined to variceal bleeding, or uncontrolled, or during the first admission or during long-term follow-up. In addition, there is non-uniformity among different trials in the definition of recurrent bleeding which may include oesophageal, gastric and ectopic varices and non-variceal sources (portal hypertensive gastropathy, treatment-induced or peptic ulcer) (Hou, 1995; Sarin, 1997). In this study these criteria were defined and the three specific and crucial time periods analyzed. The most common source of recurrent bleeding in the study patient cohort during the early phase after initiation of endoscopic therapy, and before variceal eradication, was from patent residual varices, which occurred in two-thirds of bleeding episodes while one-third

rebled from other sources. The relatively wide variations in the rates of recurrent bleeding may be in part due to technical differences among studies, such as variations in the interval between sessions or in the number of bands placed during each session. Among different trials, there are differences in the population characteristics, such as the cause or the severity of portal hypertension, or in the definition of end points such as recurrent bleeding and the calculation of recurrence i.e. the percentage of only those who recur or of patients alive at the time or the total cohort (Hou, 1995).

Current AASLD/ACG guidelines emphasize total eradication of all varices as the desired endpoint of EVL (Tripathi, 2015; Garcia-Tsao, 2023). Similarly, the reported incidence of variceal eradication varies widely, ranging from a high of 95% in RCT to a low of 55% (Table 12.4). A plausible explanation is the likely inconsistent definitions used and in some reports the definition of variceal eradication included varices too small to be ligated. The wide variation in rates may be related partly to different treatment protocols such as different treatment intervals, number of bands applied per session and selective banding of OV in some centres which band only grade 3–4 OV (Baroncini, 1997; Sarin, 1997). Ultimately the results of any long-term banding study are influenced by the diligence and regularity of follow-up endoscopy and the meticulousness and the reproducibility of the methodology and accuracy with which residual variceal size is recorded. There is increasing recognition that two important limitations of long-term EVL are the number of varices that are resistant to *complete* eradication and the substantial variceal recurrence rate after eradication. Both limitations are influenced by the design and mechanism of ligation. Experienced endoscopists know that EVL becomes increasingly difficult as varices decrease in size (Ray, 2019; Kim, 2018). Small varices are difficult to ligate effectively for two technical reasons. Grade I and 2 varices do not have sufficient variceal substance to provide purchase and grip for the constricting elastic band. In addition, mucosal fibrosis from prior banding episodes further limits mucosal pliability and the ability to suck enough tissue into the cap, thus preventing successful band

application. Of note are the number of RCTs which report higher variceal recurrence rates in patients undergoing EVL (Table 12.4).

The number of endoscopy sessions required to achieve variceal eradication has varied considerably within reported series and between centres (Table 12.4). While there is some evidence to suggest that the methodology and technique of EVL might affect the number of sessions necessary to achieve obliteration, this alone does not explain the substantial differences found between patients. Furthermore, the reproducibility, method and accuracy with which residual variceal size is recorded is dependent on the degree of insufflation used during endoscopy. Prolonged or over-inflation during endoscopy tends to flatten varices which then appear misleadingly small. Another factor influencing reporting and compounding the accuracy of data collection is the lack of a universally acceptable and standard classification to report variceal size, using either small, medium or large or grades 1-4 or 1-5. A number of studies, including a meta-analysis by Ko indicated that EVL achieved variceal eradication rates between 79% and 100% (Aggeletopoulou, 2018; Branch-Elliman, 2015; Cho, 2016; Ko, 2012).

A major drawback of EVL is the higher propensity to variceal recurrence when compared to IST in RCTs (Table 12.4). Although new varices formed following initial eradication in 31 of 50 (62%) patients, this was associated with rebleeding in only 3 (9.7%) patients. Variceal recurrence in other studies ranged between 8% and 48% after banding (Hou, 2000; Cho, 2016; Ali, 2017). More recent studies find recurrence rates of 12% to 36% (mean 25%) using EVL and NSBB (Sarin, 1997; Baroncini, 1997; Avgerinos, 1997; de la Pena, 1999). Interpretation of these results is complicated by the differences in lengths of follow up, definitions of variceal recurrence, different medications and dosage used and aetiology of portal hypertension (Krige, 2020). Accumulated evidence suggests that patent para-oesophageal and peri-oesophageal variceal feeder vessels predisposes to variceal recurrence. Data from RCTs show lower recurrence rates after IST,

probably because sclerotherapy induces fibrosis and eradication of perforating veins in contrast to band ligation, which does not affect collateral vessels in the deeper layers (Jeong, 2017).

The current study had several limitations. Firstly, as the study was conducted in a single-centre academic tertiary referral centre with experienced on-call endoscopists and staff available around the clock, patient selection and treatment bias may occur as similar advanced interventions may not be available or replicated in smaller hospitals. Secondly, half the patients in the study were Child-Pugh grade C with hepatic decompensation associated with the highest mortality and our results cannot be generalized to all other patient populations. Thirdly, the number of patients with failure was too small to identify specific criteria which may influence endoscopic failure. The use of an inclusive “all-cause” definition for rebleeding was applied to minimize bias found in previous definitions which often excluded non-variceal causes of re-bleeding. This study did not assess the important aspect of the economic consequences of variceal recurrence and rebleeding on the usage and cost of medical resources.

The strengths of this study are derived from the implementation of a modern protocol driven and standardized EVL technique in a specialist endoscopy centre. To provide the highest possible level of uniformity and to minimise differences in the zero-time entry, only patients who received their initial and subsequent treatment in our unit were included. The study design minimized possible biases that may have arisen from patient selection, referral practices and local variations in treatment strategies. The use of rebleeding and death as the main outcomes provided consistent and objective endpoints in the study. Unlike other studies which included non-consecutive patients, incomplete reporting of inclusion and exclusion criteria and have incomplete follow-up or inclusion of patients at differing disease stages without separate analyses, our study design avoided these pitfalls by excluding non-measurable biases. The robustness of this study was enhanced by the prospective data collection and an inception cohort at a well-defined stage

during cirrhosis thereby providing a homogenous study population and avoiding the error of overfitting which has influenced previous studies (Krige, 2020).

In conclusion, this study confirms that EVL provides the optimal endoscopic method both for control of acute bleeding and for the long-term treatment of varices despite the higher tendency for recurrence. Consistent with previous reports EVL in this study was safe with low procedure-related complication rates. While complete visual eradication of varices is achievable in IST and has consistently been used as the endpoint for endoscopic variceal intervention, this result may not be applicable in EVL. As alluded to above, the inherent attributes of EVL and IST are dissimilar and complete eradication may not be achievable in all patients undergoing EVL. Overall four-fifths of patients had EV that were easily managed and responded to β -blockers and EVL with no further bleeding after the initial index intervention. The remaining one-fifth however were complicated and had bleeding that was difficult to control in the short and longterm despite being on combination therapy. We have identified a subgroup of patients with small (Gr 1 and 2) varices where size and mucosal scarring preclude further safe banding. Importantly we have shown that these patients have “stable varices” with no rebleeding or progression which resulted in “functional eradication” despite the presence of residual small visible varices. The results of this study should stimulate further research to optimize robust and objective endpoints for reporting of EVL which are likely to differ from the historical outcomes reported in previous RCTs. The elusive Holy Grail of endoscopic variceal banding remains the attainment of long-term bleed-free survival.

Table 12.4 Summary of published randomized controlled trials of EVL vs IST

Author	Year	Number of patients	Number in each group		Control of bleeding		Varices eradicated		Eradication sessions		Rebleeding		Major complications		Variceal recurrence		Survival	
			EVL	IST	EVL	IST	EVL	IST	EVL	IST	EVL	IST	EVL	IST	EVL	IST	EVL	IST
Stiegmann	1992	129	64	65	86%	77%	55%	56%	4	5	36%	48%	2%	22%	33%	50%	72%	55%
Laine	1993	77	38	39	89%	89%	59%	69%	4.1	6.2	24%	31%	24%	56%	-	-	89%	85%
Gimson	1993	103	54	49	91%	92%	82%	71%	3.4	4.9	30%	53%	69%	65%	-	-	52%	18%
Lo	1995	120	61	59	94%	80%	74%	63%	3.8	6.5	11%	36%	3.3%	19%	-	-	84%	68%
Hou	1995	134	67	67	100%	88%	87%	79%	3.5	4.6	18%	33%	4%	22%	48%	30%	79%	84%
Sarin	1997	95	47	48	86%	80%	94%	94%	4.1	5.2	6.4%	20.8%	45%	50%	28.7%	7.5%	93%	89%
Baroncini	1997	111	57	54	-	-	93%	93%	3.5	4.0	16%	19%	11%	31%	30%	13%	79%	78%
Avgerinos	1997	77	37	40	-	-	95%	98%	3.7	5.8	27%	48%	35%	60%	31%	44%	80%	79%
Lo	1997	71	37	34	97%	76%	-	-	-	-	17%	33%	5%	29%	-	-	81%	65%
Siqueira	1998	40	20	20	-	-	90%	100%	3.1	3.7	0%	5%	-	-	0%	0%	100%	95%
De la Pena	1999	88	42	46	-	-	79%	71%	5.3	6.6	31%	50%	14%	41%	47%	23%	81%	78%
Masci	1999	100	50	50	-	-	88%	82%	3.4	5.3	12%	42%	18%	38%	32%	27%	80%	78%
Fakhry	2000	84	43	41	94%	94%	-	-	2.8	4.8	16%	15%	2%	65%	21%	20%	93%	93%
Zargar	2005	73	37	36	100%	83%	95%	92%	3.7	7.7	3%	19%	3%	22%	11%	9%	-	-
Villanueva	2006	179	90	89	96%	85%	-	-	-	-	7%	12%	4%	13%	-	-	87%	79%
Luz	2011	100	50	50	92%	96%	-	-	-	-	22%	14%	-	-	-	-	77%	80%
Ali	2017	124	60	64	100%	100%	87%	80%	-	-	23%	28%	10%	27%	-	-	78%	72%

EVL endoscopic variceal ligation, IST injection sclerotherapy, Bold colour highlighted comparisons are significant **p<0.05**

CHAPTER 13

Study No 4

FACTORS INFLUENCING IN-HOSPITAL MORTALITY IN CIRRHOTIC PATIENTS WITH RECALCITRANT VARICEAL BLEEDING UNDERGOING SALVAGE TIPS AFTER FAILED ENDOSCOPIC INTERVENTION.

Introduction

Acute variceal bleeding is the most serious acute life-threatening complication of portal hypertension, especially in patients with hepatic decompensation (Tapper, 2023). Rapid and sustained control of bleeding is the immediate priority but despite conventional treatment, including urgent fluid and blood resuscitation, vasoactive drugs, prophylactic antibiotics, and endoscopic intervention, treatment fails in up to 10% of patients who continue to bleed (Tripathi, 2015). In this high-risk group, further immediate options include a second attempt at endoscopic intervention and balloon or stent tamponade to temporarily control variceal bleeding. In the past patients in whom active bleeding persisted despite these treatments required surgical intervention with either a portocaval shunt or a gastric devascularization and oesophageal transection as a salvage operation which both had substantial morbidity and mortality implications (de Franchis, 2015).

Technical advances in interventional radiology have led to the evolution and implementation of transjugular intrahepatic portosystemic shunting (TIPS) as a minimally-invasive salvage alternative to surgery in patients with uncontrolled variceal bleeding (Deltenre, 2015). TIPS provides a percutaneous radiologically

created shunt between portal and hepatic veins which reduces portal vein pressure by diverting blood from the portal to the hepatic and systemic venous system through a low-resistance intrahepatic stent (Manning, 2021). TIPS is now established as the preferred rescue or salvage procedure for patients who have either uncontrolled or severe recurrent variceal bleeding unresponsive to medical and endoscopic treatment (Weichselbaum, 2022; Li, 2023). This study investigated the outcome of salvage TIPS (sTIPS) in patients who had life-threatening variceal bleeding resistant to standard treatments to identify clinical and laboratory risk factors predicting in-hospital death during the index admission.

Methods

This study is a retrospective cohort analysis of adult patients treated in the Surgical Gastroenterology Unit (SGU) at Groote Schuur Hospital and the University of Cape Town Academic Hospital, who underwent a sTIPS for life-threatening uncontrolled or severe refractory variceal bleeding between August 1991 and November 2020. The study followed the “Strengthening the Reporting of Observational Studies in Epidemiology” (STROBE) guidelines for reporting observational studies (von Elm, 2008). Baseline demographic, clinical and endoscopic data and biochemical variables were collected on admission to the Unit and the anonymized and de-identified information was later retrieved from a prospectively maintained faculty ethics approved oesophageal variceal registry (Table 10.1). In addition, the causes of portal hypertension and infection with hepatitis B or hepatitis C were documented. The model for end-stage liver disease (MELD) score, sodium MELD (MELD Na) score, Child-Pugh (C-P) score and grade (A, B, or C) were calculated.

Details of the acute bleeding management protocol and the endoscopic interventional techniques used in our unit have been published previously. An inotrope infusion was used when necessary to maintain a mean arterial pressure >65 mmHg. Urgent diagnostic endoscopy was performed to identify the source of bleeding as soon as the patient was adequately resuscitated. If bleeding oesophageal varices were encountered, injection sclerotherapy (IST) or endoscopic variceal band ligation (EVL) was used (Krige, 2023). In patients with uncontrollable bleeding a Sengstaken-Blakemore balloon tube or an oesophageal stent was inserted for tamponade. Endotracheal intubation was used for airway protection when necessary and further endoscopic procedures were performed within 24 hours. In patients who had uncontrolled variceal bleeding or those with persistent refractory bleeding despite endoscopic intervention, sTIPS was used as a rescue treatment.

Transjugular intrahepatic portosystemic shunt was performed under general anaesthesia as soon as possible after the diagnosis of active uncontrolled variceal bleeding (Krige, 2019). Imaging was reviewed to exclude portal, splenic or hepatic vein thrombosis or vascular anomalies and duplex doppler US was repeated before the TIPS to confirm patency. If large-volume ascites was present, pre-procedural paracentesis was performed. An expandable 10 mm diameter uncovered metal Wallstent (Boston Scientific, Marlborough, MA, USA) of variable length from 49 to 90 mm was placed to maintain patency of the radiologically-created shunt between the portal and hepatic veins (Krige, 2019).

Statistical methods

The primary end point of this study was in-hospital mortality. Secondary end points were control of variceal bleeding after sTIPS and variceal rebleeding after initial

control by sTIPS. The characteristics of the patients are presented as median (range) or mean ($\pm$ standard deviation) and as numbers (percentages) for categorical data. The Fisher's exact test was used for comparing dichotomous variables, and the nonparametric Mann–Whitney rank-sum test for continuous variables. All tests were two-sided. The variables listed in Table 1 were considered as potential prognostic factors associated with mortality and were tested using bivariate analysis. These factors, when significantly correlated with the primary end point, were evaluated in a univariate logistic regression analysis to identify independent predictors of survival. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using a biostatistical program package (*StatView 5.0 software*).

Ethical considerations

The study protocol was approved by the Human Research Ethics Committee (HREC Ref No. 120/2019) of the University of Cape Town and the research was conducted in accordance with the Declaration of Helsinki.

Results

A total of 564 patients with variceal bleeding were admitted to the SGU during the study period. In 530 patients (94%), bleeding was controlled by vasoactive medication and endoscopic intervention. In 34 patients (6%) bleeding was uncontrolled or persistent despite endoscopic intervention and underwent urgent TIPS and constituted the study population. Eleven of the 34 patients had endoscopically uncontrolled variceal bleeding and 23 had severe recurrent and refractory bleeding after initial endoscopic control.

The demographic, clinical and endoscopic data and biochemical variables are summarized in Table 13.1. The 29 men and five women had a median age of 52 years (range 31-80). The causes of portal hypertension were alcohol (n=24), haemochromatosis (n=2), chronic hepatitis B infection (n=2), chronic hepatitis C infection (n=1), NASH (n=2), drug-induced (n=2), or sarcoid (n=1) -related cirrhosis. Before TIPS 19 patients had a median of three (range:1-9) IST sessions, 20 had a median of two (range:1-6) EVL sessions with a median of 10 bands placed per session. Five patients had both IST and EVL. Median units of blood transfused before sTIPS was six (range:3-12), and 14 patients required either balloon tamponade (n=12) or placement of a Danis stent (n=2) to temporarily control bleeding. Eleven patients required endotracheal intubation and ventilation and nine required inotropic support.

TIPS was placed successfully in all patients and bleeding was controlled acutely in 32 of the 34 (94%) patients. Bleeding persisted in two patients (6%) despite a patent TIPS on repeat US-doppler examination. A further patient developed recurrent bleeding in hospital during the index admission after initial control of bleeding by TIPS. Overall control of bleeding by sTIPS was achieved in 31 of 34 (91%) patients.

Ten patients (29%) died in hospital (mean 4.8, range 1-10 days) of progressive liver failure (n=4), MOF (n=2), alcoholic cardiomyopathy (n=2) and uncontrolled gastric (n=1) or oesophageal (n=1) variceal bleeding. Mortality in C-P grade A was 0%, C-P grade B 16% and C-P grade C 58%. In patients who died the median C-P score was 11, (range 7-13), median MELD score was 18 (range 11-29) and median MELD Na score was 25 (range 11-33). Nine of the 12 (75%) patients who required balloon

Table 13.1. Bivariate analysis of factors associated with mortality

Risk Factor	Total Cohort (n=34)	Survived (n=24)	Died (n=10)	p-Value
Age, mean (SD)	52 ($\pm$ 11.6)	50 ($\pm$ 10.5)	57 ($\pm$ 12.9)	0.107
Sex				
Male	29	22	7	0.104
Female	5	2	3	
Cause of cirrhosis				
Alcohol related	22	15	7	0.938
Non-alcohol related	12	9	3	
Child-Pugh grade				
A	3	3	0	0.022
B	19	16	3	
C	12	5	7	
Child-Pugh score, mean (SD)	8.9 ($\pm$ 1.8)	8.2 ($\pm$ 1.8)	10.6 ($\pm$ 2.0)	0.001
MELD, median (range)	14.5 (7-29)	11.5 (7-24)	17.5 (11-29)	0.007
MELD-Na, median (range)	15.5 ($\pm$ 7-33)	13 (7-35)	25 (11-33)	<0.001
Bilirubin, median (range)	31 (8-409)	33.5 (8-152)	17.5 (9-409)	0.405
Albumin, mean (SD)	30.7 ($\pm$ 5.8)	32 ($\pm$ 5.1)	27.7 ($\pm$ 6.4)	0.020
INR, median (range)	1.4 (1-4.1)	1.3 (1-2)	1.6 (1.3-4.1)	0.009
Na, median (range)	136 (126-140)	136 (130-140)	127 (126-138)	0.002
Creatinine, median (range)	95 (49-326)	91.5 (49-126)	70 (64-326)	0.001
Encephalopathy				
1	12	9	3	0.896
2	15	10	5	
3	7	5	2	
Ascites				
1	13	12	1	0.009
2	10	8	2	
3	11	4	7	
Units blood received, median (range)	6 (3-13)	4 (3-12)	10 (4-13)	0.000
Balloon tube or stent				
Yes	14	5	9	<0.001
No	20	19	1	
Endotracheal intubation				
Yes	10	2	9	<0.001
No	24	22	1	
Inotrope requirement				
Yes	9	0	9	<0.001
No	25	24	1	

Table 13.2. Logistic Regression Analysis

Risk Factor	Univariate Logistic Regression (unadjusted)		
	Odds Ratio	95% CI	p-Value
Age	1.06	0.98 - 1.13	0.111
Sex	0.21	0.29 – 1.53	0.125
Cause of cirrhosis	1.4	0.28 – 6.83	0.677
Child-Pugh grade	8.0	1.60 – 40.4	0.011
Child-Pugh score	1.8	1.14 – 2.87	0.011
MELD	1.22	1.04 – 1.43	0.010
MELD-Na	1.27	1.08 – 1.5	0.003
Bilirubin	1.00	0.99 – 1.01	0.390
Albumin	0.85	0.72 – 1.00	0.058
INR	14.5	0.97 – 218	0.052
Na	0.66	0.51 – 0.87	0.003
Creatinine	1.06	1.01 – 1.11	0.009
Encephalopathy			
1			
2	1.5	0.27 – 8.13	0.638
3	1.2	0.14 – 9.76	0.865
Ascites			
1 – ref			
2	2.9	0.23 – 38.8	0.401
3	20.9	1.94 - 227	0.012
IST	1.15	0.83 – 1.59	0.373
EVL	0.81	0.56 – 1.19	0.303
IST plus EVL	1.75	0.24 – 12.4	0.577
Units of blood received	1.83	1.24 – 2.71	0.002
Balloon tube/oesophageal stent	34.2	3.46 - 337	0.002
Endotracheal intubation	99	7.94 - 1233	<0.001
Inotrope requirement	134	(15.3 – infinity)	<0.001
Uncontrolled variceal bleeding	28	3.92 - 199	0.001

tamponade died, while all nine (100%) who required inotropic support died. Analysis of the two subcategories shows that eight of 11 (73%) patients who had endoscopically uncontrolled variceal bleeding and required a transfusion of ≥ 8 units of blood during index hospital admission died, while two of 23 (8.7%) patients who had refractory variceal bleeding died.

On bivariate analysis, factors associated with death after sTIPS were C-P score ≥ 10 ($p=0.006$), MELD-Na ≥ 22 ($p<0.001$), ≥ 8 units of blood transfused ($p<0.001$), Sengstaken tube placement ($p<0.001$), endotracheal intubation ($p<0.001$), inotropic support ($p<0.001$) and endoscopically uncontrolled bleeding ($p<0.001$) (Table 13.2). In an unadjusted univariate logistic regression model the significant predictors of mortality were need for inotrope support (OR=134, $p<0.001$), endotracheal intubation (OR=99, $p<0.001$), endoscopically uncontrolled bleeding (OR=28, $p=0.001$), grade 3 ascites (OR=20.9, $p=0.012$) and C-P grade C (OR=8.8, $p=0.011$).

Discussion

The common characteristics in this high-risk cohort were uncontrolled or refractory variceal bleeding in patients who had portal hypertension and liver decompensation, active variceal bleeding at the time of endoscopy, failure of standard medical and endoscopic intervention to control bleeding and required urgent sTIPS placement as a life-saving procedure. TIPS was inserted successfully in all patients and overall control of bleeding was achieved in 91% of patients with 71% in-hospital survival after sTIPS. Mortality correlated with C-P grade and was 16% in grade B and 58% in grade C. Factors associated with death on bivariate analysis were C-P score ≥ 10 , MELD-Na ≥ 22 , ≥ 8 units of blood transfused, Sengstaken tube placement, endotracheal intubation, inotropic support, and endoscopically uncontrolled bleeding. The most significant predictors of mortality in an unadjusted univariate logistic regression model were the need for inotrope support, endotracheal intubation, endoscopically uncontrolled bleeding, grade 3 ascites and C-P grade C.

The prognosis of cirrhotic patients in general and after TIPS in particular depends on residual liver function, the magnitude and duration of the deleterious hepatic and renal consequences of persistent variceal bleeding, the presence of significant comorbidities and the rapidity and efficacy with which emergency treatment is initiated (Tripathi, 2020). The mortality rate in this study population should be interpreted in the context of the poor baseline liver function, 56% of whom were C-P grade B, 35% C-P grade C, and with overall median C-P and MELD scores of nine and 15 respectively. A meta-analysis evaluating sTIPS in patients with cirrhosis and refractory variceal bleeding included 23 studies and 1430 patients found that one third of patients died within the first 6 weeks (Weichselbaum, 2022). Other studies reporting rescue sTIPS for acute oesophageal variceal bleeding have shown mortality rates ranging from 15% to 75% which is significantly higher than in patients undergoing elective TIPS (Vangeli, 2002; Horhat, 2021; Bañares, 2023). In an early study from the Department of Surgery, University of Washington School of Medicine, Seattle, Helton et al. reported a 56% in-hospital mortality rate for patients who were actively bleeding or haemodynamically unstable at the time of the TIPS (Helton, 1993).

The reported mortality associated with TIPS placement varies widely with differing inclusion criteria, timing of TIPS, and the severity of underlying liver disease. Some reports combine the results of patients actively bleeding during TIPS with those of patients who were stable during the procedure. Analysis of patient factors present leading to increased mortality after TIPS placement include failure to control bleeding, C-P C stage, MELD score ≥ 30 , APACHE-II score >20 , haemodynamic instability at the time of the TIPS procedure, use of inotropes, mechanical ventilation,

balloon tamponade, the presence of comorbidities, sepsis, emergency TIPS, hyperbilirubinaemia, lactate ≥ 12 mmol/L, hyponatraemia and renal failure (Horhat, 2021; Bouzbib, 2021; Tzeng, 2009; Heinzow, 2012; Rubin, 1995; Maimone, 2019; Walter, 2021; Azoulay, 2001; Jalan, 1995; Chalasani, 2000; Rajan, 2002; Malinchoc, 2000; Brensing, 2002). Most deaths after emergency TIPS are the consequence of hepatic or multiorgan failure and sepsis and only a minority are due to recurrent variceal bleeding (Patch, 1998).

The results of this study have important implications for patients with major variceal bleeding that cannot be controlled endoscopically. We found a significant correlation between early mortality after TIPS and the need for endotracheal intubation, balloon tamponade and inotrope requirements. It is evident in several studies that as multiple unsuccessful endoscopic attempts are made to stop the bleeding, liver function deteriorates, complications supervene, and outcome worsens. Patients with major variceal bleeding are best managed in a tertiary referral unit with a skilled multidisciplinary team. Patients in whom endoscopic intervention fails to control bleeding should be identified early so that sTIPS can be performed before the deleterious consequences of deteriorating liver function and multi-organ failure occur. Other studies have identified the futility of sTIPS in patients with a C-P score >13 , MELD score ≥ 30 and lactate ≥ 12 mmol/L (Rajesh, 2020; Horhat, 2021).

The data documented must be interpreted in the light of limitations which include the long duration of the study and the relatively small patient numbers, with use of uncovered metal stents, which now have been replaced by covered stents (Krige, 2024). In addition, there may be a selection bias as the unit functions as a tertiary

referral centre for high-risk patients. A major strength of the study is the analysis of real-world data from an unselected cohort of consecutively treated patients by the same team using specific endpoints.

In conclusion, this study shows that although sTIPS controlled variceal bleeding in 94% of patients after failed endoscopic intervention, mortality remained high with 29% in-hospital deaths, especially in uncontrolled bleeding. The most significant predictors of mortality were C-P grade C, grade 3 ascites, inotrope requirement, endotracheal intubation, and endoscopically uncontrolled bleeding. Further effort is needed to reduce the high mortality and morbidity despite successful sTIPS placement. This necessitates early identification of patients unresponsive to medical treatment so that urgent TIPS for portal decompression can be initiated (Krige, 2024).

CHAPTER 14

Study No 5

INTERMEDIATE AND LONG-TERM OUTCOME AFTER SALVAGE TIPS FOR UNCONTROLLED VARICEAL BLEEDING. A STROBE COMPLIANT OBSERVATIONAL STUDY

Introduction

Acute variceal bleeding (AVB) remains the most serious acute life-threatening complication in patients who have portal hypertensive hepatic decompensation. Achieving survival in this high-risk group requires astute multidisciplinary management with urgent control of variceal bleeding, prevention of subsequent rebleeding and support of deteriorating liver function. Standard of care treatment including fluid and blood resuscitation, vasoactive drugs, prophylactic antibiotics, and endoscopic intervention is effective in controlling bleeding in over 90% of patients, but despite optimal management, up to 10% of patients fail initial endoscopic haemostasis and over 20% rebleed within 6 weeks after control of the initial bleed.

In this high-risk group with uncontrolled or persistent life-threatening bleeding, further urgent options include balloon or oesophageal stent tamponade to temporarily control variceal bleeding followed by a further attempt at endoscopic intervention. In patients who do not respond to this hierarchy of interventions, either singly or in combination, mortality rates increase inexorably and the need for a definitive rescue procedure becomes imperative. TIPS has become the preferred salvage intervention in patients who have uncontrolled variceal bleeding unresponsive to all medical and endoscopic treatment and has replaced surgical options in most circumstances. The

success rate of salvage or rescue TIPS in arresting bleeding is over 90% but outcome is burdened by an overall mortality rate that exceeds 30% and may approach 100% in patients who have sepsis, prolonged hypotension, deteriorating liver and renal function and require inotropic support and mechanical ventilation. This study investigated the clinical course and sought to identify factors influencing long-term survival in this high-risk group of patients who required a salvage TIPS (sTIPS) for life-threatening variceal bleeding resistant or intolerant to standard medical treatment.

Methods

This single centre observational retrospective cohort study evaluated patient outcome and survival after sTIPS for uncontrolled or life-threatening refractory variceal bleeding in all adult patients (>18 years) treated in the Surgical Gastroenterology Unit (SGU) at Groote Schuur Hospital and the University of Cape Town Academic Hospital between August 1991 and November 2020. Data analysis was done on 28 February 2022. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies (von Elm, 2008). Baseline demographic, clinical and endoscopic data and biochemical variables were collected on admission to the Unit and the anonymized and de-identified information retrieved from a prospectively maintained faculty ethics approved oesophageal variceal registry (Table 14.1). Survival according to model of end-stage liver disease (MELD), sodium MELD (MELD Na), APACHE II, Child-Pugh scores (C-P) and grade (A, B, or C) were calculated.

Details of the acute bleeding management protocol, endoscopic interventional techniques and TIPS method have been published previously. In patients with exsanguinating bleeding a balloon tube or temporary oesophageal stent was inserted for tamponade and endotracheal intubation was used for airway protection. In patients who, despite endoscopic intervention, had uncontrolled or life-threatening persistent variceal bleeding, an emergency sTIPS was used as a rescue treatment. Transjugular intrahepatic portosystemic shunt was performed under general anaesthesia as soon as possible after uncontrolled variceal bleeding was encountered. An expandable 10 mm uncovered metal Wallstent varying in length from 49 to 90 mm (Boston Scientific, Marlborough, MA, USA) was placed to maintain patency of the radiologically created shunt between the portal and hepatic veins (Krige and Beningfield, 2019). All patients had regular TIPS and vessel Doppler ultrasound assessment for patency during follow-up.

Outcomes

The primary end point was survival after sTIPS placement which was measured at discharge from hospital after the index admission and at 1, 3, and 5 years. Secondary end points were variceal recurrence and rebleeding and the incidence of hepatic encephalopathy post-sTIPS.

Statistical analysis

Normally distributed variables were expressed as mean $\pm$ standard deviation (SD) and compared with Student's T-tests. Non-normally distributed variables were expressed as the medians with interquartile ranges (IQR's) and compared with the Mann-Whitney U-test. Categorical variables were expressed as counts and percentages and compared with the χ^2 or Fisher's exact tests. The variables listed in Table 11.1 were considered as potential prognostic factors associated with mortality

and were tested using bivariate analysis. These factors, when significantly correlated with the primary end point, were evaluated in a univariate logistic regression analysis to identify independent predictors of survival. Survival analysis was performed by Kaplan–Meier method. Patients who died or were lost to follow-up were censored at the corresponding time point. Comparisons between cohorts were performed with the log-rank test. The Cox proportional hazards model was used to compute hazard ratios, with corresponding 95% confidence intervals. Statistical significance was established at $P < 0.05$ for all analyses. Data were analysed using Stata software version 11 (*StataCorp LP, College Station, Texas, USA*).

Ethical considerations

The study protocol was approved by the Human Research Ethics Committee (HREC Ref No. 120/2019) of the University of Cape Town and the research was conducted in accordance with the Declaration of Helsinki.

Results

In 530 of 564 patients (94%) with variceal bleeding treated in the SGU acute bleeding was controlled by standard of care management and endoscopic intervention. In 34 patients (6%) bleeding was uncontrolled or persistent despite endoscopic intervention and underwent urgent sTIPS. Eleven of the 34 patients had endoscopically uncontrolled exsanguinating variceal bleeding necessitating an emergency sTIPS, while 23 had life-threatening refractory bleeding despite endoscopic intervention and underwent an urgent sTIPS. The demographic, clinical and endoscopic data and biochemical variables are summarized in Table 14.1. Median units of blood transfused before sTIPS was six (3-12), and 14 patients required either balloon tamponade (n=12) or placement of a Danis stent (n=2) to temporarily control bleeding. Eleven patients required endotracheal intubation and

Table 14.1 Bivariate Analysis of Factors Associated with In-hospital Survival post sTIPS

Risk Factor	Total Cohort (n=34)	Survived (n=24)	Died (n=10)	p-Value
Age, mean (SD)	52 ($\pm$ 11.6)	50 ($\pm$ 10.5)	57 ($\pm$ 12.9)	0.107
Sex				
Male	29	22	7	0.104
Female	5	2	3	
CP grade				
A	3	3	0	0.022
B	19	16	3	
C	12	5	7	
CP score				
<10	22	19	3	0.006
≥ 10	12	5	7	
MELD Score				
<15	17	15	2	0.057
≥ 15	17	9	8	
MELD-Na Score				
<22	24	22	2	<0.001
≥ 22	10	2	8	
APACHE II Score				
<15	22	21	1	0.000
≥ 15	12	3	9	
Ascites				
1	13	12	1	0.009
2	10	8	2	
3	11	4	7	
Units blood, median (range)	6 (3-13)	4 (3-12)	10 (4-13)	0.000
Balloon tube or stent				
Yes	10	5	9	<0.001
No	24	19	1	
Endotracheal intubation				
Yes	10	2	9	<0.001
No	24	22	1	
Inotrope requirement				
Yes	9	0	9	<0.001
No	25	24	1	

Table 14.2 Long-Term Survival after sTIPS

Score	n	1 year survival	3 year survival	5-year survival
Overall Survival	34	n=19 (55.9%)	n=9 (26.5%)	n=7 (20.6%)
Child Pugh Grade				
A	3	3 (100%)	2 (67.8%)	2 (67.8%)
B	19	12 (63.1%)	5 (26.3%)	4 (21.1%)
C	12	4 (33.0%)	2 (16.7%)	1 (8.3%)
Child Pugh Score				
<10	22	15 (68.2%)	7 (31.8%)	6 (27.3%)
≥10	12	4 (33.3%)	2 (16.7%)	1 (8.3%)
MELD Score				
<15	17	14 (82.4%)	7 (41.2%)	6 (35.3%)
≥15	17	5 (29.4%)	2 (11.8%)	1 (5.9%)
MELD Na Score				
<22	24	18 (75.0%)	8 (33.3%)	6 (25.0%)
≥22	10	1 (10.0%)	1 (10.0%)	1 (10.0%)
APACHE Score				
<15	22	18 (81.8%)	8 (36.4%)	6 (27.3%)
≥15	12	1 (8.3%)	1 (8.3%)	1 (8.3%)

ventilation and nine required inotropic support. TIPS was placed successfully in all patients and bleeding was controlled in 32 of the 34 (94%) patients. Bleeding persisted in two patients (6%) despite a patent TIPS on repeat US-Doppler examination. A further patient developed recurrent bleeding in hospital during the index admission after initial control of bleeding by TIPS. Overall control of bleeding by sTIPS during the index admission was achieved in 31 of 34 (91%) patients.

Ten patients (29.4%) died in hospital (mean 4.8, range 1-10 days) after sTIPS. When stratified according to Child-Pugh grade, in-hospital mortality in C-P grade A was 0%, C-P grade B 16% and C-P grade C 58%. In patients who died in hospital the median C-P score was 11, (range 7-13), median MELD score was 18 (range 11-29) and median MELD-Na score was 25 (range 11-33). Nine of the 12 (75%) patients

who required balloon tamponade died, while all nine patients (100%) who required the combination of inotropic support, balloon tamponade and endotracheal intubation with ventilation died. Analysis of the two subcategories shows that eight of 11 (73%) patients who had endoscopically uncontrollable variceal bleeding, were haemodynamically unstable and required a transfusion of ≥ 8 units of blood during index hospital admission died, while two of 23 (8.7%) patients who had refractory uncontrolled variceal bleeding but were haemodynamically stable died. On bivariate analysis, factors associated with in-hospital mortality during the index admission were Child-Pugh score ≥ 10 ($p=0.001$), MELD-Na ≥ 22 ($p<0.001$), APACHE II score ≥ 15 ($p<0.000$), balloon tube placement ($p<0.001$), endotracheal intubation ($p<0.001$) and inotropic support ($p<0.001$). (Table 14.1).

Substantial morbidity was documented during follow-up after sTIPS placement. Two of 24 patients developed TIPS stent occlusion and required new stent placement. In one of these patients a patent left gastric vein was coiled during new stent placement. One patient had residual gastric varices post-TIPS placement and required endoscopic cyanoacrylate injection for resolution. One patient developed recurrent oesophageal varices during follow-up and had further treatment with band ligation. One patient developed recurrent gastric varices and endoscopically uncontrolled bleeding despite a patent stent and required surgical intervention with a gastric devascularization. Eight of 24 patients had symptomatic and clinically evident encephalopathy which responded to medical treatment without requiring revision of the TIPS stent. Four of the 24 surviving patients who left hospital developed SBP. Three responded to medical treatment but one patient had resistant *Acinetobacter* SBP which precipitated progressive liver failure and death.

Table 14.3. Bivariate analysis of factors associated with in-hospital survival after sTIPS

Risk Factor	Total Cohort (n=34)	Survived (n=24)	Died (n=10)	p-Value
Age, mean (SD)	52 ($\pm$ 11.6)	50 ($\pm$ 10.5)	57 ($\pm$ 12.9)	0.107
Sex				
Male	29	22	7	0.104
Female	5	2	3	
Child-Pugh grade				
A	3	3	0	0.022
B	19	16	3	
C	12	5	7	
Child-Pugh score, mean (SD)	8.9 ($\pm$ 1.8)	8.2 ($\pm$ 1.8)	10.6 ($\pm$ 2.0)	0.001
MELD, median (range)	14.5 (7-29)	11.5 (7-24)	17.5 (11-29)	0.007
MELD-Na, median (range)	15.5 ($\pm$ 7-33)	13 (7-35)	25 (11-33)	<0.001
Bilirubin, median (range)	31 (8-409)	33.5 (8-152)	17.5 (9-409)	0.405
Albumin, mean (SD)	30.7 ($\pm$ 5.8)	32 ($\pm$ 5.1)	27.7 ($\pm$ 6.4)	0.020
INR, median (range)	1.4 (1-4.1)	1.3 (1-2)	1.6 (1.3-4.1)	0.009
Na, median (range)	136 (126-140)	136 (130-140)	127 (126-138)	0.002
Creatinine, median (range)	95 (49-326)	91.5 (49-126)	70 (64-326)	0.001
Ascites				
1	13	12	1	0.009
2	10	8	2	
3	11	4	7	
Units blood received, median (range)	6 (3-13)	4 (3-12)	10 (4-13)	0.000
Balloon tube or stent				
Yes	14	5	9	<0.001
No	20	19	1	
Endotracheal intubation				
Yes	10	2	9	<0.001
No	24	22	1	
Inotrope requirement				
Yes	9	0	9	<0.001
No	25	24	1	

Table 14.4 Survival after salvage TIPS

Score	n	In-hospital survival	1 year survival	3 year survival	5 year survival
	34	n=24 (70.6%)	n=19 (55.9%)	n=9 (26.5%)	n=7 (20.6%)
Child Pugh Grade					
A	3	3 (100%)	3 (100%)	2 (67.8%)	2 (67.8%)
B	19	16 (84.2)%	12 (63.1%)	5 (26.3%)	4 (21.1%)
C	12	5 (41.7)%	4 (33.0%)	2 (16.7%)	1 (8.3%)
Child Pugh Score					
<10	22	19 (86.4%)	15 (68.2%)	7 (31.8%)	6 (27.3%)
≥10	12	5 (41.7%)	4 (33.3%)	2 (16.7%)	1 (8.3%)
MELD Score					
<15	17	15 (88.2%)	14 (82.4%)	7 (41.2%)	6 (35.3%)
≥15	17	9 (52.9%)	5 (29.4%)	2 (11.8)%	1 (5.9%)
MELD Na Score					
<22	24	22 (91.7%)	18 (75.0%)	8 (33.3%)	6 (25.0%)
≥22	10	2 (20.0%)	1 (10.0%)	1 (10.0%)	1 (10.0%)
APACHE Score					
<15	22	21 (95.5%)	18 (81.8%)	8 (36.4%)	6 (27.3%)
≥15	12	3 (25.0%)	1 (8.3%)	1 (8.3%)	1 (8.3%)

Overall in-hospital mortality during the index admission was 29.4%; for C-P grade C patients mortality was 58.3%, C-P score >10 58.3%, MELD score>15 47.1%, MELD Na >22 80% and APACHE II >15 75% (Table 11.2). Survival data are given in Table 11.2. In hospital and 30-day survival was 70.6%, 90-day survival 67.6%, 6 months 61.8%, 1 year 55.9%, 3 years 26.5% and survival at 5 years was 20.6%. Nine patients (26.5%) are alive at a median of 2 years (range 1-18 years) post-TIPS insertion. Seven patients survived more than 5 years post-TIPS insertion (median 7 years, range 5-18 years). Four of the seven 5-year survivors are alive and well, one underwent a liver transplant post-TIPS and is well 18 years later and one patient who

had recurrent gastric varices underwent a gastric devascularization to control bleeding. Three of the 5- year survivors have died, one at 5 $\frac{3}{5}$ years due to multicentric HCC, another at 7 years of metastatic lung cancer and the third at 16 years of sepsis due to resistant *Serratia* SBP.

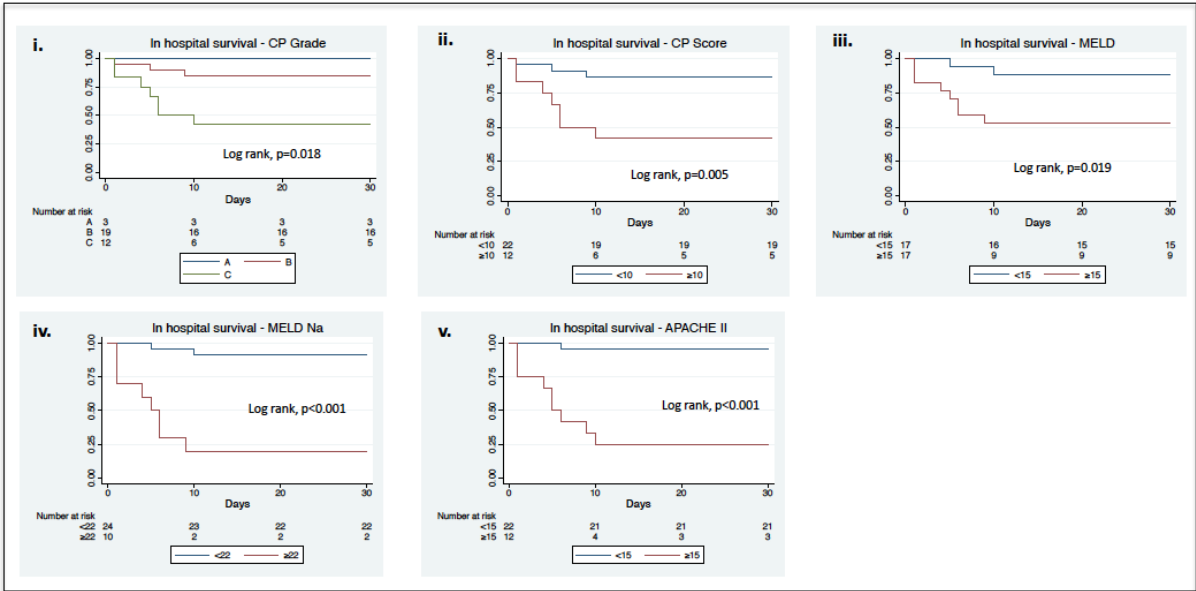
Table 14.5 Cox Proportional Hazards Univariate Analysis

In hospital survival	Hazard ratio	95% CI	p-value
CP Grade	5.1	1.3-18.5	0.015
CP Score	5.5	1.4-21.3	0.014
MELD	4.4	0.9-21	0.060
MELD Na	17.7	3.6-86	0.000
APACHE II	26.8	3.3-214	0.002
1 year survival	Hazard ratio	95% CI	p-value
CP Grade	3.1	1.2-7.9	0.017
CP Score	3.2	1.1-8.8	0.028
MELD	5.2	1.5-19	0.011
MELD Na	9.6	3.2-29	0.000
APACHE II	14.5	4.3-49	0.000
3 year survival	Hazard ratio	95% CI	p-value
CP Grade	2.1	1.1-4.3	0.032
CP Score	2.2	0.9-6.2	0.052
MELD	2.7	1.2-6.2	0.017
MELD Na	4.6	1.9-11	0.001
APACHE II	5.6	2.7-13	0.000
5 year survival	Hazard ratio	95% CI	p-value
CP Grade	2.2	1.5-4.3	0.019
CP Score	2.3	1.1-5.0	0.036
MELD	2.7	1.3-6.1	0.012
MELD Na	4.0	1.7-9.3	0.001
APACHE II	4.8	2.1-11	0.000

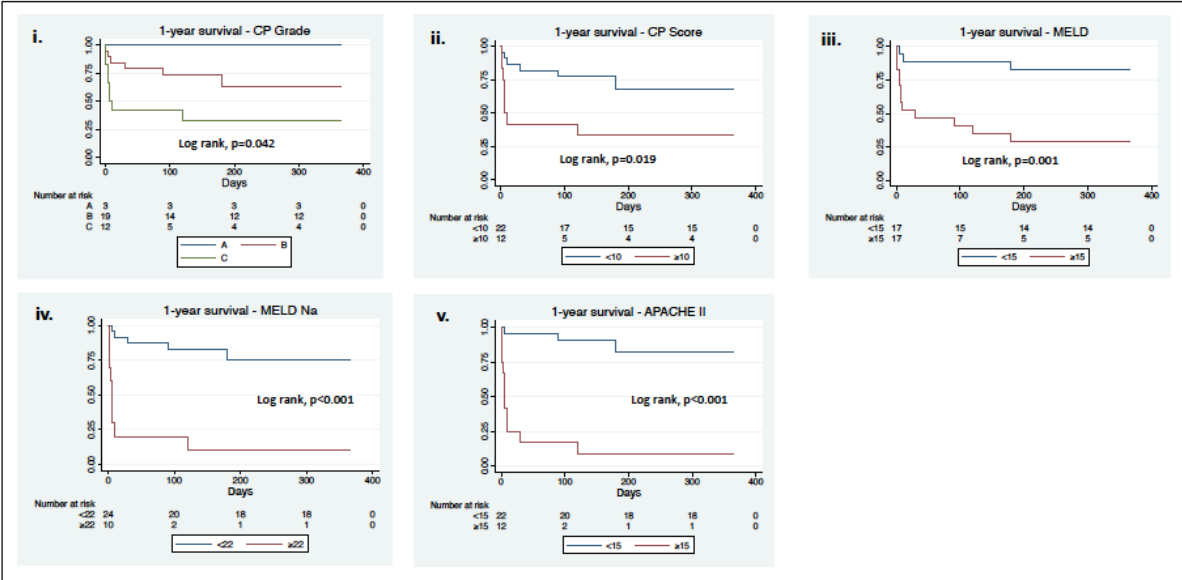
Patients with Child-Pugh grade A, Child-Pugh score <10, MELD score <15, MELD Na score <22 and APACHE II scores <15 had significantly better 1, 3 and 5-year survival rates (Tables 11.2, 11.3, 11.4, 11.5). Cox proportional hazards models showed that APACHE II had the best overall survival prediction rate (Table 14.5).

Figure 14.1 Kaplan Meier survival curves

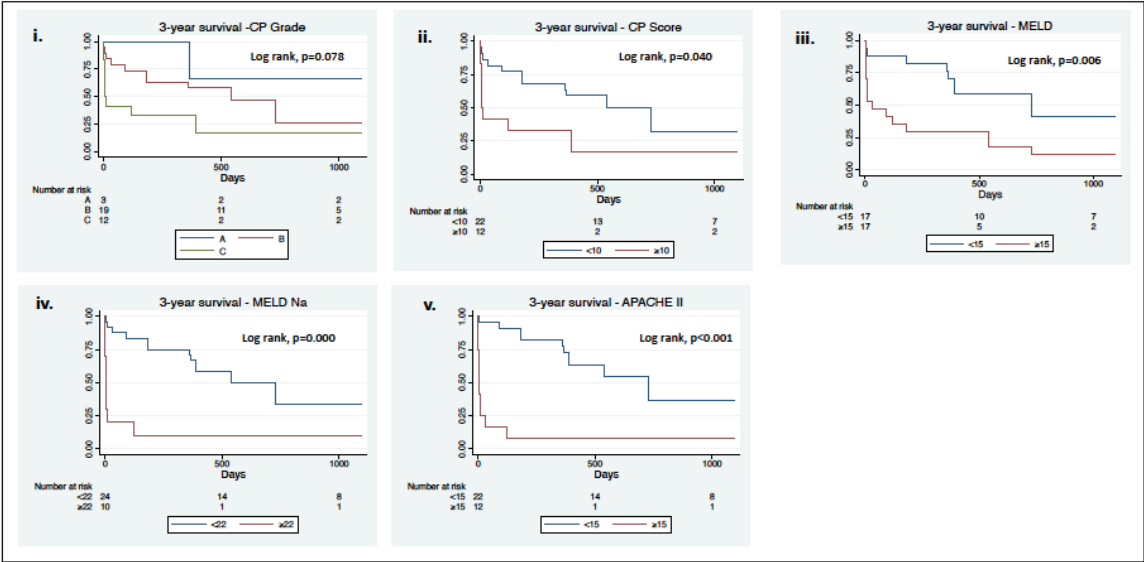
A. In hospital survival



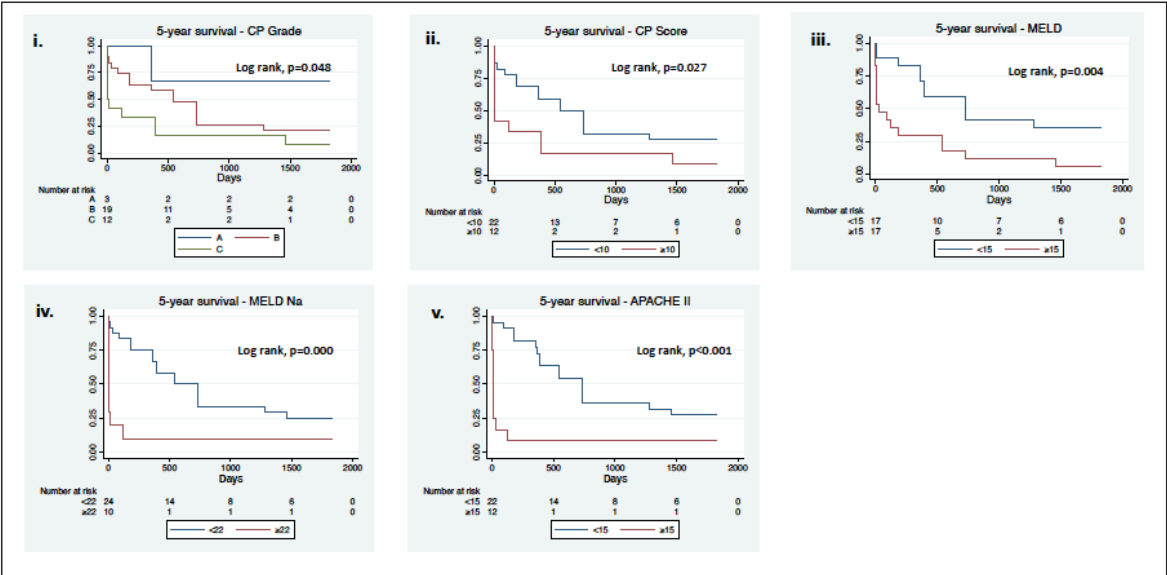
B. 1 year survival



C. 3 year survival



D. 5 year survival



Discussion

In this observational cohort study, survival and long-term outcome were assessed in a defined cohort of high-risk cirrhotic patients who had uncontrolled or life-threatening refractory variceal bleeding and required emergency rescue TIPS placement. We found two distinct and different temporal survival outcomes after

TIPS placement, an initial in-hospital peri-procedural period of increased mortality after stent insertion due to multi-organ failure precipitated by the acute bleeding episode and a subsequent lengthier phase of insidious but inexorably progressive liver failure and death unrelated to acute blood loss. Overall in-hospital mortality was 29.4% but was substantially higher in patient subgroups who had overt liver decompensation and high risk scores. In-hospital mortality increased to 47.1% in patients with MELD scores >15, 58.3% in C-P scores >10, 75% in APACHE II scores >15 and 80% in those with MELD-Na scores >22. Bleeding control was achieved in 91% of patients during the index admission and three patients subsequently required intervention for recurrent varices. Eight patients developed clinically evident or worsening encephalopathy and four of the 24 surviving patients developed SBP. Despite the need for a high-risk procedure in a group of seriously ill patients with life-threatening bleeding, two-thirds of the cohort were alive at 90 days, 61.8% alive at 6 months, 55.9% at 1 year, 26.5% at 3 years and survival at 5 years was 20.6%. As a corollary, a significantly improved five-year survival was found in patients who had preserved liver function and were C-P grade A, had a C-P score <10, a MELD score <15, MELD Na <22 and an APACHE II score <15.

The reported mortality associated with TIPS placement varies widely due to differing inclusion criteria, timing of TIPS and the severity of underlying liver disease. Some reports combine the results of patients with active bleeding during TIPS with those who were haemodynamically stable during the procedure or undergo an elective TIPS placement. Early mortality after sTIPS was 48% in the Royal Free study, predominantly in Child-Pugh C patients with a C-P score >11 (Patch, 2002), and 63% mortality due to aspiration and MOF in the study by Sanyal and colleagues (Sanyal, 1996). To identify high-risk patients after TIPS insertion, previous studies

have evaluated independent clinical and biochemical predictors of index admission mortality (Rajan, 2002). Clinical factors identified include age over 60 years (Rossle, 2013), the presence of encephalopathy and ascites, haemodynamic instability at the time of the TIPS procedure, use of inotropes, mechanical ventilation, balloon tamponade, co-morbidities and sepsis. Biochemical data identified as independent predictors of mortality include hyperbilirubinaemia, albumin $<2.7\text{g/L}$, prothrombin activity $<50\%$, lactate $\geq 12\text{mmol/L}$, hyponatraemia and renal failure (Horhat, 2021; Bouzbib, 2021; Tzeng, 2009; Heinzow, 2012; Rubin, 1995; Maimone, 2019; Walter, 2021; Azoulay, 2001; Jalan, 1995; Chalasani, 2000; Rajan, 2002; Malinchoc, 2000; Brensing, 2002). In this present study only cirrhotic patients with exsanguinating or life-threatening refractory variceal bleeding who underwent emergent rescue TIPS placement were included and bivariate analysis showed that a C-P score ≥ 10 , MELD-Na ≥ 22 , APACHE II score ≥ 15 , balloon tube placement, endotracheal intubation and the need for inotropic support were associated with increased mortality during the index admission.

Published long-term survival data following sTIPS are also widely divergent and range from 44% to 81% at 12 months, depending on the population selection, urgency of sTIPS placement and the experience of the facility in the management of critically ill patients with end-stage liver disease (Kriger 2023). The commonest cause of late deaths after a sTIPS procedure in most series is progressive liver failure. Accurate patient selection is the most important aspect of the TIPS procedure and post-TIPS outcome can reasonably be predicted after a detailed assessment of the patient's overall status and hepatic function. The principal determinant of survival in this study was the severity of the underlying liver disease. In the comparative risk

score analysis in this study the APACHE II score had higher hazard ratios for risk of death post-sTIPS at each time point than other scores; HR=26.8 (in hospital), 14.5 (1 year), 5.6 (3 years) and 4.8 (5 years), with the highest risk overall occurring while in hospital during the index admission, suggesting that the in-hospital APACHE II score is best for predicting for improving outcomes over time. The risk of death however, using MELD Na and APACHE II progressively lessened over time, whereas C-P grade, C-P scores and MELD showed a progressive decline in the risk of death from in-hospital to 3-year time points, but a slightly increased hazard of death from year 5 for C-P grade and C-P scores, and a plateauing for MELD from year 5. This suggests that to determine the one to three year prognosis, all scores are suitable, however for longer term prognosis beyond five 5 years, the MELD Na and APACHE II scores are more stable. The final goal of any therapy for variceal bleeding is to improve survival. Canizares RB To date, no therapy except liver transplantation has been shown to significantly decrease mortality in patients with advanced liver disease. In this study only one patient had a liver transplant after sTIPS which may reflect the predominantly older alcoholic population.

Technical complications associated with TIPS insertion are uncommon and in experienced units TIPS can be successfully performed in over 95% of patients (Weichselbaum, 2022). Because TIPS functions haemodynamically as a side-to-side portocaval shunt there are clinical post-shunt similarities to a central surgical shunt regarding encephalopathy, progressive liver failure and long-term survival. Most TIPS complications are predictable and are related to either technical factors during stent placement, haemodynamic consequences of portal blood flow shunting from a liver with marginal function in cirrhotic patients or shunt occlusion (Jabbour, 1996).

Hepatic encephalopathy and stent dysfunction are the two major complications that have limited the effectiveness of TIPS (Zhou, 2019). Hepatic encephalopathy is the commonest and most disabling systemic side-effect due to loss of prograde portal perfusion, compounded by arterioportal stealing and diminished sinusoidal perfusion (Friis, 2023; Trivedi, 2023; Pandhi, 2020). The incidence of clinically significant encephalopathy following TIPS is substantial and occurred in one-third of patients in this study and was well controlled with medical therapy in most patients. Sepsis due to SPB occurred in 17% of long-term survivors while recurrent varices were uncommon and required intervention in 12.5% of patients during follow-up.

The results of this study have important implications for patients with major variceal bleeding that cannot be controlled endoscopically. We found a significant correlation between early mortality after TIPS and the need for endotracheal intubation, balloon tamponade and inotrope requirements. It is evident in several studies that as multiple unsuccessful endoscopic attempts are made to stop the bleeding, liver function deteriorates, complications supervene, and outcome worsens, emphasizing that patients with major variceal bleeding are best managed in a tertiary referral unit with a skilled multidisciplinary team. Patients in whom endoscopic intervention fails to control bleeding should be identified early so that sTIPS can be performed before the deleterious and irrevocable consequences of deteriorating liver function and multi-organ failure occur. This study identified a group of patients who were Child-Pugh grade A, had a Child-Pugh score <10, a MELD score <15, a MELD-Na score <22 and an APACHE II score <15 who had substantially better 1, 3 and 5-year survival rates after sTIPS placement.

Study limitations

The data presented must be interpreted in the light of several limitations including the long duration of the study and the relatively small patient numbers, with use of uncovered metal stents, which have been replaced with covered stents. In addition, there may be a covert selection bias as our unit functions as a tertiary referral centre for high-risk patients and because sTIPS is always not readily available in some hospitals the results may not be generally applicable to all units. The intrinsic weakness due to the retrospective study analysis is partially overcome by the fact that data were recorded prospectively, and integrity maintained in a carefully controlled dedicated unit registry. Despite these obvious limitations, our study has several strengths and clinical implications. All the patients included in this database were admitted with EVB and had decompensated cirrhosis. A major strength of the study is the analysis of real-world data from an unselected cohort of consecutively treated patients by the same team using specific endpoints.

Conclusion

This study shows that sTIPS is an effective and lifesaving minimally invasive method of portal decompression that can be performed successfully with low procedural morbidity and mortality in critically ill patients with advanced liver disease, portal hypertension and uncontrolled variceal bleeding. Although sTIPS controlled variceal bleeding in 94% of patients, mortality remained high with 29% in-hospital deaths, especially in those who required balloon tube tamponade, endotracheal intubation, and inotrope support. The procedure had low rebleeding rates and encephalopathy was easily managed. Most deaths after sTIPS in this study were the consequence of hepatic or multiorgan failure and sepsis and seldom due to recurrent variceal

bleeding. The in-hospital and subsequent mortality rate in this population is high and should be interpreted in the context of the poor baseline liver function. One year survival was 55.9%, three- year survival 26.5% and 5-year survival was 20.6%. This study identified a group of patients who were Child-Pugh grade A, had a Child-Pugh score <10, a MELD score <15, a MELD Na score <22 and an APACHE II score <15 who had substantially better 1, 3 and 5-year survival rates after sTIPS placement.

CHAPTER 15

Study No 6

THE DESIGN OF A NOVEL CABIN SCORE AND COMPARISON WITH OTHER PROGNOSTIC MODELS IN PREDICTING IN-HOSPITAL MORTALITY AFTER SALVAGE TIPS FOR UNCONTROLLED VARICEAL BLEEDING.

Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) is established as the salvage procedure of choice in patients who have uncontrolled or severe recurrent variceal bleeding despite optimal medical and endoscopic treatment (Weichselbaum, 2022). Key clinical distinctions exist in the spectrum of patients undergoing TIPS, ranging from high-risk cirrhotic patients with liver decompensation and uncontrolled variceal bleeding necessitating an emergent salvage TIPS (sTIPS) to those with well-preserved liver function undergoing an elective TIPS for refractory bleeding (Pandhi, 2020). Current risk stratification of patients who have refractory variceal bleeding and require sTIPS is however imperfect (Krige, 2023). Although TIPS uses a minimally invasive technique, accurate patient selection is crucial to identify those patients who would benefit from the procedure in view of the substantial risks of hepatic encephalopathy, liver failure and increased overall morbidity and mortality in high-risk individuals (Bettinger, 2022).

Several prognostic and risk scores have been developed to distinguish patients at risk for a poor clinical outcome after sTIPS insertion. These include the Acute Physiology and Chronic Health Evaluation (APACHE) II, Bonn TIPS early mortality

(BOTEM), Child-Pugh (C-P), Emory, Freiburg index of post-TIPS survival (FIPS), Model for End-Stage Liver Disease (MELD), and Model for End-Stage Liver Disease sodium (MELD-Na) scores (Rajesh, 2022). Although each of these individual models has been correlated with TIPS outcome, their relative performances have not been assessed in a detailed analysis (Pandhi, 2020). In this comparative study the accuracy of these established risk scores to predict in-hospital mortality after salvage TIPS (sTIPS) placement was assessed and compared to a newly developed and novel CABIN score.

Methods

In this retrospective observational cohort analysis, eight risk scores were calculated for all adult patients who underwent a sTIPS for uncontrolled or life-threatening refractory variceal bleeding in the Surgical Gastroenterology Unit (SGU) at Groote Schuur Hospital and the University of Cape Town Academic Hospital between August 1991 and November 2020. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies (von Elm, 2008). Baseline demographic, clinical and endoscopic data and biochemical variables were collected on admission to the Unit and the anonymized and de-identified information retrieved from a prospectively maintained faculty ethics approved oesophageal variceal registry (Table 15.1). In patients with persistent refractory life-threatening bleeding despite endoscopic intervention, sTIPS was used as an emergency rescue treatment. Transjugular intrahepatic portosystemic shunt was performed under general anaesthesia as soon as possible after the diagnosis of uncontrolled variceal bleeding. Imaging was reviewed to exclude portal, splenic or hepatic vein thrombosis or vascular anomalies and duplex Doppler US was repeated before the TIPS to confirm vascular patency.

An expandable 10 mm uncovered metal Wallstents of variable length from 49 to 90 mm (Boston Scientific, Marlborough, MA, USA) was used to maintain patency of the radiologically-created shunt between the portal and hepatic veins (Krige, Beningfield, 2019).

Risk Scores

Eight scoring systems, the Acute Physiology and Chronic Health Evaluation (APACHE II), Bonn TIPS early mortality (BOTEM), CABIN, Child-Pugh (C-P), Emory, Freiburg index of post-TIPS survival (FIPS), model for end-stage liver disease (MELD), sodium MELD (MELD-Na) scores were calculated in the study patients. Formulas for the calculation of these scores have been previously described and are shown in *Supplementary Table 15.1*. Laboratory values obtained on admission before the TIPS procedure were used for scoring system calculation. Details of the newly developed and novel CABIN score are given in Appendix 15.1. Each of the five components of the CABIN score, **C**reatinine, **A**lbumin, **B**ilirubin, **I**NR and **N**a (sodium) were assigned five numerical levels and each increasing level from baseline scored one additional point, so that the score for each component could range from 1 to 5. The best total CABIN score would compute at 5 points, the worst at 25. Four CABIN categories (A-D) were established (A: 5-10 points, B: 11-15, C: 16-20, D: 21-25)

Measured Outcomes

The primary outcome measure of this study was in-hospital mortality. The area under receiver operating characteristic (AUROC) curves and C-statistics generated were used to evaluate the relative performances of the eight scoring models to accurately predict in-hospital mortality.

Statistical analysis

All clinical data and variables were collected and managed using *REDCap* electronic data capturing software licensed to the University of Cape Town. Statistical computations were made using IBM SPSS statistics (version 26.0, IBM, USA). Statistical significance was set as $p < 0.05$. Continuous data were reported as mean $\pm$ SD or mean $\pm$ SEM and discrete data as percentages. Associations between demographic patient characteristics and validated scoring systems with in-hospital mortality was assessed in a univariate model with no confounding variables identified as confounders in subsequent analysis. To evaluate the performance of the various scoring systems to predict in-hospital mortality following sTIPS, the concordance C-statistic [Area Under the Curve (AUC) of the Receiver Operating Characteristic (ROC) Curves] was used. The c-statistic represents a global estimate of predicting an event, which is derived from area under the ROC curve, ranged from 0 to 1. An AUROC of 0.5 indicates no predictive power, whereas AUROCs of 1–0.9, 0.9–0.8, and 0.8–0.7 indicate excellent, good, and acceptable predictive power, respectively. In addition to the evaluation of validated scoring systems, we evaluated the performance of individual clinical parameters included in these scores. To allow for a simplified point-of-care predictive model, we evaluated different combinations of clinical variables for the prediction of in-hospital death.

Ethical considerations

The study protocol was approved by the Human Research Ethics Committee (HREC Ref No. 120/2019) of the University of Cape Town and the research was conducted in accordance with the Declaration of Helsinki.

Results

Thirty-four (6%) of 564 patients with variceal bleeding which could not be controlled using pharmacological medication and endoscopic intervention underwent emergent salvage TIPS. The demographic and clinical data are summarized in Table 15.1. sTIPS was placed successfully in all patients and variceal bleeding was controlled in 32 of the 34 (94%) patients. Bleeding persisted in two patients (6%) despite a patent sTIPS on repeat US-Doppler examination. A further patient developed recurrent bleeding in hospital during the index admission after initial control of bleeding by sTIPS. Overall control of bleeding by sTIPS was achieved in 31 of 34 (91%) patients. Ten patients (29.4%) died in hospital (mean 4.8, range 1-10 days). Mortality in C-P grade A was 0%, C-P grade B 16% and C-P grade C 58%. In patients who died the median C-P score was 11, (range 7-13), median MELD score was 18 (range 11-29) and median MELD Na score was 25 (range 11-33). Nine of the 12 (75%) patients who required balloon tamponade died, while all nine (100%) patients who were hypotensive requiring inotropic support, balloon tamponade and mechanical ventilation died. Analysis of the two subcategories shows that eight of 11 (73%) patients who had endoscopically uncontrollable variceal bleeding requiring a transfusion of ≥ 8 units of blood and had an emergency sTIPS died, while two of 23 (8.7%) patients who had refractory variceal bleeding and had an urgent sTIPS but not requiring inotropic support, balloon tamponade and mechanical ventilation, died.

Table 15.1 Demographic, clinical characteristics, and Risk Prediction Scores of 34 patients undergoing salvage TIPS.

VARIABLE	TOTAL COHORT (n=34)	SURVIVED (n=24)	IN-HOSPITAL DEATH (n=10)	p- VALUE
Demographics				
Age, mean ($\pm$ SD)	52 ($\pm$ 11.6)	50 ($\pm$ 10.5)	57 ($\pm$ 12.9)	0.107
Sex				
Male	29 (85 %)	22 (92 %)	7 (70 %)	0.104
Female	5 (15 %)	2 (8 %)	3 (30 %)	
Cause of cirrhosis				
Alcohol related	22 (65 %)	15 (63 %)	7 (70 %)	0.938
Non-alcohol related	12 (35 %)	9 (37 %)	3 (30 %)	
Child-Pugh grade				
A	3 (9 %)	3 (12 %)	0	0.022
B	19 (56 %)	16 (67 %)	3 (30 %)	
C	12 (35 %)	5 (20 %)	7 (70 %)	
Risk Prediction Scores				
APACHE II score, (mean, $\pm$ SD)	13.4 ($\pm$ 4.7)	11.4 ($\pm$ 3.3)	18.3 ($\pm$ 3.8)	0.196
BOTEM score, (mean, $\pm$ SD)	5.4 ($\pm$ 1.1)	5.0 ($\pm$ 0.9)	6.3 ($\pm$ 0.7)	0.964
CABIN score, (mean, $\pm$ SD)	10.9 ($\pm$ 5.0)	8.3 ($\pm$ 1.8)	17.0 ($\pm$ 3.8)	0.133
CHILD-PUGH score, mean ($\pm$ SD)	8.9 ($\pm$ 1.8)	8.2 ($\pm$ 1.8)	10.6 ($\pm$ 2.0)	0.001
EMORY score, (mean, $\pm$ SD)	3.2 ($\pm$ 0.9)	2.8 (0.7)	4.3 ($\pm$ 0.5)	0.497
FIPS score, (mean, $\pm$ SD)	-0.3 ($\pm$ 0.9)	-0.6 ($\pm$ 0.9)	0.5 ($\pm$ 0.5)	0.205
MELD, (mean, $\pm$ SD)	15.0 ($\pm$ 6.2)	13 ($\pm$ 4.8)	19.8 ($\pm$ 6.7)	0.007
MELD-Na, (mean, $\pm$ SD)	16.9 ($\pm$ 7.4)	14 ($\pm$ 5.3)	23.9 ($\pm$ 7.1)	<0.001

Continuous variables expressed as mean ($\pm$ standard deviation) or proportions as appropriate. SD: standard deviation; APACHE II: Acute Physiology And Chronic Health Evaluation II; BOTEM: Bonn TIPS early mortality; CABIN: Creatinine Albumin Bilirubin INR Sodium score; FIPS: Freiburg index of post-TIPS survival; MELD: Model for End-Stage Liver Disease; MELD-Na: Model for End-Stage Liver Disease Sodium.

Table 15.2 details the univariate analysis between in-hospital death and risk prediction scores. Age, gender, and the cause of cirrhosis were not associated with in-hospital deaths. The univariate association of the seven established scoring

Table 15.2 Univariate analysis of demographic characteristics and scoring systems with in-hospital deaths in 34 patients undergoing salvage TIPS.

VARIABLE	β (SE)	p-Value
Age	0.068 (0.037)	0.111
Sex	-1.551 (1.011)	0.125
Cause of cirrhosis	-0.122 (0.173)	0.481
Risk prediction scores		
APACHE II	0.524 (0.200)	0.009
BOTEM	1.300 (0.340)	0.000
CABIN	8.850 (1.120)	0.000
CHILD-PUGH	0.597 (0.234)	0.011
EMORY	1.508 (0.249)	0.000
FIPS	3.442 (0.239)	0.000
MELD	0.205 (0.080)	0.010
MELD-NA	0.246 (0.084)	0.003

Continuous variables expressed as mean ($\pm$ standard deviation) or proportions as appropriate. SD: standard deviation; APACHE II: Acute Physiology And Chronic Health Evaluation II; BOTEM: Bonn TIPS early mortality; CABIN: Creatinine Albumin Bilirubin INR Sodium score; FIPS: Freiburg index of post-TIPS survival; MELD: Model for End-Stage Liver Disease; MELD-Na: Model for End-Stage Liver Disease Sodium.

systems as well as the newly developed CABIN score with in-hospital death was evaluated. All scoring systems were associated significantly with in-hospital death ($p < 0.05$). The novel CABIN score was significantly associated with in-hospital death performances

Table 15.3 Performance of various risk prediction scores in predicting in-hospital

	IN-HOSPITAL DEATHS			
	AUC	STD ERROR	p-VALUE	95 % CONFIDENCE INTERVAL
APACHE II	0.948	0.035	0.000	0.879 – 1.000
BOTEM	0.877	0.059	0.001	0.762 – 0.992
CABIN	0.967	0.028	0.000	0.912 – 1.000
CHILD-PUGH	0.802	0.084	0.006	0.638 – 0.967
EMORY	0.942	0.038	0.000	0.868 – 1.000
FIPS	0.892	0.055	0.000	0.783 – 1.000
MELD	0.792	0.082	0.008	0.631 – 0.952
MELD Na	0.865	0.077	0.001	0.713 – 1.000

Continuous variables expressed as mean ($\pm$ standard deviation) or proportions as appropriate. SD: standard deviation; APACHE II: Acute Physiology And Chronic Health Evaluation II; BOTEM: Bonn TIPS early mortality; CABIN: Creatinine Albumin Bilirubin INR Sodium score; FIPS: Freiburg index of post-TIPS survival; MELD: Model for End-Stage Liver Disease; MELD-Na: Model for End-Stage Liver Disease Sodium.

($p=0.000$). Figure 15.1 shows the graphic representation of the comparative of the eight risk scores death following salvage TIPS. The CABIN score (AUROC 0.967) had the highest discriminative ability predicting in-hospital death compared to the APACHE II (AUROC 0.948), BOTEM (AUROC 0.877), C-P (AUROC 0.802), EMORY (AUROC 0.942), FIPS (AUROC 0.892), MELD (AUROC 0.792), and MELD-Na (AUROC 0.865) scores as detailed in Table 15.3 and Figure 15.1. The mean CABIN score in the 24 in-hospital TIPS survivors was 8.25 (median = 8, range 5-18) compared to a mean of 17 (median 17, range 11-22) in the 10 deaths. Patients with a CABIN A score ranging from 5 to 10 had a 100% survival, while a CABIN B score of 11 to 15 score had a 25% survival and a CABIN C score of 16-20 had a 12.5%

survival. A CABIN score of 11 provided a clear survival cut-off. Only 3 of 24 patients with a CABIN score <10 died while 21 of 24 survived. All ten patients with a CABIN score >11 died.

Discussion

The unique safety and minimally invasive characteristics of TIPS which provide an effective reduction in portal pressure make the procedure the ideal rescue intervention in high-risk patients with liver decompensation and endoscopically uncontrolled variceal bleeding (Garcia-Pagan, 2020). In this study the relative capabilities of eight scoring models, including a novel CABIN score, to predict survival in a high-risk cohort of patients who underwent an emergency sTIPS placement were compared. Although sTIPS controlled variceal bleeding in 94% of patients, overall in-hospital mortality was 29.4% and increased exponentially in those who required >8 unit blood transfusion, inotropic support, oesophageal balloon tamponade, and mechanical ventilation. Log-rank comparisons of survival curves showed that of the eight scores evaluated, the CABIN, APACHE II and Emory scores had the highest AUROC values and the best discriminatory ability with C-statistic values all exceeding 0.9. Of these three top contenders, the novel CABIN score (0.967) had the best discriminatory and predictive capacity. As a corollary, this study demonstrates excellent predicted survival in a select patient group with a CABIN A score or <10 CABIN score points after salvage TIPS.

The reported mortality rate after TIPS placement however varies widely due to differing inclusion criteria, timing of TIPS, severity of underlying liver disease and inclusion in some reports of both actively bleeding patients during TIPS and those who were stable during the procedure or had an elective TIPS (Weichselbaum,

2022; Lee, 2023). In studies exclusively reporting salvage or rescue TIPS in patients with uncontrolled life-threatening or endoscopically unmanageable variceal bleeding, as in this study, mortality rates range from 15% to 75% which are significantly higher than elective TIPS (Table 15.1). Accurate prediction of outcome in high-risk emergency sTIPS patients is a crucial element of management and the optimal prognostic score should ideally be able to differentiate two groups, patients with a better prognosis and likely to survive and those with a prohibitive risk of death.

Most of the current prognostic scores used for sTIPS have intrinsic limitations due to the selection and weighting of the constituent components. Currently the MELD score, which was initially created to predict survival following elective placement of TIPS, is the most widely used liver-related prognostic score both in clinical practice and research. Although MELD was a prospectively developed and validated indicator of the severity of end-stage liver disease that utilizes quantitative, objective measures, including bilirubin, creatinine and INR values, the score has potential limitations and caveats include the maximum assigned value of serum creatinine which is capped at 4 even when the measured serum level is higher. Modifications to overcome MELD shortcomings have included reweighting the model's coefficients, altering the laboratory components and the addition of new variables including serum sodium ('MELD-Na') and albumin (termed '5-variable MELD [5vMELD]') which is more discriminative than both MELD and MELD-Na in transplant assessment and use similar elements as the CABIN score (Myers, 2014).

The inclusion of subjective clinical components in other proposed prognostic models may limit precision and reproducibility of score assignments. The C-P, Emory and

BOTEM scores all have at least one component that may be perceived as subjective while the APACHE II and BOTEM scores lack specificity to liver disease which limits their capacity to predict outcomes after liver interventions such as TIPS. In addition, the C-P, Emory, and BOTEM scores are limited by a ceiling effect in which laboratory values above a particular cutoff level are not distinguished from one another in terms of higher scoring. The Freiburg index of post-TIPS survival (FIPS) uses age, bilirubin, albumin, and creatinine levels.

In a meta-analysis which included 11 studies and 2037 patients Zhou found that MELD was superior to the C-P score in predicting 3-month survival after TIPS but the predictive 1-month, 6-month and 12-month survival was not significant (Zhou, 2015). Zhang found that C-P grade C and MELD >10 but not Emory, BOTEM or SB/PLT scores were predictors of survival in Chinese cirrhotic patients treated with TIPS (Zhang, 2014) while Gaba reported that MELD and MELD-Na scores had the best capability to predict early mortality compared with bilirubin, C-P, Emory, PI, APACHE II, and BOTEM, with statistical superiority over bilirubin, Emory, and BOTEM scores in an American population (Gaba, 2013). In a comparison of MELD, C-P and Emory risk scores in TIPS patients, Schepke found that all three models predicted short-term 3-month survival with similar accuracy and the MELD model was marginally superior to C-P for both 12-month and 36-month survival (Schepke, 2003). In patients with refractory variceal bleeding Rubin found that survival was inversely proportional to Child-Pugh class and APACHE II scores (Rubin, 1995). The single determinant most closely associated with decreased survival in the month after TIPS was the APACHE II score, a score of 18 stratifying patients into those at low and high risk of mortality. Only 1 of 13 patients with Child-Pugh C cirrhosis and

an APACHE II score exceeding 18 survived >30 days (Rubin, 1995). In the Hermie study early mortality was associated with a MELD score of at least 19 and haemodynamic instability at time of admission and if hemodynamic instability was combined with a high MELD score, the 6-week mortality peaked at 77.8% (Hermie, 2018). In the multicentre French study Walter et al reported that sTIPS mortality was >90% in patients who had lactate levels ≥ 12 mmol/L and/or a MELD score ≥ 30 (Walter, 2021).

In view of these differing outcomes, it is therefore important to develop a convenient, effective, and accurate prognostic model which stratifies the risk of patients undergoing salvage TIPS in order to guide treatment. The novel CABIN score used in this study was developed as a point-based tool to improve prognostic predictability in patients specifically undergoing emergency salvage TIPS placement. This new score which comprises five laboratory measurements without any clinical or subjective elements can be calculated at the bedside from a minimal laboratory dataset and provides a refined, granular grading system with scores ranging from 5 to 25. The CABIN score achieved significant prognostic discrimination reflected by in-hospital survival of 100% in patients in the CABIN A category with a score ranging from 5 to 10 while CABIN B scores of 11 to 15 score had a 25% survival and a CABIN C score of 16-20 had a 12.5% survival. This new model predicted in-hospital mortality with high accuracy and showed statistic superiority over the other seven contenders, including MELD and C-P scores. Moreover, of all examined models, CABIN, APACHE II and Emory scores were the only scores that exceeded a C-statistic values of greater than 0.9.

There are inevitable and specific limitations to this study. Firstly, this investigation is limited by its small size, retrospective design, and lack of a control group. Secondly, the study has a clear selection bias and restricted generalizability as these patients were treated in a well-resourced, single tertiary care referral centre with round the clock skilled endoscopic and TIPS access. Thirdly, because patients were accrued over three decades, technical differences in TIPS placement and improvements in medical care during the study period would have contributed to differences in clinical outcomes over time. However, the robustness of this study is enhanced by the prospective data collection, supervision by the same investigators during the study period, restriction of subjects to a well-defined cohort of cirrhotic patients with uncontrolled exsanguinating bleeding and complete follow-up. The use of all-cause mortality as the primary outcome provided a consistent and objective end point.

In conclusion, the novel CABIN liver-specific prognostic model which is objective, quantitative and reproducible, combines five easily obtained laboratory test results and provides a new score with improved statistical power predicting in-hospital mortality in patients with uncontrolled variceal bleeding undergoing salvage TIPS. The CABIN score identifies high-risk patients and outperformed other scoring systems in predicting in-hospital mortality. Even though mortality was 75% for CABIN B, 87.5% for CABIN C, and 83% for CABIN scores >10 in this study, this high-risk category should not be denied consideration for a sTIPS and should be assessed on a case-by-case basis especially in units where there is prompt access to liver transplantation after sTIPS. Of importance is that this study was based on a small defined cohort of predominantly alcoholic decompensated cirrhotic patients

undergoing emergent TIPS and the CABIN score will need further prospective external validation in a larger sample before being considered for clinical application.

CHAPTER 16:**THESIS SYNOPSIS****A: SUMMARY OF THE SIX CLINICAL RESEARCH INVESTIGATIONS****B: RECOMMENDATIONS FOR FUTURE RESEARCH**

This thesis focussed on the complex nature and the critical outcomes of uncontrolled and refractory variceal bleeding which occurs in a subgroup of high-risk patients who, despite receiving conventional pharmacological and endoscopic treatment, fail to respond and continue to bleed, ultimately to exsanguinate if not effectively treated. The dissertation analysis has identified deficiencies in the literature related to high-risk variceal bleeding management and has addressed these limitations in a series of clinical investigations with advanced proposals for more effective management, tailored to individual patient needs. The research investigations undertaken and reported in this thesis are novel, relevant, and important and make a substantial contribution to the existing body of knowledge. As the six studies are clinically based and involve portal hypertensive patients with acute and life-threatening variceal bleeding which has a substantial mortality rate, any improvement in outcome will have a beneficial impact on existing patient care.

Identification and knowledge of accurate prognostic data predicting early rebleeding should ideally provide a powerful tool to identify at an early stage those patients in whom conventional treatment is likely to be unsuccessful and those who require accelerated and escalated intervention. The course and outcome of bleeding oesophageal varices due to chronic liver disease is notoriously difficult to predict and an important component of future medical care therefore is the

acquisition and application of robust, reliable, and validated prognostic tools to predict the likely outcome in individual patients. To improve the accuracy of prognostic models, better prognostic variables that are central to the disease process are required and has been addressed in two clinical investigations in the thesis.

A major strength of these studies is that they were conducted in a single centre in a well-defined population of consecutive patients using standard endoscopic techniques and supervised by the same group of investigators during the study period. All included patients were at a well-defined stage during cirrhosis (inception cohort) thereby homogenising the study population and avoiding the error of overfitting which has influenced a significant proportion of previous studies. To provide the highest possible level of uniformity and to minimise differences in the zero-time entry, only patients who received their initial and subsequent treatment in the unit were studied. The robustness of the studies is enhanced by the prospective data collection and the use of rebleeding and death as the main outcomes which provided consistent, objective and definitive hard endpoints.

The essential future requirements necessary to improve survival in these high-risk patients are self-evident and include effective control of acute variceal bleeding, prevention of further rebleeding and minimizing deterioration of liver function. The early recognition of endoscopic failures and implementation of newer technologies for local control including self-expanding oesophageal metal stents, enhanced efficacy of long-acting drugs and improved quality PTFE coated TIPS stenting should provide better haemostasis in this high-risk cohort.

A: SUMMARY OF THE SIX CLINICAL RESEARCH INVESTIGATIONS

Study 1

Identification and knowledge of accurate prognostic data predicting early rebleeding should ideally provide a powerful tool to identify those patients in whom conventional treatment is likely to be unsuccessful at an early stage and who require urgent implementation of an aggressive salvage strategy or identify those with a very poor prognosis in whom chances of survival are slim. There remain deficiencies in the common scoring systems widely used for predicting early rebleeding and death after a major variceal bleed. To rectify these shortcomings, this study investigated the relative predictive performances of the original Child-Pugh, Model for End stage Liver Disease and a newly designed four-category recalibrated Child-Pugh (rC-P) score were compared by area under receiver operating characteristic curves for in-hospital rebleeding and death in alcoholic cirrhotic patients during the index admission.

The new rC-P score demonstrated a significantly improved ability to predict death, compared to both the C-P and MELD scores but ultimately was no better in predicting rebleeding. The new 4-category rC-P scoring system provides a refined stratification of patients in the C category of the original C-P, in that patients with scores of 14 and 15 are allocated to a category D. The results show that the rC-P score may be better than C-P and MELD scores at predicting in-hospital death but not rebleeding in patients who present with variceal bleeding secondary to alcoholic liver cirrhosis. This proposed modified and recalibrated C-P model will need to be

validated in prospective studies including a wider spectrum beyond alcoholic cirrhosis.

Study 2

This study was clinically important and relevant because no detailed comparative data exist on the relative efficacies, safety, and outcome of EVL versus IST in controlling *actively* bleeding (“spurting”) oesophageal varices. Forty patients with actively bleeding oesophageal varices who were treated with endoscopic variceal ligation were matched and compared with 40 who underwent endoscopic injection sclerotherapy. Control of variceal bleeding, rebleeding, variceal recurrence, endoscopic complications, eradication, and survival were recorded using Baveno assessment criteria. Primary endoscopic failure to control acute bleeding during the first endoscopic intervention occurred in 2.5% in the EVL group and 10% in the IST group. Secondary 5-day failure of bleeding control was 20% in the EVL group and 25% in the IST group. Overall successful endoscopic variceal bleeding during the index admission was similar. Endoscopic-related complications and bleeding from treatment-induced esophageal ulceration were less common in EVL than in IST. Oesophageal variceal eradication was similar and there was no significant difference in mortality rates during the index admission, at 6 weeks and total subsequent deaths. Survival outcome was similar.

The study found that EVL performed better than IST in achieving initial primary acute variceal bleeding control and secondary bleeding control at 5 days, with lower rebleeding rates and fewer procedure-related complications but had no influence on 6 week or ultimate survival. Variceal eradication rates were similar. The study

conclusions were that EVL is safe and effective and should be the preferred endoscopic method of treatment in patients with actively bleeding oesophageal varices. This study also demonstrated that endoscopic therapy was highly effective in controlling acute bleeding from oesophageal varices and that ultimate survival was influenced by both rebleeding and underlying liver reserve. Sustained control of acute bleeding has been shown to be a critical requirement in variceal management because each subsequent bleed worsens marginal liver function. In addition, the study showed that in this high-risk group, even when EVL and IST successfully controlled variceal bleeding, progressive liver failure resulted in high mortality rates in the first 6 weeks after admission, especially in Child-Pugh patients scoring >13 with an 80% mortality.

Study 3

Although endoscopic variceal ligation is now widely used to control acute variceal bleeding and prevent recurrent bleeding, detailed outcome analysis using specific and validated endpoints is poorly defined. This study assessed the efficacy of EVL in controlling acute variceal bleeding, preventing variceal recurrence and rebleeding and achieving *complete* eradication of oesophageal varices in patients who present with bleeding varices. One hundred and fourteen (81%) of the 140 patients had variceal bleeding that was effectively controlled during the index banding procedure and never bled again from oesophageal varices, while 26 (19%) patients had complicated and refractory variceal bleeding. EVL controlled the acute sentinel variceal bleed during the first endoscopic intervention in 134 of 140 patients (95.7%). Overall 5-day endoscopic failure to control variceal bleeding was 7.1%. Index admission mortality was 14.2%. OV were completely eradicated in 50 of 111 patients

(45%) who survived >3 months, of whom 31 recurred and 3 rebled. Sixteen (13.3%) of 120 surviving patients subsequently had 21 EV rebleeding episodes and 10 patients bled from other sources after discharge from hospital. The 6-month incidence of EV rebleeding per patient was 8.3%, 12 month incidence was 12.5%, 2 year incidence 12.5% and beyond 2 years the total cumulative EV rebleeding rate was 13.3%. Overall rebleeding from all sources after 2 years was 21.7%. Cumulative survival for the 140 patients was 71.4% at 1 year, 65% at 3 years, 60% at 5 years and 52.1% at 10 years. The study found that EVL was highly effective in controlling the sentinel variceal bleed with an overall 5-day failure to control bleeding of 7.1%. Although repeated EVL achieved complete variceal eradication in less than half of patients with BOV, there was a significant reduction in subsequent rebleeding. Varices recurred in 62% of patients but with minimal rebleeding.

Study 4

This study investigated the outcome of salvage TIPS (sTIPS) in patients who had life-threatening variceal bleeding resistant to standard treatments in order to identify clinical and laboratory risk factors predicting in-hospital death during the index admission. In a total of 564 patients treated for acute variceal bleeding, 530 (94%) had control of bleeding by vasoactive medication and endoscopic intervention. In 34 (6%), bleeding was uncontrolled or persistent despite endoscopic intervention and underwent urgent sTIPS. Ten patients (29%) died in hospital after the procedure. Mortality in C-P grade A was 0%, in C-P grade B 16% and in C-P grade C 58%. In the patients who died, the mean (SD) C-P score was 10.6 (2.0), the median MELD score 18 (range 11-29) and the median MELD-Na score 25 (11-33). On bivariate analysis, factors associated with death after sTIPS were C-P score ≥ 10 , MELD-Na

≥22, ≥8 units of blood transfused, Sengstaken tube placement, endotracheal intubation, inotropic support and endoscopically uncontrolled bleeding (all $p < 0.001$). In an unadjusted univariate logistic regression model, the significant predictors of mortality were need for inotropic support, endotracheal intubation, endoscopically uncontrolled bleeding, grade 3 ascites and C-P grade C.

The results of this study have important implications for patients with major variceal bleeding that cannot be controlled endoscopically. There was a significant correlation between early mortality after TIPS and the need for endotracheal intubation, balloon tamponade and inotropic support. This study shows that although sTIPS controlled variceal bleeding in 94% of patients after failed endoscopic intervention, mortality remained high with 29% in-hospital deaths, especially in patients with uncontrolled bleeding. The most significant predictors of mortality were C-P grade C, grade 3 ascites, inotrope requirement, endotracheal intubation, and endoscopically uncontrolled bleeding. Further effort is needed to reduce the high mortality and morbidity despite successful sTIPS placement. In order to achieve this goal, early identification of patients unresponsive to medical treatment is crucial so that urgent sTIPS for portal decompression can be initiated without delay.

Study 5

This study compared the efficacy of current prognostic scoring models in predicting 90-day, 1-, 3- and 5-year survival after salvage transjugular intrahepatic portosystemic shunt when endoscopic control of variceal bleeding had failed. While the success rate of sTIPS in arresting bleeding is over 90%, this outcome is negated by mortality rates that can exceed 30% and may approach 100% in patients with

associated sepsis, prolonged hypotension, deteriorating liver and renal function and who require inotropic support and mechanical ventilation. Accurate patient selection is therefore vital and this study compared the efficacy of current prognostic scoring models. On bivariate analysis, C-P score ≥ 10 , high C-P grade, MELD ≥ 15 , MELD Na score ≥ 22 and APACHE II score ≥ 15 predicted 90-day mortality. Individual clinical characteristics associated with 90-day mortality were grade 3 ascites, >10 units of blood transfused, balloon tube placement, endotracheal intubation and inotrope support. The overall 90-day, 1-, 3- and 5-year survival rates were 67.6%, 55.9%, 26.5% and 20.6% respectively due to progressive liver failure. Nine patients (26.5%) were alive at a median of two years (range 1-18 years) post-TIPS. Patients with C-P grade A, C-P score <10 , MELD score <15 , MELD Na score <22 and APACHE II score <15 had significantly better 90-day, 1-, 3- and 5-year survival rates.

Patients with C-P grade A, C-P score <10 , MELD score <15 , MELD Na score <22 and APACHE II scores <15 had significantly better 90-day, 1, 3 and 5-year survival rates at 67.6%, 55.9%, 26.5% and 20.6% respectively. The Cox proportional hazards models showed that at 1, 3 and 5 years the APACHE II score had higher hazard ratios for risk of death post-sTIPS than the other scores: HR=14.5, 5.6 and 4.8 respectively, with the highest risk overall at 1 year. Conversely, for 90-day survival, MELD was the only score that predicted death with a HR=13.5, suggesting that the best score to predict post-sTIPS survival at 90 days is the MELD score and at 1 year, the APACHE II score. Although sTIPS controlled variceal bleeding in 94% of patients after failed endoscopic therapy, in-hospital mortality was 29% and less than one quarter were alive after five years. C-P score ≥ 10 , high C-P grade, MELD Na score ≥ 22 , and APACHE II score ≥ 15 predicted 90-day mortality, while C-P grade A,

C-P score <10, MELD score <15, MELD Na score <22 and APACHE II score <15 predicted long term survival.

In conclusion, this study confirms that sTIPS is an effective and lifesaving minimally invasive method of portal decompression that can be performed successfully with low procedural morbidity and mortality in critically ill patients with advanced liver disease and uncontrolled variceal bleeding. Although in the short term sTIPS controlled variceal bleeding in 94% of patients, mortality remained high with 29% in-hospital deaths. Most deaths after sTIPS were the consequence of hepatic or multiorgan failure and sepsis, and seldom due to recurrent variceal bleeding. However because this study was based on a small cohort of predominantly alcoholic decompensated cirrhotic patients, the high-risk category identified should not be denied consideration for a sTIPS. Each patient should be assessed on a case-by-case basis especially in units with liver transplantation available after sTIPS.

Study 6

Current risk stratification of patients who have refractory variceal bleeding and require sTIPS is imperfect. Although TIPS is a minimally invasive procedure, appropriate patient selection is crucial to identify patients who would benefit from the procedure, considering the substantial risks of hepatic encephalopathy, liver failure and increased overall morbidity and mortality in high-risk individuals. In the newly developed CABIN score which was devised to overcome limitations of existing scoring systems, each variable is scored from one to five and the cumulative total is calculated by adding together the individual values of the five biochemical components (**C**reatinine, **A**lbumin, **B**ilirubin, **I**NR (international normalized ratio) and

Na (sodium). The best total CABIN score computes at 5 points and the worst at 25 points. Four CABIN categories (A-D) were established (A: 5-10 points, B: 11-15, C: 16-20, D: 21-25). The CABIN score and seven previously described scoring systems, APACHE II, BOTEM, Child-Pugh, Emory, FIPS, MELD, and MELD-Na scores were calculated based on clinical evaluation and laboratory values obtained before the sTIPS procedure. In this study the accuracy of the CABIN score was compared to established risk scores for the prediction of in-hospital mortality following sTIPS. Log-rank comparisons of survival curves showed that of the eight scores evaluated, the CABIN, APACHE II and Emory scores had the highest AUROC values and the best discriminatory ability with C-statistic values all exceeding 0.9. Of these three top contenders, the CABIN score (0.967) had the best discriminatory and predictive capability. As a corollary, this study also demonstrates the predictive ability of the CABIN score with 100% survival observed in patients in the CABIN A category (<10 points) after sTIPS.

The CABIN score used in this study was developed as a point-based tool to improve prognostication specifically for patients undergoing emergency sTIPS and circumvents the complex computations of the MELD and other scores. This new score avoids subjective elements and can be calculated at the bedside providing a refined, granular grading system from a minimal laboratory dataset with scores ranging from 5 to 25. The CABIN score achieved significant prognostic discrimination reflected by in-hospital survival of 100% in patients in the CABIN A category (5-10 points), while patients in the CABIN B category (11-15) score had 25% survival and those in the CABIN C category (16-20) 12.5% survival. Our model predicted in-hospital mortality with high accuracy and showed statistical superiority over the other

seven contenders, including MELD and C-P scores. Moreover, of all the examined models, only the CABIN, APACHE II and Emory scores exceeded a C-statistic value of 0.9.

In conclusion, the novel CABIN prognostic score, which is objective, quantitative, and reproducible, combines five easily obtained laboratory test results and provides improved statistical power of predicting in-hospital mortality in patients with uncontrolled variceal bleeding undergoing sTIPS. The CABIN score identified high-risk patients and outperformed other scoring systems in predicting in-hospital mortality. Even though mortality was 75% for CABIN B, 87.5% for CABIN C, and 83% for CABIN scores >10 in this study, this high-risk category should not be denied consideration for an emergency TIPS but should be assessed on a case-by-case basis, especially in units where there is prompt access to liver transplantation after sTIPS. This study was based on a small defined cohort of predominantly alcoholic decompensated cirrhotic patients undergoing emergency TIPS and this newly developed derivative CABIN score will need further prospective external validation before being considered for general clinical application.

B: RECOMMENDATIONS FOR FUTURE RESEARCH

1. Prognostic scoring incorporating artificial intelligence, machine learning algorithms and neural network models

Since the outcome of patients with bleeding oesophageal varices and progressive liver decompensation is particularly difficult to predict, the acquisition and application of robust, reliable, validated, real-time prognostic tools to forecast the likely outcome in individual patients is an essential clinical requirement. To improve the accuracy of

existing prognostic models, improved selection of variables central to the disease process are required. Although the new rC-P score in study #1 is an improvement in identifying high-risk patients, validation of future prospective studies incorporating and evaluating the full spectrum of prognostic factors including clinical variables, renal function and liver biochemistry, endoscopic criteria and findings, quality of intervention and portal pressure readings in order to create a new comprehensive scoring system will be a valuable addition to improving the effective management of patients with bleeding oesophageal varices and portal hypertension.

To achieve this objective, the future management of portal hypertensive bleeding will benefit from the application and integration of artificial intelligence, machine learning algorithms and neural network models in patient assessment to enhance scoring systems and predictive analysis. An unexplored research area is the combination of these three elements that may offer a potentially promising avenue for non-invasive, accurate prediction, theoretically surpassing traditional methods. Utilizing data from electronic health records, machine learning algorithms can efficiently identify high-risk patients, triggering risk prediction tools for consistent decision support to clinicians. Neural network models will be able to provide continuous risk predictions, aiding in triaging higher-risk patients to appropriate levels of care, thus enhancing decision-making and improving patient outcomes and healthcare efficiency.

2. Definition of clear and specific endpoints

There is international consensus that the assessment of the efficacy of treatment of bleeding oesophageal varices should be based on specific clinical outcomes. Published results are variable and conflicting because of small sample sizes, referral bias, dissimilar study endpoints, differences in patient selection, methods and

techniques of endoscopic intervention and the precise definition of rebleeding as indicated in study #2. In order to provide a consistent measure of standardisation and accuracy in the interpretation of data from different studies, specific and uniformly defined endpoints which incorporate rebleeding and death are required. Quality of life and cost effectiveness issues are also now increasingly important concepts to consider and to include in future trial design.

3. Technical aspects of endoscopic therapy and strategies to prevent endoscopic-related complications

Endoscopic failure to control variceal bleeding is encountered by even the most experienced endoscopists. Up to 20% of variceal bleeding episodes are refractory to standard therapy and are associated with increased mortality. Mature clinical judgment is necessary in acute problematic or complex cases and careful supervision of trainees and assistance by an experienced endoscopist becomes essential when critical decisions are required. The early recognition of endoscopic failures and the implementation of local control methods including self-expanding oesophageal metal stents and improved quality PTFE-coated TIPS stenting is anticipated to improve bleeding control and survival in this high-risk cohort.

The rational treatment of oesophageal varices requires a clear understanding of the risks of rebleeding, the hazards of liver decompensation and the likely response and benefits of each specific intervention in the treatment hierarchy. Complications related to endoscopic intervention occur mostly during active bleeding when endoscopic vision is obscured or limited. The incidence of complications varies widely in reported studies because of variations in patient population, the type and

severity of the underlying liver disease and the different banding techniques used. In addition, the incidence of complications is higher when carefully documented in prospective studies. Optimal treatment should be offered by a dedicated variceal bleed team which includes a skilled endoscopist and support staff.

4. Prospective documentation of endoscopic adverse events

There is a need to stimulate further research and analysis to clearly define objective endpoints when reporting the results of endoscopic ligation and procedural adverse events. These are likely to differ from the less clear historical outcomes reported in previous randomized controlled trials as indicated in study #3. The elusive goal of effective and safe endoscopic variceal banding remains the attainment of long-term bleed-free survival with a minimum of procedure-related adverse events.

5. The future role of TIPS

Several important and unresolved issues relating to the specific role of salvage TIPS in the management of patients with actively bleeding uncontrolled oesophageal varices remain as indicated in studies #4 and #5. Published results are variable and conflicting because of referral bias, dissimilar or erratic study endpoints including documentation of portal pressure gradients, either as direct measurements or using surrogate markers, differences in patient selection and the precise definition of rebleeding. Despite the widespread use of TIPS, few studies have specifically evaluated these endpoints in patients undergoing salvage TIPS for uncontrolled variceal bleeding. Consequently, there are a paucity of accurate data on the efficacy of salvage TIPS in these circumstances as well as survival in this high-risk cohort, as suggested in study #6. A further goal would be to define and identify the specific

target population that would benefit or not from salvage TIPS, while another objective should be to identify stable recurrent variceal bleeders who would benefit from pre-emptive or early-TIPS.

6. Eliminating variations in the quality of randomised trials and deficiencies in the standardised definitions of critical endpoints.

The literature review in this thesis has shown considerable variation in the quality of the randomised trials evaluated, especially regarding generation of allocation sequence and allocation concealment that raises concern about patient selection, assessment, and attrition bias. Despite the number of concluded studies, there are unresolved questions. Understanding the problems inherent in the design, execution, and interpretation of clinical trials in portal hypertension is critical to eliminating quality variations and addressing these deficiencies as well as answering these questions when planning future studies. In addition, the statistical power of trials remains a major problem in portal hypertension trials, where modest survival advantages are unlikely to be detected unless large-scale, multicentre randomised trials are undertaken incorporating sufficient patient numbers. A further limitation is that only a modest number of published trials have performed blinded outcome assessment. The implications for future research into variceal bleeding are that adequately powered, meticulously conducted, properly reported multicentre trials need to continue to address unresolved issues. As patient recruitment becomes an increasing impediment, future studies require internationally accepted standard protocols to facilitate aggregate analyses and future meta-analyses. In addition, the increasing demand for medical fiscal discipline and logistic efficiency require the

issue of cost to be adequately addressed in prospective studies, issues raised at Baveno Consensus Conferences.

7. Future clinical trials

Variceal haemorrhage remains a significant medical challenge that requires ongoing research and the development of new treatment approaches. Optimal advancements in management of variceal bleeding necessitate the implementation of large-scale clinical trials and prospective cohort studies to explore innovative therapeutic approaches and technological applications. These are important not only to enhance patient outcomes but also to establish up to date evidence-based guidelines. The effective management of bleeding oesophageal varices requires a holistic approach considering ethical principles, regulatory standards, and patient-centred care. By balancing these factors, medical interventions are more likely to be clinically successful and aligned with the values and preferences of the individuals receiving care. This reflective approach should contribute to a comprehensive and compassionate model of healthcare delivery.

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Supplementary Table S1 Complications after endoscopic variceal banding for bleeding oesophageal varices. Search strategy.

PUBMED

Search	Query	Records retrieved
#1	"Esophageal and Gastric Varices/therapy"[Mesh]	7,792
#2	"varice"[All Fields] OR "variceal"[All Fields] OR "varicose veins"[MeSH Terms] OR ("varicose"[All Fields] AND "veins"[All Fields]) OR "varicose veins"[All Fields] OR "varices"[All Fields] OR ("oesophageal varices"[All Fields] OR "esophageal and gastric varices"[MeSH Terms] OR ("esophageal"[All Fields] AND "gastric"[All Fields] AND "varices"[All Fields]) OR "esophageal and gastric varices"[All Fields] OR ("esophageal"[All Fields] AND "varices"[All Fields]) OR "esophageal varices"[All Fields]) OR ("oesophageal varices"[All Fields] OR "esophageal and gastric varices"[MeSH Terms] OR ("esophageal"[All Fields] AND "gastric"[All Fields] AND "varices"[All Fields]) OR "esophageal and gastric varices"[All Fields] OR ("esophageal"[All Fields] AND "varices"[All Fields]) OR "esophageal varices"[All Fields])	40,369
#3	((("endoscope s"[All Fields] OR "endoscoped"[All Fields] OR "endoscopes"[MeSH Terms] OR "endoscopes"[All Fields] OR "endoscope"[All Fields] OR "endoscopical"[All Fields] OR "endoscopically"[All Fields] OR "endoscopy"[MeSH Terms] OR "endoscopy"[All Fields] OR "endoscopic"[All Fields]) AND ("varice"[All Fields] OR "variceal"[All Fields] OR "varicose veins"[MeSH Terms] OR ("varicose"[All Fields] AND "veins"[All Fields]) OR "varicose veins"[All Fields] OR "varices"[All Fields]) AND ("banded"[All Fields] OR "banding"[All Fields] OR "bandings"[All Fields])) OR ((("endoscope s"[All Fields] OR "endoscoped"[All Fields] OR "endoscopes"[MeSH Terms] OR "endoscopes"[All Fields] OR "endoscope"[All Fields] OR "endoscopical"[All Fields] OR "endoscopically"[All Fields] OR "endoscopy"[MeSH Terms] OR "endoscopy"[All Fields] OR "endoscopic"[All Fields]) AND ("varice"[All Fields] OR "variceal"[All Fields] OR "varicose veins"[MeSH Terms] OR ("varicose"[All Fields] AND "veins"[All Fields]) OR "varicose veins"[All Fields] OR "varices"[All Fields]) AND ("ligate"[All Fields] OR "ligated"[All Fields] OR "ligates"[All Fields] OR "ligating"[All Fields] OR "ligation"[MeSH Terms] OR "ligation"[All Fields] OR "ligations"[All Fields])) OR ((("endoscope s"[All Fields] OR "endoscoped"[All Fields] OR "endoscopes"[MeSH Terms] OR "endoscopes"[All Fields] OR "endoscope"[All Fields] OR "endoscopical"[All Fields] OR "endoscopically"[All Fields] OR "endoscopy"[MeSH Terms] OR "endoscopy"[All Fields] OR "endoscopic"[All Fields]) AND ("varice"[All Fields] OR "variceal"[All Fields] OR "varicose veins"[MeSH Terms] OR ("varicose"[All Fields] AND "veins"[All Fields]) OR "varicose veins"[All Fields] OR "varices"[All Fields]) AND ("band"[Journal]	147,690

	OR "band"[All Fields]) AND ("ligate"[All Fields] OR "ligated"[All Fields] OR "ligates"[All Fields] OR "ligating"[All Fields] OR "ligation"[MeSH Terms] OR "ligation"[All Fields] OR "ligations"[All Fields])) OR "EVL"[All Fields] OR "EL"[All Fields]	
#4	#1 OR #2	40,369
#5	#4 AND #3	2,085

PMC

Search	Query	Records retrieved
#1	((("Esophageal and Gastric Varices/therapy"[Mesh]) OR (varices OR oesophageal varices OR esophageal varices)) AND (endoscopic variceal banding OR endoscopic variceal ligation OR endoscopic variceal band ligation OR "EVL" OR "EL"))	3,917
#2	(complications OR side-effects OR adverse effects OR reaction OR reactions OR contra-indications OR treatment failure)	4,414,636
#3	#1 AND #2	3,524

Web of Science

Search	Query	Records retrieved
#1	ALL=(varices OR oesophageal varices OR esophageal varices)	14,960
#2	ALL=(endoscopic variceal banding OR endoscopic variceal ligation OR endoscopic variceal band ligation OR "EVL" OR "EL")	651,202
#3	#1 AND #2	1,304

SCOPUS

Search	Query	Records retrieved
#1	ALL(varices OR "oesophageal varices" OR "esophageal varices")	53,250
#2	ALL("endoscopic variceal banding" OR "endoscopic variceal ligation" OR "endoscopic variceal band ligation")	2,845
#3	#1 AND #2	2,614

PRIMO

Search	Query	Records retrieved
#1	ANY FIELD varices OR (oesophageal varices) OR (esophageal varices)	48,983
#2	ANY FIELD (endoscopic variceal banding) OR (endoscopic variceal ligation) OR (endoscopic variceal band ligation)	6,659
#3	#1 AND #2	6,053
	Apply filter to include only articles, conference proceedings, reports	5,845

