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Predictors of Good Outcome in Upper Gastrointestinal Bleeding (UGIB)

Sebastiana Zimba Kalula

B Sc (Human Biology), MB ChB (Zambia), LRCP & S (Edin, Glasgow), MRCP (UK), M.Med (Med) (UCT)

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Declaration

I, Sebastiana Zimba Kalula, hereby declare that the work on which this thesis based is my original work (except where acknowledgements indicate otherwise), and that neither the whole work nor any part of it has been, or is to be submitted for another degree in this or any other university.

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ABSTRACT

Back ground and literature review

Introduction

Acute upper gastrointestinal bleeding is a common cause of emergency hospital admission. It is also not uncommon in patients already in hospital.
The bulk of severe morbidity and mortality occurs in patients with recurrent bleeding or significant comorbid illness. The use non-steroidal anti-inflammatory drugs (NSAID), which is more common in the elderly, more than doubles the mortality associated with peptic ulcer complications. Endoscopy and endotherapy have improved outcome in patients with continued or recurrent bleeding.

Clinical Predictors of Outcome

Despite improved technology in the management of upper gastrointestinal bleeding (UGIB), mortality has remained high. This has been attributed to the increase in the population of elderly people who tend to have other underlying diseases leading to the high mortality rate. From international literature, mortality varies from 4-10%. Most of the reports reflect mortality around 8%. A local retrospective study by Van Stiegmann et. al. (1983) on patients with bleeding peptic ulcer had an overall mortality of 5.4 %, and mortality of 9.8% in those treated surgically.

Ideally to avoid waste of resources and time, emergency endoscopy should primarily be considered in relatively few patients at risk of further haemorrhage. In this class of patients endoscopy is used not only for diagnosis but also for endoscopic treatment to control massive ulcer bleeding. This approach is worthy of consideration in a "resource poor" environment.

Most previous studies have employed endoscopic criteria for identifying patients at high risk of poor outcome. These data are not available at the time of admission. This is therefore not helpful in the triage of patients prior to endoscopy.

Groote Schuur Hospital (location for the current study) has experienced a significant staff cutback over the past 5 years. Few of our regional hospitals and none of our primary health care facilities have endoscopy facilities and endoscopic expertise is similarly limited. Given the pressures on the limited endoscopy services, there is a need for guidelines for the referral of patients to centres with these facilities. There is a possibility that the number of potential referrals of patients with upper gastrointestinal bleeding (UGIB) will increase as the primary health care services improve, a rational review of criteria for referral appeared timely. There would be need to triage patients into:

i). those who must have endoscopy urgently and

ii). those who could be safely referred for elective endoscopy.

Most previous studies have looked at predictors of adverse outcome. To our knowledge no study has been done in South Africa to determine clinical predictors of good outcome prior to endoscopy, that would help determine patients who would recover uneventfully without urgent endoscopy.

Study Rationale

Given the scarcity of both endoscopy resources and of information for the triage of patients who would recover uneventfully following UGIB without urgent endoscopy in our setting, this study set out to answer the question:

Is it possible to identify clinical criteria that will predict patients with UGIB in whom endoscopy could be safely deferred?

OBJECTIVES:

1. To identify clinical criteria that predict uneventful recovery.
2. To determine the accuracy of individual symptoms and signs or combinations of symptoms or signs at the time of presentation in predicting uneventful recovery.

Study population and Methods

Study design and study setting:

The design was a prospective, descriptive, cross sectional study with an analytical component.

The study was conducted at Groote Schuur Hospital (GSH), which is a tertiary referral teaching hospital with 1470 beds. It is affiliated to the University of Cape Town.

Subjects:

Two hundred consecutive patients over the age of 12 years, presenting with haematemesis and/or melaena but without history of varices or gastrointestinal neoplasm were included into the study over a 10 month period (1997-1998). The

median age was 57.5 years (range 43.7-71.4 years). There were 112 males and 78 females. Predictor variables prior to endoscopy were collected and all patients underwent endoscopy.

Independent variables (potential predictors) and dependent variable

The clinical predictors of interest were pre-syncope or syncope, use of non-steroidal anti-inflammatory drugs (NSAID), salicylates, or warfarin, history of ingestion of alcohol, history of previous peptic ulcer disease, haemoglobin concentration, pulse, systolic blood pressure, postural hypotension, age and comorbidity.

The study outcome criterion (dependent variable) was good outcome (i.e. no blood transfusion or endoscopic therapy or surgery, and alive one month after presentation).

The relative risk of good outcome for each predictor variable was calculated. Multiple stepwise logistic regression analysis was used to identify the combinations of variables that best predicted outcome. Sensitivity, specificity, predictive values and likelihood ratios were calculated for these combinations of variables.

Results

Of the 200 patients, 102 (51%) had blood transfusion, 35 (17.5%) patients had endoscopic therapy and 8 (4%) underwent surgery, 4 (50%) had surgery for a malignant ulcer and 4 (50%) for benign peptic ulcer disease. The total mortality rate was 6.5%.

Eighty (40%) of the patients had a good outcome (i.e. no blood transfusion or endoscopic therapy or surgery, and alive one month after presentation).

Haemoglobin concentration greater than 10 g/dl (OR 25.5; 95% CI, 8.9-74.8; p = <0.001), absence of melaena (OR 4.8; 95% CI, 1.8-12.9; p =0.002) and absence of history of syncope (OR 4.0; 95%CI, 1.7-9.5; p = 0.002) were independent predictors of good outcome. A combination of all three variables had the best association with good outcome when compared to a single variable or a combination of any two of these variables. The model with all three variables had sensitivity for good outcome of 34% (27-40%), specificity of 98% (95-100%), positive predictive value of 90% (86-94%) and negative predictive value of 69% (62-75%). The likelihood ratio for a positive test was 13.5 (5.3-54) and the likelihood ratio for a negative test was 0.68 (0.57-0.79).

Of the 200 patients, 30 (15%) had the combination for the prediction rule (haemoglobin greater than 10 g/dl, no melaena and no syncope). These patients would have not been referred for urgent endoscopy. Three (10%) of these i.e.1.5% of the total sample had a poor outcome. They all required sclerotherapy to control haemorrhage and none of them died.

Conclusion

Thus, in this study population with a 40% prevalence of good outcome, haemoglobin greater than 10g/dl, absence of syncope and absence of history of melaena were independent predictors of good outcome. The best prediction rule for good outcome was the combination of all the 3 variables. This had sensitivity for good outcome of 34% and specificity of 98%, the likelihood ratio for positive and negative test of 13.5 and 0.68 respectively. These test characteristics indicate that the test was accurate at excluding poor outcome, which is a priority in the clinical context. The test was not accurate at predicting good outcome. The clinical implications of these findings are

that there would be a 15% reduction in unnecessary endoscopies with 5% or less of the patients with poor outcome sent home without endoscopic examination.

The findings of this study may have clinical relevance especially in under-resourced healthcare environment in which we practice. However the test needs validation before being confidently applied into clinical practice.

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CHAPTER 1 INTRODUCTION

1.1 Background and Literature Review

Acute upper gastrointestinal bleeding is a common cause of emergency hospital admission. A study from the United States of America reported approximately 300,000 hospitalisations with health expenditure in excess of $2.5 billion per year for acute upper gastrointestinal bleeding (Cutler 1981, Gostout 1998). It is also not uncommon in patients already in hospital (Johnston 1973).

Despite improved technology in the management of upper GIT bleeding (UGIB), mortality has remained high. This has been attributed to the increase in the population of elderly people who tend to have other underlying diseases leading to the high mortality rate. From international literature, mortality varies from 4-10%. Most of the reports reflect mortality around 8% (Mueller 1994, Clements 1991, Katschinski 1994, Steffes 1992, Sugawa 1990, Silverstein 1981,Turner 1991). The bulk of severe morbidity and mortality occurs in patients with recurrent bleeding or significant comorbid illness (Terdiman 1998, Jaramillo 1994, Zimmerman1995).

The use non-steroidal anti-inflammatory drugs (NSAID), which is more common in the elderly, more than doubles the mortality associated with peptic ulcer complications (Armstrong 1987). A local retrospective study by Van Stiegmann et al. (1983) on patients with bleeding peptic ulcer had an overall mortality of 5.4 %, and mortality of 9.8% in those treated surgically.

1.1.1 Incidence and epidemiology of UGIB

Earlier local studies have reported occurrence of peptic ulcer disease rather than that of UGIB. In South Africa these have shown a rising trend in the proportion of peptic ulcer disease, which is the most common cause of UGIB. The proportion rose from 0.9 per 1000 hospital admissions between 1943-1948 (Charlewood and Frylinck 1951) to 4.5 per 1000 in 1977 (Segal et. al.). In the study by Segal et al., 28% of the patients with peptic ulcer disease presented with haematemesis and/or melaena. A 4-year study (1978-1981) at Groote Schuur hospital had an average of 437.5 admission per year for UGIB (Van Stiegmann et. al.1983). The total number of admissions per year for the period was not stated.

Earlier European series indicate that between 40 and 120 persons per 100 000 population are admitted to hospital with haematemesis and/or melaena (Schiller et.al.1970, Johnson et al. 1973). The incidence in Denmark in 1987 was 90 per 100 000 adults per year (Wara 1987). Two large population-based studies (Longstreth 1995, Rockall 1995) showed the yearly incidence of upper gastrointestinal bleeding requiring hospitalisation to be about 100 per 100 000 adults. The incidence varies with age; rising from 23 in those aged under 30 to 485 in those aged over 75 years (Rockall 1995*)*. It was twice as high in men as in women (Rockall 1995, Longstreth 1995*)*. The increasing age of the population presenting with UGIB that has been documented by many researchers is a reflection of the increasing age of the general population. In the United Kingdom a study by Johnson et al. (1973) of 817 patients found that 49% were over the age of 60. In the study of Rockall et al (1995) of 4185 patients, the proportion of patients over the age of

60 was 68%. Over the same period (1941-1991) the age structure of the population had changed considerably with the proportion of those aged over 60 years increasing from 15% in 1941 to 21% in 1991 (Rockall 1995).

1.1.2 Causes of upper gastrointestinal haemorrhage

Peptic ulcer remains the commonest cause of acute non-variceal upper gastrointestinal haemorrhage. Ulcer bleeding accounts for 50% of the cases, although the incidence may be expected to fall with wider use of *Helicobacter pylori* eradication therapy and as COX2-specific non-steroidal anti-inflammatory drugs are developed (Palmer 2000). The proportion of variceal bleeding in a study population is dependent on the population under study. A study done on a population with a high incidence of alcoholism showed a greater proportion of varices (22%) and erosive disease (24%) in comparison to other series (Sugawa et al. 1990). In the United Kingdom varices have been reported to represent 2-4% of the patients presenting with upper gastrointestinal bleeding (UGIB) (Report of a Joint Working Group 1992). The other commonly reported causes are oesophagitis (10%), gastritis (3%), Mallory-Weiss tear (3%) and malignancy (2%) (Wara 1987). In the local study (Van Stiegman et al. 1983), of 1750 patients presenting with UGIB 55% had peptic ulcer disease as the source of their bleed. The source of bleeding in the remaining 45% was not stated.

1.1.3 Risk Factors for Gastrointestinal Bleeding and Peptic ulcer bleeding

- **Nonsteroidal anti-inflammatory drugs (NSAID) and salicylates**

Significant association between use of NSAID and salicylates and upper gastrointestinal bleeding from peptic ulcers, oesophagitis and gastric erosions has been reported in several studies (Sommerville et. al. 1986, Levy et. al. 1988, Holvoet et al. 1991). In some series over one third of all haemorrhages from peptic ulcers can be attributed to NSAID or aspirin use (Holvoet et.al. 1991).

NSAIDs cause damage to the gastroduodenal mucosa via several mechanisms, including the topical irritant effect to the epithelium, impairment of the barrier properties of the mucosa, suppression of prostaglandin synthesis through a systemic effect which is independent of route of administration (prostaglandins play a role in modulating mucosal defence), reduction of the mucosal blood flow and interference with the repair of superficial injury (Wallace 2000).

Administration of NSAIDs as suppositories, has been shown to increase the risk of upper gastrointestinal bleeding because of the higher dosages administered by this route. Thus Henry et al. (1993) in their case-control study found NSAID by the rectal route to have an odds ratio of 11.4 compared to 2.3 by oral route.

Carson et al. (1987) and Henry et al. (1993) in their case-control studies found that the increased risk of upper gastrointestinal bleeding in patients taking NSAID followed a linear dose-response relationship.

Weil et al. (1995) in a case-control study investigated the association of aspirin with gastrointestinal bleeding in a study involving 1121 patients presenting with UGIB and 1126 hospital and 989 community matched controls. The odds ratio for aspirin was dose

dependent: 2.3 for 75mg (CI 1.2-4.4), 3.2 for 150 mg (CI 1.7-6.5) and 3.9 for 300 mg (CI 2.5-6.3). The risk was higher with regular aspirin (OR= 4, CI 2.8-5.8) than for enteric-coated aspirin (OR=1.1, CI 0.4-3.3). Short-term use for less than a month was associated with highest risk (OR =9.2, CI 2.3-160.1). Laszlo et al. (1998) found that the combination of over the counter aspirin or NSAID plus alcohol was associated with the highest odds ratio (OR 4.47, 95% CI 2.73 to 7.32) for bleeding when compared to controls or any of these factors alone.

- **Alcohol**

Alcohol causes injury to gastric mucosa by interrupting the gastric mucosa barrier, thus permitting back-diffusion of hydrogen ions. This results in cellular injury and damage to small blood vessels and thus mucosal damage and superficial ulceration (Friedman 1998). The severity of mucosal damage is directly related to the local ethanol concentration and length of exposure (Domschke et al. 1984). Although there are no controlled studies to show that alcohol causes clinically significant UGIB, acute haemorrhagic gastritis accounts for 25% of cases of major haemorrhage in alcoholics compared to 5% in non-alcoholics (Domschke et al. 1984). The combination of alcohol and another "barrier breaker" e.g. salicylates increases the risk of gastrointestinal blood loss (Kaufman et al. 1999).

Despite the common belief that alcohol increases the risk of peptic ulcer disease, the evidence for this is still conflicting. Some studies have shown no relationship between intake of alcohol and increased risk of developing peptic ulcer disease (Friedman 1974, Ivey.1981)

- ***Helicobacter pylori* (in relation to peptic ulcer disease)**

Case-control studies have shown reduced rate of recurrent bleeding in patients who had received ulcer therapy that included eradication therapy for *H. pylori* (Jaspersen 1995, Rokkas 1995, Santander 1995). The findings in these studies were similar, with rebleed rates of 27% and 33% in controls and none in those who received eradication therapy. The longest follow-up period for these studies has been two and half years hence long-term effects of *H. pylori* eradication cannot be defined (Rollhauser 1997). Contrary to this, Pilotto et al. (1997) in a case–control study on elderly patients presenting with UGIB found an inverse relationship between *H. pylori*–positivity and bleeding in patients with gastric erosions and a lower overall risk for bleeding in *H pylori*-positive NSAID users than *H pylori*-negative NSAID users. *H. Pylori* infection was thought to increase gastric prostaglandin synthesis, which has a protective mechanism on the mucosa, resulting in a protective effect against UGIB in the elderly who normally have age related decreases in prostaglandin E_2.

- **Gastric acid and Pepsin (in relation to peptic ulcer disease)**

In the past ideas concerning the pathogenesis of peptic ulcer disease, which count for half the admissions for acute UGIB, focused on the role of acid and pepsin. Medical therapy for peptic ulcer has centred on inhibition of gastric acid secretion. Gastrin is the most potent stimulant of gastric acid secretion. The final step in the secretion of the hydrogen ion is accomplished by an H^+, K^+-ATPase 'proton pump' located in the structure of the parietal cell. Proton pump inhibitors (omeprazole, lansoprazole and pantoprazole) are

specific inhibitors of the H^+, K^+-ATPase 'proton pump', and potent inhibitors of gastric acid secretion. These drugs are substituted benzimidazoles that bind to the proton pump and irreversibly inactivate it (Friedman1998).

Gastric mucosa also contains large amounts of histamine in cytoplasmic granules of mast cells and enterochromaffin-like cells. Histamine is an important stimulant of gastric acid. Recognition of the role of histamine in acid secretion led to the discovery of $Histamine_2$ receptor antagonists (e.g. cimetidine, ranitidine, famotidine and nizatidine).

1.1.4 CLINICAL PREDICTORS OF OUTCOME

Most previous studies have employed endoscopic criteria for identifying patients at high risk of poor outcome (Wara 1985; Storey 1981; Longstreth 1995; Rockall 1996). These data are not available at the time of admission. This is therefore not helpful in the triage of patients prior to endoscopy.

It is commonplace that manifestations of acute UGIB result in reflex interventions and care driven by established practice patterns. Ideally, to avoid waste of resources and time, it would be helpful to identify those patients in whom endoscopy could be delayed without deleterious outcome. Emergency endoscopy should primarily be considered in patients at risk of further haemorrhage. In this class of patients endoscopy is used not only for diagnosis but also for endoscopic treatment to control massive ulcer bleeding (Wara 1985). This approach is worthy of consideration in a "resource poor" environment.

The major task in patients with upper gastrointestinal haemorrhage is to select those patients with bleeding requiring haemostatic intervention. The widely used endpoints in

patients with bleeding ulcers are the number of units of blood transfused, the need for urgent surgery and death. The determinants of these endpoints are the magnitude of initial bleeding episode, whether bleeding persists or recurs, patient's age and overall health (Braniski 1990; Armstrong 1987; Schiller 1970).

Clinical markers that indicate a high risk of further haemorrhage and therefore poor outcome include haemodynamic instability on presentation, bleeding manifested as repeated red haematemesis, haematochezia (passage of red blood per rectum) and failure to respond to resuscitative measures. Haemodynamic assessment includes measures of blood pressure, pulse and their postural changes (Laine 1994).

Contrary to studies that emphasise the importance of clinical predictors, Wara et al. (1987), reported that bleeding pattern before admission and other clinical factors were not reliable predictors of major haemorrhage in a number of studies.

Research and debate on important factors influencing the outcome of acute upper gastrointestinal haemorrhage began in the 1940's (Rockall 1996). Risk factors associated with both re-bleeding and death are well known. However, there has been no agreement on a set of risk factors as different researchers have put a different emphasis on each of these according to their experiences (Northfield 1971; Mayberry 1981; Katschinski 1994). Age, comorbidity, shock, admission haemoglobin values, presentation (either haematemesis, melaena or both), ulcer type, ulcer size, stigmata of recent haemorrhage (visible vessel in an ulcer bed, ooze, fresh clot), and transfusion requirement have all been described as significant risk factors for further haemorrhage and death. The risk of

rebleed and death is well known to be related not to an individual factor but to many factors which tend to interact with each other (Rockall 1996).

There is still controversy as to the significance of these clinical factors and endoscopic findings in predicting outcome. The problem with comparing findings of different studies is that most of the studies done have been small (Rockall 1995, Turner 1991). Turner et al. reported a variation in mortality in upper gastrointestinal bleeding due to variation in sample size with small studies having sample sizes ranging from 66 to 148 patients and larger studies with samples of 387-1427 patients.

On the small samples, it has been impossible to assess the impact of individual factors, while controlling for confounding effects from other factors on the outcome of bleeding. The other problem in comparing different series is the variable patient selection criteria. This introduces selection bias in the study results (Turner 1991). This could explain the variability in the clinical predictions of adverse outcome in the different studies.

Another source of discrepancy is the follow up period. Earlier studies have followed up patients only up to the date of discharge. It has been shown in some studies that death from upper gastrointestinal bleeding does not occur only during the first few days following the bleed but is evenly distributed over the one month following the episode (Hasselgren 1998, Provenzale 1987).

Furthermore, some studies have been done retrospectively. Retrospective studies have a problem of bias as the data collected were not intended for the study and record retrieval may be incomplete (Rockall 1995).

Some studies have validated their findings while others have not.

- **Identification of low-risk patients presenting with UGIB**

Until recently, no study had attempted to devise a simple and therefore clinically useful risk scoring system that would be readily available to the clinician for categorising patients by risk. As junior doctors manage most cases of acute upper gastrointestinal bleeding, a risk scoring system would be a useful aid to patient selection (Rockall 1996). Of the studies that have investigated predictors of outcome, a large number have looked at predictors of adverse outcome (rebleed, death, and surgery). Very few studies have looked at predictors of good outcome. Even then, most of these studies have included endoscopic findings in their decision criteria (Rockall 1996, Longstreth 1995, Longstreth 1998, Lai 1997). Endoscopy facilities are not readily available to "resource poor" communities. The clinical factors in some scoring systems are cumulatively of greater predictive value than endoscopic findings if one removes patients with advanced liver disease, varices and suspected variceal bleeding, a group at greater risk of adverse outcome (Goustout1998).

Except for studies by Bordley et al. (1985) and Kollef et al (1995), most previous studies selecting patients at low risk of adverse outcome have included endoscopic features in their patient selection. Bordley et al. (1985) concluded that patients at low risk of poor outcome, i.e. with none of the following: death, emergency surgery, rebleed or significant complications were unlikely to benefit from early endoscopy and could be managed as out-patients. The predictors of good outcome in this study were: age less than 75 years; no unstable comorbid illness; no ascites on physical examination; normal prothrombin time and within one hour after presentation, a systolic blood pressure of 100 mm Hg or more and nasal gastric aspirate free of fresh blood. Caution must be exercised in

adopting the results of this study because of the small sample size (see table 1), as chance plays a major role in such situations.

Kollef et al. (1995) found from their study that patients classified as being at low risk of adverse outcome had significantly lower rates of re-bleed (3.6% versus 22.5%; $p = 0.022$) and had lower mortality (0.0% versus 21.3%; $p = 0.008$) compared to patients classified as being at high risk. Low risk patients were defined according to the following criteria: (a) haemodynamically stable before ICU admission (i.e. mean arterial pressure of >60 mm Hg and systolic blood pressure >100 mm Hg); (b) not requiring the use of vasopressors; (c) not having evidence of other organ failure requiring ICU admission; and (d) not having evidence of active, ongoing gastrointestinal haemorrhage at the time of triage determination. The results of this study are not applicable to all categories of patients presenting with upper gastrointestinal bleeding as the study population included only patients managed in the intensive care unit. These patients would have had quite a significant bleed and had invasive procedures such as intra-arterial blood pressure readings prior to triage. These facilities are not available at the local primary and most secondary level hospitals.

A summary of studies that investigated predictors of good outcome or low risk of adverse outcome are shown in table 1.

Table 1: Studies of predictors of good outcome or low risk of adverse outcome

Study/Type/Sample	Endpoint	Scope	validated	Significant variables
Rockall 1996 Prospective multicentre (4185). **Risk score**	Low risk (no rebleed, no death)	Yes	Yes	Age (0-2), Shock (0-2), Comorbid (0-3), Diagnosis (0-2), SRH (0-2) **Score ≤ 2 = low risk**
Bordley et. al. 1985 Retrospective (162)	* Good outcome	No	Yes (111 patients prospectively)	Age < 75, no comorbid, no ascites, normal PT, BP > 100, NG aspirate no blood
Longstreth et. al. 1998 176 selected using **pre-selected guidelines**	Out patient treatment. Risk of rebleed or death	Yes	**1% hospitalisation, 1% rebleed, no death**	No SRH, no varices or portal HGP, no debilitation, no orthostatic signs, no severe liver disease or concomitant disease, no anticoagulants or coagulopathy, no fresh haematemesis or melaena, Hb >8 g/dl
Lai et. al. Retrospective **Pre-selected criteria (72 patients)**	Low risk of re-bleed	Yes	Yes (75 patients with DU) No re-bleed in all	Age < 60, stable vital signs, no SRH, no serious comorbidity
Kollef MH et. al. 1995 Prospective (108 ICU patients)	Low risk of rebleed or death	No	Yes **Used pre-selected criteria**	Mean arterial BP < 60 mmHg, no vasopressors used, BP > 100 mmHg, no unstable comorbid

* None of these features: death, emergency surgery, rebleed, significant complications. Scope = endoscopy

SRH= endoscopic stigmata of recent haemorrhage, PT = prothrombin time, BP = blood pressure in mm Hg NG= nasogastric tube, Hb = haemoglobin, DU = duodenal ulcer, ICU = intensive care unit, HGP = hypertensive gastropathy.

- **Studies that used risk scores or other pre-determined criteria to categorise patients into high or low-risk of adverse outcome.**

A number of studies derived a risk score or guidelines that were used to classify patients into high or low risk of poor outcome following upper gastrointestinal haemorrhage (Rockall 1996, Provenzale 1987, Bordley 1985, Kollef. 1995, Kollef 1997, Morgan 1988, De Dombal 1986, Longstreth 1998).

i. Studies including endoscopy features as a method of triage

In Britain, Rockall et al. (1996) assigned a weighed "risk score" from five variables to predict outcome in patients with UGIB. The British scoring system was drawn from a two-phased questionnaire type prospective population based study designed to establish the relative risk for mortality after acute UGIB. The variables were: (1) age in years (< 60 = 0, 60-79 = 1 and ≥ 80 = 2), (2) shock (systolic blood pressure ≥ 100 and pulse < 100 beats/min = 0, systolic blood pressure ≥ 100 and pulse ≥ 100 beats/min = 1, systolic blood pressure < 100 = 2), (3) comorbidity (none = 0, cardiac failure, ischaemic heart disease, or other major comorbidity = 2, and renal failure, liver failure or disseminated malignancy = 3), (4) endoscopic diagnosis (Mallory- Weiss tear, no lesion found at endoscopy, and no endoscopic stigmata of recent haemorrhage (SRH) = 0, all other diagnoses = 1, and malignancy of the upper gastrointestinal tract = 2) and (5) major stigmata of recent haemorrhage (SRH) (none or dark spot only = 0, blood in upper gastrointestinal tract, adherent clot, visible vessel or spurting vessel = 2). Not included as risk factors were haemoglobin, gender, use of certain drugs (NSAID and anticoagulants, and presentation other than shock, e.g. haematemasis and /or melaena. A patient scored a maximum of 7 points prior to endoscopy and a maximum of 11 points after endoscopy. They concluded that patients with a score of ≤ 2 should be considered for early discharge or be treated as out-patients as rebleeding occurs in less than 5% and mortality is virtually zero. The British investigators concluded that their risk score could identify 15% of all cases of acute UGIB on presentation and 26% of all cases after endoscopy who were at

low risk of recurrent bleeding and death. The study results are not applicable to our needs as the risk score is inclusive of endoscopic diagnosis.

Longstreth and Feitelberg (1998) utilised pre-set guidelines (see table 1) derived from their earlier study (Longstreth et. al 1995) to select patients for outpatient treatment. An important addition to their criteria was the availability of adequate social support at home. Patients with liver disease, varices or portal hypertensive gastropathy were excluded for their known increased risk of adverse outcome. With these guidelines hospitalisation was required in 1%, recurrent bleeding occurred in 1% and there were no deaths during 5 to 27 months period of follow up of the selected patients. These authors applied the British "risk score," mentioned above to their patient population. One third of the patients who were successfully managed as outpatients had scores greater than two and would have been assessed as high risk by the British system. The guidelines from the study by Longstreth and Feitelberg just as the risk score from the British study would not be applicable to our needs as the decision criteria included endoscopic features.

Hay et al. (1996), from literature review, derived clinical guidelines in form of a scoring system using 4 variables. These were scored as: (a) haemodynamics (stable = 0 points, intermediate = 1, unstable =2), (b) time from bleeding (> 48 hours = 0, < 48 hours = 1, in hospital = 2), (c) comorbidity ($\leq 1 = 0$, 2 = 1, 3 = 2, $\geq 4 = 3$) and (d) upper gastrointestinal endoscopy (0-4 points, with stigmata of recent haemorrhage scoring 3 points, and persistent UGIB, varices and UGI malignancy scoring 4 points). The hypothesis of the study was that the proposed guidelines would reduce length of hospital stay for low-risk patients with acute UGIB while maintaining or improving quality of care compared to the standard practice. A recommendation for continued hospital stay was given for a total

score of ≥3. The scoring system was applied retrospectively on 500 patients with UGIB, and it was noted that 70% of their patients achieved low-risk status and could therefore undergo early discharge with a complication rate of 0.6%; 95% CI, 0.07-2.1, and no worsening of quality of care. Complications were defined as in-hospital death, emergency surgery, recurrent bleeding, decompensated chronic or new unstable comorbid illness and readmission within 30 days. An acceptable risk of recurrent bleeding was 3% or less. Ninety-four percent of recurrent bleeding and 92% of complications occurred within 72 hours. Although their focus was on reducing hospital stay, the ability to identify low risk patient group would be a move towards outpatient management. Of note as in the fore-mentioned studies, is the use of urgent endoscopy as a method of triage.

ii. Studies that did not include endoscopy features as a method of triage

Provenzale et al. (1987) investigated predictors of outcome prior to endoscopy. The predictors used and their scores were: (a) melaena (absent = 0, present = -1) as melaena was a negative predictor of mortality; (b) haematochezia (absent = 0, present = 1); (c) drop in haematocrit of 5% (absent = 0, present = 1); (d) level of systolic blood pressure in mm Hg (>100 = 0, 90-99 = 1, 80-89 = 2, <80 =3); (e) chronic renal disease (absent = 0 present = 1), (f) liver disease: (i) encephalopathy (absent = 0, present = 1), (ii) spider naevi (absent = 0, present = 1), (iii) prothrombin time in seconds (<12 = 0, 12-15 = 1, >15 = 2) and (g) duration of the bleed in hours (>12 = 0, 3-12 = 1, <3 = 2). The minimum score was minus 1 and maximum score was 12. They concluded that patients with scores ≤ 2 were less likely to die while those with a score > 6 were at a high risk of

dying. The patients at high risk of dying would be candidates for aggressive management and therapeutic endoscopy. This study did not state the management plan for patients with scores between 3 and 5. Management decisions would presumably be at the discretion of the attending physician.

Kollef et al. (1997) reported that patients at high risk had significantly greater rates of in-hospital complications (RR 2.47; 95% CI, 1.38-4.44, p <0.001) at Barnes hospital and RR 8.94; 95% CI, 3.92-20.49; p <0.001 at Jewish Hospital. The classification tool they used was called BLEED standing for: on going **b**leeding, **l**ow systolic blood pressure, **e**levated prothrombin time, **e**rratic mental state, unstable comorbid **d**isease. This classification tool would not be applicable to our needs, as some laboratory investigations such as prothrombin time are not readily available in all centres.

Morgan et al. (1988) used a computer programme to categorise patients. According to presenting symptoms (age, liver disease, heart failure, alcohol history, drug history, continuing bleeding, confusion, dehydration, jaundice, ascites, haemoglobin concentration and systolic BP), patients were classified by a computer programme into very high, high, medium, low and very low risk categories of adverse outcome. Rate of rebleed decreased with reduction in computer-predicted risk of rebleed. In the very high-risk category, 60% of patients re-bled and 32% died while in the low risk group only 4% re-bled and there were no deaths. The variables associated with adverse outcome are as shown in the table 2. The problem with computer aided analysis is the assumption that every centre would have access to a computer.

De Dombal et al. (1986) conducted a similar study and their findings were similar to those of Morgan et al. except that De Bombal included endoscopic features in categorising their patients.

Table 2. Studies using risk score or other pre-determined criteria to categorise patients into high or low-risk of adverse outcome.

Study/Type/Sample	Endpoint	Scope	Validated	Significant variables
Rockall et. al. 1996 Prospective multicentre (4185). **Risk score**	Low risk (no rebleed, no death)	Yes	Yes	Age (0-2), Shock (0-2), Comorbid (0-3), Diagnosis (0-2), SRH (0-2) **Score ≤2 = low risk**
Provenzale et. al. 1987 retrospective (153) **Risk score**	Mortality	No	Yes (104 patients)	Liver disease, Renal disease, continued bleeding **Score ≤ 2 low risk** **Score > 6 high risk**
Kollef et. al. 1997 Prospective (465)	High risk of rebleed, surgery, death	No	Yes **Used predetermined classification tool**	Continued bleeding, BP <100 mm Hg, PT > 1.2, Erratic mental state, Unstable comorbid
De Dombal et. al. 1986 Prospective (4010, O.M.G.E Survey)	High risk of rebleed or death	Yes	No	Age > 60, History of heart or liver disease, confusion, dehydration, jaundice, ascites, Hb < 10 g/dl, BP <90 mm Hg, bleeding from cancer or varices
Morgan et. al. 1988 Prospective (2623)	Risk of Re-bleed, mortality	No	Yes **Used prognostic factors from a previous study (1434 patients)**	Age > 60, liver disease, jaundice, ascites, heart failure, BP < 90 mm Hg, confusion, dehydration, Hb < 10 g/dl
Longstreth et. al. 1995 Retrospective (933) **(78 for outpatient treatment, no complication)**	Low risk patients (out-patient treatment)	Yes	Yes 141 patients **(34 outpatient treatment), 1 re-bleed**	Age < 60, Hb > 10 g/dl, no alcoholism, no syncope or pre-syncope, no unstable comorbidity, BP > 100 mmHg, pulse < 100, no orthostatic signs, no SRH

SRH= endoscopic stigmata of recent haemorrhage, PT = prothrombin time, BP = blood pressure, Hb = haemoglobin, O.M.G.E = Organisation Mondiale De Gastroenterologie (World organisation of gastroenterology). Scope=endoscopy

- **Local studies**

To our knowledge no study has been done in Cape Town to determine clinical predictors of good outcome prior to endoscopy, that would help determine patients who would recover uneventfully without urgent endoscopy.

Van Stiegman et al. (1983) retrospectively analysed 967 patients admitted to Groote Schuur hospital (Cape Town) with bleeding peptic ulcer between 1978-1981. This study looked at predictors of mortality, which included endoscopic features. The predictors of mortality were identified to be age > 50 years, shock (systolic blood pressure <90 mm Hg re-bleed, comorbidity, multiple or stomal ulcers and transfusion > 10 units. Like most international studies, the results of this study are not applicable to our current needs as it includes endoscopic features and there was only one endpoint, mortality. This study also has the above-noted problems associated with retrospective studies.

1.1.5 Why the need to have predictors of good outcome?

Of principal concern is the safety of patients who would to be discharged from primary and secondary health care facilities for deferred endoscopy examination. Reducing the number of urgent endoscopies at the expense of patients' safety would be deleterious. There is a need to isolate predictors of good outcome with a discriminatory ability to accurately classify patients that would be safely discharged on medical therapy without prior endoscopy and recover without any adverse event. Most studies have looked at predictors of adverse outcome. One could argue that we should implement the opposite of the predictors from these studies if we require good outcome measures. This is not possible for the reasons previously stated, such as the use of different endpoints in these studies to the current study. Studies that devised risk scores had groups of patients that did not exactly fit into the low-risk or high-risk groups. The management of this group of patients also needs to be clearly defined.

The commonly used variables in studies on risk factors in UGIB and their association with outcome are summarised in table 3.

Table 3. Summary of frequently tested predictors of outcome in UGIB

Predictors commonly associated with outcome	Predictors uncommonly associated with outcome
Age	Gender
Blood pressure	Previous peptic ulcer disease
Pulse	Previous surgery
Haemoglobin	Melaena
Comorbidity	Salicylates or NSAID
Haematemesis	Anticoagulants
Transfusion requirements	Alcohol
Re-bleed	Smoking
Stigmata of recent haemorrhage	Ulcer location
varices	
Liver disease	

1.2 MANAGEMENT OF UPPER GASTROINTESTINAL BLEEDING

1.2.1 The role Endoscopy and Endoscopy Therapy

Endoscopy has provided physicians with a view of the gastrointestinal tract unprecedented in the history of medicine. However, in the initial phase, the precise role of endoscopy had been argued (Petrini Jr 1988). This was because the anticipated benefits of early diagnosis offered by endoscopy had little effect on overall management such as, reduced transfusion requirements, more rational use of surgery, decreased hospital stay and the overall mortality had remained unchanged (Graham 1980, Eastwood 1981). But if diagnostic and therapeutic techniques were not improving, mortality rate would have worsened with the increasing age of patients presenting with upper gastrointestinal bleeding, as mortality is highest in the elderly (Whigham 1991). Optimal management of a patient presenting with upper gastrointestinal bleeding includes endoscopy (Terdiman 1998). Endoscopic management of upper gastrointestinal bleeding has been expanded from a purely diagnostic role to a therapeutic role (Steffes 1992). Meta-analyses based on systematic literature reviews of randomised controlled trials have demonstrated that endoscopic therapy in peptic ulcer disease is effective in reducing the rate of rebleeding, the need for surgery and the mortality rate (Henry 1988, Cook 1992). Not only is endoscopy useful in improving outcome in UGIB but it is the most sensitive and specific diagnostic procedure for determining the cause and site of bleeding. It provides information regarding (a) location and identity of the bleeding source, (b) bleeding rate and (c) whether stigmata of recent haemorrhage (SRH) (active bleeding at endoscopy, an old or fresh clot, a visible vessel or an ooze) are present (O'Connor 1992).

Despite its sensitivity and specificity, repeat endoscopy may be required in 8 to 10% in whom the bleeding source is undetermined (O'Connor 1992).

Peptic ulcer is the most common bleeding lesion accounting for 50% of all bleeding from upper gastrointestinal tract (Silverstein 1981). Bleeding ceases spontaneously in 75% to 85% of the cases (Gilbert 1981). Not all patients with upper gastrointestinal bleeding require or should be considered as candidates for endoscopic therapy. Age is a primary consideration since mortality appears to be higher in patients over the age of 60 years in whom prolonged bleeding or delay of treatment may increase the likelihood of a poor surgical outcome (Morris 1984). Active bleeding, fresh red clot adherent to ulcer base or a visible vessel indicates a tendency towards rebleed with a recurrence rate of nearly 40% (Griffiths 1979, Wara 1985). The probability of continued bleeding or rebleed may be as high as 85% for active arterial bleeding, approximately 40% for a fresh clot on an ulcer and 5 to 10% for a flat, pigmented spot. A clean base on an ulcer reliably indicates that the ulcer is not likely to bleed (O'Connor 1992)

Endoscopic sclerotherapy is a reasonable therapeutic alternative for varices that have bled once, as rebleed is likely (Graham 1981). Arteriovenous malformations and the lesion associated with Osler-Weber Rendu disease (hereditary haemorrhagic telangietasia) are also likely to rebleed, although the bleeding is usually not life-threatening. The primary goal of therapy in these situations is elimination of the need for continued transfusion (Petrini Jr 1988). Mallory-Weiss (oesophageal) tear rarely requires therapy, since bleeding stops spontaneously in about 90% of cases (Sugawa 1983).

1.2.1.1 Specific Endoscopic Treatments

Specific endoscopic therapeutic techniques greatly increase the utility of upper endoscopy in patients with gastrointestinal bleeding. These are: injection, thermal, combination thermal and injection treatments and mechanical haemostasis.

- **Injection treatment**

This is the treatment of choice in many institutions. The injection commonly consists of dilute epinephrine (adrenaline), which causes vasoconstriction. This is injected around and into the bleeding point. Other materials used are ethanol or hypertonic saline and a combination of thrombin and fibrinogen (fibrin tissue glue). Studies have not shown definitive evidence as to which material is superior. Benefit has been shown in treatment groups compared to controls (Pascu 1989, Rutgeerts 1989, Balanzo 1990, Chung 1991 Asaki 2000) in that need for surgery and overall mortality were reduced.

- **Thermal treatments**

Laser thermocoagulation was the first endoscopic therapy used to treat bleeding ulcers. This has been replaced by cheaper and more user-friendly methods. Most institutions use heater probe thermal haemostasis but recently argon plasma coagulator (APC) has been instituted (Palmer 2000). APC is a no-touch treatment with relatively superficial damage and therefore low risk of complications such as ulceration, induction of bleeding and perforation associated with other modes of therapy (O'Connor 1992).

- **Combination injection and thermal treatment**

Studies have failed to demonstrate significant overall benefit for combination therapy. Chung et al. (1991) compared combination of epinephrine and heater probe coagulation versus epinephrine alone. They demonstrated slight benefit in a subgroup of patients who had most severe active haemorrhage, as they tended to have fewer rebleeding episodes and required surgical intervention less often when treated by combination method. Though this may demonstrate some clinical benefit, supportive evidence is currently lacking to translate this into standard clinical practice (Palmer 2000).

- **Mechanical haemostasis**

A range of physical methods has been used to arrest ulcer bleeding. The most promising of which is the use of haemoclips. Studies comparing injection treatment with haemoclip or a combination of the two have demonstrated a slightly better outcome in the haemoclip or combination therapy. In a study by Chung et al. (1999) of 124 patients with actively bleeding or visible vessel who were randomly allocated to the treatments, rebleeding rate was lowest (2.4%) in those receiving haemoclip alone, 9.5% in those receiving combination treatment (haemoclip and hypertonic saline-epinephrine injection) and 14.6% in patients treated by injection alone. Total haemostasis was achieved in 95% of patients receiving haemoclip or combination treatment and 85% of those treated with injection alone. Villanueva et al. (1996) similarly randomised 79 patients to epinephrine injection or combination of epinephrine injection and haemoclip. The rebleeding rate was lower in the combination group, hospital stay was shorter and transfusion

requirements lower in the haemoclip group, but no difference in mortality and requirement of surgery was noted.

1.2.1.2 Failure of Endoscopic therapy

Endoscopy therapy is unsuccessful in 15-20% of patients (Palmer 2000). Patients at highest risk of failing endoscopy therapy are those who present with anaemia, shock and active arterial bleeding from a posterior duodenal ulcer (Villanueva 1993). Lau et al. (1999) have studied outcome in patients who rebleed following initial endoscopic haemostasis. They compared outcome in patients who were randomised either to repeat endoscopic therapy (48 patients) or surgery (44 patients) over a 40 month period. In 73% of patients haemostasis was achieved after repeat endoscopy but the remaining 27% had surgery (23% for failure of treatment and 4% for perforation resulting from thermocoagulation). The complication rate was 36% in the surgical group and 14% in the endoscopy group. The mortality rate was 18% in the surgical group and 10% in the endoscopy group. The length of hospital stay and blood transfusion requirements was similar in the two groups. On multivariate analysis, hypotension at randomisation ($p = 0.01$) and ulcer size of at least 2 cm ($p = 0.03$) were independent predictors of failure of endoscopy therapy. The conclusion from this study was that when patients rebleed after initial haemostasis has been achieved, it is worthwhile to re-treat using endoscopic methods.

1.2.2 Role of Medical Therapy

- **Inhibitors of Acid Secretion**

Studies have so far not demonstrated any practical and beneficial medical therapy in the management of acute upper gastrointestinal bleeding. The primary role of medical therapy is in the healing of peptic ulcers.

The first pharmacological treatment which promoted the healing of peptic ulcers were the histamine$_2$ (H_2) receptor antagonists e.g. cimetidine and ranitidine which inhibit gastric acid secretion. Later, proton pump inhibitors (PPI), e.g. omeprazole and lansoprazole were introduced. These are more potent inhibitors of acid secretion than the H_2-antagonists.

There is conflicting evidence about the role of these drugs in the control of upper gastrointestinal bleeding (Jenkins 1999). Daneshmend (1992) in a placebo-controlled trial of omeprazole failed to demonstrate any difference between treatments with respect to recurrent bleeding, transfusion requirement, need for surgery and mortality. The problem with this study is that they included all patients with UGI bleeding, 80% of whom would have stopped bleeding spontaneously as a result of intrinsic haemostatic mechanisms (Steffes 1992), diluting any difference in effect. However, omeprazole has been found to improve outcome and reduce need for invasive therapy in placebo-controlled trials that only included patients with prognostic signs indicative of rebleeding (Khuroo 1997, Hasselgreen 1997, Schaffalitzky de Muckadell 1997).

Some studies have compared omeprazole versus H_2-receptor antagonists in the setting of acute UGI bleeding. Lin et al. (1996) randomised 31 patients to omeprazole and 32 patients to cimetidine intravenously for 3 days. Both groups received endoscopic therapy

for actively bleeding ulcers and non-bleeding visible vessels. This study reported a significantly different rebleeding rate of 3.2% versus 28.1% in favour of omeprazole. Lanas et al. (1995) randomised 51 patients with acute UGI bleeding to intravenous omeprazole and ranitidine. Baseline characteristics were matched in both groups; none received endoscopic therapy. Re-bleeding rate and surgery requirements were significantly reduced in favour of omeprazole. Gastric juice alkalisation has been shown to reduce clot lysis (Patchett 1995). This could explain the beneficial effect of acid inhibition in the setting of acute gastrointestinal bleeding. In contrast to the findings of Lanas et al. (1995), Villanueva (1995) noted no difference in the rate of rebleed, emergency surgery, need for transfusion and length of hospital stay in two groups of patients randomised to receive intravenous omeprazole (45) or intravenous ranitidine (41). Lau et al. (2000) in a double blind trial, randomised 240 patients with actively bleeding ulcers or ulcers with nonbleeding visible vessel to high dose intravenous omeprazole or placebo (120 in each group) for 72 hours followed by oral omeprazole for 8 weeks. These patients were all treated with an epinephrine injection followed by thermocoagulation prior to randomisation. The primary end point was recurrent bleeding within 30 days after endoscopy. Bleeding recurred within 30 days in 6.7% in the omeprazole group, and 22.5% in the placebo group.

The use of standard or high dose H_2-receptor antagonists or omeprazole to prevent recurrence of bleeding is currently controversial as there has been no consistently demonstrable benefit in patients with acute gastrointestinal bleeding (Peterson and Cook 1998). A pooled analysis of different studies has been difficult because of the heterogeneity of the patients enrolled to these studies, the variable endoscopic stigmata of

recent haemorrhage (SRH) and different baseline risks of rebleeding, different dosages and duration of trial medication and different cointerventions (Peterson and Cook 1998). Treatment should however be initiated to promote ulcer healing (Laine 1994).

There is nothing to choose between the currently available PPIs (omeprazole, lansoprazole and pantoprazole). The speed of healing is proportional to the intensity of acid suppression and the duration for which gastric pH is kept above 3. H_2-receptor antagonists maintain the pH above 3 for 8-12 hours and PPIs for 15-17 hours (Tytgat 1998).

- **Somatostatin and Octreotide**

Somatostatin is a hormone and octreotide is its synthetic analogue.

Somatostatin exerts a number of effects on the gastrointestinal tract that may be beneficial in the control of non-variceal UGI haemorrhage.

a) It inhibits basal and stimulated gastric acid and pepsin secretion (Konturek 1985, Mogard 1985), thereby promoting platelet aggregation and facilitating the formation of occlusive thrombus.

b) It reduces gastric mucosal blood flow (Li 1996) and gastric perfusion (Panés 1994), thus may be beneficial in decreasing the risk of rebleeding.

c) It stimulates mucous protection, which forms the main protective barrier between the gastric mucosa and digestive actions of acid and pepsin. This may be beneficial in both preventing early recurrent bleeding from ulcers and in promoting ulcer healing (Jenkins 1999).

Octreotide inhibits basal and stimulated gastric acid secretion (Whitehouse 1986, Olsen 1987) but it is not yet known whether it has an effect on gastric blood flow, pepsin secretion or mucous production (Jenkins 1999). The inhibitory effects on gastric acid secretion of octreotide are short lived being lost after 7 days of continuous, low dose, subcutaneous administration, owing to down regulation or internalisation of somatostatin receptors involved in inhibiting acid secretion (Londong 1989).

- **Comparative Studies of Somatostatin and Octreotide in UGI Bleeding**

Trials comparing the effects of somatostatin versus H_2-receptor antagonists, omeprazole, or placebo (Coraggio 1989, Tulassay 1989) suggest that somatostatin significantly reduced the rate of rebleeding compared with ranitidine and omeprazole. These studies only included patients with stigmata prognostic of recurrent bleeding. Preliminary results of a randomised controlled trial have a similar findings with rate of rebleeding of 6% in those treated with somatostatin and 18% in those treated with either ranitidine or omeprazole following endotherapy (Jenkins 1999).

Randomised trials that included low risk patients have failed to demonstrate any beneficial effects of somatostatin (Somerville 1985, Panés 1994, Basso 1986). Inclusion of such low risk patients would probably have diluted the effects of somatostatin as in 80% bleeding will cease spontaneously (Steffes 1992).

Imperiale and Birgisson (1997) conducted a meta-analysis based on systemic English-language literature review of randomised clinical trials comparing somatostatin or octreotide with H_2 blockers or placebo in patients with clinical or endoscopic diagnosis of acute nonvariceal upper gastrointestinal haemorrhage. There was a reduced rate of re-bleeding or continued bleeding (RR 0.53; 95% CI, 0.43-0.63) in favour of somatostatin. The efficacy of somatostatin was more in peptic ulcer bleeding (RR 0.48; CI, 0.39-0.59) than in non-peptic ulcer haemorrhage (RR 0.62; CI, 0.39-1.002). The overall result suggested a decreased need for surgery in the somatostatin group, but a subgroup analysis of investigator-blinded trials revealed a more modest effect that was not statistically significant (RR 0.94; CI, 0.87-1.001).

Octreotide has not been well studied. Small randomised controlled trials with this drug suggest that its effect on control of bleeding is lower than that of somatostatin (Jenkins 1999).

On the basis of available data, it would seem that somatostatin may be of value in the treatment of acute UGI bleeding. Because of conflicting findings from various studies its use has not gained popularity and further studies are required (Jenkins 1999). Wider use of naturally occurring somatostatin may be further curtailed by its high cost (Shields 1992). The analogue octreotide is much cheaper but not as effective.

- **Eradication of *H. pylori***

A number of studies have demonstrated that successful eradication of *H. pylori* in the long term reduces recurrent ulcer bleeding and subsequent complications (Graham 1993, Rokkas 1995, Santander 1996, Labenz 1994 Jaspersen 1995). Tygat et al. (1993)

reviewed seventeen trials in which patients with or without *H pylori* were compared. The follow-up period varied from 6 to 48 months after healing. The relapse rate was 71% (range 20-100%) in patients with persistent infection and 0% (0-22%) in those in whom *H. pylori* had been eradicated. It is suggested that only therapies that achieve over 90% cure rate per protocol and over 80% per intention to treat should be employed (Hunt 1997, Maastricht Consensus Report 1997). The commonly used regimens consist of PPI-Clarithromycin-Amoxycillin or PPI-Clarithromycin-Metronidazole. These have an efficacy range of 85-95% (Tytgat 1998). The regimen used will depend on the local prevalence rates of microbial resistance.

Studies have shown that PPIs are superior to H_2-receptor antagonists or other pharmacological modalities in healing and maintenance of duodenal ulcers with known *H. pylori* status (Hunt 1997, Howden 1997).

1.2.3 Role of Surgery in the bleeding patient

Surgery has had a role in the following situations: (1) non-response to medical therapy; (2) pyloric stenosis or hourglass contracture of the stomach from scarring; (3) suspicion of malignancy; (4) complications, such as haemorrhage and perforation. Except for the last indication, improvement in medical therapy has not changed the indications for surgical therapy in upper gastrointestinal bleeding (Jamieson 2000).). Other reports have suggested that emergency surgery is on the increase because of a decrease in elective surgery and an increase in the incidence of NSAID-associated complications (Bliss 1991).

- **Emergency surgery in Haemorrhage**

The advent of endoscopic therapies such as thermal therapy and injection sclerotherapy has greatly diminished the need for emergency surgery in bleeding peptic ulcer. Eradication therapy for *H pylori,* where it is affordable, has changed the natural history of peptic ulcer disease and diminished the need for surgery (Jamieson 2000).

In the past emergency surgery would have been indicated in patients presenting with shock and acute anaemia; coagulopathy; other significant comorbidity and visible vessel or active bleeding at endoscopy (Meilahn and Ritchie 1994). Endoscopic therapy controls bleeding in 80% to 90% of these patients. For those where bleeding recurs or is not controlled, surgery is indicated (Meilahn and Ritchie 1994). Evaluation of operative treatment in peptic ulcer bleeding has been difficult because randomised controlled trials, which are the preferred scientific standards for investigating treatments are rare in this field (Ohmann 2000). In many trials involving medical or endoscopic therapy, surgery is considered as an outcome criterion rather than a treatment option (Ohmann 2000). Gralnek et al. (1997) in their prospective, randomised-controlled study confirmed the widespread belief that endoscopic forms of therapy are superior when compared to traditional medical/surgical therapies. Lau et al. (1999) confirmed the superiority of endoscopic therapy in patients with recurrent bleeding after endoscopic haemostasis. They randomised patients to repeat endoscopy and surgery. The surgical group had more complications than the group that had the repeat endoscopy group (Lau 1999).

Surgical procedures vary from local (under-running the vessel or ulcer excision) to conventional (partial gastrectomy). From the available evidence, there is no difference

between local and radical surgery concerning mortality, although the rebleeding rate may be higher in the local group (Ohmann 2000).

1.3 How should patients with Upper Gastrointestinal Bleeding be managed?

Profile of international accepted practices:

Important clinical questions in the management of UGIB include:

- Should a patient be admitted to hospital?
- How soon should endoscopy be performed?
- Who should take responsibility (surgeons or physicians)?

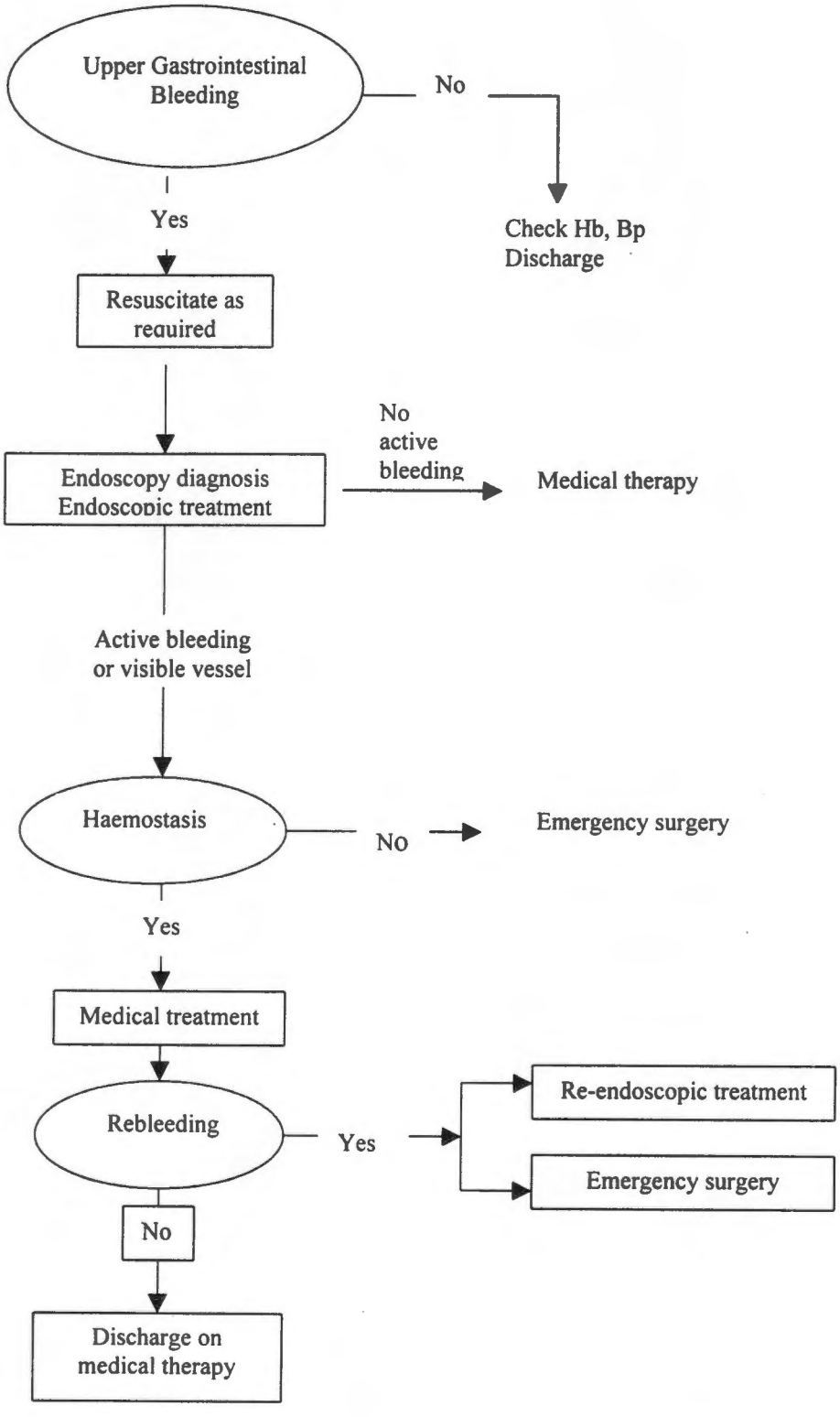
Experts in this field emphasise a team approach to the management of patients with UGIB where surgeons and physicians have jointly agreed policy guidelines for management of such patients (Sanderson 1990, Clements 1991). Patients should preferably be admitted to medical wards or specialised gastrointestinal (GI) units with close medical-surgical liaison and managed according to strict protocols for resuscitation, transfusion and surgery (Mueller 1994).

In some centres the decision as to whether to manage a particular patient as an in- or outpatient is made after clinical and endoscopic evaluation. In such situations there are guidelines encompassing absolute and less clearcut recommendations for discharge (Longstreth 1995).

On the whole, accepted practice is that endoscopies are done on the next endoscopy list usually within 24 hours unless the case is deemed to be an "emergency" (i.e. experiencing life threatening UGIB) (Report of Joint Working Group 1992).

Ideally patients presenting with upper gastrointestinal bleeding should have the severity of the bleeding assessed. If the patient presents with haemoglobin < 10 g/dl, shock (systolic blood pressure < 100 mmHg) or has other risk factors (age > 60 years, comorbidity) the bleeding should be regarded as serious. Such patients should have adequate resuscitation with blood and be admitted where they can be adequately observed for rebleeding. If these patients rebleed or have continued bleeding, emergency endoscopy should be arranged or endoscopy should be carried out on the next available list. The previously fit patient can be observed in a general medical ward and undergo endoscopy on the next available list to document the source of bleeding. A protocol of patient management has been derived (Figure 1).

Fig: 1 Management of patients with upper gastrointestinal bleeding



Adapted from report of Joint working group 1992 and Ohmann et al. 2000

1.4 CURRENT PRACTICE AT GROOTE SCHUUR HOSPITAL (GSH):

- **Admission policy**

All patients with upper gastrointestinal bleeding present to the Emergency Unit. Those with obvious melaena or haematemesis are admitted to the emergency medical admission ward for further management. Patients with known oesophageal varices (which is often the most rapid type of UGIB and known not to benefit from medical therapy) (Elta 1991) and those presenting in shock are referred to surgeons to expedite endoscopic and surgical intervention if necessary.

Patients with less clear history of UGIB who are faecal occult blood negative and haemodynamically stable are discharged on antacids and referred for routine outpatient endoscopy.

Patients over the age of 60 years with any history of gastrointestinal tract (GIT) bleeding are all admitted for endoscopy.

- **Endoscopy policy**

All patients who are admitted have endoscopy on the next day's routine endoscopy list. Over the weekends (when such services are not available) endoscopy is usually performed on the first weekday slate. Emergency endoscopy services are always available.

There are currently 4 different waiting lists for upper gastrointestinal endoscopy:

1. Emergency (available at all times);

2. Urgent routine (next morning);

3. Delayed urgent routine i.e. patient presenting Friday midday to Monday morning all have endoscopy on Monday;

4. Elective (out patient list usually entailing a waiting list of up to 2 months).

For patients from G.F. Jooste and Conradie Hospitals, which are regional hospitals in the drainage area of GSH, endoscopy is available once a week at GSH, unless the bleeding does not settle in which case patients are promptly transferred to GSH and endoscopy performed as indicated above.

- **Resuscitation practice**

Physicians operating the endoscopy service require that all patients should have been adequately resuscitated, with stable haemodynamic parameters and a haemoglobin of at least 10 g/dl prior to endoscopy. In the case of life threatening bleeding resuscitation is performed during endoscopy, usually in an operating theatre.

Endoscopy typically reveals one of the following common situations:

- Patient with an actively bleeding ulcer - the ulcer is injected with submucosal adrenaline (1:10 000 – 20 000) to bring about haemostasis.
- Patient with features suggesting a high risk of rebleed (active bleeding at endoscopy, an old or fresh clot, a visible vessel or an ooze) is observed for a further 92 hours in hospital regardless of endotherapy as re-bleeding has been commonly found to occur within three days (Laine 1994).

- Patient with gastric ulcers - routinely have biopsies taken from the wall of the ulcer to exclude gastric carcinoma unless they are actively bleeding in which case they are rescoped once bleeding has settled. All patients with gastric ulcers are rescoped after one month of medical ulcer healing therapy after which time the ulcer is expected to have healed. If the ulcer hasn't healed repeat biopsies are taken, compliance with therapy is reviewed and medical therapy is given for a prolonged period depending on biopsy results.
- Patient with bleeding varices - the varices are injected with sclerosant (Ethanolamine oleate) or banded to secure haemostasis.

All patients with non-bleeding gastric and duodenal ulcers are discharged soon after endoscopy on ulcer healing therapy that commonly consists of a proton pump inhibitor with or without antibacterial therapy for eradication of *H. pylori*. Indications for the latter therapy are a positive urease test for *H. Pylori* (Laine 1994).

- **Criteria for Emergency scope:**

The general practice in the hospital is that following admission the patients are resuscitated and endoscopy is performed on the next available list unless:

1. Patient has known oesophageal varices;
2. Patients presents evidence of a rebleed (hypovolaemia, fresh haematemesis or drop in haemoglobin of >3g when there is no evidence of bleeding);
3. Patient continues to bleed (haemoglobin and blood pressure and pulse not stabilising despite resuscitative measures).

These patients are generally referred to surgeons, as they would possibly require surgical intervention.

Patients found to have gastric, oesophageal or other gastrointestinal malignancy are also referred to surgeons.

1.5 Pressures on local endoscopy services

Groote Schuur Hospital (location for the current study) has experienced a significant staff cutback over the past 5 years. Few of our regional hospitals and none of our primary health care facilities have endoscopy facilities and endoscopic expertise is similarly limited. Given the pressures on the limited endoscopy services, there is a need for guidelines for the referral of patients to centres with these facilities. Diagnostic endoscopy without a therapeutic procedure does not alter mortality (Dronfield 1982, Erickson 1986), though in most cases it provides information on the source of bleeding. Our community would benefit more if these services were aimed at patients to whom it would be most beneficial, that is in whom it would alter management decisions. If only the deserving patients were to undergo endoscopy, the waiting list for non-urgent endoscopies which is currently stands at 2 months would be shortened as the need for emergency endoscopy would diminish, leaving time for elective endoscopy. It would hence be beneficial to be able to predict patients who would do well regardless of whether they underwent endoscopic examination or not.

There is a possibility that the number of potential referrals of UGIB cases will increase as the primary health care services improve, a rational review of criteria for referral appeared timely. There would be need to triage patients into:

i). those who must have endoscopy urgently and

ii). those who could be safely referred for elective endoscopy.

1.6 Study Rationale

Given the scarcity of both endoscopy resources and of information for the triage of patients who would recover uneventfully following UGIB without urgent endoscopy, this study set out to answer the question:

1.6.1 QUESTION:

Is it possible to identify clinical criteria that will predict patients with UGIB in whom endoscopy could be safely deferred?

1.6.2 PURPOSE:

To identify patients at low risk for an adverse outcome following an upper gastrointestinal bleed.

1.6.3 AIM:

- To identify patients who would not require in-patient hospital care following upper gastrointestinal bleeding (UGIB) by:
- Identifying the key clinical variables prior to endoscopy that predict uneventful recovery.

1.6.4 OBJECTIVES:

- To identify clinical criteria that predict uneventful recovery.
- To determine the accuracy of individual symptoms and signs or combinations of symptoms or signs at the time of presentation in predicting uneventful recovery.

CHAPTER 2: METHODS

2.1 Study population and Methods

2.1.1 Study Design:

The design was a prospective, descriptive, cross sectional study with an analytical component.

2.1.2 Study population

Inclusion criteria

The study population included consecutive patients over the age of 12 years presenting to the Emergency unit of GSH with haematemesis and/or melaena between October 1997 to August 1998.

Exclusion criteria

Patients were excluded:

- If their initial presentation was to another hospital that instituted resuscitative measures;
- If they were known to have oesophageal varices or upper gastrointestinal malignancy;
- If they presented with anaemia without a clear history of UGIB;
- If they developed UGIB during the course of hospitalisation for another problem.

2.1.3 Study setting

Groote Schuur Hospital (GSH) which is a tertiary referral teaching hospital with 1470 beds. It is affiliated to the University of Cape Town. The hospital provides both secondary and tertiary care to a racially and socio-economically mixed patient population.

All patients admitted to GSH with upper gastrointestinal bleeding (UGIB) initially present to the Emergency Unit.

2.1.4 Independent variables (potential predictors)

The clinical predictors of interest were presyncope or syncope, use of non-steroidal anti-inflammatory drugs (NSAID), salicylates, or warfarin, history of alcohol ingestion (see definitions), history of previous peptic ulcer disease, haemoglobin concentration, pulse, systolic blood pressure, postural hypotension, age and comorbidity.

2.1.5 Outcome (dependent) variable considered:

i Good outcome

1. Non-performance of: -

a. an endoscopic procedure (endotherapy) to control bleeding,

or

b. a therapeutic surgical procedure,

or

c. a blood or blood product transfusion,

and

2. Alive on discharge and no death related to UGIB within the month of initial presentation.

ii **Poor outcome,** i.e. any patient who had anyone of the above events.

Death in hospital or in the first month of presentation. The deaths were divided into: i) those that were directly related to the gastrointestinal bleeding and ii) those that were not directly related to gastrointestinal bleeding.

2.1.6 Management criteria

Criteria for admission changed in that all patients who presented with UGIB during the period of the study were admitted to the emergency admission ward regardless of severity of bleed. Timing of endoscopy remained as is currently practiced (see under current practice at Groote Schuur Hospital).

Referral to surgeons was maintained as is currently practiced.

2.1.7 Data collection

Data was collected on a structured clerking sheet (see appendix A), which was designed for the study. On admission every patient had this clerking sheet filled in by the casualty officer who collated the patient's history, findings and management prior to endoscopy.

No formal training was given to the casualty officers in the use of the clerking sheet but they were informed of the study and use of the study questionnaire as a clerking sheet for all patients presenting with UGIB. A written note was left in the casualty unit informing the casualty officers of the ongoing study.

A pilot study was conducted using the first ten patients. The casualty officers were asked for their input on any ambiguities. Except for the layout, no major changes

were made to the questionnaire.

History

Information collected from history included: -

- Demographic data (name, age gender, race, hospital number, home address, telephone number (home or work where applicable), date of admission and date of discharge or death);
- History of the current bleed, which included duration of the current bleed (in hours) and any other recent episode of bleeding (in days);
- Whether the bleed was a haematemesis or melaena or both;
- Pre-syncope or syncope;
- Medication use, particularly use of salicylate, non-steroidal anti-inflammatory drugs and anticoagulants at the time of the bleed;
- Social habits (smoking and alcohol use) at the time of the bleed;
- History of previous peptic ulcer;
- History of other underlying disease (obtained from the patient and hospital notes where these were available).

Physical examination

Physical examination at the time of admission included: -

- Haemoglobin (gm/dl) by fingerprick method, using a BMS Haemoglobinometer (Linegar 1991);
- Blood pressure (in millimetres of mercury) measured by the admitting doctor with a mercury sphygmomanometer. This was done in a supine, sitting and where

possible also in a standing position;

- Pulse measured in beats/min using a watch with a second hand counted over one minute.

Following admission, nursing staff checked blood pressure and pulse every 6 hours or half-hourly if on blood transfusion. Haemoglobin was checked every 12 hours.

Other examination included:

- Palpation for lymphadenopathy including a Virchow's (VT) node which is a palpable lymph node in the supraclavicular fossa as a sign of metastatic gastric carcinoma;
- Abdominal examination for tenderness, abdominal mass, visceromegaly, rectal examination, inspection of vomit/stool (noting colour) and testing for occult blood in stools with Haemoccult test (Rockey 1999);
- Examination of cardiovascular, central nervous, musculoskeletal, renal and respiratory systems for evidence of other underlying disease.

Endoscopic findings

At endoscopy the endoscopist recorded the following:

- Identification of the source of bleed;
- Stigmata of recent bleeding. These were any of the following: - a bleeding visible vessel, a visible vessel, an adherent clot, ooze or a fresh clot;
- Endoscopic diagnosis, that is, oesophageal varices, a Mallory-Weiss tear, oesophagitis, gastritis, duodenitis, peptic ulcer, neoplastic disease, any other

specific pathology or no pathology at all found;

- Any specific therapeutic procedure done during endoscopy, for example sclerotherapy.

At endoscopy biopsy samples were obtained where judged clinically indicated, to identify the presence or absence of *Helicobacter pylori* by rapid urease test and histology (Isenberg et al. 1991), or to determine whether the ulcer was benign or malignant.

2.1.8 Management based on endoscopy as advised by the endoscopists

At endoscopy the endoscopist filled into the clerking sheet the endoscopic findings, procedures and recommendations on further management of the patient (see appendix A). The recommendation ranged from:

- Medical therapy in the form of one of the following: antacids, sucralfate, histamine$_2$-antagonists, proton pump inhibitors, with or without antibiotic therapy for *Helicobacter pylori*;
- Referral for "surgical" management either to expedite endoscopy or for the surgical control of the bleeding or for definitive surgery for a malignant ulcer;
- Prolonged hospital stay because of signs seen at endoscopy that indicated an increased likelihood of recurrent bleeding;
- No therapy recommended, but advice on further investigation (e.g. to investigate the lower gastrointestinal tract).

The principal investigator checked every admission before discharge to record the outcome in each patient and ensure that study pro forma had been completed.

2.1.9 Status at one-month follow-up

Patients were followed up within a month of discharge from hospital by the fieldworker with extensive previous experience in fieldwork. She was trained by the principal investigator on use of the follow-up questionnaire (see appendix B) and the importance of the patients being reviewed within a month following discharge.

The follow-up questionnaire had the same study number as the main questionnaire for each patient. The questions in the questionnaire related to how the patient rated their health at the time of the follow-up, whether they had been booked for a repeat endoscopy, whether the symptoms had resolved and whether they had a recurrent bleed. If they had died, the principal investigator made a judgement as to whether death was related or unrelated to the bleed. This was determined by interviewing relatives and reviewing hospital notes where death occurred in hospital.

Before discharge from the hospital all patients consented to the telephonic contact or home visit that would be made by the fieldworker to check on their progress. The follow up was done telephonically in the majority of cases. Where a telephone was unavailable, the patient was visited at his/her home address.

Patients that could not be contacted after five telephone calls or three home visits were classified as "lost to follow-up". For every patient lost to follow-up, the field worker made a comment as to why contact was not made.

2.2 Sample size calculations

There were 11 clinical predictors (variables) of interest for this study. These were: age, use of NSAID and/or salicylates, use of anticoagulation (warfarin), history of ingestion of alcohol, history of previous peptic ulcer disease, a history of pre-syncope or syncope, the presenting blood pressure, pulse and haemoglobin and comorbidity

status. Using general guidelines that at least 10 events are required for each independent variable included in a logistic regression model, a sample with 110 or more patients was considered adequate (Peduzzi 1996). Since comorbidity had 7 subgroups (cardiac, renal, pulmonary, hepatic, haematology, central nervous system, musculoskeletal) and history of ingestion of alcohol had 2 subgroups (alcohol binge and alcoholism) bringing the total variables to 20, a target sample size was set at 200 patients.

2.3 Instruments used: validity and reliability

- **Questionnaire:**

Most of the questions were closed with space provided for comments. Old hospital records in those patients who previously had been seen at the hospital supplemented this information.

- **Measurement of Haemoglobin (gm/dl)**

Due to cost constraints, laboratory haemoglobin by Coulter counter was not routinely done. The haemoglobin was measured using the Buffalo Medical Specialities (BMS) Haemoglobinometer Model 10-101DR. This is a compact battery powered Miniature Photometer. It measures haemoglobin content of blood by the oxyhaemoglobin method. The BMS Haemoglobinometer compares the absorption of light through a layer of haemolysed blood (oxyhaemoglobin) to that of a standardised glass wedge. If regularly calibrated this is accurate to 5% (0.6 gm/dl) of the true haemoglobin value over the range of 4-20 gm/dl [Manufacturer's manual]. The validity and reliability of the BMS haemoglobinometer has been tested in a local study of 100 consecutive

venous samples submitted to the haematology laboratory, and has been found to be good. The average error was between 5% and 6% (0.6 g/dl) of the laboratory haemoglobin value (Linegar 1991).

Nursing staff check haemoglobin. If the reading is low or it does not match the clinical context, then a doctor or another nurse is asked to recheck the colour co-ordination. In this study some readings, especially if very low (8gm/dl or low), were verified with a second sample that was sent to the laboratory. This was done at the discretion of the attending doctor.

- **Blood pressure**

Blood pressure (systolic and diastolic) readings were measured using a mercury sphygmomanometer. There was no special training for the study in taking these measurements, as this forms part of the routine measurements done on all patients presenting to the emergency unit. Every member of the staff used the standard method of recording blood pressure as recommended by the American Heart Association (1967).

A specific requirement for the study was that the admitting doctor took the initial measurements in a supine, sitting and standing position. This was to check for a postural drop in blood pressure, which, if present, would suggest volume depletion. Blood pressure was measured 4 hourly thereafter. In situations of continued bleeding the measurements were done at hourly intervals.

Blood pressure measurements are liable to a number of errors:

i) Inter-observer variation as they were recorded by different nursing staff on the ward;

ii) Use of a wrong sized cuff e.g. an obese patient using a standard size cuff will

give falsely high readings;

ii) An instrument that is not well calibrated;

iii) Changing emotional state and position of the patient.

- **Pulse recording**

The radial pulse was counted over one minute, using a watch with a second hand. *The blood pressure and pulse rate values used in the text were those measured at the time of presentation to hospital.*

- **Haemoccult test (Bayer)**

This is a guaiac-based test that relies on peroxidase activity of heme in haemoglobin. Theoretically it should be able to detect blood in the stool from all parts of the gastrointestinal tract. However, in bleeding from the upper gastrointestinal tract, false negative results may occur as intestinal enzymes and/or bacteria degrade haemoglobin introduced into the upper gastrointestinal tract to porphyrin. The proportion of positive tests increases with increased amounts of blood loss (Rockey 1999). Feacal haemoglobin levels must exceed 10 mg/g (10 ml daily blood loss) before the haemoccult test is positive at least half the time. Certain fruit and vegetables such as turnips, cauliflower, grapes and broccoli have a perioxidaselike activity giving false positive reactions (Macrae 1982).

- **Endoscopy**

This is prone to inter-observer variation even when done by physicians experienced in endoscopy. The higher the number of such endoscopists involved the lower the inter-observer agreement. This has been demonstrated in the following studies.

i. Twenty- five videotapes from endoscopic examinations of patients with recent non-variceal upper gastrointestinal haemorrhage were shown to 47 expert endoscopists. The endoscopists were asked to classify every lesion for features of stigmata of recent haemorrhage according to Forrest's classification. Forrest classified endoscopic appearance of lesions into: FIA, FIB, FIIA, FIIB, FIIC and FIII (see definitions). Three independent experts had agreed on the Forrest's classification of each lesion. Agreement was expressed as of kappa statistics (see definitions). Kappa statistics were calculated for each class of Forrest's classification. For FIA, kappa = 0.76 and FIB, kappa = 0.61. For other lesions kappa varied from 0.44 to 0.49 (Mondardini 1998).

ii. Gastroenterologists were shown videos of endoscopic images to investigate whether they would agree on the definitions of lesions within the stomach seen at endoscopy. There was a 100% overall agreement (kappa = 1.0) for patients not taking non-steroidal anti-inflammatory drugs (NSAID). For lesions in patients taking NSAID, the overall agreement was 52% with a kappa statistic of 0.37. Ulcers in patients on NSAID are often more superficial and difficult to distinguish from erosions (Hudson 1994).

2.4 Statistical Methods

Data was entered into a standard spreadsheet (Excel) and univariate, bivariate and multivariate descriptive statistics were derived using STATISTICA VERSION 5.1 1998 software. Bivariate analysis for the individual predictive factors for a good

outcome was performed using the Chi-square test (with a Yates correction) or Fisher exact test. Continuous variables were compared using the two-tailed Student t-test. To increase clinical relevance the continuous variables were also converted into categorical variables by grouping them into ranges. The cut-off values were determined before analysis, and are those that are internationally accepted as defining severity of an UGIB. Associations were expressed as relative risk with 95% confidence intervals for bivariate analysis and odds ratios with 95% confidence intervals for multiple logistic regression analysis. A 5% level of significance was used.

Clinical predictors that showed significant association with good outcome on bivariate analysis ($p = 0.10$ for inclusion and 0.05 for retention) were entered into multiple logistic regression models. A final model was selected using stepwise multiple logistic regression analyses. Variables with $p > 0.05$ were excluded from the model.

Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio for a positive test and likelihood ratio for a negative test were calculated individually and in combination for the variables that were found to be independently associated with outcome. Ninety-five percent confidence intervals for sensitivity, specificity and likelihood ratios were calculated using standard methods (Simel 1991).

2.5 ETHICAL AND LEGAL CONSIDERATION

The study was approved by the Ethics and Research Committee of the Medical School of the University of Cape Town. There were no major ethical considerations as far as the patients were concerned as there was no major change in their management except

that patients with non-significant UGIB were admitted. A verbal consent for completion of the questionnaire and for a follow up visit or telephone call was obtained from each patient.

CHAPTER 3: RESULTS

Results

3.1 Data capture

Over the 10 month period of the study, a total of 306 patients were admitted to the emergency admission ward with a diagnosis of haematemesis and/or melaena. Of these, 218 (71.24%) had their data captured on the questionnaire. A total of 200 (91.7%) of these patients met the inclusion criteria and were included in the final analysis. The reasons for the exclusion of the 18 were varied: 2 were known to have oesophageal varices; 2 were unfit for endoscopy (end stage chronic obstructive airways disease); 3 refused endoscopy; 7 did not have haematemesis or melaena at presentation; 3 did not co-operate with the endoscopic procedure and 1 was a readmission within 4 weeks of the initial admission.

3.2 Patient characteristics

3.2.1 Age and gender

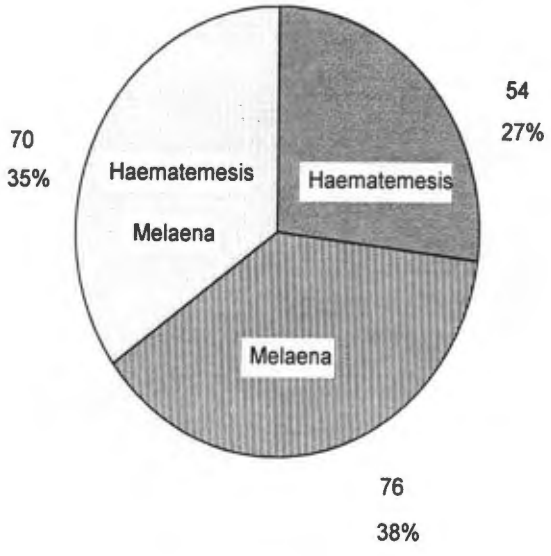
The median age for the 200 patients was 57.5 years and the interquartile range 43.7-71.4 years. The male: female ratio was 1.6:1 with 122 (61%) males and 78 (39%) females.

3.2.2 Manifestation of haemorrhage

- **History of haematemesis and melaena**

All patients included in the study presented with either a history of haematemesis or melaena, or both. The proportion of patients with haematemesis, melaena, or both is shown in figure 2.

Figure 2: The proportion of patients with haematemesis and/or melaena



- **Faecal occult blood (FOB) test and history of haematemesis and melaena.**

One hundred and sixty nine (84.5%) of the 200 patients had a faecal occult blood test performed. The numbers and percentages of their FOB test status is shown in table 4.

A larger proportion of patients with a history of melaena had positive FOB test than those with history of haematemesis alone. The difference in proportions was significant ($p < 0.001$)

Table 4: History of melaena and FOB test status

Presentation	FOB +ve	FOB-ve	Total	*p
Melaena	121 (94.5%)	7 (5.5%)	128 (75.7%)	
No melaena	25 (61%)	16 (39%)	41 (24.3%)	<0.001
Total	146 (86.4%)	23 (13.6%)	169 (100)	

+ve= positive; -ve = negative; *chi square test

3.3 Potential risk factors present on history:

3.3.1. Previous peptic ulcer disease (PUD)

Fifty-nine (29.5%) gave a history of previous peptic ulcer disease. One hundred and twenty three (61.5%) gave no history of previous peptic ulcer disease, whereas 18 (9%) did not know whether they had had previous peptic ulcer disease or not.

3.3.2. NSAID and Salicylate intake at time of the bleed

Thirty-eight (19%) of patients were taking non-steroidal anti-inflammatory drugs (NSAID) while 66 (33%) were taking salicylates. Seventeen (8.5%) admitted taking NSAID and salicylates concurrently. Therefore, a total of 87 (43.5%) of patients were taking ulcerogenic drugs at the time of presentation. Eleven (5.5%) did not know whether they were taking NSAID or salicylates. For analysis, these were regarded as not taking these drugs.

3.3.3. History of current anticoagulant consumption

Twenty (10%) patients were taking warfarin at the time of presentation (1 for deep vein thrombosis and 19 for cardiac disease of whom 9 had atrial fibrillation and 10 had valvular heart disease either with or without valvular surgery). The median international normalised ratio (INR) at presentation was 4.1, with a range from 0.9 to greater than 10, and an interquartile range of 2.5-6.4.

3.3.4. Alcohol

Forty-one (20.5%) gave a history of an alcohol binge prior to onset of symptoms. Thirty-five (17.5%) gave a history of chronic alcoholism.

3.3.5. Comorbid diseases

- **Cardiac disease**

A history of cardiovascular disease was present in 71 (35.5%). The disease distribution was as follows: hypertension 22 (30.9%), ischaemic heart disease 37 (52.1%), arrythmias 14 (19.7%), peripheral vascular disease 1 (1.4%) and pulmonary embolism 1 (1.4%). The commonest arrhythmia was atrial fibrillation occurring in 9 (64%) of the 14 patients with arrythmias. Of those with cardiac disease, 17 (23.9%) were in congestive cardiac failure at the time of presentation. Note that some patients had a combination of these cardiac diseases.

- **Pulmonary disease**

A history of pulmonary disease was present in 29 (14.5%). This included chronic obstructive airways disease (COAD) 21 (72.4%), asthma 4 (13.8%), bronchiectasis 3 (10.3%) and chronic fibrosing alveolitis 1 (3.4%).

- **Renal disease**

A history of renal disease was present in 14 (7%). Of these 9 (64.3%) had chronic renal failure.

- **Hepatic disease**

Ten (5%) patients had hepatic disease. Of these 5 (50%) had liver cirrhosis (4 of the 5 gave history of excessive alcohol intake), 1 (10%) had cancer of the breast with metastasis to the liver and 4 had hepatomegaly of unknown etiology. None had a past history of oesophageal varices.

- **Haematological disease**

Three (1.5%) had a history of haematological disease. All had lymphoma.

- **Neurological disease**

Twelve (6%) patients had neurological disease. These included previous stroke 5 (42%) of whom 2 were taking salicylates, encephalopathy due to alcoholic liver disease 5 (42%), peripheral neuropathy 1 (8%) and dementia 1 (8%).

- **Musculoskeletal disease (MSS)**

Twenty-six (13%) patients had a history of musculoskeletal disease. Twenty-one (81%) of the 26 were due to arthritis, either rheumatoid or osteoarthritis. One (4%) had gout arthritis and 4 (15%) had undiagnosed musculoskeletal aches and pains. Eighteen (69%) of the 26 patients were taking NSAIDs.

3.3.6. Pre-syncope and syncope

One hundred and six (53%) of the patients had symptoms of pre-syncope or syncope.

3.4 Haemodynamic Assessment

- **Blood pressure**

At the time of admission, 21 (10.5%) patients had a systolic blood pressure (SBP) of less than 100 mm Hg. The median (SBP) was 130 mm Hg with a range of 70 to 220 mm Hg. The interquartile range was 110 to 150 mm Hg.

- **Pulse**

Eighty (40%) had a pulse rate of greater than 100 beats per minute. The median pulse rate (interquartile range) was 97 (80-104) beats per minute.

- **Postural blood Pressure**

Supine and sitting blood pressure were recorded in 136 (68%) of the patients. Of these, 25 (12.5%) had a postural drop in blood pressure of greater than 20 mm Hg.

- **Patients with shock at presentation**

Eleven (5.5%) patients met the study criteria for shock of a systolic blood pressure of less than 100 mm Hg and a pulse rate of greater than 100 beats per minute. An additional 10 (5%) had systolic blood pressure less 100 mm Hg but a pulse rate of less than 100 beats per minute. In total 21 (10.5%) had blood pressure less than 100 mm Hg at presentation.

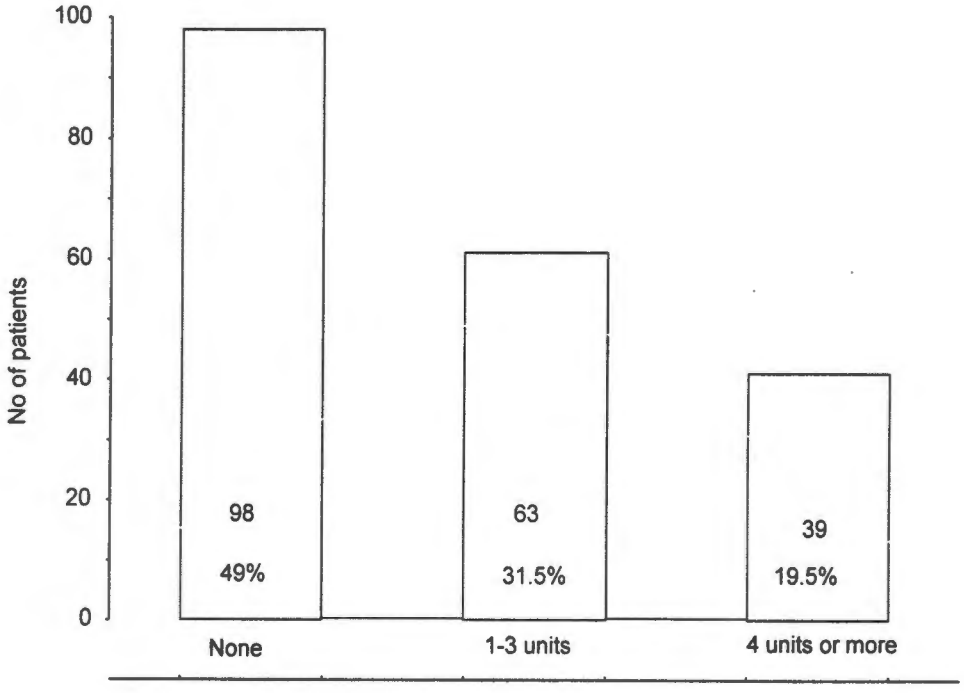
- **Haemoglobin**

Ninety-two (46%) had a haemoglobin concentration of less than 10 grams per decilitre (gm/dl). The median (interquartile range) was 10 (7.5-12.8) gm/dl. The range was 3 - 18 gm/dl.

3.5 Transfusion requirements

One hundred and two (51%) of the 200 patients required blood transfusion. The minimum number of units transfused was 1 unit and the maximum was 10 units. The mean and median were both 3 units with an inter-quartile range of 2-4. Thirty-nine (19.5%) were transfused 4 units of blood or more. See figure 3. Six patients received transfusion of fresh frozen plasma to control bleeding that was associated with a raised INR, the result of an excessive anticoagulant effect.

Figure 3: Transfusion requirements



3.6 Endoscopic diagnoses

The largest group had peptic ulcer disease. The second largest group had gastritis, which included erosive gastritis. There were a substantial number of patients where the cause for the bleed was unknown.

- **Peptic ulcer**

Of the 95 (47.5%) patients who had peptic ulcer disease diagnosed on endoscopy, the majority were gastric ulcers 60 (63%), 32 (34%) had duodenal ulcers, 2 (2%) had both gastric and duodenal ulcers and 1 (1%) had a stomal ulcer. Other causes of UGIB are reflected in table 5.

Table 5: Source of bleed found on endoscopy

Diagnosis	number	% of total (N 200)
Peptic ulcer	95	47.5
Gastritis	53	26.5
Oesophagitis	26	13
Duodenitis	15	7.5
Mallory Weiss Tear	9	4.5
Malignancy	8	4.0
Varices	4	2.0
Miscellaneous	9	4.5
Unknown diagnosis	19	9.5

The miscellaneous group consisted of 2 patients with telangiectasia, 2 with gastric vascular malformation, 2 with duodenal polyps, 2 with Dieulafoy lesion and 1 with oesophageal candidiasis

3.7 Relation between presenting factors and outcome

The study outcome criterion was good outcome (i.e. no blood transfusion or endoscopic therapy or surgery, and alive one month after presentation). Eighty (40%) patients of the 200 had a good outcome.

One hundred and two (51%) were transfused. Thirty-five (17.5%) patients had endoscopic therapy. Eight (4%) underwent surgery. Of these 4 (50%) had surgery for malignant ulcer and 4 (50%) for benign peptic ulcer disease.

There were 13 (6.5%) deaths. Of these, 8 (61.5%) deaths were related to gastrointestinal haemorrhage but 7 (87.5%) had other underlying comorbidity. Five (38.5%) deaths of the 13 were unrelated to UGIB, they were due to underlying comorbidity (2 had cardiac and chronic renal failure, 1 had chronic renal failure, 1 had

metastatic breast cancer and 1 had pneumonia). One patient died from gastrointestinal bleeding without associated comorbidity.

3.7.1 Bivariate analysis

3.7.1.1. Previous peptic ulcer disease and outcome

Previous history of peptic ulcer disease was not associated with outcome. A relative risk (RR) of 0.90 was indicative of a 10% reduction in the likelihood of a good outcome, but the 95% confidence interval (CI) did not exclude 38% reduction or 32% increase in likelihood of a good outcome in patients with previous peptic ulcer disease. See table 6.

Table 6: History of previous peptic ulcer disease and outcome

	Outcome					
	Good	Poor	Total	RR	95% CI of RR	P*
Prev.PUD +ve	23	36	59	0.90	0.62-1.32	0.59
Prev. PUD -ve	53	70	123			
Total	76	106	182			

*Chi square test; Prev. PUD +ve = Previous peptic ulcer disease present; Prev. PUD -ve = Previous peptic ulcer disease absent

3.7.1.2. Previous PUD and endoscopic diagnosis of peptic ulcer

A history of previous peptic ulcer disease was not significantly associated with the endoscopic diagnosis.

Though the RR was 1.35, history of previous peptic ulcer disease was not statistically significantly associated with endoscopically proven PUD as the 95% CI for the relative risk included 1. However, this is more likely to be associated with endoscopic

diagnosis of PUD as lower CI (0.99) is almost equal to "1" and the upper CI (1.84) does not exclude an 84% increase in the relative risk. See table 7.

Table 7: Significance of previous PUD on endoscopic diagnosis of peptic ulcer.

	PUD on endoscopy					
	+ve	-ve	Total	RR	95% CI of RR	P*
Prev.PUD +ve	33	26	59	1.35	0.99-1.84	0.06
Prev. PUD -ve	51	72	123			
Total	84	98	182			

*Chi square test; Prev.PUD +ve = prev. peptic ulcer disease present; Prev. PUD –ve = previous peptic ulcer disease absent.

3.7.1.3. Ulcerogenic drugs (NSAID and salicylates) and outcome

Current intake of NSAID and salicylates had no association with outcome (table 8). The RR 0.82; 95% CI, 0.58-1.17; p = 0.26. Though the RR was suggestive of a reduced likelihood of a good outcome, the 95% CI for the RR included 1 indicating that the association was not significant.

Table 8: Association of ulcerogenic drug intake and outcome

	outcome					
	Yes	No	Total	RR	95% CI of RR	P*
Drugs	31	56	87	0.82	0.58 - 1.17	0.26
No drugs	49	64	113			
Total	80	120	200			

*Chi-square test. Drugs refers to NSAID and salicylates

- **Drug history and proportion of endoscopic diagnosis of peptic ulcer**

The risk of finding a peptic ulcer at endoscopy was increased by 79% (95% CI 33%-140%) in patients taking ulcerogenic drugs. The association between use of NSAID or salicylates with diagnosis of peptic ulcer disease is shown in table 9.

Table 9: Association of ulcerogenic drug intake with a diagnosis of peptic ulcer.

	PUD on endoscopy					
	+ve	-ve	Total	RR	95% CI of RR	P*
Drugs	55	32	87	1.79	1.33-2.40	<0.001
No drugs	40	73	113			
Total	95	105	200			

*Chi-square test; PUD= peptic ulcer disease; Drugs refers to NSAID and salicylates

- **Drug history and Gastritis**

Forty-seven (23.5%) were found to have gastritis on endoscopy. Of these, 16 (30.2%) were taking either NSAID or salicylates.

Table 10: Association of ulcerogenic drug intake with gastritis.

	Gastritis					
	Yes	No	Total	RR	95% CI of RR	P*
Drugs	16	71	87	0.67	0.39 - 1.14	0.13
No drugs	31	82	113			
Total	47	153	200			

*Chi-square test. Drugs refers to NSAID and salicylates

There was no association between ingestion of NSAID or salicylates and the diagnosis of gastritis on endoscopy. The 95% CI did not exclude a 61% reduction or 14% increase in development of gastritis in those taking ulcerogenic drugs (table 10).

3.7.1.4. Warfarin intake and outcome

Sixteen (80%) of the 20 patients taking warfarin to achieve anticoagulation, required blood transfusion. Six patients were transfused with fresh frozen plasma as well. Four (67%) of the six were on warfarin and 2 (33%) had deranged liver function. Significantly more patients on warfarin required blood transfusion compared to those not taking warfarin. See table 11.

Table 11: Warfarin intake and transfusion requirements

	Blood transfusion					
	yes	no	Total	RR	95% CI of RR	P*
Warfarin	16	4	20	1.67	1.28-2.19	0.006
No warfarin	86	94	180			
Total	102	98	200			

*Chi-square test

3.7.1.5. Alcohol

A history of alcohol intake was not associated with outcome.

Alcohol binge had no association with outcome. The RR of 1.19 is suggestive of a weak association with a good outcome but the 95% CI for the RR indicates that this association was not significant. See table 12. In 5 patients information on alcohol binge drinking was not available.

Table 12: History of alcohol binge and outcome

	Outcome					
	Good	Poor	Total	RR	95% CI of RR	P*
Alcohol B +ve	19	22	41	1.19	0.81-1.75	0.39
Alcohol B -ve	60	94	154			
Total	79	116	195			

*Chi square test; Alcohol B. = Alcohol binge

Alcoholism had no association with outcome. The RR of 1.27 was suggestive of an association with a good outcome but the 95% CI for the RR indicates that the association was not significant. See table 13.

Table 13: History of alcoholism and outcome

	Outcome					
	Good	Poor	Total	OR	95% CI of OR	P*
Alcolism +ve	17	18	35	1.27	0.86-1.88	0.25
Alcolism -ve	63	102	165			
Total	80	120	200			

*Chi square test; Alcolism. = Alcoholism

3.7.1.6. Comorbid diseases and outcome

- **Cardiac disease**

Thirty-eight (19%) of the 200 patients had cardiac disease both on history and examination. Cardiac disease was significantly associated with outcome. Patients with cardiac disease were 53% less likely to have a good outcome. The 95% CI

indicates that these patients were 10 - 75% less likely to have a good outcome when compared to those without cardiac disease. See table 14.

Table 14: Presence of cardiac disease and outcome

	Outcome					
	Good	Poor	Total	RR	95% CI of RR	P*
Cardiac +ve	8	30	38	0.47	0.25-0.90	0.008
Cardiac -ve	72	90	162			
Total	80	120	200			

*Chi square test; Cardiac +ve = presence of cardiac disease; Cardiac -ve =absence of cardiac disease

- **Renal disease and outcome**

Renal disease was not significantly associated with outcome. The RR showed a 73% reduction in the likelihood of a good outcome in those with renal disease but the 95% CI for the RR indicated that a 96% reduction to a 72% increase in the likelihood of a good outcome could not be excluded. (Note the small sample of those with renal disease). See table 15.

Table 15: Presence of renal disease and outcome

	Outcome					
	Good	Poor	Total	RR	95% CI of RR	P*
Renal +ve	1	8	9	0.27	0.04-1.72	0.08
Renal -ve	79	112	191			
Total	120	80	200			

*Chi square test; Renal +ve = presence of renal disease; renal -ve = absence of renal disease

- **Pulmonary disease and outcome**

Thirty (15%) of the 200 patients had signs of pulmonary disease on examination. Presence of pulmonary disease was not associated with outcome. The RR of 0.72 was suggestive of a 28% reduction in the likelihood of a good outcome in those with pulmonary disease. The 95% CI for the RR of 0.40-1.28, p=0.22 indicates that the association was not significant as it does not exclude a 60% reduction or a 28% increase in the likelihood of a good outcome.

- **Hepatic disease and outcome**

Hepatic disease was not associated with outcome. A RR of 1.27 is suggestive of an association with a good outcome but the 95% CI of 0.67-2.41; p = 0.51 indicates that the association was not significant.

- **Haematological disease and outcome**

The number of patients with haematological disease was too small for a meaningful statistical analysis. However, none of the 3 patients with haematological disease had a good outcome. They all required blood transfusion. Two were transfused 1-3 units of blood, while one was transfused at least 4 units of blood. None had endoscopic therapy or surgery and there were no deaths.

- **Neurological disease and outcome**

Presence of a central nervous system disease was not associated with outcome. The RR of 0.82 suggested that the likelihood of a good outcome was reduced but the 95% CI for the RR of 0.36-1.87, p = 0.76 indicates that the association was not significant.

- **Musculoskeletal disease and outcome**

Presence of musculoskeletal disease was not associated with outcome. The RR of 0.74 was suggestive of a 26% reduction in the likelihood of a good outcome but the 95% CI for the RR of 0.41-1.36, p = 0.30 suggests that the association was not significant.

- **Comorbidity and outcome**

When all diseases (cardiac, pulmonary, renal, hepatic, haematological, neurological and musculoskeletal) were combined, the likelihood of a good outcome was reduced by 33% (6% – 52%) in patients with other underlying disease when compared to those with no other underlying disease. See table 16.

Table 16: Association between comorbidity and outcome

	Outcome					
	Good	Poor	Total	RR	95% CI of RR	P*
Comorbid.+ve	41	81	122	0.67	0.48-0.94	0.02
Comorbid -ve	39	39	78			
Total	80	120	200			

*Chi square test; Comorbid =comrbidity;

3.7.1.7. Age and outcome

Age was associated with outcome. Patients under the age of 60 years were 58% more likely to have a good outcome compared to those patients aged greater than 60 years. See table 17

Table 17: Association between age and outcome

	Outcome					
	Good	Poor	Total	RR	95% CI of OR	P*
Age < 60 yrs	52	56	108	1.58	1.10-2.28	0.01
Age > 60 yrs	28	64	92			
Total	80	120	200			

*Chi square test

Comorbidity increased with increasing age (RR 1.75; 95% CI, 1.39-2.20; $p < 0.001$) for those over the age of 60 years.

3.7.1.8. History of melaena or haematemesis and outcome.

Presentation with haematemesis alone was associated with good outcome. The likelihood of a good outcome was 72% higher in those who presented with haematemesis alone when compared to those who presented with melaena alone. See table 18.

Table 18: Influence of haematemesis on outcome

	Outcome					
	Good	Poor	Total	OR	95% CI of OR	P*
Haemat. +ve	59	65	124	1.72	1.14-2.59	0.005
Haemat. -ve	21	55	76			
Total	80	120	200			

*Chi square test; Haemat. +ve = positive history of haematemesis; Haemat. -ve = melaena

3.7.1.9. Haemodynamic assessment and outcome

Patients with a good outcome had significantly higher blood pressure, lower pulse rate and higher haemoglobin levels compared with those with a poor outcome. See table 19.

Table 19: Haemodynamic assessment and outcome

	outcome		
	Good	Poor	p
Systolic BP; median, (I-Q range)	135 (120-159)	120 (105-140)	0.002
Pulse; median, (I-Q range)	86 (80-100)	100 (90-110)	<0.0001
Hb (median, I-Q range)	13 (10.8-14)	8 (5.5-10.5)	0.0001

I-Q range = interquartile range

Though the results show a difference in systolic blood pressure, pulse and haemoglobin between those who had a good outcome and those who had a poor outcome, there were no clear-cut values separating these two groups except for haemoglobin that shows a cut-off of below 8 gm/dl. See figures 4-6.

Figure 4: Systolic blood pressure distribution in the good and poor outcome groups.

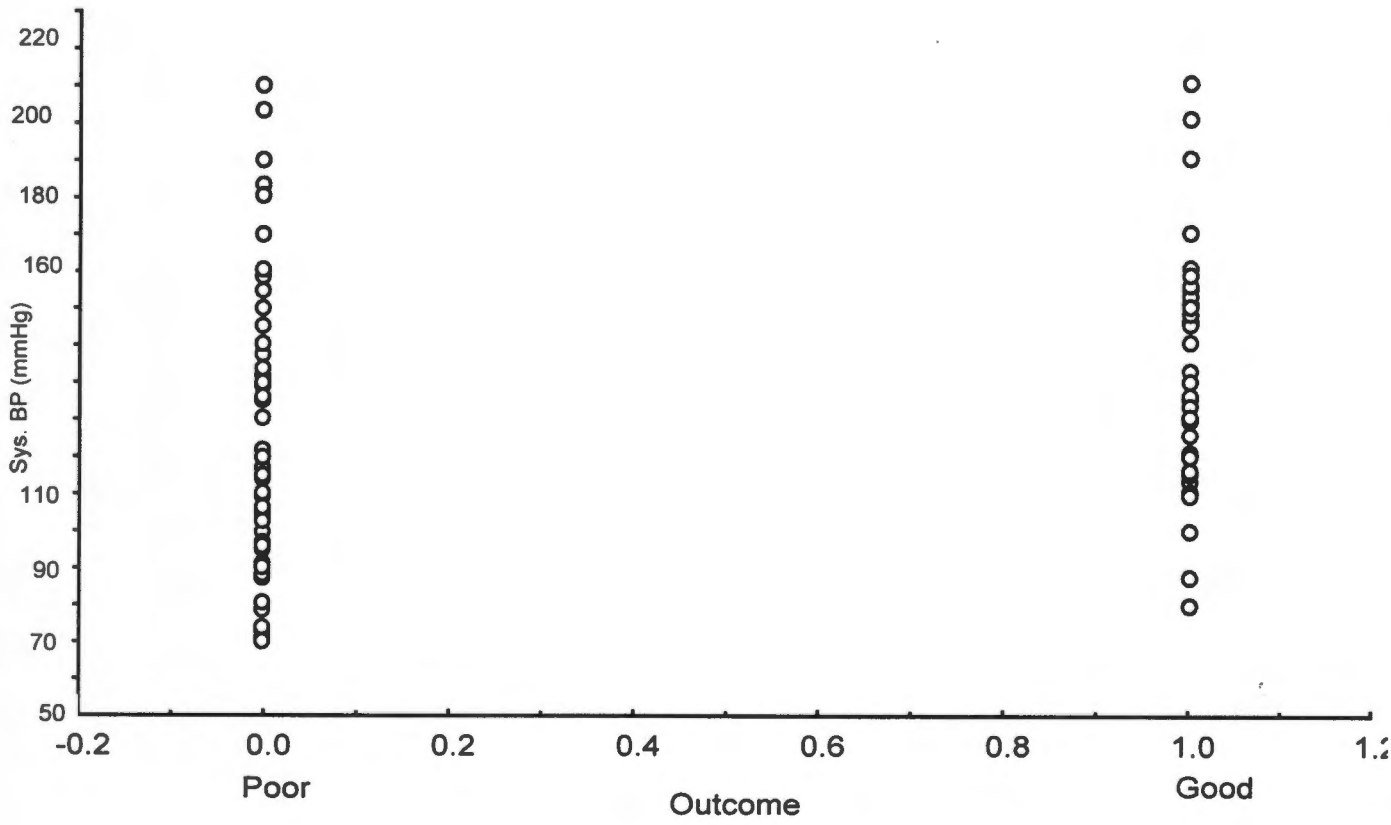


Figure 5: Pulse (beats / minute) distribution in the good and poor outcome groups.

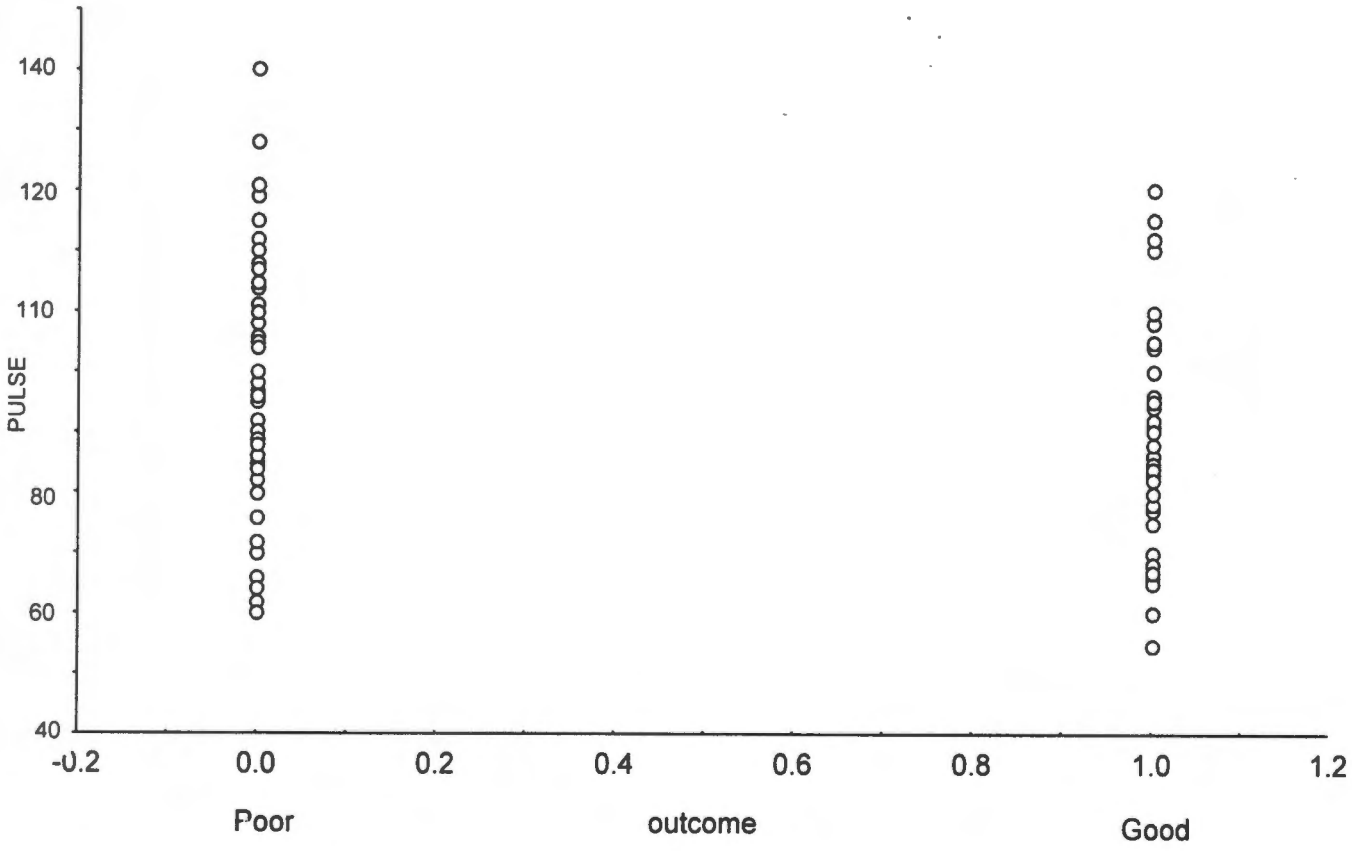
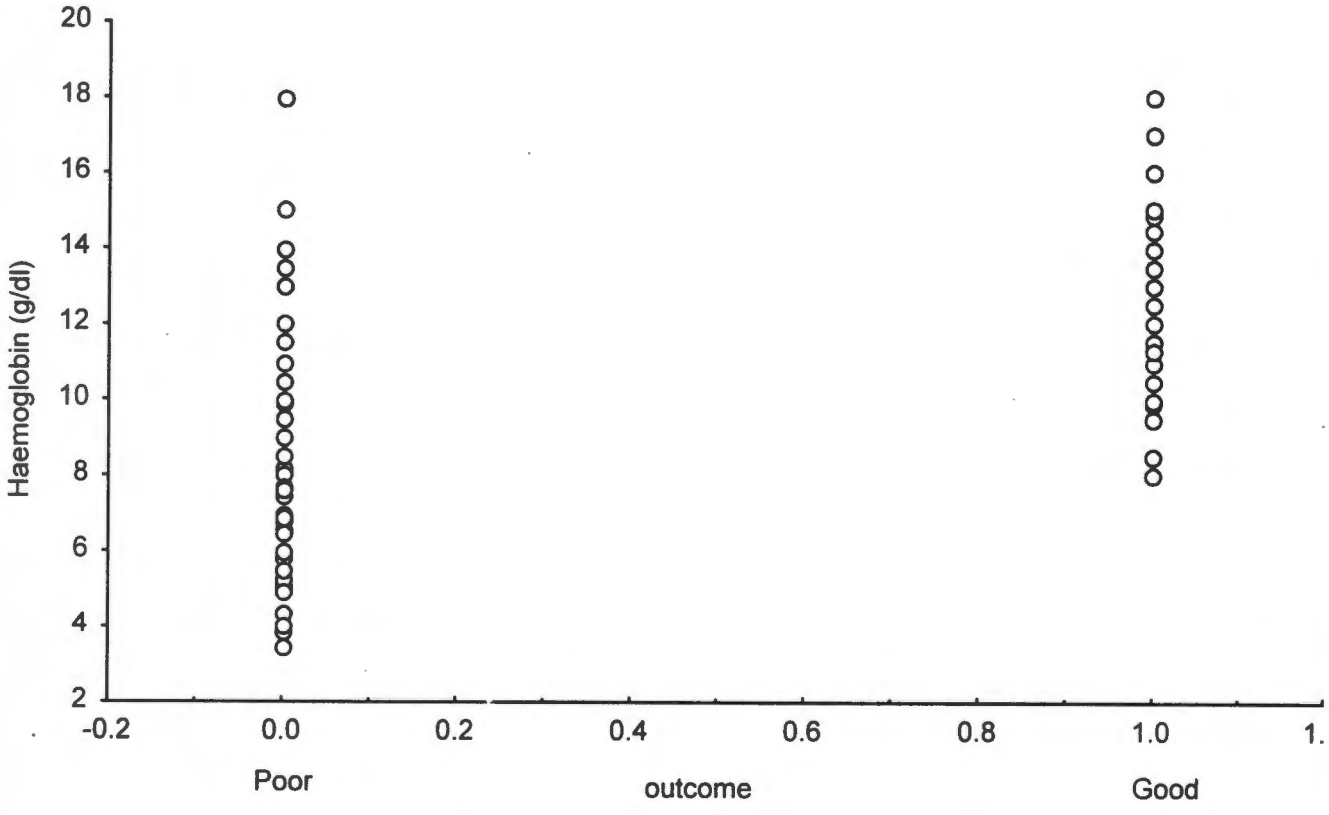


Figure 6: Haemoglobin (g/dl) distribution in the good and poor outcome groups.



On bivariate analysis haemoglobin greater than 10 g/dl (RR 10.5; 95% CI, 4.8-23 = < 0.001), pulse rate less than 100 beats per minute (RR 1.76; 95% CI, 1.18-2.6; p = 0.003) and systolic blood pressure greater than 100 mm Hg (RR 4.58; 95% CI, 1.2-17.3; p = 0.002) were significantly associated with a good outcome. As continuous

variables, an increase in blood pressure was associated with good outcome (OR 1.01 for each unit increase in systolic blood pressure (mm Hg); 95% CI, 1.0-1.02; p= 0.016 and increase in pulse rate was associated with poor outcome (OR 0.97 for each unit increase in pulse rate per minute; 95% CI, 0.95-0.99; p= 0.0006).

3.7.1.10 Pre-syncope or syncope and haemodynamic assessment

One hundred and six (53%) of the patients had symptoms of pre-syncope or syncope. Significantly more patients presenting with syncope or pre-syncope had a pulse rate greater than 100 beats per minute and haemoglobin less than 10 g/dl while the proportion presenting with blood pressure less 100 mm Hg was not significantly different.

There was a very significant association between presentation with syncope and the level of haemoglobin. The risk of syncope was increased in those who had haemoglobin less than 10 g/dl. The association between syncope and pulse rate of greater than 100 beats per minute or systolic blood pressure of less than 100 mm Hg closely approached significance. See tables 20-22.

Table 20: Association between pre-syncope or syncope and haemoglobin

	Syncope			
Hb g/dl	Yes	No	Total	P*
<10	60	32	92	0.002
>10	46	62	108	
Total	106	94	200	

* Chi square test

Table 21: Association between pre-syncope or syncope and pulse rate

	Syncope			
Pulse b/min	Yes	No	Total	P*
>100	49	31	80	0.056
<100	57	63	120	
Total	106	94	200	

* Chi square test

Table 22: Association between pre-syncope or syncope and blood pressure

	Syncope			
BP mm Hg	Yes	No	Total	P*
<100	6	15	21	0.07
>100	88	91	179	
Total	94	106	200	

* Chi square test

3.7.1.11. Syncope and outcome

Presentation with pre-syncope or syncope was significantly associated with outcome. Patients presenting with pre-syncope or syncope were 57% (38% - 71%) less likely to have a good outcome than those who had no pre-syncope or syncope. See table 23.

Table 23: Association between pre-syncope or syncope and outcome

	Outcome					
	Yes	No	Total	RR	95% CI of RR	P*
Syncope +ve	26	80	106	0.43	0.29 – 0.62	<0.0001
Syncope -ve	54	40	94			
Total	80	120	200			

* Chi square test

3.7.1.12. Postural blood pressure and outcome

The presence of a postural drop in blood pressure was recorded in 136 of the patients. Postural drop in blood pressure at presentation was not associated with outcome. The 95% CI for the RR included 1. See table 24.

Table 24: Relationship of postural hypotension to outcome

	Outcome					
	Good	Poor	Total	RR	95% CI of RR	P*
Post. hypo.+ve	12	13	25	1.09	0.69-1.72	0.72
Post. hypo. -ve	49	62	111			
Total	61	75	136			

*Chi square test; Post. hypo. = Postural hypotension (postural drop in blood pressure).

3.7.1.13. Shock on presentation and outcome

All but 1 of the 11 patients presenting with shock (blood pressure < 100 mm Hg and pulse > 100 beats/min) and all but 1 of the 10 patients presenting with blood pressure less than 100 mm Hg and pulse less than 100 per minute received blood transfusion. Presentation with shock was associated with poor outcome. This association remained significant after inclusion of patients who had blood pressure less than 100 mm Hg but normal pulse rate (< 100 beats per minute). See table 25.

Table 25: Relationship of shock to outcome

	Outcome					
	Good	Poor	Total	RR	95% CI of RR	P*
Shock +ve	2	19		0.22	0.06-0.83	0.002
Shock -ve	79	110				
Total						

*Chi square test; +ve= Presence; -ve = absence of shock at presentation

Summary of the Bivariate analysis

The bivariate analysis showed that all variables except NSAID, salicylates, alcohol, previous peptic ulcer disease, comorbidities (renal, pulmonary, hepatic, neurological and musculoskeletal) when analysed individually, and postural hypotension were predictors of outcome at the 5% level of significance.

3.7.2. Multivariate analysis

Tables 26 and 27 show all variables entered into a multiple logistic regression model and show the combination of variables that was associated the closest with good outcome, after controlling for confounders. Continuous variables (haemoglobin, pulse, blood pressure and age) were analysed both as continuous and as categorical variables.

Table 26: Predictors of good outcome (no transfusion, no endoscopic therapy no surgery and alive at 1 month) *(multiple logistic regression)*

***AIC for the model =147.7 Full model**

Variable	Parameter Estimate	SE	Odds Ratio	95%CI	P value
No melaena	1.66020	0.68887	5.26	1.35 – 20.53	0.01
No haematemesis	-0.02864	0.59433	0.96	0.3 – 3.1	0.96
No syncope	1.239209	0.492880	3.45	1.3 – 9.1	0.01
No NSAID	0.283486	0.600553	1.33	0.41 – 4.35	0.64
No Salicylate	0.524279	0.521431	1.69	0.60 – 4.74	0.31
No Previous PUD	0.444832	0.528617	1.56	0.54 – 4.43	0.40
No warfarin	-0.33172	0.98839	0.72	0.10 – 5.1	0.74
HB >10 g/dl	3.07708	0.61554	21.69	6.43 – 73.25	<0.0001
Pulse b/min	-0.02125	0.01623	0.98	0.94 – 1.01	0.19
BP mm Hg	0.00756	0.00885	1.0	0.99 – 1.03	0.39
Age < 60 years	0.153419	0.564174	1.17	0.38 – 3.56	0.78
No comorbidity	0.095521	0.553404	1.1	0.37 – 3.29	0.86

SE = standard error; *AIC = Akaike's Information Criterion (see definition)

With haemoglobin and age as categorical variables and pulse and blood pressure as continuous variables.

Haemoglobin and age were entered as categorical variables because they were not accepted into the model as continuous variables.

3.7.2.1. Predictors of good outcome (no transfusion, no endoscopic therapy, no surgery and alive at one month) *(multiple logistic regression).*

All variables were entered into a multiple logistic regression model with continuous variables entered as categorical variables using pre-determined cut-off values. This was done to test whether the result would be different when continuous variables were used as categorical variables.

Table 27: Predictors of good outcome (no transfusion, no endoscopic therapy, no surgery and alive at one month) *(multiple logistic regression).*

AIC for the model = 146.8 **Full model**

Variable	Parameter Estimate	SE	Odds Ratio	95%CI	P value
No melaena	1.65034	0.67878	5.21	1.36 – 19.93	0.01
No haematemesis	-0.03461	0.59676	0.96	0.29 – 3.1	0.95
No syncope	1.33823	0.49249	3.8	1.44 – 10.09	0.006
No NSAID	0.33823	0.593162	1.39	0.43 – 4.5	0.57
No Salicylate	0.548433	0.522767	1.73	0.61 –4.86	0.29
No Previous PUD	0.596731	0.548508	1.81	0.61 – 5.37	0.27
No warfarin	-0.27043	0.97533	0.76	0.11 – 5.25	0.78
HB >10 g/dl	3.13403	0.61192	22.97	6.85 – 76.98	<0.0001
Pulse < 100 b/min	0.862019	0.555835	2.37	0.78 – 7.1	0.12
BP >100 mm Hg	0.90916	1.00267	2.48	0.34 – 18.01	0.36
Age < 60 years	0.09078	0.56496	1.09	0.36 – 3.35	.87
No comorbidity	0.02899	0.56359	1.03	0.34 – 3.14	0.95

SE = standard error. With haemoglobin, pulse, blood pressure and age as categorical variables.

In both full models, whether variables were used as continuous or categorical, absence of melaena, absence of syncope and haemoglobin value of > 10 g/dl were significant in predicting a good outcome. The strength of associations (i.e. p values) were also very similar in the 2 models.

3.7.2.2. Stepwise selection of the final model

Using stepwise logistic regression with an inclusion criterion of p = 0.10 and retention criterion of p = 0.05 a final model was selected. This was done in order to select the best predictive variables and assess their interaction once all variables not

significantly associated with outcome were excluded. Age, haemoglobin, pulse and blood pressure were entered as categorical variables.

The final model had absence of melaena, haemoglobin greater than 10 g/dl and absence of syncope as predictors of good outcome. See table 28.

The last 2 variables to leave the model were absence of previous history of peptic ulcer disease ($p = 0.1$) and pulse of < 100 beats/min ($p = 0.07$) respectively.

Table 28: Final Model: Predictors of a good outcome

AIC for the model = 139.0

Variable	SE	Z	P value	OR	95% CI for OR
No melaena	2.429009	3.115	0.002	4.8	1.79 – 12.94
HB >10g/dl	14.01974	5.995	<0.0001	25.8	8.9 – 74.8
No Syncope	1.762506	3.120	0.002	3.98	1.67 – 9.48

This model has sensitivity for good outcome of 34% (27-40%), specificity of 98% (95-100%), positive predictive value of 90% (86-94%) and negative predictive value of 69% (62-75%). The LR^+ was 13.5 (5.3-54) and LR^- was 0.68 (0.57-0.79). With this model 72% of the patients were correctly classified. Table 29 shows 2x2 tables for the model.

Table 29: 2x2 table for final model (no melaena, no syncope, Hb> 10 g/dl)

	Outcome		
	Good	Poor	Total
All three variables	27	3	30
≤ 2 variables	53	117	170
Total	80	120	200

A model combining any 2 of the 3 variables had sensitivity for good outcome of 74% (68-80%), specificity of 83% (78-88%), positive predictive value of 75% (69-81%) and negative predictive value of 83% (77-88%). The LR^+ was 4.4 (2.8-6.6) and LR^- was 0.32 (0.21-0.45). With this model 79.5% of the patients were correctly classified. Table 30 shows 2x2 tables for the model.

Table 30: 2x2 table for a combination of any 2 of the 3 variables

	Outcome		
	Good	Poor	Total
Combination of any 2 variables	59	20	79
< 2 variables	21	100	121
Total	80	120	200

With this model more patients were correctly classified and it had a higher sensitivity but the specificity was lower than the model combining all 3 variables.

3.7.2.3. Multiple logistic regression analysis with age, haemoglobin, pulse and blood pressure as continuous variables.

When the variables (age, haemoglobin, pulse and blood pressure) entered the model as continuous variables rather than categorical variables, the final model had haemoglobin p = <0.0001, pulse (p = 0.041) and absence of syncope (p = 0.003) as predictors of good outcome. See table 31. The last 2 variables to leave the model were absence of melaena (p =0.23) and age (p = 0.08) respectively.

Table 31: Final model: predictors of good outcome (pulse and haemoglobin) as continuous variables.

	SE	Z	P value	OR	95% CI for OR
Haemoglobin	0.2123625	6.315	<0.0001	1.97	1.59 – 2.44
Pulse	0.0142896	-2.047	0.041	0.97	0.94 – 0.99
No syncope	1.921189	2.990	0.003	4.08	1.62 – 10.27

The model where all variables were categorical was used for simplicity of implementation in clinical practice.

3.8 Test characteristics of different combinations of variables that were significant in predicting a good outcome.

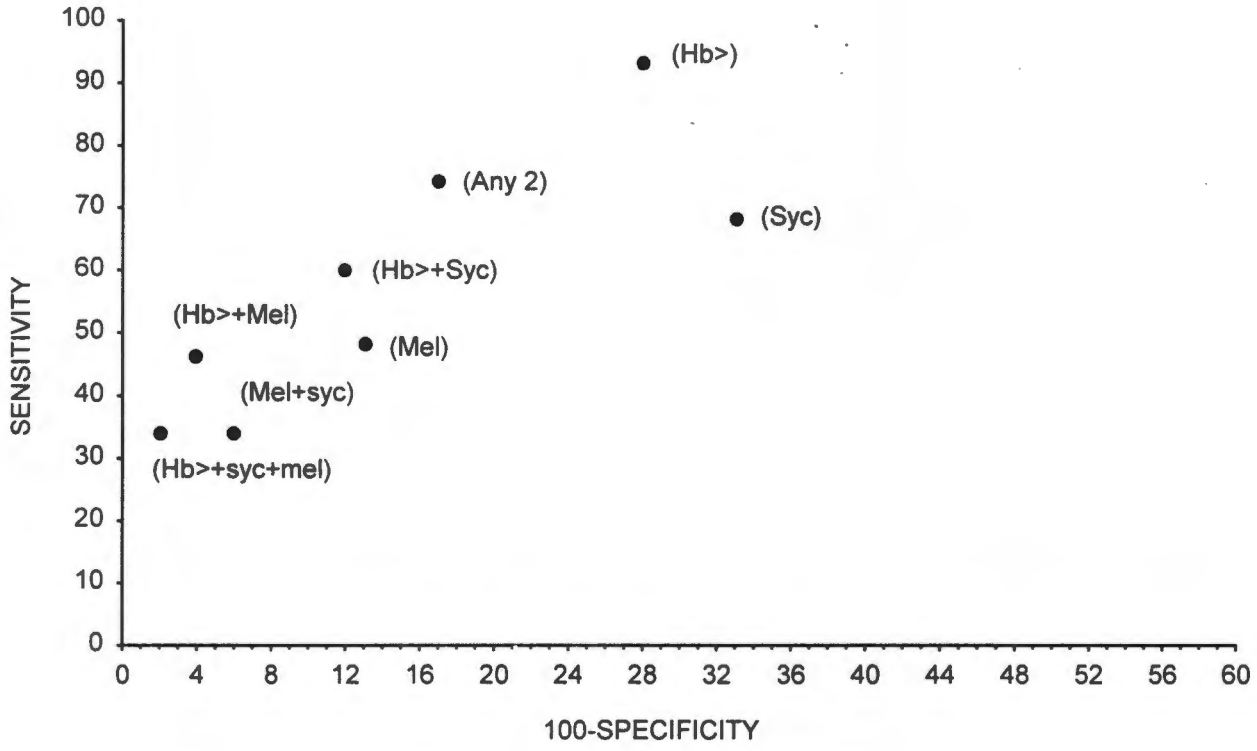
Table 32 shows a summary of sensitivity, specificity, positive predictive value, negative predictive value and their 95% CI, percentage of patients correctly classified, the likelihood ratio for a positive test and likelihood ratio for a negative test and 95% CI for the different combinations of variables.

Table 32: Tests characteristics of different combinations of variables that were significant in predicting a good outcome

Variables	Sensitivity (95% CI)	Specificity (95% CI)	+ve pred. (95% CI)	-ve pred. (95% CI)	% cor.cl	LR^+ & (95% CI)	LR^- & (95% CI)
Hb >10g/dl	93 (89-96)	72 (65-78)	69 (62-75)	93 (90-97)	80	3.3 (2.5-4.4)	0.10 (0.04-0.21)
No melaena	48 (41-54)	87 (82-91)	70 (64-77)	71 (65-78)	71	3.6 (2.2-6.5)	0.61 (0.48-0.75)
No syncope	68 (61-74)	67 (60-73)	57 (51-64)	75 (70-81)	67	2.0 (1.5-2.7)	0.49 (0.33-0.67)
Hb >10g/dl & no syncope	60 (53-67)	96 (84-93)	77 (72-83)	77 (71-83)	77	5.1 (3.0-8.2)	0.45 (0.33-1.6)
Hb >10g/dl & no melaena	46 (39-53)	96 (93-99)	88 (84-93)	73 (67-79)	76	11.1 (4.7-28)	0.56 (0.45-0.69)
No melaena & no syncope	34 (28-42)	94 (91-97)	80 (74-86)	68 (62-75)	70.5	6.0 (2.6-12.3)	0.69 (0.59-0.83)
Hb >10g/dl, no melaena & no syncope	34 (27-40)	98 (95-100)	90 (86-94)	69 (62-75)	72	13.5 (5.3-54)	0.68 (0.57-0.79)
Combination of any 2 of the 3 variables	74 (68-80)	83 (78-88)	75 (69-81)	83 (77-88)	79.5	4.4 (2.9-6.6)	0.32 (0.21-0.46)
Hb >10g/dl, no melaena no syncope & pulse<100	26 (20-32)	98 (95-100)	88 (83-92)	66 (60-73)	69	10.5 (4.0-42)	0.76 (0.66-0.86)

+ve pred. = positive predictive value; -ve pred = negative predictive value; cor. cl. = correctly classified; LR+ve = likelihood ratio for a positive test; LR-ve = Likelihood ratio for a negative test.

Figure 7: A graphic representation of True Positive Rates (sensitivity) and False Positive Rates (1-Specificity) for different combinations of predictor variables



Hb> = Haemoglobin > 10g/dl; Mel. = No melaena; Syc. = No syncope; any 2 = combination of any 2 of the 3 variables

Figure 7 shows that the model with all the three variables (Hb>10 g/dl, absence of melaena and absence of syncope) had the highest specificity but a low sensitivity.

3.9 Models with additional variables

The last three variables to leave the model were BP > 100 mm Hg ($p = 0.124$), history of previous peptic ulcer disease ($p = 0.103$) and pulse < 100 beats/min ($p = 0.076$). Tables 33 and 34 show models that included these variables.

- **Predictors of good outcome (no transfusion, no endoscopic therapy, no surgery and alive at 1 month)** ***(multiple logistic regression)***

Pulse rate as a categorical variable was included in the model because it had the lowest p value of the excluded variables.

Table 33: No melaena, no syncope, Hb >10 g/dl and pulse<100 b/min ***(multiple logistic regression)***

AIC for the model = 137.5

Variable	Parameter Estimate	SE	Odds Ratio	95%CI	P value
No melaena	1.70407	0.57198	5.49	1.77 - 17.01	0.003*
No syncope	1.308161	0.473578	3.69	1.45 - 9.43	0.006*
Hb>10 g/dl	3.08298	0.491782	21.8	7.15 - 66.59	<0.0001*
Pulse<100 b/min	0.620391	0.491782	1.8	0.7 – 4.9	0.207

SE = standard error; pulse, haemoglobin and blood pressure as categorical variables

This model has sensitivity for good outcome of 26% (20-32%), specificity of 98% (95-100%), positive predictive value of 88% (83-92%) and negative predictive value of 66% (60-73%). The LR^+ was 10.5 (4.0-42) and LR^- was 0.76 (0.66-0.86). This model was not as good a predictor of outcome as the final model (no syncope, no melaena and Hb >10 g/dl). The model correctly classified 69% of the patients compared to 72% with the final model.

- **Predictors of good outcome (no transfusion, no endoscopic therapy no surgery and alive at 1 month)** ***(multiple logistic regression)***

Pulse as a categorical variable and previous peptic ulcer disease were included in this model because they had the lowest p values of the variables excluded from the final model. See table 34.

Table 34: No melaena, no syncope, no previous PUD, Hb >10 g/dl and pulse<100 b/min ***(multiple logistic regression)***

AIC for the model = 137.1

Variable	Parameter Estimate	SE	Odds Ratio	95%CI	P value
No melaena	1.311646	0.463938	3.7	1.49 – 9.27	0.005*
No syncope	1.167762	0.407117	3.2	1.44-7.17	0.004*
Hb>10 g/dl	3.19514	0.49489	24.4	9.2 - 64.7	<0.0001*
Pulse <100 b/min	0.548248	0.422089	1.73	0.75 - 3.97	0.194
No Previous PUD	-0.081511	0.084544	0.92	0.78 - 1.09	0.334

SE = standard error; PUD = previous peptic ulcer disease

This model had sensitivity for good outcome of 16% (11-21%), specificity of 99% (98-100%), positive predictive value of 93% (89-96%) and negative predictive value of 64% (57-71%). The LR^+ was 19.5 (10-25) and LR- of 0.84 (0.76-1.07). With this model 66% of the patients were correctly classified. This combination of variables has a higher specificity and LR +ve than all the other models but sensitivity and negative predictive values were very low compared to other models.

CHAPTER 4: DISCUSSION AND CONCLUSION

4.1 DISCUSSION

This prospective study was undertaken to find predictors of good outcome (i.e. no transfusion or endotherapy or surgery and alive at one month) in patients presenting with upper gastrointestinal bleeding, with a view to identifying criteria for the selection of patients who will recover without interventions requiring endoscopy. Since availability of endoscopy is limited in our setting, there is a need to select those patients who would benefit from it the most, i.e. those in whom it could not only help establish the source of bleeding but also change management decision.

4.1.1 Endpoints

Blood transfusion was taken to be a poor outcome event because it requires admission to hospital, laboratory, medical and nursing expertise. The need for blood transfusion implies significant bleeding and possible need for endotherapy or surgical intervention to control bleeding. Endotherapy and surgery both require the services of a trained specialist. These latter services are available at only some secondary and at no primary level hospitals. Hence, all patients with UGIB requiring such interventions need to be referred to centres where facilities are available for endoscopy, endotherapy, and surgery.

Death is the end point that we all strive to reduce.

4.1.2. Patient Characteristics

- **Age and gender**

Our study population had a median age of 57.5 years (interquartile range 43.7-71.4) and a male preponderance. This is consistent with findings from other studies (Longstreth 1995 and 1998, Silverstein 1981).

The finding reflects an increase in the age of patients presenting with upper gastrointestinal bleeding over the past 50 years as reported by Allan and Dykes in 1976, that the percentage of patients over the age of 60 years had increased from 2% - 48%. Gustavsson et al. (1988) also reflected a rise in median age of patients from 51.5 to 64.5 over a 30-year period (1956–1985).

- **Mode of presentation**

More patients presented with melaena alone (76, 38%) or with both melaena and haematemesis (70, 35%) than with haematemesis alone (54, 27%). This is in agreement with a study by Terdiman et al (1997) that had a similar age distribution and found similar proportions in the mode of presentation.

- **Positive Faecal Occult Blood (FOB) Test**

Patients presenting with haematemesis alone may have a negative FOB test because of the transit time before blood reaches the rectum (Rockey 1999). Of the patients that had a FOB test done, not surprisingly a higher proportion of patients presenting with melaena {121 (94.5%) of 128 patients} had a positive FOB test compared to 25 (61%) of the 41 patients presenting with haematemesis alone.

4.1.3. Potential Risk Factors identified on Clinical Assessment and Outcome

- **History of previous peptic ulcer disease and outcome**

Previous history of peptic ulcer disease did not predict outcome. These results are consistent with the results of previous studies. Katschinski et al. (1994) found no association between history of previous peptic ulcer disease and rebleed or death. Similarly, Jaramillo (1994) found no association between past history of peptic ulcer and prediction of further haemorrhage. Likewise Corley (1998) found that history of previous peptic ulcer disease was not a predictor of outcome.

A few studies have reported a higher mortality rate in first time bleeders as compared to those with previous history of peptic ulcer disease (Hasselgren 1998, Braniski 1990, Schiller 1970, Johnson 1973).

Hasselgren (1998) argued that patients with previous peptic ulcer disease represent a separate group with chronic disease and a low case-fatality rate. Schiller (1970) pointed out that decisions in the management of patients could not be based on whether or not they have had previous peptic ulcer disease, as this is a poor predictor of outcome. The findings of this study support this view.

- **Association between history of NSAID intake and Endoscopic Diagnosis of Peptic Ulcer.**

The risk of finding a peptic ulcer at endoscopy was higher in patients taking NSAID or salicylates (RR 1.79; 95% CI, 1.33 – 2.40; $p < 0.001$). These findings are in keeping with the general consensus that the use of NSAID

increases the risk of peptic ulcer occurrence, ulcer complication (haemorrhage or perforation) and death by a factor of between 2 and 4 (Carson 1987, Griffin 1988, Jick 1987). Nevertheless in our study, though current intake of ulcerogenic drugs was associated with an increased risk of peptic ulcer disease, it was not significantly associated with outcome (RR 0.82; 95% CI, 0.58–1.17; p = 0.26). The RR suggests association with poor outcome, a lower 95% CI of 0.58 includes a clinically meaningful association, but with our sample size we cannot say whether there is a meaningful association as the upper 95% CI does not exclude a 17% chance of good outcome. This might be due to inclusion of patients on minimal doses of NSAID; information on dosage and duration of intake was not collected. Case-control studies have found the increased risk of upper gastrointestinal bleeding in patients taking NSAID to have a linear dose-response relationship (Carson et al. 1987 and Henry et. al. 1993).

- **Warfarin and outcome**

Our study showed that significantly more patients who were taking warfarin required blood transfusion (RR 1.67; 95% CI, 1.28 – 2.19; p 0.006). Anticoagulation will increase bleeding as it causes coagulopathy. Warfarin itself has no known causative role in peptic ulcer disease. Though it increases bleeding in patients with peptic ulcers, placebo-controlled trials that excluded patients with known ulcer disease, have not documented a significant increase in bleeding ulcers (Laine 1994).

Rockall et al. (1996) did not find anticoagulation to be a significant predictor of mortality. However anticoagulation has been used in patient selection. In

studies that selected patients with UGIB for outpatient treatment, or low intensity care, one of the requirements was that the patient was not on anticoagulants (Longstreth 1995, Kollef 1995).

- **Alcohol and outcome**

The severity of mucosal damage by alcohol is directly related to the local ethanol concentration and length of exposure (Domschke 1984). This results in inflammation of the stomach (gastritis) and of the oesophagus (oesophagitis). Both gastritis and oesophagitis can present as UGIB. Chronic heavy drinking if associated with violent vomiting can produce a Mallory-Weiss tear (longitudinal tear at the gastro-oesophageal junction), which presents as UGIB.

We found no association between alcohol intake and outcome. The results were similar for those who gave history of alcohol binge and those who gave history of alcoholism, (RR 1.19; 95% CI, 0.81–1.75; p = 0.39) and (RR 1.27; 95% CI, 0.86–1.88; p = 0.25) respectively. The confidence intervals for both estimates include a greater than 50% increase in the chance of a good outcome. A weakness of our study is that we did not quantify the amount of alcohol consumed. It is possible that this obscured the effect of alcohol on outcome, but it should be noted that those who gave history of chronic alcoholism were analysed separately and still there was no significant association with outcome.

The rate of peptic ulcer disease was significantly lower in those with a history of alcohol binge or alcoholism. History of alcohol binge or alcoholism appeared to reduce the likelihood of finding of peptic ulcer at endoscopy (RR

0.56; 95% CI, 0.34–0.92; p = 0.007 and RR 0.62; 95% CI, 0.37–1.03; p = 0.05 respectively). There was no association between gastritis and alcohol binge (RR 1.48; 95% CI, 0.86–2.54; p = 0.16) or alcoholism (RR 1.62; 95% CI, 0.94–2.79; p = 0.09).

Ostensen et al. (1985) in a case-control study found an increased alcohol intake in controls as compared to cases with peptic ulcer. In this study the amount of alcohol taken was not quantified. It is possible that the cases modified their habits due to symptoms.

Kelly (1995) found a significant association between alcohol intake and the risk of peptic ulcer disease after controlling for potential confounders such as smoking and NSAID. Compared to drinkers of less than one drink per week, the relative risks among other current drinkers ranged from 0.8 for 1-6 drinks per week to 6.3 for more than 35 drinks.

In contrast other authors have argued that complications of alcohol such as hepatic cirrhosis and portal hypertensive gastropathy increase incidence of peptic ulcer and UGIB. But this association is probably related to cirrhosis rather than to alcohol (Langman 1976).

- **Comorbidity and outcome**

Active comorbidity must be identified, and treated energetically at an early stage, in patients admitted with acute upper gastrointestinal bleeding. This is because most people who die following UGIB have significant comorbidity putting them at risk of decompensation of their comorbid disease and of post-operative complications in the event that they have to undergo surgery (Wara 1983, Terdiman 1998).

On bivariate analysis we found comorbidity to be a predictor of poor outcome (RR 0.67; 95% CI, 0.48–0.94; p = 0.02). However this association was lost on multivariate analysis.

When the underlying diseases were analysed individually only cardiac disease was found to be associated with poor outcome (RR 0.47; 95% CI, 0.25–0.90; p= 0.008). Pulmonary, renal, hepatic, haematological, neurological and musculoskeletal diseases were not individually associated with outcome. The small number of patients with a particular comorbidity however, resulted in wide confidence intervals.

In a study by Rockall et al. 1996, hepatic (OR 8.6) and renal disease (OR 10.3) were most predictive of adverse outcome. Hepatic disease was not associated with outcome in our study but it must be noted that the number of patients with hepatic disease was small (10, 5%). Five were known to have liver cirrhosis, one had breast cancer with liver metastasis and the remaining 4 were reported as having a palpable liver, which does not necessarily indicate active liver disease. It must be emphasised that patients with a known history of portal hypertension and varices were excluded from the study, thus reducing the number of patients in the sample with liver disease.

Renal failure was not a predictor of outcome as very few patients (9, 4.5%) had renal failure. This number was insufficient for meaningful analysis, but despite this only one out of the nine had a good outcome. The wide confidence intervals (RR = 0.27; CI, 0.04–1.72) include the plausible possibility of a meaningful association.

The role of comorbidity as a predictor of adverse outcome has been confirmed in other studies (Silverstein and ASGE 1981, Braniski et al. 1990, Kollef et al. 1997)

However, some studies have found comorbidity not to be a significant predictor of outcome. Wara et al. (1985) examined predictors of major haemorrhage. Cormobidity was recorded only if it predated the bleed and required specific treatment. Cormorbidity was found in 65% of both the self-limited and the major haemorrhage groups. Jaramillo et al. (1994) looked at predictors of further haemorrhage in 567 patients. Comorbidity was a significant predictor on bivariate but not on multivariate analysis. Clason et al. (1986) examined 326 admissions prospectively to predict factors of further haemorrhage or mortality. Though comorbidity was a significant predictor on bivariate analysis, this was lost on multivariate analysis.

Corley et al. (1998) stratified 335 patients into good outcome (discharged alive, no surgery and no persistent or recurrent haemorrhage) and adverse outcome (patients with any of the above factors). On bivariate analysis comorbidity was a significant predictor of adverse outcome but on multivariate analysis only evidence of portal hypertension was a predictor of poor outcome.

In these studies, comorbidity lost significance on multivariate logistic regression analysis presumably because of the association of comorbidity with other risk factors for poor outcome. Once the multivariate model adjusted for these other variables, no independent association with comorbidity persisted. Most studies have however confirmed the significant role of active comorbidity in predicting poor outcome. In the study by Rockall et al. (1996),

presence or absence of comorbidity is one of the risk factors used in the scoring system they devised to predict outcome.

Longstreth et al. (1998) used a number of criteria to select patients for outpatient treatment using absence of active comorbidity as one of the factors. They selected 176 patients for outpatient care who on follow-up for a period of 6–26.8 months had 0% mortality, 1% recurrent bleeding and 1% hospitalisation.

- **Age and outcome**

Many other studies have found age to be significantly associated with adverse outcome (Rockall 1996, Morgan 1988, Zimmerman 1995, Katschinski 1994, Jaramillo 1994, Clason 1986, Longstreth1995). Advancing age in the population of patients presenting with UGIB has been blamed for lack of improvement in mortality rate despite diagnostic and therapeutic improvements. This is because there is an increase in concomitant disease with increasing age (Berstad 1982, Wara 1983).

We found an increased risk of comorbidity in those over the age of 60 years when compared to patients below this age. (RR 1.75; 95% CI, 1.39–2.20; $p < 0.001$).

On bivariate analysis age was a predictor of outcome. Patients less than 60 years old had a better outcome than those over the age of 60 years, (RR 1.58; 95% CI, 1.10–28; p=0.01). This was similar to findings from previous studies that identified low risk patients with upper gastrointestinal haemorrhage (Bordley et al. 1985, Rockall et al. 1996).

On multivariate logistic regression analysis, however, age was not a predictor of outcome. This reflects to findings from previous studies (Wara et. al. 1983, Corley et al. 1998, Turner et al. 1991, Northfield et al. 1971, Chojkier et. al. 1986) and could be explained by the adjustment for other variables such as comorbidity in the multivariate model. However, in this study both age and comorbidity were not associated with outcome on multiple logistic regression analysis suggesting that they were both associated with identified predictors (haemoglobin concentration, syncope and melaena)

- **Mode of presentation (haematemesis, melaena or both) and outcome**

On bivariate analysis haematemesis alone was associated with good outcome (RR 1.72; 95% CI, 1.14–2.59; p = 0.005 while presentation with melaena alone (RR 0.58; 95% CI, 0.39–0.87; p <0.005) was associated with a poor outcome. This is unlike findings in most studies where haematemesis is associated with an adverse outcome (Terdiman 1997, Wara 1985, Jaramillo 1994, Silverstein et. al and ASGE 1981, Northfield 1971 and Schiller 1970). Schiller et al. (1970) had a fatality rate of 12% in those who presented with haematemesis, 5.4% in those who presented with melaena and 9.4% in those who presented with both haematemesis and melaena.

Wara et al. (1985) recommended from their study that patients presenting with haematemesis and melaena or haematemesis alone should have endoscopy as the risk of massive haemorrhage is increased.

Silverstein and the National ASGE found that presence of haematemesis with any stool colour, whether melaena or not, had an average mortality rate of

20.7%, in absence of haematemesis mortality was 6.6% but rose to 11.7% in the presence of history of coffee ground vomiting.

In the study by Northfield (1971), the rate of rebleed was 20% in patients presenting with haematemesis and 3% in those presenting with melaena.

The difficulty in comparing these studies with our study is that all these studies included patients with varices who tend to present with haematemesis and are at high risk of a poor outcome.

The other problem is that the end points differ in the different studies.

We included blood transfusion as part of the poor outcome measures. Patients presenting with melaena alone tend to present late to hospital, as the bleeding is less brisk and less alarming. Therefore, they present with much lower haemoglobin levels and need blood transfusion. However, there are studies that have found the presence of melaena to be a predictor of an adverse outcome. Katschinski et al. (1994), in a study of 2217 patients, showed that melaena (OR 1.6; 95% CI, 1.1–2.4) was a predictor for rebleeding. Macleod et.al. (1982), in a study of 389 consecutive patients with UGIB, found that patients presenting with melaena or with both haematemesis and melaena were at greater risk of further haemorrhage compared to those presenting with haematemesis alone.

A weakness of our study is that haematemesis included both patients with red haematemesis and with coffee ground vomit, the former being associated with brisker UGIB. It is possible that if these were analysed separately the association with outcome would have been different (Silverstein et. al and ASGE 1981). The other weakness is that haematemesis was not always

witnessed in hospital but obtained from history. This might not have always been reliable.

- **Pre-syncope or Syncope and outcome**

Patients presenting with pre-syncope or syncope had significantly lower haemoglobin (RR 1.5; 95% CI, 1.17–2.0; p = 0.001) than those who did not have these symptoms. Pulse rate (RR 1.29; 95% CI, 1.0–1.67; p = 0.056) and systolic blood pressure (RR 0.58; 95% CI, 0.29–1.16; p = 0.07) did not differ significantly between the two groups though the difference in pulse rate reached borderline significance. History of syncope was associated with poor outcome (RR 0.43; 95% CI, 0.29–0.62; p = < 0.001).

Syncope is correlated with rapidity of blood loss. This variable has been incorporated as a predictor of outcome in very few studies. This is despite the fact that this information can easily be obtained on history at the time of presentation and that it costs nothing.

Silverstein et al. (1981) and the National ASGE survey showed that syncope was not associated with high mortality rate or an increased incidence of complications but it was associated with blood transfusion > 5 units and surgery. Longstreth et al. (1995) using variables identified from a prior retrospective study, prospectively selected patients for treatment as outpatients. Of the patients managed as out-patients, 29% had history of syncope compared to 53% of those managed as in-patients. There were no deaths among the 34 patients who were treated as outpatients and only 1 rebled. Zimmerman et al. (1995) did not find syncope to predict mortality (OR 2.6; 95% CI, 0.8–8.2; p = 0.114) but the trend is toward an association

with increased mortality, and the CI is very wide. Nevertheless, we cannot compare our findings to those of this study, as their only end point was mortality. They did not use transfusion requirements as an outcome measure.

- **Haemoglobin, Pulse and Blood Pressure and outcome**

Haemoglobin, pulse and blood pressure are all measures of severity of the bleed (Booker et. al. 1987). These variables have been used in many studies as predictors of outcome.

We did not find clear-cut threshold levels between those who had a good outcome and those who had a poor outcome. However no patient with a haemoglobin level of less than 8 g/dl had a good outcome. This is artefactual, as the presence of low haemoglobin would dictate transfusion in our practice. For the purposes of our study, however, the aim of which was to identify criteria that indicated the patients that would not require urgent hospital admission and management, this was a relevant outcome. In the analysis we used internationally used cut-off levels for low risk of adverse outcome. Longstreth et al. 1995 in a retrospective study of 933 patients stratified patients into those who received outpatients and inpatient care. The cut-off values for pulse, haemoglobin and blood pressure for those who received out patient care were similar to those used in this study.

In our study, on bivariate analysis haemoglobin greater than 10 g/dl (RR 10.5; 95% CI, 4.8–23; $p = < 0.001$), pulse rate less than 100 beats / minute (RR 1.76; 95% CI, 1.18–2.6; $p = 0.003$) and systolic blood pressure of greater than 100 mm Hg (RR 4.58; 95% CI, 1.2–17.3; $p = 0.002$) were significantly associated with a good outcome. As continuous variables, a higher blood

pressure was associated with good outcome (OR 1.01 for each unit increase in systolic blood pressure (mm Hg); 95% CI, 1.0–1.02; p = 0.016) and increase in pulse rate was associated with poor outcome (OR 0.97 for each unit increase in pulse rate per minute; 95% CI, 0.95–0.99, p = 0.0006). On multiple logistic regression analysis, pulse rate and blood pressure lost statistical significance. This is probably due to association between pulse rate, blood pressure levels and haemoglobin value that was adjusted for in the multivariate model.

Pulse rate and systolic blood pressure have been used in some studies to predict outcome. Rockall et al. (1996) used pulse and blood pressure in the model from which a risk score was generated. Bordley et al. (1985) stratified patients into high risk and low risk for poor outcome with systolic blood pressure of greater than 100 mm Hg being one of the six variables that were associated with good outcome.

Turner et al. (1991) found no association between presence of shock (blood pressure <100 mm Hg and pulse rate >100 beats per minute), haemoglobin less than 10 g/dl on presentation and outcome. This study, like our study, excluded patients with varices. Similarly these variables did not predict the risk of major haemorrhage in a study by Wara et al. 1985, nor did they in the study by Perng C-L et al. (1994).

This may be because in patients who are initially haemodynamically stable, but subsequently rebleed, the initial values of haemoglobin, pulse rate and blood pressure are poor predictors of major haemorrhage.

4.1.4 Multiple Logistic Regression analysis

On bivariate analysis all predictor variables were significantly associated with outcome except current intake of NSAID and/or, salicylates, history of ingestion of alcohol, previous peptic ulcer disease, comorbid conditions (renal, pulmonary, hepatic, haematological, neurological and musculoskeletal) when analysed individually and postural drop in blood pressure. Though ulcerogenic drugs were associated with increased incidence of peptic ulcer disease they did not predict outcome of UGIB. Multiple logistic regression analysis controlled for the effect of confounders.

Absence of melaena, absence of syncope and haemoglobin greater than 10g/dl were the predictors of good outcome in our final model. Haemoglobin greater than 10g /dl (OR 25.8; 95% CI, 8.9–74.8; p = <0.001) was most significantly associated with outcome. As demonstrated in the scatter plots, no patient with a haemoglobin level of less than 8 g/dl had a good outcome, as this was an indication for transfusion. Melaena (OR 4.8; 95% CI, 1.8–12.4; p = 0.002) and syncope (OR 4.0; 95% CI, 1.7–9.5; p = 0.002) were similar in the strength of their association with outcome. A combination of two or of all three variables significantly improved the association. The improved specificity, predictive values and likelihood ratios of the combined variables demonstrate this. It must be emphasised that the good test characteristics shown by haemoglobin, as a single variable is artefactual as its presence determined transfusion.

Further increasing the number of variables in the model did not improve its prediction of the outcome and the sensitivity decreased further. The final

model had slightly higher Akaike Information Criteria (AIC) than some of the models. In general, the smaller the value of this statistic the better the model and the fewer the number of variables the greater the clinical simplicity and usefulness. When unnecessary variables are added there is little change in the value or its value will increase (Collet 1994). However the AIC is only a guide for selecting the best set of predictors.

4.1.5 Clinical relevance of the test characteristics

- **Likelihood ratios**
- Likelihood ratios (LRs) are measures of the accuracy with which a diagnostic test identifies its target disorder in an individual patient. They are regarded as the most useful indicators of test accuracy in a clinical context involving individual patients (Jaeschke 1994). The likelihood ratio represents the direction and magnitude of change from pre-test to post-test probability. The higher the ratio is above 1, the greater the change in probability in favour of the condition of interest, and the lower the ratio below 1 the greater the change in probability against the condition of interest. Ranges of ratios have had suggested clinical meaningfulness attached to them (Jaeschke 1994) as shown in the table 35.

Table 35: Magnitude of change to post-test probability of the disorder

Shifts in the probability	Ratio
Conclusive	> 10 or <0.1
Moderate	5-10 or 0.1-0.2
Small (sometimes important)	2-5 or 0.2-0.5
Small (rarely important)	1-2 or 0.5 –1.0

The LRs for the selected model were 13.5 and 0.68 for positive and negative "tests" respectively. This suggests important usefulness of a positive test (haemoglobin > 10 g/dl, no syncope and no melaena) in identifying patients with good outcome but limited usefulness of a negative test in excluding a good outcome. Positive predictive value was 90% and negative predictive value was 69%. These values represent the post-test probabilities in a population with a 40% prevalence of good outcome. The predictive values of a test are influenced by the prevalence of the condition under study, so they are not applicable to populations with a different prevalence.

- **Sensitivity and specificity** (Jaeschke 1994)

Although LRs are more meaningful expressions of the clinical usefulness of a test for individual patients, sensitivity and specificity are more helpful in selecting tests for use in populations (such as our study sample).
Sensitivity is the proportion of people with the target disorder in whom the test result is positive and specificity is the proportion of people without the disorder in whom the test is negative. The closer the proportion is to 1 the better the test. The sensitivity and specificity for good outcome for the test (final model) is 34% and 98% respectively, i.e. 66% false negatives and 2% false positives test (with good outcome as the condition of interest). In this clinical context the predictive test needs to have a high specificity for good outcome, thereby reducing the number of false positives (patients sent home wrongly). A larger number of false negatives is more acceptable but at the cost of patients being kept in hospital who would have had a good outcome.

The alternative model that includes any two of the selected variables has unacceptably low specificity to be of clinical value. With a specificity of 83%, 17% of patients whose management might have required urgent endoscopy would be sent home without endoscopy.

From table 32, it can be seen that the increase in specificity with the increase in the number of predictor variables is at such cost to sensitivity that it makes the prediction rule worthless in selecting anyone for management without urgent endoscopy. Therefore a further increase in the prediction variables above 3 would mean that the criteria would not alter current clinical practice. The investigator's judgement is that a predictive tool with a specificity of not less than 95% is acceptable. That is, no more than 5% of the patients with poor outcome should miss urgent endoscopy. Our predictive model meets these requirements as the specificity is 98%, and 95% CI (95–100).

Of the 200 patients in our study, 30 (15%) satisfied the prediction rule (haemoglobin greater than 10 g/dl, no melaena and no syncope). These would have been sent home without endoscopy. However, 3 of those who satisfied the prediction rule (1.5% of the total sample) had a poor outcome (see table 29). Thus, with the prevalence of good outcome in this study, there would have been a 15% reduction in the number of urgent endoscopies. Sixty percent of all patients with UGIB, including 10% (3 of the 30) of those sent home without endoscopy had poor outcome. All 3 patients who were false positives according to the test criteria required sclerotherapy to control haemorrhage. They did not have blood transfusion or surgery, and were alive at one month. These patients presumably presented early with their bleed and thus did not to require transfusion. If the prediction rule were in practice they

would have been observed at a primary health care facility and referred at a later stage.

The predictor variables could be easily applied even in poorly resourced health centres, as they do not involve much expense or sophisticated equipment. Presence or absence of melaena can be objectively confirmed by rectal examination and haemoglobin values can be measured without much expense using a haemoglobinometer, and the symptom of syncope is easy to elicit as it involves transient loss of consciousness. The symptom of pre-syncope is problematic, as it is subjective.

It should be noted that these criteria help identify those who will get better anyway, regardless of endoscopy. It does not necessarily identify those who will benefit from endoscopy.

4.1.6 Validation

A clinical decision rule is "data driven" in that it is derived from a specific sample of patients. The test may not perform as well in a different population, and thus needs to be validated (Wasson 1985). The rule can be tested on the patients in the study from which the rule was derived (cross-validation methods). Another approach is to test the prediction rule on a new group of patients in the same setting from which the rule was derived or from a different clinical environment. The preferable way is to embark on a second independent study in the same location, as this is a much more stringent test. None of these validations have been performed, given the constraints of time and patient numbers.

For the validation studies to be comparable, the protocol of the original researcher should be followed. Diagnostic and follow-up techniques should be rigorous. A co-ordinated prospective evaluation between original and subsequent investigators is preferable to numerous, poorly standardised attempts at validation.

The most rigorous evaluation of the impact of these criteria on patient well being would be a randomised controlled trial of the effect on outcome of the use of the study criteria compared to performing endoscopy on everyone.

4.1.7 Sample size and power

Although some subgroups of the predictor variables (e.g. individual comorbidities) had too few patients to detect meaningful association with outcome, our sample was adequate to identify 3 predictors of high statistical significance. The confidence intervals for specificity for the selected model on a sample of 200 (95–100%) was sufficiently narrow to enable a decision to be made regarding acceptability of the test. This test however requires validation. If greater precision were required, the following would be the 95% CIs for an estimated specificity of 98%: 96–99% with 400 patients, 96–99% with 800 patients and 97–99% with 1600 patients. Thus the 95% confidence interval would not change meaningfully with feasible increases in sample size.

4.1.8 General applicability

Patients included in the study are not representative of the population,

as patients who can afford private health care are cared for in private hospitals. Patients presenting to private hospitals with UGIB may be different at presentation from the study population in that they may present earlier, or they might have different degrees of exposure to risk factors for UGIB. Their outcome may differ due to different management strategies, such as transfusion practices.

4.2 CONCLUSION

- In this study absence of syncope, haemoglobin concentration greater than 10 g/dl and absence of a history of melaena were independent predictors of outcome. This is a test of good outcome regardless of endoscopy as findings post endoscopy were not included in its derivation.
- The best predictive rule was a combination of all the 3 variables.
- When this was used as a "test" for good outcome, the sensitivity was (34%) and specificity (98%). The likelihood ratios were 13.5 and 0.68 for positive and negative tests respectively. These test characteristics indicate that the test was accurate at excluding poor outcome, which is a priority in the clinical context. The test was however not accurate at predicting good outcome.
- The clinical implications of these findings are that the test would have resulted in a moderate impact on the reduction of unnecessary endoscopies (15% of admissions) with 5% or less of patients with poor outcome (1.5% of all patients) being sent home. In the judgement of

the investigator, this is an acceptable trade-off between benefits and costs.

- The findings of this study may have clinical relevance, especially in under-resourced health care environment in which we practice.
- The test however needs validation, preferably a second independent study in the same location, before being confidently applied to local practice.
- The findings appear generalisable to similar patient populations.

4.3 Future directions

A validation study is required before these clinical prediction rules can be applied confidently to local practice.

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UPPER GASTROINTESTINAL BLEEDING AUDIT

(1) **Study no** | | | | (3) **Ward** | |

(2) **Date** | | | **19** | **Address:**

dd mm yy

Label or Surname:
First

Folder no

Phone (H)
(W)

DOB ___/___/19___

Dr (PRINT)	BLEEP

CLINICAL DIAGNOSIS/CONDITION:

Upper GI Bleed:

Cause.....

Other conditions

1. _____
2. _____
3. _____
4. _____
5. _____
6 _____

MANAGEMENT:

_____

_____

_____

_____

_____

Date **CONTINUATION SHEET**

APPENDIX A
HISTORY

1. Bleeding

(4)	duration of bleed that caused patient to present	0 - 24 hrs	>24-48 hrs	>48-72 hrs	>72hrs
(5)	melaena	no	yes		
(6)	haematemesis	no	yes		
(7)	other recent episode of bleeding	no	<72 hrs	72 hrs to 7 days	>7 days

2. Symptoms of major bleed

(8)	symptoms	none	presyncope lightheaded	syncope

3. Predisposing factor

					details (specify drug and dose)
(9)	drugs (other than 5, 6 & 10 below)	no	yes	unknown	
(10)	nsaid (rheumatic pills)	no	yes	unknown	
(11)	salicylates Grand Pa, Aspirin, Disprin	no	yes	unknown	
(12)	previous peptic ulcer	no	yes	unknown	
(13)	smoking	no	yes	unknown	
(14)	alcohol (binge in past week)	no	yes	unknown	
(15)	anti coagulant	no	yes then INR		*result

4. Underlying conditions

			comment
(16)	cardiac	no	yes	
(17)	pulmonary	no	yes	
(18)	renal	no	yes	

***To be filled in before discharge**

4. Underlying conditions continued

				comment
(19)	hepatic	no	yes	
(20)	haematological	no	yes	
(21)	alcoholism (chronic)	no	yes	
(22)	other	no	yes	

5. Examination

(23)	lymph nodes (incl Virchow-Trossier)					
(24)	telangiectasis					
(25)	Hb	%				
(26)	pulse					
(27)	BP supine	____/____				
(28)	BP sitting	____/____				
(29)	BP standing	____/____	cannot be done specify reason:			
(30)	abdomen	NAD	tender	mass	visceromegaly	
(31)	vomit	NAD	fresh blood	coffee grounds	both	no sample
(32)	stool	NAD	fresh blood	melaena	both	no sample
(33)	occult blood	-ve	+ve	no stool on PR		
(34)	Cardiovascular System		NAD	abnormal		
(35)	CNS		NAD	abnormal		
(36)	Musculoskeletal System		NAD	abnormal		
(37)	Respiratory System		NAD	abnormal		

6. Haemoglobin status

(38)	Hb on admission		
*(39)	Hb drop(after admission)	no	yes
*(40)	transfusion requirements		units

7. Assessment

(41)	insignificant bleed	admit	if discharged, comment:
	significant bleed	admit	if discharged, comment:

NB If discharged arrange OPD scope

8. Assessment of endoscopy timing

(42)	Endoscopy appointment	emergency	routine urgent(next list)	elective within 1/52

9. Clinical Diagnosis by assessing doctor

Cause of UGIB

				comment
(43)	varices	no	yes	
(44)	Mallory -Weiss	no	yes	
(45)	oesophagitis	no	yes	
(46)	gastritis	no	yes	
(47)	peptic ulcer	no	yes	
(48)	Ca	no	yes	
(49)	other	no	yes	
(50)	unknown	no	yes	

10. If endoscopy was unavailable on site I would

(51)	Treat empirically	
or	Transfer for endoscopy	

***To be filled in before discharge**

11. Endoscopy

(52) Source of bleed identified

(53) stigmata of recent haemorrhage

no		yes	
no		bleeding visible vessel	
visible vessel	adherent clot	ooze	fresh blood

12. Diagnosis at Endoscopy

		details
(54) varices	no	yes	
(55) Mallory -Weiss	no	yes	
(56) oesophagitis	no	yes	
(57) gastritis	no	yes	
(58) peptic ulcer	no	yes	
(59) Ca	no	yes	
(60) other	no	yes	
(61) unknown	no	yes	

13. Sclerotherapy

(62) sclerotherapy

(63) treatment

(64)

no	success	failed
adrenaline dilution	volume	
sclerosant etholamine	volume	

14. Management based on scope

(65) treatment

nil	antacids	H^2 blockers	PPI	surgery
Other:		Comment		

15. Pathology

(66)	Biopsy	no		yes	
(67)	Histolology	benign		malignant	not done
(68)	H pylori hist status	antrum	-ve	+ve	not done
(69)	RUT (rapid urea test)	antrum	-ve	+ ve	not done

16. Surgery

(70)	surgery	no	yes
	specify		under-running
			under-running with Hp eradication
			definitive

17. Date of Discharge

Date

(71). | | | 19 |
|---|---|---|
| dd | mm | yy |

18. Status at one month

Date

(72). | | | 19 |
|---|---|---|
| dd | mm | yy |

(73)	resolved	rebleed	died (related)	died (unrelated)	unknown

APPENDIX B

UPPER GASTROINTESTINAL BLEEDING AUDIT

FOLLOW-UP AT ONE MONTH

Study No | | | |

Date first seen | | | | | | | D D M M Y Y

Review Date | | | | | | | D D M M Y Y

LABEL or
Surname: ..... Address: .....

First name: ....

Folder No: ..... Phone (H) .....
(W) .....

Date of Birth: | | | | | | | D D M M Y Y

R/S: ..... Language: .....

1. Marital status: | Married | Single | Divorced | Widowed | Separated |

2. Source of income: |

3. How do you rate your health? | Excellent | Good | Fair | Poor |

4. Did you have repeat endoscopy? | Yes | No |

5. Status at one month

Resolved	Rebleed	Died Related	Died Unrelated	Unknown
Comment:				