Abdominal surgery in very low birth weight neonates in a developing world neonatal unit- Short term outcomes and risk factors for mortality

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List of abbreviations:

VLBW	Very Low Birth Weight (<1500g)
ELBW	Extremely Low Birth Weight (<1000g)
NICU	Neonatal Intensive Care Unit
TPN	Total Parenteral Nutrition
PN	Parenteral Nutrition
NEC	Necrotizing Enterocolitis
SIP	Spontaneous intestinal perforation
PD	Peritoneal Drainage
IQR	Interquartile Range
CI	Confidence Interval
CRIB	Clinical Risk Index for babies
SNAPPE	Score for Neonatal Acute Physiology Perinatal Extension
IRA	Intestinal rotational abnormality
LMIC	Low- and middle-income countries
GA	Gestational Age

BW Birthweight

1. Literature Review

1.1. Objectives

The objectives of this literature review were twofold:

1. To review the short-term survival to discharge in very low birthweight infants following abdominal surgery and factors associated with mortality in the immediate post-surgical period.
2. To review the validity of the CRIB or SNAPPE scores for predicting neonatal morbidity and mortality.

1.2. Background

The surgical neonate, defined as a neonate predisposed to surgery between birth and 28 days of life, requires specialized care in centres that offer high risk neonatal support. [1] Surgical conditions seen include congenital diaphragmatic hernias, oesophageal atresia, NEC/ gastric perforation, small bowel obstruction/atresia, anorectal malformations, Hirschsprung's disease, omphalocele, gastroschisis and bladder exstrophy. [1]

Anaesthetic and operative interventions remain hazardous in this vulnerable population. These infants often have several risk factors including preterm birth, low birth weight, chromosomal defects, genetic syndromes or serious illness with multiple organ dysfunction requiring care in dedicated neonatal intensive care units. [1] Risk factors such as decreasing gestational age, decreasing birthweight and severely ill infants in combination with life threatening surgical conditions, mostly related to preterm and low birth weight, have been found to have an increased risk for poor outcomes in this population group. A higher 30-day post-operative mortality are seen in infants with severe or life-threatening systemic disease [1]

In 2010, 15 million babies were born preterm with more than 1 million deaths as a result of preterm birth. Sixty percent of preterm births occur in Africa and South Asia. [2]

Necrotizing enterocolitis (NEC) and spontaneous intestinal perforation (SIP) are two of the commonest surgical complications of preterm infants. [3-6] NEC is a potentially devastating condition and most commonly affects preterm and low birth weight infants. Surgical NEC is associated with a 35% mortality with approximately 50% of preterm infants with NEC requiring surgery. [4,7]

A number of strategies are implemented to prevent NEC, these include the promotion of human breastmilk as a feeding choice as well as different enteral feeding initiation and establishment strategies. Fear of causing NEC may lead to unnecessarily cautious slow feeding in Very Low Birth Weight (VLBW) infants which could cause postnatal growth restriction and potentially adverse effect on neurodevelopmental outcome. The desire to strike a balance between avoiding NEC and postnatal growth restriction causes a variation in feeding practices. [4,5,8]

A retrospective study conducted in Kwazulu Natal showed that gastrointestinal perforation in neonates occurred more commonly in males and that the main cause was NEC. Preterm birth was seen to be the leading comorbidity, however sepsis was the leading complication and highest cause of mortality. [9]

SIP occurs more commonly in Extremely Low Birth Weight (ELBW) infants (weighing <1000g) and usually present early in life (< 7 days) just prior to or shortly after initiating enteral feeds. Infants with SIP are prone to feeding difficulties and prolonged hospitalization but has also been shown to be at an increased risk for poor long-term neurodevelopmental outcome.[3]

A large multi-centered prospective United States study showed that infants with laparotomy confirmed SIP had a significantly lower mortality than laparotomy confirmed NEC [6].

Mortality in both NEC and SIP groups decreased with increasing birth weight and mortality was significantly higher for NEC than SIP in each birth weight category. SIP was also more commonly associated with exposure to early postnatal steroids or non-steroidal anti-inflammatory agents in that study. [6]

Infants are sometimes treated with peritoneal drainage (PD) but may often require multiple surgeries and may take longer to start enteral feeds or achieve full enteral feeds than those undergoing a salvage laparotomy. [3] The role of PD as a sole procedure in patients with NEC has been questioned beyond the initial stabilization of the infant, as PD alone does has not been shown to improve long term survival. [10] There is no clear consensus on the optimal surgical approach between peritoneal drainage and laparotomy and the best management plan is guided by the presence of comorbidities, haemodynamic status, size and extent of disease involvement as well as available resources.

Aside from increased mortality, VLBW surgical infants are at risk for significant short term morbidity such as sepsis and surgical site infections, delayed enteral feeding and long hospital stays. [3,6,9-11] Postoperative complications occurred in 47% of the patients in one study with the most common complications identified being: sepsis, intestinal stricture, and short gut. Wound infections occurred in 6%, and the incidence of intraabdominal abscess formation was 2.3%. [12]

Infants with surgical NEC have much longer lengths of stay, exceeding those of controls by 60 days in one case-controlled study, whereas lengths of stay among infants with medical NEC exceeded those of controls by 22 days hereby impacting the cost of hospital stay. [13] NEC is associated with a worse neurodevelopmental outcome than preterm birth alone. Advanced stage NEC as well as the need for surgery, further increases the risk. [4,14] Other long-term implications in survivors include short bowel syndrome and growth failure. [4] Strategies to improve outcomes following surgery could decrease the burden of many of these complications.

The ability to predict neonatal mortality and establishing illness severity can be a useful tool especially in resource limiting settings especially if it aids resource allocation and better and more appropriate counselling of patients.

Different Scoring systems have been developed and used to assess the severity of the illness and to predict the mortality, morbidity and prognosis of neonates in neonatal intensive care units (NICU). These have been devised to overcome differences imposed by varying birth weights, causes of neonatal mortality, care given in neonatal units and risk factors predisposing to neonatal mortality. Some of the scores developed are Clinical Risk Index for Babies (CRIB), CRIB II (An update of the clinical risk index for babies score), Score for Neonatal Acute Physiology (SNAP), SNAP Perinatal Extension (SNAP-PE), SNAP II, and SNAPPE-II. [2,15]

Variables such as birthweight, gestational age and APGAR score were previously used to predict mortality and morbidity, but these variables alone were not very accurate in mortality prediction.

SNAPPE II (Score for Neonatal Acute Physiology with Perinatal extension-II) score was found to be a useful tool in predicting neonatal mortality with a score of > 38 associated with a higher mortality. [15]

Both scores CRIB II and SNAPPE II have been found useful as a tool in predicting neonatal mortality but not useful in determining morbidity, the use of CRIB II is recommended in a busy neonatal department as it requires less variables for its calculation. [16]

1.3. Search strategy

In order to achieve the objectives, a search of the published literature in the medical database Pubmed was conducted online on 20/5/2020. Two searches were performed.

1. Short term survival to discharge in very low birthweight infants following abdominal surgery and factors associated with mortality in the immediate post-surgical period.

1st SEARCH STRING:

((((("very low birthweight"[Title/Abstract] OR "VLBW"[Title/Abstract]) OR "infant, newborn"[MeSH Terms]) AND "abdominal surgery"[All Fields]) AND English[lang] AND "infant"[MeSH Terms]) AND (("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonatal"[All Fields]) AND ("mortality"[Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms])) AND (English[lang] AND "infant"[MeSH Terms])

Filters included were: humans and infants from birth to 23 months and only English articles were included.

This search yielded 86 articles of which 17 were applicable to the study topic. The abstract of all articles was read and irrelevant studies excluded.

8 articles were reviewed, 9 excluded due to full article not being obtainable.

2. To review the validity of the CRIB or SNAPPE scores for predicting neonatal morbidity and mortality

2nd SEARCH STRING:

((("SNAPPE"[Title/Abstract]) OR ("CRIB Score"[Title/Abstract])) AND (neonate[MeSH Terms])) AND ("very low birth weight") AND ((fft[Filter]) AND (humans[Filter]) AND (english[Filter]) AND (allinfant[Filter]))

Filters included were: humans and infants from birth to 23 months and only English articles were included.

This search yielded 56 articles of which 11 were applicable to the study topic. The abstracts of all articles were read, and irrelevant studies excluded.

7 articles were reviewed, 4 excluded due to full article not being obtainable.

1.4. Results

Most of the studies reviewed were retrospective cohort studies. *Table 1* illustrates a summary of the findings of the first objective i.e. a review of short-term survival to discharge in very low birthweight infants following abdominal surgery and factors associated with mortality in the immediate post-surgical period.

Because there is an increased survival amongst ELBW infants, there is an increased number of infants who develop conditions which present with an acute abdomen. [17]

In a study published by Byun et al. [17] in 2019, 805 ELBW infants admitted over a 12-year period were retrospectively evaluated, 8.1% of whom required abdominal surgery. The most common causes of abdominal pathology found in this study were: NEC, SIP, Meconium related ileus and non-meconium related ileus respectively. Infants that had intestinal resections and primary anastomosis had a higher rate of complications than infants in whom intestinal stoma were created. All infants without intestinal stoma creation had experienced reperforation. NEC was found to be a poor prognosticator for survival outcome. Eight infants had a 30-day postoperative mortality, seven of which had NEC, with the most common cause of death being attributed to septic shock.

Pathologies in a small retrospective study of 16 infants undergoing a trans-umbilical mini-laparotomy included: intestinal atresia, meconium peritonitis, bowel obstruction, necrotizing enterocolitis, segmental volvulus with necrosis and malrotation. Procedures performed through this technique were: primary intestinal repair, LADDs procedure and ileostomy. Complications seen included anastomotic leak, adhesion ileus and missed rectal atresia. One

mortality was reported in an ELBW infant with poor lung maturation. Low birth weight was compared to normal birthweight infants and it showed that this technique could be applied to both. Therefore with enough surgical experience, this minimally invasive procedure could be used to perform complicated surgery. [18]

In a prospective cohort study by *Lindsay M Ryerson et al.* [19] of infants recruited over a 4-year period, evaluated the incidence and natural history of intestinal rotational abnormalities (IRA) in infants with heterotaxy syndrome. These infants have abnormal lateralization of body organs along the right-left axis, this coupled with IRA further contributes to morbidity and mortality. Most of the infants were asymptomatic. It was concluded that the majority of infants with heterotaxy syndrome had IRA and that expectant management of asymptomatic infants was a reasonable management option. [19]

Fullerton et al. [20] studied infants with gastroschisis and demonstrated that, in the study population, sepsis remained the single independent risk factor for mortality where as other determinants of length of stay included: bowel resection, sepsis, presence of other congenital abnormalities, diagnosis of NEC and small for gestational age which was the biggest contributor to length of stay. This study demonstrated that although the overall survival of neonates with gastroschisis is good, they are still at risk for sepsis, longer hospital stays, NEC, multiple abdominal operations and malnutrition at discharge. No significant change in outcome was observed by different delivery modes. The most important prevention strategies would include prevention of sepsis and optimal nutritional support. [20]

Preterm infants have an underdeveloped immune system and epidermal skin barrier. Blood stream infections and sepsis in infants are associated with long term adverse neurological outcome and an increased risk for mortality. Low birthweight, preterm birth, young chronological age and an underlying metabolic disorder have been found to be risk factors for central line associated blood stream infection (CLABSI). The presence of active intrabdominal pathology increasing the risk of CLABSI by 6 fold. [21]

Hartel et al. [7] evaluated the outcome of a cohort of VLBW infants who were administered prophylactic probiotics namely, Lactobacillus acidophilus/ Bifidobacterium infantis in the

German Neonatal Network. [7] They found that the use of probiotics was associated with a reduced risk for NEC, any abdominal surgery and the combined outcome abdominal surgery and/or death. No effect was seen on the risk of blood culture confirmed sepsis and infants were noted to have improved weight gain per day.[7] NEC and sepsis are the leading cause of morbidity and mortality in the vulnerable VLBW group and has a negative impact on long term neurodevelopment. [7]

More extremely low birthweight infants are surviving which places them at an increased risk of prematurity related complications including NEC. Arbell et al. demonstrated that bedside laparotomy is feasible for these patients and avoids the risks of transferring an unstable child as well as the need for a dedicated intensive care bed at the surgical centre. [22] The 30-day post-operative survival rate was 81% in this study.

Complications due to the need for parenteral nutrition (PN) in surgical infants have been noted. A retrospective study by Javid et al. found that cholestasis secondary to PN was more common in infants with a lower gestational age. [23]

Very low birth weight infants remain a vulnerable population of patients despite advancement in neonatal care such as surfactant therapy and antenatal glucocorticoid administration. Understanding the risk factors and outcomes of mortality will aid in protecting this population. Mortality has been linked to decreasing age with preterm birth and its complications being the leading cause of death. Scoring systems have been used in order determine the risk of adverse outcomes in this population. Table 2 illustrates a summary of the findings of the second objective i.e. to review the usefulness of the CRIB or SNAPPE scores for predicting neonatal morbidity and mortality.

Using tools that could predict mortality may aid in better planning of perinatal care and appropriate parental counselling. [24] A study by Kardum et al. [24] found that the contributors to death until hospital discharge included: a 4-week lower gestational age than surviving infants, lower birth weight, low 5 min Apgar score, higher CRIB score and more frequently resuscitated at birth. The survivors were more likely to receive CPAP at birth and were small for gestational age. The CRIB score was found to have the highest association for death until

discharge. NEC was the most common cause of death after the first 7 days postnatally and death was more commonly as a result of preterm birth in the first 7 days. [24]

The CRIB score can only be used on patients < 32 weeks and < 1500g, SNAPPE II can be used on all birthweights. Hüseyin Selim Asker et al. found that SNAPPE II was a better predictor of mortality than CRIB score and that it more accurately predicted mortality in infants receiving antenatal steroids. [25]

Baird et al. compared outcomes of peritoneal drainage with/without delayed laparotomy vs primary laparotomy using SNAPPE II as a predictor of mortality. [26] The primary outcome was 30-day mortality from the time of diagnosis of perforation, other secondary outcomes evaluated included: in hospital mortality, number of days fasted, time to extubation and length of stay. Patients with a higher SNAPPE II score had a higher mortality rate and patients with a peritoneal drain alone did worse than the primary laparotomy group.

A small retrospective study of 39 infants by Bonnard et al. evaluating the modified SNAPPE score at various intervals, demonstrated that a high modified SNAPPE score post peritoneal drain insertion, was associated with a higher risk of mortality irrespective of whether the patient had a laparotomy or not. The modified SNAPPE score did not differ at birth between the PD group and the PD and laparotomy group. [27]

A study by Kaaresen et al. found the use of CRIB score superior in predicting hospital mortality when compared to GA and birthweight only. [28] Comparisons were made over different time periods taking into consideration clinical advancements such as antenatal steroids and surfactant administration. CRIB scores were significantly lower in infants whose mother's received antenatal steroids than those who did not, but it was not an independently associated with survival, but surfactant was. In this study the CRIB score was found to be a better predictor of hospital mortality than gestational age and birthweight and served as good predictor irrespective of surfactant administration. [28]

Simon J Broughton et al. studied the use of a modified CRIB score are a triage tool in neonatal transport. [29] The common reasons for required transportation include: preterm

birth, RDS, MAS, sepsis, major surgical abnormality requiring urgent surgery, major congenital cardiac abnormality, congenital metabolic abnormality and chromosomal and other genetic abnormalities. The modified CRIB score was noted to be a useful adjunct to the prediction of neonatal mortality particularly when a situation arises where a prioritisation of medical care has to be decided upon. The CRIB score was also found to be more accurate than gestational age and birthweight in predicting neonatal mortality. [29]

Table 1: Short term outcomes in VLBW infants following abdominal surgery including risk factors for mortality

Study	Author	Aim	Population	Findings
1	Byun et al. [17]	Comparison of acute abdominal surgical outcomes of ELBW infants according to differential diagnosis	ELBW infants: 805 infants admitted over a 12-year period retrospectively evaluated, 65 requiring abdominal surgery.	Of the 65 infants: NEC(n=29) was most common followed by SIP (n=18), meconium related ileus (n=13) and meconium non-related ileus (n=5). 93.8% of these infants had a stoma formation done as opposed to 6.2% with primary anastomosis. Mean gestational age was 26+1 weeks (22+3–33+0), mean birth weight was 695.9 g (355–990 g) and the mean age of operation 12.4 days. The total mean hospital stay was 107.8 days.

				Mean postoperative duration of TPN was 39.7 days and 26 infants had Parenteral associated liver disease. NEC was found to be a poor prognostic factor for survival outcome ($P = 0.033$).
2	Chia-Yu Chang et al. [18]	To evaluate the outcome of trans umbilical mini-laparotomy and compare low birth weight and normal birthweight infants	Infants (Low birth weight(n=11) and normal birthweight(n=5)) Retrospective study including 16 infants conducted over a 7-year period.	Mean gestational age 32 weeks, median weight 1731g and the median age at the time of surgery being 3 days. The pathologies seen included: intestinal atresia, meconium peritonitis, bowel obstruction, necrotizing enterocolitis, segmental volvulus and necrosis and malrotation.

				Procedures performed through this technique: primary intestinal repair(n=14), LADDs procedure(n=1), ileostomy(n=1). Complications seen included anastomotic leak, adhesion ileus and missed rectal atresia. One mortality was reported in an ELBW infant with poor lung maturation Trans umbilical mini-laparotomy is a feasible and an alternative option for minimally invasive surgery in newborns. This technique can be applied to term and preterm infants with low bodyweights. With good surgical experience, surgeons will be able to perform complicated surgery using this technique.

3	Ryerson et al. [19]	Evaluate incidence and natural history if intestinal rotation abnormalities (IRA) in patients with heterotaxy syndrome	Infants recruited over a 4-year period.	29 evaluated, 8 symptomatic and 21 asymptomatic using upper gastrointestinal imaging. Of the 29 infants, 21 had IRA (14 with malrotation and 7 with non-rotation) The median age at presentation was 46 days (5-171 days) Most infants screened with heterotaxy syndrome had IRA, upper gastrointestinal imaging is a good tool for screening, expectant management of asymptomatic infants is a reasonable management strategy.
4	Fullerton et al. [20]	To quantify outcomes and analyze predictors of morbidity and	Infants - A multicenter cohort study in America,	

		mortality in infants with gastroschisis.	evaluated 4420 diagnosed with gastroschisis	The median birthweight in the study population was 2410g with median length of stay 37 days. Survival (discharge home or alive in hospital at 1 year) was 97.8% with a 37-day median length of stay. Sepsis was found to be the only significant independent predictor of mortality (P = .04). Significant independent determinants of length of stay included: bowel resection (9.8%), sepsis (8.6%), presence of other congenital anomalies (7.6%, including 5.8% with intestinal atresia), NEC (4.5), and small for gestational age (37.3%). Abdominal surgery in addition to gastroschisis repair occurred in 22.3%, with 6.4% receiving gastrostomy or jejunostomy tubes and 6.3% requiring ostomy creation. At discharge, 57.0% were less than the 10th percentile weight for age. The mode of delivery (52.4% cesarean delivery)

				was not associated with any differences in outcome. Of the group included, very low birth weight infants and those less than 29 weeks' gestation were excluded to avoid the impact this high-risk group would have on outcomes, this accounted for 4.2% (193) of the study population. However, this group had a mortality of 20.2% (significantly lower survival) and median length of stay of 80 days. 16% of these infants developed sepsis.
5	Dahan et al. [21]	To determine whether intra-abdominal pathology is an independent risk factor for central line associated blood stream infections	Infants admitted to NICU	120 cases and 293 controls were included in the study. Active intrabdominal pathology, abdominal surgery in the prior seven days, male sex, >= 3 heel punctures were found to be significant risk factors for CLABSI whereas >= 3 heel punctures and intra-abdominal pathology served as

				independent risk factors for CLABSI with intrabdominal pathology increasing the risk by 6-fold.
6	Härtel et al. [7]	To evaluate the outcome of VLBW infants administered prophylactic probiotics	VLBW infants	The infants were observed over a period of 28 months and classified in to 3 groups: 1) no prophylactic use, 2) changed to use of probiotics during this period and 3) use of probiotics prior to this period. Probiotics were found to reduce the risk of NEC and any abdominal surgery as well at the combined outcome of abdominal surgery/mortality. No effect was seen on the outcome of confirmed sepsis.

7	Arbell et al.[22]	To determine whether bedside laparotomy is safe at the referring Centre and if it is beneficial for the infant	ELBW infants (< 1000g) who were ventilated, haemodynamically unstable and required abdominal surgery were included.	12 infants qualified for the study, the median weight at operation was 850g and median age at birth was 25 weeks. Of the 12 infants: 11 survived the acute event, 9 survived more than 30 days and 5 survived to discharge. The study concluded that bedside laparotomy was feasible in this study population and avoids the risks involved with the transfer of an unstable infant.
8	Javid et al. [23]	To determine incidence and risk factors for cholestasis associated with parenteral nutrition	Infants who underwent abdominal surgery.	The median exposure to PN in this study was 28 days and development of cholestasis occurred with a median duration of 23 days.

				Retrospective study over 5 years with 176 infants, 24% developed cholestasis Cholestasis with higher in infants with lower gestational age and not influenced by surgical pathology

Table 2: Clinical use of SNAPPE and CRIB scores in predicting neonatal mortality.

Study	Author	Aim	Population	Findings
1	Gagliardi et al. [30]	To compare discriminatory ability of CRIB I, CRIB II and SNAPPE II	VLBW infants	CRIB and CRIB II was superior to SNAPPE II, CRIB 1 and II were equal in accuracy. Both scores do not estimate risk of death
2	Kardum et al. [24]	Describe mortality, timing, causes of death until hospital discharge	VLBW infants- a retrospective study with 252 VLBW	The CRIB score was found to have the highest association for death until discharge. Contributors to death until hospital discharge included: a 4-week lower gestational age than surviving infants, lower birth weight, low 5 min Apgar score, higher CRIB score and more frequently resuscitated at birth. The survivors were more likely to receive CPAP at birth and were small for gestational age.

				NEC was the most common cause of death after the first 7 days postnatally and death was more commonly as a result of prematurity in the first 7 days. The mortality until hospital discharge was 30.5%.
3	Asker et al. [25]	Determine mortality risk using SNAPE II and CRIB score as well as to evaluate use of antenatal steroids and surfactant on mortality	VLBW infants	SNAPE II was found to have a higher predictor of mortality in infants < 1500g and also noted to be more accurately assessed in patients who had received antenatal corticosteroids.
4	Baird et al. [26]	Compare outcomes of peritoneal drainage and delayed laparotomy vs primary laparotomy using SNAPPE II as a predictor of mortality	VLBW- 52 infants reviewed.	Mortality rates in the peritoneal drainage and primary laparotomy groups were 32% and 7.4% respectively with predicted mortality rates using the SNAPPE II score: 15.7% and 7.4% respectively.

				The delayed laparotomy group had a 30-day mortality of 6.3% and a predicted mortality rate of 9.3%. The secondary outcomes all favoured the primary laparotomy group. From this it is evident that 30-day mortality in the primary laparotomy group correlated to the SNAPPE II scores. Infants with a higher SNAPPE II score had a higher mortality rate and patients with peritoneal drain alone had a poorer outcome than the primary laparotomy group.
5	Bonnard et al. [27]	Determine the clinical use of the modified SNAPPE in making a surgical decision with regards to PD vs PD and laparotomy in low	VLBW infants-retrospective study of 39 patients.	A total of 39 infants were included, 20 of them had peritoneal drainage alone and 19 of them had both PD and a laparotomy.

		birthweight infants with perforated NEC		The mean gestational age in the PD and combination group: 25.6 and 26.6 respectively and mean birth weight 795g and 910g respectively. No Difference in SNAPPE scores were noted between the two groups when calculated on the day of admission, day before drain insertion and the day after drain insertion. The modified SNAPPE score was found to be a good predictor of mortality. A high SNAPPE score post PD insertion was associated with a higher risk of mortality irrespective of whether infants had a laparotomy or not.

6	Kaaresen et al.[28]	Two outcomes: To compare the use of the CRIB score to gestational age and birthweight in predicting hospital mortality in VLBW infants If the CRIB score was useful, to use it as a measure of the performance of the NICU by using the CRIB score to adjust the initial risk	VLBW infants-retrospective study of data collected on 398 infants.	Easy score to use, CRIB score found to be significantly better than birthweight and gestational age in predicting hospital mortality. The CRIB score can adjust for differences in illness severity and management prior to NICU admission such as antenatal steroids and can therefore be used as a marker to audit a neonatal unit. The study showed a survival rate of 78% and more girls were likely to survive than boys.
7	Broughton et al. [29]	The use of modified CRIB score as a triage tool when used at the first telephonic consult with a transport service comparing death in the neonatal period between infants retrieved	Infants	Modified CRIB (only maximum FiO2 calculated and not both minimum and maximum) score was better in predicting mortality than birthweight and gestational age.

				CRIB score is easy to use, SNAP is limited due to extensive variables and unable to be applied at the first telephone contact. A modified CRIB score of 6 and higher had a 90% sensitivity and 36% specificity. Repeated assessments of illness severity improve mortality prediction.

1.5 Summary and Conclusion

The successful management of a surgical infant requires access to an intensive care unit that offers high risk neonatal support including ventilatory and inotropic support.

Due to advancements in neonatal care, there is an increased trend in survival of ELBW infants and with this an increase in preterm related complications including more abdominal emergencies.

Risk factors such as decreasing gestational age, decreasing birthweight and severely ill infants in combination with life threatening surgical conditions have been associated with a poorer neonatal outcome.

NEC and SIP are the two most common surgical complications of preterm birth with an increase in mortality with decreasing gestational age. Approximately half of the patients with NEC require surgery. NEC has a higher mortality than SIP with sepsis being the leading complication , particularly in premature infants with underdeveloped immune systems, increasing the risk for mortality.

Certain surgical conditions such as gastroschisis have a good overall survival but these patients are still at risk for complications.

Various techniques and preventative strategies, such as different feeding practices or the prophylactic use of probiotics, have been looked at to improve outcomes in these patients.

There is no consensus on the optimal surgical approach in managing patients with surgical conditions. PD alone did not improve survival; trans-umbilical mini laparotomy has been considered a feasible minimally invasive approach, but this requires advanced surgical skills. Bedside laparotomy in ELBW neonates could improve 30-day postoperative survival and unnecessary transfers of unstable infants.

Using tools that could predict mortality may aid in better planning of postnatal care and parental counselling. The CRIB score is a better predictor of mortality than weight and gestational age but is limited to patients < 32 weeks' gestation.

Identifying and understanding the short-term outcomes and risk factors associated with mortality and severe morbidity, different management practices may be applied to improve overall healthcare for this group of infants. While re-enforcing preventative strategies like exclusive human milk feeding is imperative, identifying the infants at highest risk could improve vigilance for surgical complications, manage parental expectations by appropriately counselling parents about the risks of surgical complications, but also identifying the infants whose prognosis is promising in order to prioritise their surgical care. Effective prognostication could facilitate the appropriate utilization of restricted resource and limit prolonged discomfort, pain and parental distress in cases where aggressive and invasive attempts might be futile.

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2. Manuscript in publication ready format

2.1 Title page

Title: Abdominal Surgery in very low birth weight neonates in a developing world neonatal unit- Short term outcomes and risk factors for mortality

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2.2 Abstract

Background

The surgical infant requires care in specialized neonatal units. Very low birth weight (VLBW) infants are a group particularly vulnerable to the risks and outcomes associated with preterm birth. There is an increased number of abdominal emergencies seen, attributed to improved survival in this birthweight category.

Objectives

To describe the short-term survival to discharge in VLBW infants following abdominal surgery at a South African public tertiary hospital and to examine the utility of common scoring systems for prognostication.

Methods

A retrospective study of VLBW infants with abdominal surgery was conducted in patients admitted to the neonatal unit at Groote Schuur Hospital between 2012 and 2016. CRIB and SNAPPE scores were calculated for patients where sufficient data was available.

Results

Fifty-two patients were included. The mean gestational age (GA) and birthweight (BW) were 29.5 weeks (SD 2.1) and 1102g (SD 197.8) respectively.

Necrotizing enterocolitis was the most common (50%) surgical emergency. The leading post-operative complication was sepsis (37%).

Fourty-two (81%) infants survived to discharge, the mean age at presentation 21 days (SD 21.1) with a mean hospital stay of 74 days in survivors vs 52 days in the non-survivors (p=0.06).

There was no statistically significant difference in SNAPPE scores between survivors and non-survivors.

Conclusion

Abdominal emergencies have a high mortality and adds to the overall length of stay in VLBW infants.

Neonatal scoring systems have proven to be useful adjuncts in predicting neonatal mortality, further study is warranted in infants who deteriorate due to surgical abdominal complications.

2.3 Background

Highly specialized neonatal care is required for the preterm infant requiring surgery due to the hazards of anaesthesia and operative interventions. [1] In addition, risk factors such as decreasing gestational age, decreasing birthweight and severely ill infants in combination with prematurity-related life-threatening surgical conditions are associated with poor outcomes in the infant. [1].

Necrotizing enterocolitis (NEC) and spontaneous intestinal perforation (SIP) are the commonest emergencies, 50% of which require surgery and prolonged hospitalization. [2-4] Greater survival is seen in infants with larger birthweights, [5] but postoperative complications are common with sepsis being the leading cause of mortality. [6] There is a concern of poorer neurodevelopmental outcome in survivors with NEC compared to those without surgical NEC. [2]Other complications include intestinal strictures, wound infections and malabsorption syndromes. [7]

Sixty percent of preterm births occur in lower- and middle-income countries (LMIC). [8] The ability to predict neonatal mortality and establishing illness severity can be a useful tool especially in resource limited settings if it aids resource allocation with improved and more appropriate counselling of parents. Different Scoring systems have been developed and used to assess the severity of the illness and to predict mortality, morbidity and prognosis of infants in neonatal intensive care units (NICU). These have been devised to overcome differences imposed by varying birth weights, causes of neonatal mortality, care given in neonatal units and risk factors predisposing to neonatal mortality. [8,9]

CRIB II (An update of the clinical risk index for babies score) and SNAPPE (Score for Neonatal Acute Physiology Perinatal Extension) have been found useful as a tool in predicting neonatal mortality. [10]

2.4 Objectives

The primary objective of this study is to describe the short-term survival to discharge in VLBW infants following abdominal surgery at a neonatal unit in a middle-income African country.

The secondary objectives are to describe the conditions requiring abdominal surgery in the study population as well as identifying factors associated with mortality during the post-surgical period. Additionally, to examine the differences between the CRIB II and SNAPPE scores as tools for predicting mortality in infants.

2.5 Methods

This is a descriptive retrospective study conducted at Groote Schuur Hospital (GSH) Neonatal Unit in Cape Town, South Africa. It is a tertiary level neonatal unit that admits approximately 2400 infants per annum. The unit cares for approximately 500 VLBW infants, a group particularly vulnerable to the risks and outcomes associated with preterm birth. Infants with surgical complications are referred to Red Cross War Memorial Children's Hospital for definitive surgical management. VLBW infants born between 2012 and 2016, who have had abdominal surgery, identified from a patient database using The Vermont Oxford Network Database (VON) which records details of all very low birth weight neonates admitted to the neonatal unit. All infants transferred to Red Cross Hospital with the intention of abdominal surgery were included. A folder review of these infants was then conducted, collecting information from both hospitals. Ethical approval was obtained by the Faculty of Health Sciences Human Research Ethics Committee of the University of Cape Town. Information recorded included infant demographics, resuscitation at birth, inborn vs outborn, indication for abdominal surgery, type of abdominal surgery, cause for mortality, length of stay, length of total parenteral nutrition (TPN) duration, initiation of enteral feeds, ventilatory requirements, variables for CRIB II and SNAPPE scores.

Variables used to calculate CRIB II included: gestational age, birthweight, sex, base excess and temperature on admission. SNAPPE scores were calculated using variables such as: mean blood pressure, lowest temperature and serum pH, presence of seizures, Apgar score, birthweight, gestational age, urine output, PO2/FiO2 traditionally collected within 12 hours of admission. In this study, the score was calculated at the time of deterioration prior to surgery.

The information from both facilities was captured and recorded with the use of predesigned digital data collection sheets using EpiData Manager (V4.6.0.2) and Entry Client (V4.6.0.2). Data was exported to Microsoft Excel ® and Stata ® V 13.0 statistical software for analysis. Demographic and clinical data were presented with descriptive statistics and statistical analysis utilizing univariate analysis to compare survivors to non survivors. The Student's t-test was used for comparison of parametric continuous variables and the Wilcoxon rank-sum test and Kruskal Wallis for non-parametric comparison. The χ^2 test or Fisher's exact test was used for categorical comparisons. Statistically significant results considered with ($p<0.05$).

2.6 Results

A total of 52 VLBW infants were included in the study. Complete information was available on 44 infants.

The infant and perinatal characteristics of the cohort are shown in Table 1. The mean gestational age (GA) and birthweight (BW) were 29.5 weeks (standard deviation (SD) 2.1) and 1102g (SD 197.8) respectively. The majority of the patients in the cohort are male (65%). Approximately half (28/52, 54%) the patients were delivered via caesarian section, followed by normal vaginal delivery (23/52, 44%). One infant was a breech vaginal delivery.

Outcomes and potential risk factors are described in Table 2. Fourty-two (81%) of the cohort survived to discharge. The presence of culture proven sepsis (including both early and late

sepsis) was not statistically different between survivors (26/42 62%) and infants who died before discharge (8/10 80%) (p=0.28).

Of the total cohort, 51 of the 52 infants had a definitive surgical procedure, one infant with a spontaneous intestinal perforation (SIP) was managed palliatively with a peritoneal drain.

The pathology seen in the cohort include necrotizing enterocolitis (NEC) (26/52 50%), SIP (13/52 25%) and other pathologies including intestinal malrotation and duodenal atresia. Table 3 tabulates the pathologies seen.

The most common post-operative complication seen was sepsis (19/51 37%) followed by high output stoma losses (11/51, 22%) . Fourty-four infants received TPN but complete data was only available for 40 infants. The most common TPN complication observed was electrolyte abnormalities (33/40, 83%) followed by thrombosis (17/40, 43%). Table 4 illustrates the complications observed in the cohort.

Survivors had a higher mean BW and GA compared to non-survivors, 1126g (SD 197.2) vs 1004g (SD 177) (p=0.09) and 29.6 weeks (SD 2.2) vs 28.6 (SD 1.6) (p=0.27) respectively but this was not statistically significant.

The mean age at presentation 21 days (SD 21.1) and mean corrected gestational age (CGA) 32.4 weeks (SD 3.6). The mean overall hospital stay between both hospitals was 74 days in survivors compared to 52 days in the non-survivors (p=0.06). Infants with NEC were more likely to require longer hospitalization than infants with spontaneous intestinal perforation (SIP) (p=0.005).

The mean duration of TPN was 16 days (SD 9.5). One infant received TPN for 43 days. NEC was the diagnosis in 22/44 patients that required TPN, and 21/22 (95%) received this for more than 1 week compared to 8/13 (62%) of patients with SIP (p=0.016). Infants with other pathologies all required TPN for more than 1 week.

Post-operative length of hospital stay had a median of 44 days (IQR 27-72.5). Sixty percent of infants that died, demised within 30 days from the time of surgery. Post-operative length

of hospital stay in survivors was longer with a median of 45.5 (IQR 33-72) versus non-survivors 23.5 (IQR 11-73) (p=0.08).

Cause of death in non-survivors include most commonly sepsis (5/10, 50%). The causes of death are tabulated in Table 5.

CRIB II scores could be only be determined in 7 patients due to incomplete data. All seven of these infants survived. SNAPPE II scores were determined in 34 infants. Survivors had a lower median score of 31 (95% Confidence Interval (CI) 25.4 – 38.2) compared 47 (CI 26.0 -68.0) in patients who demised (p=0.08).

2.7 Discussion

Most studies of surgical outcomes in infans are from settings in high income countries. This study adds to the limited body of literature on abdominal surgery outcomes coming from Low- or Middle-income countries that are resource restricted. In this study 10 out of 52 infants referred for abdominal surgery demised. The mean age of presentation of the surgical emergencies was 21 days. While most of the non-survivors (90%) were very preterm with a lower mean GA this was not found to be statistically significant. The mortality of 19.2% of infants in this cohort is comparable to other studies which found mortality rates up to 30,5% in VLBW infants[11,12]. A study by Arbell et al. [13] including a cohort of 12 ELBW infants with 58% in-hospital mortality in infants who received bedside abdominal surgery. Groote Schuur Hospital where the study was performed is a state sector hospital with restricted resources serving a largely impoverished community with challenges in health care access and antenatal care. The neonatal unit has 8 out of a total of 14 funded neonatal intensive care beds that service the greater western metropole of Cape Town where approximately 40 000 births occur annually. [14] The restricted available ICU beds place a great emphasis on the prioritization of care for infants with better prognosis. As such, extreme preterm infants may not survive to an age where they may present with abdominal surgical emergencies, which may explain the favourable mortality rate. Härtel et al. [3] demonstrated that prophylactic

probiotics reduced the rate of NEC, any abdominal surgery and the combined outcome of surgery and/or death, though not specifically documented, this study was conducted at a time where prophylactic antibiotics were routinely prescribed to any VLBW infant.

Half of the infants in our study had NEC requiring abdominal surgery also found in other studies to be the most common reason for surgery in preterm and low birthweight infants [2,3], followed by SIP which was also commonly observed in prior studies. [2,4,5,15]

In one of the few studies from resource restricted settings, Kuremu et al. reported a retrospective study conducted in Kwazulu Natal that showed gastrointestinal perforation occurred more commonly in males and the main cause was NEC. [6] While we did not specifically look at intestinal perforation as a reason for surgery, we also found a male predominance in our cohort.

This study found sepsis (confirmed on blood culture) to be the leading postoperative complication. This was not unsurprising as several studies on surgery in neonatal populations comment on sepsis as the leading complication with the highest cause of mortality especially with preterm birth as a comorbidity. [3,12]. Dahan et al. found that intraabdominal pathology is an independent risk factor for central line associated bloodstream infections, increasing the risk by 6-fold [16]. Post-operative sepsis was observed in 37% of our infants. While most infants received TPN this study did not record whether infants received this via central lines, percutaneous intravenous catheters or peripheral lines.

The overall mean length of hospital stay between survivors and non-survivors trended towards statistical significance. We suspect that had the cohort been larger, the result may have been statistically significant. The type of pathology significantly impacted on length of hospital stay with NEC requiring longer hospitalization than SIP or the other pathologies found in our study which has been observed in previous studies [11,17]. Bisquera et al. showed that infants with surgical NEC had much longer hospital stays than their control counterparts, exceeding them by 60 days[17].

We found sepsis contributed to half of the mortality of infants in this cohort with no statistical significance between NEC, SIP and the other pathologies which could be explained by the relatively small number of deaths in this study. Byun et al. reported that NEC was the most common pathology followed by SIP and that NEC was considered a poor prognosticator for survival with the most common cause of death due to septic shock. They noted a longer duration of TPN and length of hospital stay than our study which could be due to a lower mean GA in their study cohort and only extremely low birthweight (ELBW) infants enrolled [18]. Baird et al. demonstrated in their study that infants with peritoneal drain alone had a poorer outcome than infants who had a primary laparotomy [19]. Only one infant in our study had a peritoneal drain alone and was managed conservatively due several either comorbidities, which makes comparisons difficult.

Four (40%) of the infants that died, demised more than 1 month after surgery. Short bowel syndrome was the cause of death in one of these infants and one died due to sepsis. Records were unclear for cause of death of the remaining two infants.

A study by Kardum et al. found that contributors to death until hospital discharge included: 4 week lower gestational age than survivors, lower birth weight, low 5 min Apgar score, higher CRIB score and more frequently resuscitated at birth and the survivors were more likely to receive continuous positive pressure (CPAP) at birth[12]. In our study there were no observable significant differences seen in maternal or perinatal characteristics, as well as no significant differences between the need for early or late respiratory support. However, there was a trend towards a lower duration of early oxygen therapy in survivors that could be a potentially significant association.

The surgical infant requires care in highly specialized units, with increasing survival it means that more infants are at risk of abdominal emergencies. Given the resource limitation that we face in South Africa, a tool that is able to accurately predict mortality would be very useful in our setting. The SNAPPE score in our study was calculated on 34 infants who had the relevant information, traditionally the score is calculated within 12 hours of admission to the neonatal intensive care unit (NICU), as this information was not available, the score was

done within 12 hours of deterioration. Survivors had a lower median score (31) compared to non-survivors (47), although this is not statistically significant (p=0.08) we can speculate that with a larger cohort it could have been.

In our study, 79% of survivors had a SNAPPE score of more than 38. Muktan et al. found that a SNAPPE score> 38 was associated with a higher mortality. [9] Bonnard et al. looked at the clinical use of the SNAPPE score in making a surgical decision with regards to patients who had a peritoneal drain(PD) alone vs patients who had both a PD and laparotomy in patients with perforated NEC. No differences were found in scores between the 2 groups when measured at three different intervals, on the day of admission, day before drain insertion and the day after drain insertion [20].

We only had sufficient information on 7 infants to calculate the CRIB score and all of these infants survived, therefore no mortality analysis could be conducted on the use the CRIB score as a predictor of mortality.

This study was limited as it was a small study population, was retrospective in design and minimal data was available for collection for use of SNAPPE score as a routine gas in the first 12 hours is not a standard practice. Several analyses that showed a trend towards significance may have been affected by size of the cohort.

2.8 Conclusion

Very low birth weight infants remain a population at risk of serious complications associated with preterm birth despite advancements in neonatal care. While NEC and SIP are the most common surgical complications seen, NEC especially is a potentially devastating condition that not only serves as a cause of mortality but also impacts on overall length of hospital stay. These factors contribute to the financial implications for the treating institution particularly in a LMIC neonatal unit where we are faced with resource constraints.

Optimal surgical approaches are still being sought in order to reduce the potential risk of these infants. Feeding practices and the use of probiotics have been implemented as preventative strategies in order to improve outcomes in these infants and although these are all important in their management , identifying infants at risk, based on a scoring system, would help alert us to potential serious surgical complications and allow us to provide appropriate counselling to parents sparing them unnecessary despair. Similarly, infants with a good prognosis could be identified and offered optimal care in our resource limited setting.

Although this study was limited in demonstrating the potential effectiveness of a patient scoring tool for prognostication, further prospective studies are warranted especially in resource restricted setting.

Table 1: Characteristics of study cohort

(n=52 unless different N specified in first column)

	Total	Survivors (42)	Non-survivors (n=10)	p-value
Infant Characteristics				
Male gender, **n** (%)	**34** (65)	**29** (85)	**5** (15)	0.26
BW(g), **mean** (SD)	**1102** (197.8)	**1126** (197.2)	**1004** (177)	0.09
500-1000g, **n** (%)	**16** (31)	**11** (69)	**5** (31)	0.14
1001-1500g, **n** (%)	**36** (69)	**31** (86)	**5** (14)	
GA(weeks), **mean** (SD)	**29.5** (2.1)	**29.6** (2.2)	**28.6** (1.6)	0.27
GA: n (%)				0.26
< 32 weeks	**46** (88)	**37** (80)	**9** (20)	
≥ 32 weeks	**6** (12)	**5** (83)	**1** (17)	
Maternal Characteristics				
Antenatal Steroids[‡] **n** (%)	**20** (38)	**15** (75)	**5** (25)	0.48[†]
Maternal Hypertension,**n/N** (%)	**13/50** (26)	**10/40** (76)	**3/10** (23)	0.70

Maternal HIV-positive, **n** (%)	**15** (29)	**13** (87)	**2** (13)	0.70
Birth Characteristics				
Inborn, **n** (%)	**41** (79)	**34** (83)	**7** (17)	0.45*
Delivery Mode				
NVD, **n** (%)	**23** (44)	**18** (78)	**5** (22)	0.83*
Breech, **n** (%)	**1** (2)	**1** (100)	0	0.79†
Caesarian Section, **n** (%)	**28** (54)	**23** (82)	**5** (18)	0.83*
Apgar Score				
1 min: **n**; mean; (SD)	**50**; 6; (2.4)	**41**; 6;(2.4)	**9**; 7; (2.5)	0.94
5 min: **n**; mean; (SD)	**12**; 7; (2.6)	**10**; 7; (2.8)	2; 8; (1.4)	0.86
CPR at birth, **n** (%)	**10** (19)	**9** (90)	**1** (10)	0.66†
Neonatal Period				
Surfactant, **n** (%)	**17** (33)	**13** (76)	**4** (24)	0.58*
Mechanical Ventilation				
Early (before 7 days), **n** (%)	**8** (15)	**7** (88)	**1** (13)	0.73*
Late (after 7 days), **n** (%)	**19** (37)	**15** (79)	**4** (21)	0.91*

Duration of early oxygen therapy(days), **n**; mean; range; (SD)[§]	**41**; 6; 1-34; (5.9)	**33**; 5; 1-22; (4.2)	**8**; 10, 3-34; (10)	0.08[**]
Duration of late oxygen therapy(days), **n**; mean; range; (SD)[§]	**41**; 12; 1-40; (10.8)	**33**; 11; 1-40; (10.7)	**8**; 17; 8-40; (10.5)	0.60[**]
Feeding(until point of deterioration)				0.62[†]
EBF, **n** (%)	**35** (67)	**27** (77)	**8** (23)	
EFF, **n** (%)	**4** (8)	**4** (100)	0	
Mixed, **n** (%)	**13** (25)	**11** (85)	**2** (15)	

Abbreviations: BW=Birthweight; g=grams; SD= standard deviation; GA=gestational age; EBF=Exclusive breastfeeding; EFF= Exclusive Formula feeding; mixed= both breast and formula milk; IQR=interquartile range; med= median

[*] Chi-Square test, [†] Fisher's exact test, [**] Wilcoxon Rank Sum test

[‡] 2 doses of steroids

[§] Includes all forms of ventilation(Mechanical, CPAP, Both)

Table 2: Outcomes of study cohort: survivors vs non-survivors

	Total(n=52)	Survivors(n=42)	Non-Survivors(n=10)	p-value
Age at presentation (days), **n**, mean, (SD)	**52**[¶], 21, (21.1)	**42**, 22, (22.6)	**10**, 16.7, (18.6)	0.53[**]
CGA at time of surgery (weeks), **n**; mean; (SD)	**52**[¶]; 32.4; (3.6)	**42**; 32.8; (3.8)	**10**; 31; (2.7)	0.15[**]
< 32 weeks, **n** (%)	**27** (52)	**20** (74)	**7** (26)	0.87[*]
≥ 32 weeks, **n** (%)	**25** (48)	**22** (88)	**3** (12)	
Pathology, n (%)				0.41[*]
NEC	**26** (50)	**21** (81)	**5** (19)	
SIP	**13** (25)	**8** (62)	**5** (38)	
Other	**13** (25)	**13** (100)	0	
Length of hospital stay(overall days in hospital), n; mean; (SD)	52; 70; (32.1)	42; 74; (31.4)	10; 52; (30.1)	0.06[¥]

By Pathology: *NEC*, **n**; mean; (SD)	**26**; 82; (26.4)			0.005
SIP, **n**; mean; (SD)	**13**; 47; (25.3)			
Other, **n**; mean; (SD)	**13**; 69; (37.6)			
Length of stay following surgery (days), **n**; med; (IQR)	**52**; 44; (27-72.5)	**42;** 45.5; (33-72)	**10**; 23.5; (11-73)	0.08**
30-day post-operative length of stay, **n** (%)	**15** (29)	**9** (60)	**6** (40)	0.02†
TPN initiation: **n** (%)				
Pre-surgery	**31** (62)	**25** (81)	**6** (19)	0.90*
Within 24 hrs of surgery	**7** (14)	**5** (71)	**2** (29)	
Within 48hrs of surgery	**11** (22)	**9** (82)	**2** (18)	
48hours of surgery	**1** (2)	**1** (100)	0	

Total Duration of TPN in days; **n**, mean, range, (SD)	**44**, 16, 5-43, (9.5)	**35**, 16, 5-43, (9.4)	**9**, 15, 10.3, (5-40)	0.76
		TPN Category (days), n (%)‖		
By pathology		1-7 days	7-28 days	>28 days
NEC (**n**=22)	**22**, 18.6, (10-25)	**1** (5)	**16** (73)	**5** (23)
SIP (**n**=13)	**13**, 8.9, (7-11)	**5** (38)	**8** (62)	0
Other (**n**=9)	**9**, 18.2, (12-23)	0	**8** (89)	**1** (11)
Any Proven Sepsis[ij], n (%)	**34** (65)	**26** (62)	**8** (80)	0.28*
Early Sepsis, **n** (%)	**6** (12)	**4** (67)	**2** (33)	0.35*
Late Sepsis, **n** (%)	**31** (60)	24(77)	**7** (23)	0.46*
SNAPPE Score; **n**, med, CI	**34**, 34, 0-74	**29**, 31, 25.4-38.2	**5**, 47, 26.0-68.0	0.08**
SNAPPE Score less than 38; **n** (%)	**20** (59)	**18** (90)	**2** (10)	0.35*
SNAPPE Score greater than 38; **n** (%)	**14** (41)	**11** (79)	**3** (21)	0.35*

Abbreviations: TPN=total parenteral nutrition; CGA= corrected gestational age in weeks; NEC= necrotizing enterocolitis; SIP= spontaneous intestinal perforation; hrs= hours; SNAPPE score= Score for Neonatal Acute Physiology Perinatal Extension; CI= confidence interval; IQR=interquartile range; med= median

[i]Proven Sepsis (Early< 7days; Late>7 days)

[*] Chi-Square test; [†] Fisher's exact test; [‡] 2 doses of steroids; [**] Wilcoxon Rank Sum test

[¶] One patient was conservatively managed

[‖]p=0.016: statistical significance between TPN duration and pathology

Table 3: Classification of pathology

Pathology	**n=52**
NEC	26
SIP	13
Other:	13
Malrotation	3
Duodenal Atresia	4
Cholangiography for conjugated hyperbilirubinaemia	1
Bilateral Inguinal Hernias	1
Gastroschisis	1
Stomach Perforation	1
Right upper quadrant inflammatory mass	1
Jejunal Atresia with microcolon	1

Table 4: Total Parenteral (TPN) and Postoperative Complications

Complications in patients receiving TPN, n=40		
	n	**%**
Electrolyte abnormalities	33	83
Thrombosis (Large vessel)	17	43
Sepsis	11	28
Hyperglycaemia	9	23
Hypoglycaemia	9	23
Anaemia	8	20
Cholestasis	6	15
Thrombocytopaenia	4	10
Hypoalbuminaemia	2	5
Coagulopathy	2	5
FTT	1	3
None	1	3
Post-operative Complications, n=51		
Sepsis	19	37
High output stoma losses	11	22
Anaemia	9	18
Wound infection	9	18
Wound Dehiscence	8	16
DIC	6	12
Thrombocytopaenia	5	10
DVT	5	10
Electrolyte Abnormalities	3	6
Feed intolerance/delay in initiating feeds	3	6
Acute Kidney Injury	2	4
Short Bowel Syndrome	2	4
Stricture	2	4
Inguinal Hernia	2	4
Bowel Obstruction	1	2
Compartment Syndrome	1	2
Urethral Injury	1	2
None	1	2

TPN= Total parenteral nutrition; Electrolyte Abnormalities= Changes in sodium, potassium, magnesium, phosphate; DVT= Deep Vein Thrombosis; DIC=Diffuse intravascular coagulopathy; Anaemia= Haemoglobin < 10g/dl; FTT= failure to thrive

Table 5: Cause of death and days post-surgery at time of death

Causes of death	**n=10**	**%**	**Length post-surgery at time of death(days)**
Sepsis	5	50	4, 11, 18, 29, 43
Respiratory Failure	1	10	11
Short Bowel Syndrome	1	10	83
Unknown	3	30	1, 73, 75

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3. Appendices

Addendum 1 Data Collection Sheet

Case Report Form:

VON Case Number:

Study Number:

Neonatal factors:

<table>
<tr><td colspan="3">Gestational Age (weeks and days):</td><td colspan="3"></td></tr>
<tr><td colspan="3">Weight(g):</td><td colspan="3"></td></tr>
<tr><td colspan="3" rowspan="2">Sex:</td><td colspan="2">Male</td><td>Female</td></tr>
<tr><td colspan="2"></td><td></td></tr>
<tr><td colspan="3" rowspan="2">Apgars:</td><td>1min</td><td>5min</td><td>10min</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td colspan="3">Year of birth:</td><td colspan="3"></td></tr>
<tr><td rowspan="2">Ventilation:</td><td>CPAP</td><td>Mechanical</td><td>Early</td><td colspan="2">Late</td></tr>
<tr><td></td><td></td><td></td><td colspan="2"></td></tr>
<tr><td colspan="3">Mortality:</td><td>Yes</td><td>No</td><td>Cause for mortality:</td></tr>
<tr><td colspan="3"></td><td></td><td></td><td>Withdrawal/Limitation of care:</td><td>Yes</td><td>No</td></tr>
<tr><td colspan="3"></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

Inborn			Outborn			
CPR at birth			Yes			No
Adrenaline						
Temperature on admission:			°C			
Base Deficit in first 12 hours			mmol/l			
Inotropes			Yes			No
Surfactant:			Insure		Ventilated	
Congenital malformations			Yes			No
			Type			
Genetic Syndromes/associations			Yes			No
			Type			
Feeds			Breastmilk		Formula	
Day of initiation post-surgery						
TPN	Yes	No	Day of initiation post-surgery		Complications	
Positive Blood Culture			Proven early sepsis	Proven late sepsis	Treated for suspected late sepsis	

Maternal Factors:

Mode of Delivery	NVD	Breech	C/S
Booking bloods	Rhesus	RPR	HIV Status
	Yes	No	
Chorioamnionitis			
Antenatal Steroids	1 dose		
	2 doses		
Hypertension			
Magnesium Sulphate			

Surgical Outcomes:

Indication for abdominal surgery		
Type of Surgery		
Corrected gestational age and weight at time of surgery	CGA	Weight
Post-operative complications		
Length of stay following abdominal surgery	Days:	
Is there a correlation between type of surgery and mortality		
Are there any predictors of mortality		
Discharged:	Yes	No
If no, number of days of survival post-surgery at time of death:	Days:	
Days post-surgery at time of discharge:	Days:	

Addendum 2 Crib Score

CRIB II SCORE:

11

Birthweight (g) and gestation (weeks):

The maximum (worst) score for birthweight and gestation is 15, which is obtained for a 22 week male infant of less than 501 g birthweight

Male infants

Birthweight (g)	22	23	24	25	26	27	28	29	30	31	32
2751 to 3000											0
2501 to 2750										1	0
2251to 2500									3	0	0
2001to 2250									2	0	0
1751to 2000								3	1	0	0
1501to 1750						6	5	3	2	1	0
1251to 1500					8	6	5	3	3	2	1
1001to 1250		12	10	9	8	7	6	5	4	3	3
751 to 1000		12	11	10	8	7	7	6	6	6	6
501 to 750	14	13	12	11	10	9	8	8	8	8	
251 to 500	15	14	13	12	11	10	10				

Gestation (weeks)

Female infants

Birthweight (g)	22	23	24	25	26	27	28	29	30	31	32
2751 to 3000											0
2501 to 2750										1	0
2251 to 2500									2	0	0
2001 to 2250									1	0	0
1751 to 2000								3	1	0	0
1501 to 1750						6	4	3	1	0	0
1251 to 1500					7	5	4	3	2	1	1
1001 to 1250		11	10	8	7	6	5	4	3	3	3
751 to 1000		11	10	9	8	7	6	5	5	5	5
501 to 750	13	12	11	10	9	8	8	7	7	7	
251 to 500	14	13	12	11	10	10	10				

Gestation (weeks)

Temperature at admission (˚C)

≤29·6	5
29·7 to 31·2	4
31·3 to 32·8	3
32·9 to 34·4	2
34·5 to 36	1
36·1 to 37·5	0
37·6 to 39·1	1
39·2 to 40·7	2
≥40·8	3

Base excess (mmol/L):

<−26	7
−26 to −23	6
−22 to −18	5
−17 to −13	4
−12 to −8	3
−7 to −3	2
−2 to 2	1
≥3	0

Sex, birthweight (g) and gestation (weeks): _____

Temperature at admission (˚C): _____

Base excess (mmol/L): _____

Total CRIB II Score ☐

The logistic regression equation relating CRIB II to mortality (CRIB II algorithm) is:

Log odds of mortality = G = −6·476 + 0·450×CRIB II

Probability of mortality = exp(G)/[1+exp(G)]

The range of possible CRIB II scores is 0 to 27

Addendum 3 SNAP-II and SNAPPE-II

Scoring systems for ICU and surgical patients:

SNAP-II and SNAPPE II (Score for Neonatal Acute Physiology and SNAP Perinatal Extension)

Variables	Values	Points
Mean Blood Pressure		0
Lowest temperature		0
$P0_2$ (mmHg) / FIO_2 (%)		0
Lowest serum pH		0
Multiple seizures		0
Urine output (mL/kg.h)		0
SNAP II :	0	
Apgar score		0
Birth weight		0
Small for gestational age (help)		0

SNAPPE II : 0 In- hospital mortality : see below Data are collected within the first 12 hours after admission to the NICU

Gestational age (wk)	3rd percentile birth weight (g)
	0

		Observed deaths		Expected deaths	
SNAPPE-II	Total	No.	%	No.	%
		For all birth weights			
0-9	16,274	48	0.3%	51	0.3%
10-19	3,923	61	1.6%	61	1.6%
20-29	1,952	74	3.8%	71	3.6%
30-39	1,262	93	7.4%	101	8.0%
40-49	790	124	15.7%	116	14.7%
50-59	476	105	22.1%	102	21.4%
60-69	310	101	32.6%	100	32.3%
70-79	142	55	38.7%	63	44.4%
> = 80	141	94	66.7%	90	63.8%

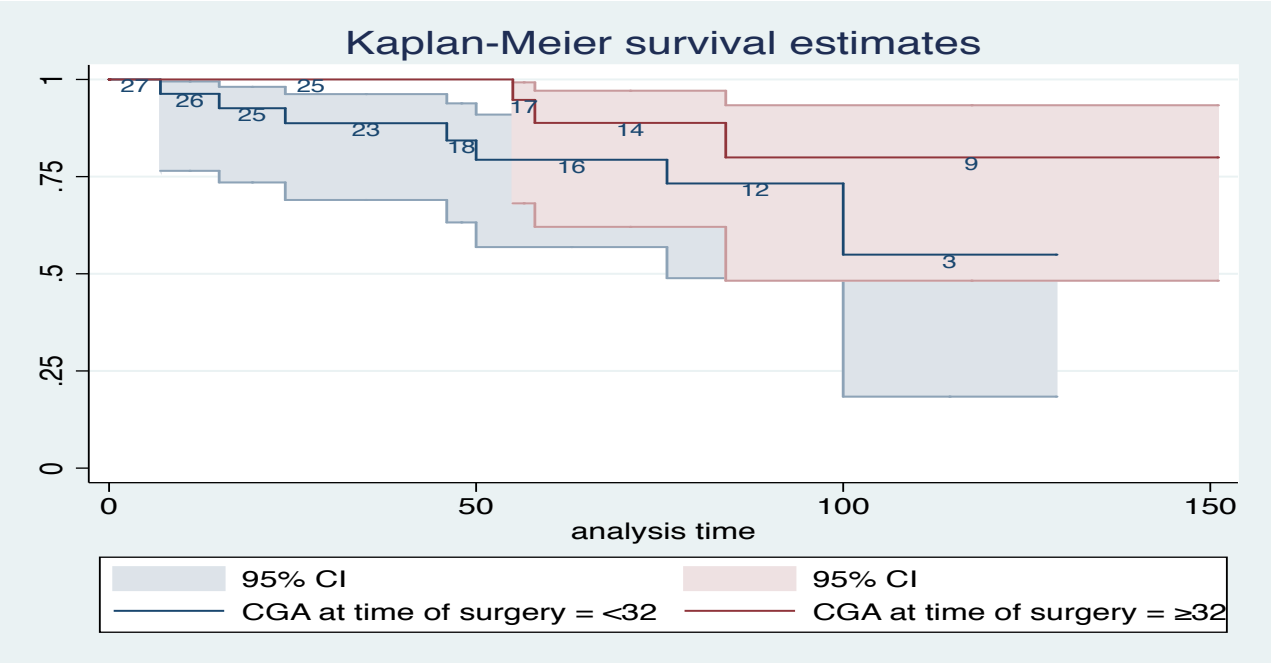
		Observed deaths		Expected deaths	
SNAPPE-II	Total	No.	%	No.	%
		For <1500 g			
0-9	1,526	9	0.6%	7	0.5%
10-19	1,092	30	2.7%	24	2.2%
20-29	772	40	5.2%	38	4.9%
30-39	645	61	9.5%	60	9.3%
40-49	497	79	15.9%	78	15.7%
50-59	318	72	22.6%	72	22.6%
60-69	260	85	32.7%	84	32.3%
70-79	121	46	38.0%	53	43.8%
> = 80	132	88	66.7%	85	64.4%

		Observed deaths		Expected deaths	
SNAPPE-II	Total	No.	%	No.	%
		For >=1500 g			
0-9	14,748	39	0.3%	45	0.3%
10-19	2,831	31	1.1%	37	1.3%
20-29	1,180	34	2.9%	33	2.8%
30-39	617	32	5.2%	40	6.5%
40-49	293	45	15.4%	38	13.0%
50-59	158	33	20.9%	30	19.0%
60-69	50	16	32.0%	16	32.0%
70-79	21	9	42.9%	10	47.6%
> = 80	9	6	66.7%	5	55.6%

Addendum 4: Budget

Item	*Cost*
Travel to hospital site	R 1 500
Printing and office consumables	R 1 500
Research assistant	R 4 500
Citation Software (Papers3)	R 600
Total	R 8 100

Addendum 5 Kaplan-Meier Graph for Corrected Gestational Age



Letter of Ethics Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

22 June 2018

HREC REF: 399/2018

Dr Yaseen Joolay
Neonatology
Red Cross War Memorial Children's Hospital

Dear Dr Joolay

PROJECT TITLE: SHORT TERM OUTCOMES AND RISK FACTORS IN VERY LOW BIRTH WEIGHT (VLBW) NEONATES FOLLOWING ABDOMINAL SURGERY IN A DEVELOPING WORLD NEONATAL UNIT (MMED CANDIDATE - DR N ALLIE) (Study linked to R040/2013)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 June 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that the student, Dr Nazneen Allie will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 399/2018

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Instructions to authors of chosen journal: South African Medical Journal (SAMJ)

SAMJ Policies

Type of articles considered by the SAMJ

The *SAMJ* will no longer limit the articles accepted to those that have 'general medical content', but is intending to capture the spectrum of medical and health sciences, grouped by relevance to the country's burdens of disease. This content will include research in the social sciences and economics that is relevant to the medical issues around our burden of disease. Please see 'A new vision for the *SAMJ* – and a call for papers' for a full discussion of the new directions for the *SAMJ*.

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Research

Reviews

Clinical trials

Editorials

In Practice (Previously Forum incl. Case Reports)

Correspondence

Obituaries

Book reviews

Ad hoc supplements e.g. guidelines, conference/congress abstracts, Festschrifts*

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Guest editorial

Continuing Medical Education (CME)

*Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

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Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.
Author contributions should be listed/described in the manuscript.

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Research ethics committee approval

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whether individual deidentified participant data will be shared;
what data in particular will be shared; whether additional, related documents will be available;
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Preparing an article for anonymous review

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Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
Mask self-citations by referring to your own work in third person.

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Please make your article concise, even if it is below the word limit.
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Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state ‘none’.
Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.

Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:
- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.
**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.
- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:
Human Gene Mapping Workshop (HGMW): genetic notations and symbols
HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.
Preparation notes by article type
Research
Editorials
CME
In Practice and Case reports
Reviews
Clinical trials
Correspondence

Obituaries

Book reviews

Guidelines

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.
Do not replicate data in tables and in text .

Structured abstract

This should be 250-400 words, with the following recommended headings:

Background: why the study is being done and how it relates to other published work.

Objectives: what the study intends to find out

Methods: must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
Results: first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
Conclusion: must be supported by the data, include recommendations for further study/actions.
Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article
All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.
The following are additional heading or section options that may appear within these:
Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.

Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

Start with description of the population and sample. Include key characteristics of comparison groups.

Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.

Do not replicate data in tables and in text.

If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:

E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).

Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

Statement of principal findings

Strengths and weaknesses of the study

Contribution to the body of knowledge

Strengths and weaknesses in relation to other studies

The meaning of the study – e.g. what this study means to clinicians and policymakers

Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

expert opinion

personal clinical experience

observational studies

trials

systematic reviews.

CME (by invite only)

CME is intended to provide readers with practical, up-to-date information on medical and related matters. It is aimed at those who are not specialists in the field.

From January 2016, all CME articles will be printed in full in the *SAMJ*. Please try to adhere strictly to the guidelines on word count as we have a page limit for the print issue of the *SAMJ*. We reserve the right to place some tables and reference lists online if this is necessary for space.

In practice, this means that each CME topic usually covers two issues of the print issue of the *SAMJ*.

The guest editor, in consultation with the editor, is responsible for convening a team of authors, deciding on the subjects to be covered and for reviewing the manuscripts submitted. The suggestion is for 4 - 5 articles, although there is some room for flexibility contingent on discussions with the editor.

For queries about these guidelines please feel free to contact the CME editor, Dr Bridget Farham, by email (ugqirha@iafrica.com) or telephone (+27 (0)82 452 2860)

Review process

The guest editor reviews the articles and returns them to the CME editor for review and final approval.

Guest editorials

Guideline word limit: 1 000 words

Include the guest editor's personal details (qualifications, positions, affiliation, e-mail address, and a short personal profile (50words)).

If possible, include a photograph of the author(s) at high enough resolution for print. It is preferable to provide two guest editorials, one for each issue, so that the content of the articles in each issue is covered.

Articles

Guideline word limit: 2 000 - 3 000 words

Each article requires an abstract of ±200 words.

The editor reserves the right to shorten articles but will send a substantially shortened article back for author approval.

Personal details

Please supply: Your qualifications, position and affiliations and MP number (used for CPD points); Address, telephone number and fax number, and your e-mail address; and a short personal profile (50words)and a few words about your current fields of interest.

In Practice

Guideline word limit: 2 000 - 3 000words

This section includes articles that would previously have been accepted into the Forum section, and case reports.

In practice articles are those that draw attention to specific issues of clinical, economic or political interest regarding medicine and healthcare in southern Africa. They are assigned to a topic:

Case report
Clinical practice
Clinical alert
Issues in medicine
Issues in public health
Healthcare delivery
Medicine and the environment
Medicine and the law
Cochrane corner

An In Practice article should follow the following format – sub-headings are not necessary, but may be used for clarity:
Author affiliations and qualifications: to be the same as for Research. Provide all authors' names and initials, qualifications and full affiliations, and corresponding author.
Short abstract: does not need to be structured, but should capture the essential features of the article
Introduction: the reason for the article and the issue being addressed
Recent research, discussion, local policy around the issue – include your own research where appropriate
All statements should be referenced and, if opinion only, this should be stated
Discussion: how this article adds to the discussion around a particular topic
If a clinical practice or policy point is at issue, this needs to be emphasised, using a box with highlights if appropriate.

Essentially In practice is an opportunity for a more discursive approach to topics of clinical, economic or political importance in southern African health systems. It is not an opportunity to put forward unsubstantiated opinions!

Case reports
The *SAMJ* has recently started to accept case reports. The cases must come from Africa, preferably southern Africa unless the condition is common to all African countries, and must

be either a completely new description of a clinical condition or result (use Google!) or a case that highlights important practice or management issues.

Please use the following format for case reports:
Title of case: do not include the words ‘a case report’ in the title
Summary/abstract: up to 150 words summarising the case presentation and outcome
Background: why is this case important and why did you write it up?
Case presentation: presenting features, medical, social, family history as appropriate
Case management: should be according to best practice, and if not, please explain why
Investigations, if relevant: save space by simply saying ‘normal’ if, for example, renal function was completely normal, rather than listing normal results, highlight the abnormal – or indeed the normal if this is clinically significant
Differential diagnosis, if relevant
Treatment, if relevant
Outcome and follow-up
Discussion – a VERY BRIEF review of similar published cases
Teaching points: 3 - 5 bullet points
References: as per the *SAMJ* house style
Tables and figures: keep to a minimum. Use clinical images where relevant – we need hi-res versions for print, and identifiable persons must have a consent form
Patient consent: please include a statement about patient consent to a written case report. This should be uploaded as a supplementary file.

Clinical trials

Guideline word limit: 4000 words

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the

abstract. Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register.
The *SAMJ*therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Review articles

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners.

Please ensure that your article includes:
Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 500 words

Letters to the editor should relate either to a paper or article published by the SAMJ or to a topical issue of particular relevance to the journal's readership

May include only one illustration or table
Must include a correspondence address.

Book reviews

Guideline word limit: 400 words

Should be about 400 words and must be accompanied by the publication details of the book. Provide a hi-res image of the cover if possible (with permission from the copyright holder).

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Guidelines

Guidelines should always be discussed with the Editor prior to submission.

Because of the intensive review process required to ensure Guidelines are independent, evidence-based and free from commercial bias, they are usually published as a supplement to the *SAMJ*, the costs of which must be covered by sponsorship, advertising or payment by the guideline authors/association. We will provide a quote based on the expected length of the guideline and whether it is to appear online only, or in print, which must be accepted by the body putting the guidelines together before submitting the work to the SAMJ.

The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.

All guidelines should include a clear, transparent statement about all sources of funding and an explicit, clear statement of conflicts of interest of any of the participants in the guidelines about industry funding for lectures, research, conference participation etc.
All guidelines should be structured according to Agree II.
Please access this website before putting the guidelines together, download the Agree 11 instrument and use this to put the guidelines together.
All submitted guidelines will be sent to the local Agree II appraisal committee for review and must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed.

A structured abstract not exceeding 400 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2.etc.) and summarised in a Table of Contents.

Illustrations/photos/scans
If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
All images must be of high enough resolution/quality for print.
All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

Tables should be constructed carefully and simply for intelligible data representation.
Unnecessarily complicated tables are strongly discouraged.
Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
Ensure each table has a concise title and column headings, and include units where necessary.
Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:
Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:
Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:
Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

Authors must verify references from original sources.

Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]

All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).

Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.

Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.

Volume and issue numbers should be given.

First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.

Wherever possible, references must be accompanied by a digital object identifier (DOI) link).

Authors are encouraged to use the DOI lookup service offered by CrossRef:

On the Crossref homepage, paste the article title into the 'Metadata search' box.

Look for the correct, matching article in the list of results.

Click Actions > Cite

Alongside 'url =' copy the URL between { }.

Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182

Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.

Chapter/section in a book: Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

Legal references

- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996. In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

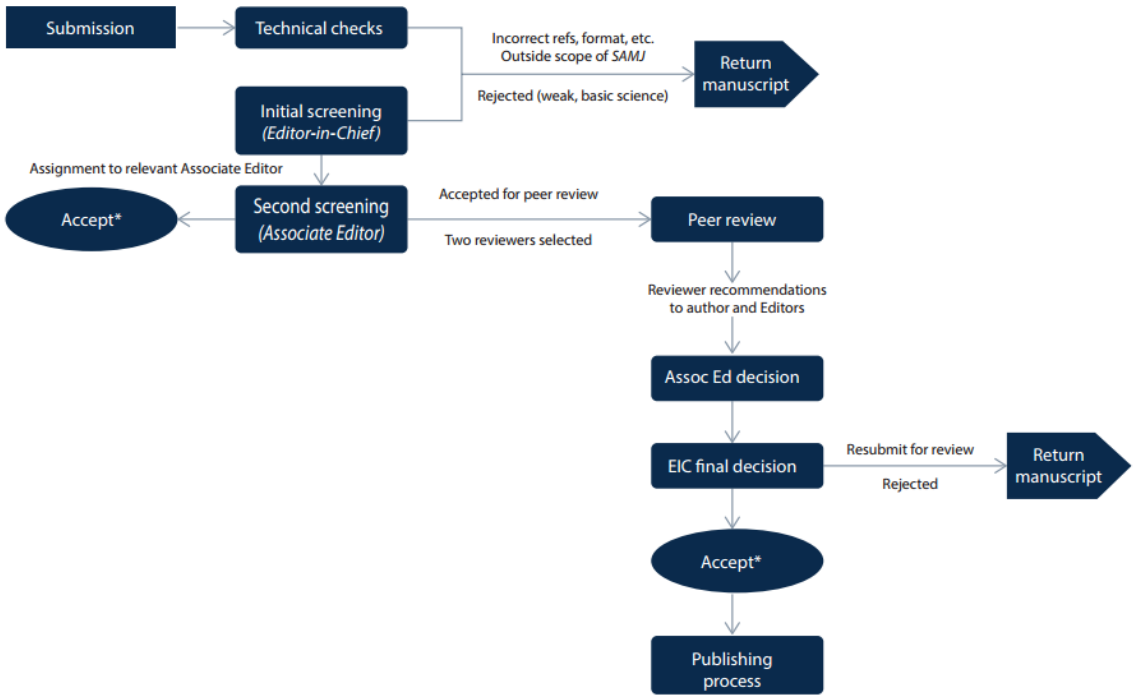
SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.
NOTE: no . after the v
Other references (e.g. reports) should follow the same format: Author(s). Title. Publisher place: Publisher name, year; pages.
Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

From submission to acceptance
Submission and peer-review
To submit an article:
Please ensure that you have prepared your manuscript in line with the SAMJ requirements.
All submissions should be submitted via Editorial Manager
The following are required for your submission to be complete:
Anonymous manuscript (unless otherwise stated)
Manuscript
Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer-review process



*Manuscripts accepted at this point are limited to Editorials, Correspondence, Obituaries, Book reviews, Abstracts, CME
**Some minor revisions may be requested

Production process

Please note that there is a 6-month waiting time for publication, once an article has been sent to the production team.

The following process will follow:

An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).

The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.

If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.

The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.

The CE will finalise the article and then it will be typeset.

Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.
The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship
Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Publication
Online v. print
The *SAMJ* is an online journal. The online version of the journal is the one that has the widest circulation, is indexed by bibliographic databases including PubMed and SciELO, and is accessible in academic libraries. A printed edition , containing material selected by the Editor is also published each month and distributed to the membership of the South African Medical Association.

Online
The full text of all accepted articles is published in full online, open access.
Citation information of each article is based on its online publication.
You may want to make use of the advantages of online publication e.g. specify web links to other sources, images, data or even a short video.

Print
Not all articles will be selected for print.
An article may be selected for print in a different month from that in which it was published online.
Research articles will appear *in abstract form only*, if selected for a print edition.

Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@hmpg.co.za,including the following details:

Journal, volume and issue in which published

Article title and authors

Description of error and details of where it appears in the published article

Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish anerratum in the next issue. The correction will be indexed, as PubMed has a function for linking errata back to the original article. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

Retractions

Retraction of an article is the prerogative of either the original authors or the editorial team of HMPG. Should you wish to withdraw your article before publication, we need a signed statement from all the authors.

Should you wish to retract your published article, all authors have to agree in writing before publication of the retraction.

Send an email to publishing@hmpg.co.za, including the following details:

Journal, volume and issue to which article was submitted/in which article was published

Article title and authors

Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or

professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

Indexing

The *SAMJ* has an impact factor of 1.5.

Published articles are covered by the following major indexing services. As such articles published in the *SAMJ* are immediately available to all users of these databases, guaranteed a global and African audience:

Index Medicus (Medline/PubMed)

ExcerptaMedica (EMBASE)

Biological Abstracts (BIOSIS)

Science Citation Index (SciSearch)

Current Contents/Clinical Medicine

Scopus

AIM

AJOL

Crossref

Sabinet

Scielo

Sponsored supplements

Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

Named authors consent to publication and meet the requirements of authorship as set out by the journal.
The submission has not been previously published, nor is it before another journal for consideration. All research already published as 'Conference proceedings' needs to be substantially re-written, with a new title, a new abstract and new and important results to back up any study before it will be considered for a new publication.
The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
The manuscript is in Microsoft Word document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (PDF or jpeg). These must be submitted individually as 'supplementary files' (not solely embedded in the manuscript).
For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
Where possible, references are accompanied by a digital object identifier (DOI).
An abstract has been included where applicable.
The research was approved by a Research Ethics Committee (if applicable)
Any conflict of interest (or competing interests) is indicated by the author(s).

Privacy Statement

The *SAMJ* is committed to protecting the privacy of the users of this journal website. The names, personal particulars and email addresses entered in this website will be used only for the stated purposes of this journal and will not be made available to third parties without the user's permission or due process. Users consent to receive communication from the *SAMJ* for the stated purposes of the journal. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

4. Acknowledgements

I wish to thank Dr Yaseen Joolay, who has supervised this research study and edited this dissertation. His support through this process has been invaluable.

I wish to acknowledge and thank the secretary, Mrs. Gabeba Abass at Groote Schuur hospital for her help in obtaining folders as well as her endless help and encouragement, may her soul rest in peace.

I would also like to thank all the clerical staff at both Groote Schuur and Red cross Hospital for their help in acquiring folders.