ARE ADMISSION LABORATORY VALUES IN ISOLATION VALUABLE IN PREDICTING SURGICAL OUTCOME IN PATIENTS WITH PERFORATED PEPTIC ULCERS: A RETROSPECTIVE, COHORT ANALYTICAL, OBSERVATIONAL STUDY

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Submitted in partial fulfillment of the requirements in respect of the Master's Degree MMed in the Department of Surgery in the Faculty of Health Sciences at the University of the Free State.

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Declaration of Authorship

I, Wikus Wessel Mulder, declare that the coursework Master's Degree mini-dissertation that I herewith submit in a publishable manuscript format for the Master's Degree Qualification MMed (Surgery) at the University of the Free State is my independent work, and that I have not previously submitted it for a qualification at another institution of higher education.

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"The symptoms are so typical; I hardly believe it possible that anyone can fail to make the correct diagnosis" Edward Crisp 1843

"Every doctor, faced with a perforated duodenal ulcer of the stomach or intestine, must consider opening the abdomen, sewing up the hole, and averting a possible inflammation by carefully cleansing of the abdominal cavity" Johan Mikulicz-Radecki (1850-1905)

Table of Contents

Abstract

Background:

Perforated peptic ulcer carries a noteworthy mortality, and admission status is a significant prognosticator thereof. Laboratory values are objective and readily available and therefore ideal for risk stratification. The objective of the study is to calculate the predictive value of admission laboratory values in patients with perforated peptic ulcers.

Methods:

A retrospective, cohort analytical, observational study was performed. All patients with surgically confirmed perforated peptic ulcers at Pelonomi Tertiary Hospital from July 2014 to June 2019 were considered. Demographic data and admission laboratory values were collected from hospital and laboratory electronic databases and theatre books. Outcomes measured were in-hospital mortality, ICU admission and length of stay in ICU and in hospital. The significance of categorical variables was calculated by Chi-square and Fisher's exact test. Logistic regression analysis considered univariately statistically significant variables. A p-value of < 0.05 was considered statistically significant.

Results:

Over the 5 years 188 patients met the inclusion criteria. The median age was 46 years (15-87) with a male predominance of 71.3 % (N=134). The median length of hospital stay was 7 days (1-94) and 31.4% (N=59) of patients were admitted to the Intensive Care Unit. Operative in-hospital mortality was 25.0% (N=47).

Predicting the two categorical outcomes of in-hospital mortality and ICU admission abnormal haemoglobin, platelet count, urea, creatinine and potassium were all found to be statistically significant in univariate analysis. For in-hospital mortality age (OR 1.03 [95% CI 1.01-1.06]), haemoglobin (OR 4.36 [95% CI 0.98-19.39]),) and creatinine (OR 7.76 [95% CI 2.90- 20.74]),) were significant in multivariate analysis and for ICU admission age (OR 1.03 [95% CI 1.00-1.05]),), platelet count (OR2.94 [95% CI 1.24-7.01]),) and creatinine (OR 6.90 [95% CI 2.87-16.61]),). Urea $\geq$ 10.9mmol/L showed a sensitivity of 70.2% and specificity of 82.1% (AUC 0.79) and creatinine $\geq$ 109umol/L a sensitivity of 80.9% and specificity of 67.7% (AUC 0.80) in predicting in-hospital mortality.

Conclusions:

The mortality rate in patients with perforated peptic ulcer disease is still substantial. Admission laboratory values shows statistical significance as outcome indicators and are valuable to assist in

predicting prognostication. Abnormal high serum creatinine was the strongest single predictor of both mortality and ICU admission.

Keywords

Peptic ulcer perforation, mortality, laboratory values, prognostic factors, emergency surgery

List of Abbreviations

ASA	American Society of Anaesthesiologist physical status classification system
CI	Confidence interval
CORES score	Calculation of post-operative risk in emergency surgery
HSREC	Health Science Research Ethics Committee
ICU	Intensive Care Unit
IQR	Interquartile range
Meditech	Medical technology system data storage
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds Ratio
POMPP score	Prediction of mortality in perforated peptic ulcer
PPI	Proton Pump Inhibitor
P-POSSUM score	Portsmouth Physiological and operative severity score for the enumeration of mortality and morbidity (Portsmouth modification of the original POSSUM score)
PPU	Perforated peptic ulcer
PULP score	Peptic Ulcer Perforation score
UFS	University of the Free State
WCC	White Blood Cell Count

List of Appendices

CHAPTER 1

Most of the symptomatology already described by Crisp in 1843 for stomach ulcer perforations still holds true even today[1]. Peptic ulcer disease is the consequence of a disparity between pepsin and acid in the stomach and the defensive barriers of stomach mucosa[2,3]. Annually over 4 million people are affected by peptic ulcer disease worldwide[4]. Peptic ulcer disease is complicated by bleeding, obstruction, perforation and penetration[5]. These complications come with a significant economic burden on the health care system[6]. Perforation is after bleeding, the second most common complication[7].

The incidence of perforation is 4-10/100 000 population per annum and can be the first hospital presentation of patients with peptic ulcer disease[8,9]. In patients known with peptic ulcer disease, the lifetime prevalence of perforation is about 5%[2]. Endoscopic management and modern interventional radiology techniques have improved outcomes for bleeding ulcers, but outcomes for perforation have remained mostly unchanged[10,11]. In 1880 Mikulicz-Radecki described suturing of these ulcers for the first time, and the most common operation remains a form of simple closure using sutures[8,11,12]. The surgical benchmark is still omental patch repair during explorative laparotomy, with laparoscopic surgery considered if expertise is available[2,3,13]. Gastrectomy and gastric resections are considered in patients with larger or malignant ulcers, but the outcomes in these patients remain inferior[2,13].

Even though surgical therapy has not changed much over the last few decades, perforated peptic ulcer disease remains a dangerous surgical condition with morbidity and mortality not to be underestimated[14]. Perforation is the cause of more than 70% of deaths associated with peptic ulcer disease[14]. Sepsis and septic shock is common and a frequent ultimate cause of mortality[15–17]. Perforated peptic ulcer carries a mortality of 1.3% to 40%[5,6,20–25,7,11,13,15–19]. Mortality due to a perforated peptic ulcer is ten times greater than other emergency abdominal pathologies like acute cholecystitis and acute appendicitis[26].

A classic triad of tachycardia, acute onset abdominal pain and abdominal rigidity has been described, but patients can present with a wide array of gastrointestinal or systemic symptoms[2,18,24]. Between 70% and 85% of patients demonstrate free air under the diaphragm on chest X-ray, and CT scan has shown a sensitivity of 98% in diagnosing a perforated peptic ulcer[2,14,15,24]. Diagnosis must be made early, resuscitation efforts initiated swiftly and rapid surgical intervention initiated to improve patient outcome[2,18]. Admission status has been described as a significant prognostic indicator in patients with peptic ulcer perforation[19]. Early identification of high-risk patients for an adverse outcome is crucial to guide the level of monitoring peri-operatively and targets of treatment[27,28].

Investigations into risk factors for perforation are complicated by the wide variation in demographics, socioeconomic status, the prevalence of Helicobacter pylori, and medication and substance use in different population groups[24]. Cohorts from other African countries show a male predominance of 6-13:1 to females[24]. In developing countries, young (predominantly male) smokers make up the most significant patient group. In contrast, in the developed world, elderly patients (increase in females) with other co-morbidities and use of NSAIDs are more commonly found[2,14,19]. Significant inequality in South Africa leads to a broad spectrum of socioeconomic circumstances in our study population, and both these population groups might be included[29]. The prevalence of Helicobacter pylori is also suspected to be higher in our study population than in the developed world[4].

Scoring systems are used to provide an objective description of the patient's condition at a specific stage in the disease process to try and assist the physician with the diagnosis, guide him in the course that the disease is taking within the particular patient and help him to follow the appropriate management and treatment algorithm[5]. A perforated peptic ulcer is a multifactor disease, and multiple scoring systems have been suggested and used as outcome predictors thereof [7]. Scoring systems range from simple to complex (combining demographical data, history, vital signs and clinical findings, chosen surgical intervention and management options as criteria), sometimes making practical implementation more difficult[5,27]. The ASA and Boey scores are the most regularly validated scores for patients with perforated peptic ulcers[2]. The ASA score is the oldest available scoring system and not explicitly intended for perforated peptic ulcer patients, but a generic surgical risk score was introduced in 1941 to assess patients' fitness level[7,30,31]. Literature shows that it can predict mortality well in different patient groups but has the shortcoming of inter-observer variability as it is not an objective score[7,26,30]. The ASA grading is also dependent on whether the acute state of the assessed patient is taken into consideration which can lead to underscoring if not considered[10,26]. ICU and other standard surgical scores have also been evaluated in patients with perforated peptic ulcers [24]. Replication of original high positive predictive values of used scores has not always been shown in other study populations, and there is a lack of external cohort validation [5,24,27]. There is still no agreed standard scoring system, and investigation towards an optimal prediction model in terms of outcome for patients with perforated peptic ulcers in today's setting is still not saturated[10,24]. The reason for none of the multiple scoring systems being widely accepted in clinical practice can be due to the complexity, non-specificity or subjective points of these scoring systems[26]. The goals of being easy to calculate, accurate in predicting outcomes and being reproducible across different populations have not been comprehensively satisfied by any score[30]. Although most scoring systems have the potential to be used as a comparison of risk-adjusted mortality across hospitals, prognostication and identification of high-risk patients that needs aggressive management protocols can only be done using scores based on preoperative criteria[30].

The time from ulcer perforation until surgical intervention is one of the criteria used in the Boey score[20]. There is uncertainty about the external validation of the Boey score[7]. It has been described as a significant predictor of mortality in some studies[15,19], but found not to be significant in others[22,27,32]. Due to the wide rural drainage area of our hospital, a large number of our patients have a late presentation that already falls outside the 24-hour window by the time of theatre. Literature from South Africa demonstrates a late presentation in patients with perforated peptic ulcers, outside of the 24-hour window from onset of symptoms[13]. Cultural beliefs guide the use of alternative medication, and symptomatic treatment at primary care centres also contribute to late presentation in the African healthcare setting[23]. Record bias in terms of pre-hospital data plays a part in retrospective studies. Patient recall bias in terms of medical and complaint history can also be possible. Patients with pre-existing peptic ulcer disease might experience pain or symptoms for some time and are, therefore, unable to pinpoint precisely when pain was exacerbated[32]. Accurate patient history might not be possible due to the patient's clinical condition (e.g. Decreased level of consciousness, elderly patients), which will influence patient medical history in terms of other comorbidities and medication use at the time of admission[26]. All these risk factors have been questioned due to lack of objectivity and have been reported to lack sensitivity and specificity [32]. However, these risk factors still form part of scoring systems (PULP score, Mannheim Peritonitis score, Hacettepe score) previously described in predicting patient outcome[21,22].

Acute renal failure and a WCC of more than 20 x 109/l are significant factors influencing mortality in perforated peptic ulcers. With male sex, they contribute 3 out of the 4 scoring criteria used in the Hacettepe Score, which showed a predictive accuracy of 93%[22]. WCC and C-reactive protein values can increase due to infection or inflammation[2]. A study in Japan found a low WCC (<9.500/mm3) to be an age-dependent, significant risk indicator[25].

The POMPP score was developed in 2015 as a practical scoring system to assist in calculating mortality risk in patients with perforated peptic ulcers. It indicated age, albumin and urea levels to be three variables that are statistically relevant in multivariate analysis. This new scoring system compared well to ASA, PULP and Boey scoring systems but was found less complex as it only made use of age and two admission laboratory values (albumin and urea)[26].

A contemporary study done among an African population in Côte d'Ivoire who had operative interventions for perforated peptic ulcer disease showed a high median value of WCC ($p < 0.0001$), low level of natraemia (134 vs 137, $p = 0.02$) and low potassium (3.6 vs 3.7, $p = 0.01$) in patients that had postoperative complications or mortality compared to those who didn't. Patients with hyponatremia had a twofold increase in the risk of complications or death in this study population[23]. Hyponatremia is seen in perforated peritonitis as a consequence of gastroduodenal fluid leakage into the peritoneal cavity causing third spacing[33].

Elevated serum creatinine levels can be due to untreated peritonitis or pre-existing renal disease (known or unknown before diagnosis). Together with elevated urea level and metabolic acidosis, it can be indicative of pre-renal injury and SIRS (Systemic inflammatory Response Syndrome)[2]. With a delay in medical attention, there is a deficit in total body water, which leads to hypotension. Uninterrupted hypotension can then also progress to acute kidney injury[2]. During construction of the Hacettepe Score, serum creatinine concentration of greater than 177mol/L; urea concentration of greater than 8.9 mol/L or progressively rising urea concentration with or without oliguria were used as criteria for acute renal failure[22]. The POMPP score used an Urea value of > 16,07mmol/L (45mg/dl) and the CORES score an Urea of > 14.28mmol/L (≥ 40mg/dl) as scoring criteria [26,30]. Acute kidney injury can be a reflection of dehydration, shock or sepsis and loss of renal function is a poor prognostic sign[10,34]. In the development of the Mortality Probability Models (MPM II), patients who were admitted to ICU with acute renal failure were 4.4 times more likely to die in the hospital (OR 4.4 [95% CI 3.7-5.2])[35]. In the era before Proton Pump Inhibitor (PPI) therapy, preoperative serum creatinine has already been shown to be the single most important predictor of survival, with patients with a normal serum creatinine 25.5 times more likely to survive with a perforated gastroduodenal ulcer regardless of the type of surgery that was performed[32]. It has been shown that the ICU mortality rate increases with increasing serum creatinine concentration[36]. Elevated serum creatinine was also associated with mortality during the Jabalpur prognostic scoring system development and formed one of its criteria[37]. Another multivariable regression analysis found hypoalbuminaemia, hyperbilirubinaemia, and increased creatinine to be predictive of 30-day post-operative mortality[10]. During the development of the PULP score, a nationwide cohort study was performed using a collection of prospective information from 2668 patients who were surgically treated for peptic ulcer perforations at hospitals in Denmark[21]. It demonstrated a better prediction of 30-day mortality than the ASA score and Boey score in the same population group, and elevated serum creatinine (>130 umol/L) was also one of the factors with the highest prognostic impact[21]. Therefore elevated serum creatinine may be an indicator for other underlying factors like pre-existing disease or the state of the acute disease[10]. A mortality of 75% has been demonstrated in patients with perforated gastroduodenal ulcer and renal failure[25].

A model to calculate post-operative risk specifically for emergency surgery (CORES) was developed in Japan in 2012. It uses five preoperative variables, including WCC, platelet count and blood urea nitrogen as laboratory values, and reproducibly predicted postoperative mortality in the validation and multicentre subgroups. It was postulated that the better prediction in the General Surgery patient subset compared to the P-POSSUM score could be due to the inclusion of platelet count, as thrombocytopenia has been shown as a risk factor for mortality in ICU patients and is the most commonly cited manifestation of haematological dysfunction[36,38]. Patients with a high platelet count (

>300,000) interestingly also had higher mortality rates demonstrated in the study used to develop the CORES model[38].

In a condition such as perforated peptic ulcer disease, electrolyte disturbances, anaemia, hypoalbuminaemia, renal failure and leucocytosis can all be described as part of the sepsis syndrome[7]. Multi-organ dysfunction progressing to multi-organ failure is known to have a dreadful outcome independent of management course[5].

A perforated peptic ulcer diagnosis cannot be made using laboratory values in isolation, and these values are non-specific[18]. Laboratory values are, however, good indicators of organ dysfunction, local and systemic inflammation. They are also used to rule out other pathologies on the differential diagnosis, like acute pancreatitis[2,14,24]. Even though admission laboratory values are not as amenable to intervention, such as time to operating theatre, they play a crucial role in our approach and management of the patient from the time of diagnosis[8]. The most significant advantage for the use of laboratory values in risk stratification is that they are objective, routinely done and readily available[10]. Laboratory values form part of most perforated ulcer and other prognostic scoring systems used currently:

Table 1: Laboratory values that form part of scoring systems used for prediction models in patients with perforated peptic ulcers[7,30]:

Scoring system used for outcome prediction	**Target population**	**Outcome measured**	**Laboratory values used as part of scoring system**
Hacettepe score[22]	Patients with perforated peptic ulcer	30-day mortality	Acute renal failure, White blood cell count
Jabalpur score[37]	Patients with perforated peptic ulcer	30-day mortality	Serum creatinine
PULP (Peptic ulcer perforation score)[21]	Patients with perforated peptic ulcer	30-day mortality	Liver failure, serum-creatinine
POMPP (Prediction of mortality in perforated peptic ulcer) score [26]	Patients with perforated peptic ulcer	30-day mortality	Albumin, urea
Mannheim Peritonitis	General peritonitis	Preoperative	Organ failure

index		prediction of outcome	
APACHE II *(Acute physiology and chronic health evaluation II)[34]	Critically ill patients	Prediction of outcome in ICU patients	White blood cell count, creatinine, Potassium, Sodium
SAPS II (Simplified acute physiology score II)[39]	Critically ill patients	Prediction of outcome in ICU patients	White blood cell count, Bilirubin, Urea, Potassium, Sodium
MPM II (Mortality Probability Models)[35]	Critically ill patients	Prediction of outcome for ICU patients	Liver failure, Renal insufficiency
POSSUM (Physiological and operative severity score for the enumeration of mortality and morbidity score)[40]	Surgical patients	Prediction of mortality	White blood cell count, Haemoglobin, Urea, Potassium, Sodium
CORES (Calculation of postoperative risk in emergency surgery)[38]	Patients who underwent emergency surgery	In hospital mortality	White blood cell count, urea, platelet count
Multiple organ dysfunction score[36]	Critically ill patients	Prediction of mortality and outcome for ICU patients	Serum creatinine, platelet count

As described, all these scoring systems use a different subset of available laboratory values in an attempt to predict mortality. The question remains whether admission laboratory findings are of any importance in isolation, and can they be used as a reliable indicator of prognosis?

The diagnosis of perforated peptic ulcer disease is made using a combination of history, clinical and radiological findings. Surgical intervention with explorative laparotomy, ulcer biopsy, primary repair and omentoplasty is the preferred surgical source control and management of perforated peptic ulcers in our institution, followed by postoperative Proton Pump Inhibitor and Helicobacter Pylori eradication therapy.

The study's primary aim is to use in-hospital mortality as a comparative outcome, with secondary aims being ICU admission and length of stay in hospital and ICU. In-hospital mortality is defined as any death occurring during or after surgical intervention before hospital discharge.

The objective of the study is to calculate the predictive value in terms of surgical outcomes of different routine admission laboratory values in patients with perforated peptic ulcers. Secondary outcomes are the predictive value of demographic data, comparison of predictive value between laboratory results, and the prediction of length of ICU and hospital stay.

The study hypothesis is that routine admission laboratory values can be used in isolation to accurately predict surgical outcomes in patients with perforated peptic ulcers that were confirmed and managed via explorative laparotomy.

The research findings will assist in the practical usage of readily available laboratory values in predicting outcomes in patients with perforated peptic ulcers. It can lead to better clinical decisions and cost-benefit strategies, promote optimal management and facilitate better assignment of resources. Patients identified as higher risk could have earlier access to organ support, intensive care and more aggressive resuscitation. Outcomes can then be improved based on individual risk stratification. It has been proven that extra perioperative care and management protocols for high-risk patients improve in-hospital mortality[16,26]. Results will also enhance patient counselling in terms of risks, possible complications and outcome expectations. The surgeon's knowledge of significant independent risk factors will assist in confident judgment about operative planning and appropriateness[22]. Naturally, an individual predictor can't be ascribed to a single patient, but the presence of a significant or more than one risk factor presents a much higher mortality risk in contrast to patients with none[10].

These findings can also be used in combination with other preoperative information or in further prospective studies to develop appropriate prediction and scoring systems for this health care setting or used in different populations as a comparison. Most of the studies available in the literature were done mainly in western and Asian countries[23]. In the era of hand-held devices and smartphones, more complex scoring systems might be easier to calculate at the bedside than before[30]. It might be challenging to develop a universally reproducible scoring system due to geographical variation in age, gender and patterns of presentation[24]. However, laboratory values have the advantage of being an objective variable not influenced by subjective interpretation and therefore ideal for validation between different patient cohorts and demographic regions[10].

Limitations of this study are that it is a retrospective, single-centre study. Laboratory values might be indicators for other underlying factors like chronic disease[26]. Therefore, further investigation into causality from the findings in the study might be warranted at a later stage. Long term outcome after hospital discharge for our patient group was also not assessed.

To minimise bias in terms of our literature review, we tried to include and evaluate all the recognised scoring systems. We included up to date and older studies of proposed outcome predictors that were still used popularly or acknowledged in high regard.

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CHAPTER 2

ARE ADMISSION LABORATORY VALUES IN ISOLATION VALUABLE IN PREDICTING SURGICAL OUTCOME IN PATIENTS WITH PERFORATED PEPTIC ULCERS: A RETROSPECTIVE, COHORT ANALYTICAL, OBSERVATIONAL STUDY

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Abstract

Purpose:

The objective of the study is to calculate the predictive value of admission laboratory values, as they are objective and ideal for risk stratification, in patients with perforated peptic ulcers.

Methods:

A retrospective, cohort analytical, observational study was performed. All patients with surgically confirmed perforated peptic ulcers over 5 years were considered. Demographic data and admission laboratory values were collected from hospital electronic databases. Outcomes measured were in-hospital mortality, ICU admission and length of stay. The significance of categorical variables was calculated by Chi-square and Fisher's exact test. Logistic regression analysis considered univariately statistically significant variables. A p-value of < 0.05 was considered statistically significant.

Results:

Over the 5 years, 188 patients met the inclusion criteria. The median age was 46 years (15-87) with a male predominance of 71.3 % (N=134). The median length of hospital stay was 7 days (1-94) and 31.4% (N=59) of patients were admitted to the Intensive Care Unit. Operative in-hospital mortality was 25.0% (N=47). Predicting the categorical outcome of in-hospital mortality abnormal haemoglobin, platelet count, urea, creatinine and potassium were all found to be statistically significant in univariate analysis; age (OR 1.03), haemoglobin (OR 4.36) and creatinine (OR 7.76) were significant in multivariate analysis.

Conclusions:

The mortality rate in patients with perforated peptic ulcer disease is still substantial. Admission laboratory values shows statistical significance as outcome indicators and are valuable to assist in predicting prognostication. Abnormal high serum creatinine was the strongest single predictor of both mortality and ICU admission.

Keywords

Perforation, mortality, laboratory values, emergency surgery

Declarations

Funding

The research was self-funded by the authors.

Competing interest

The authors declare that they have no competing interests.

Availability of data and materials

The data that support the findings of this study are available from the Department of Biostatistics, University of the Free State, but restrictions apply to the availability of these data and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Department of Biostatistics, University of the Free State.

Code availability

Not applicable.

Authors' contributions

WWM was the principal investigator and wrote the study protocol, performed the data collection, interpreted the results and wrote the manuscript. EAC supervised the study and reviewed the study protocol and final manuscript. GJ reviewed the study protocol, performed the statistical analysis, assisted with data interpretation and reviewed the manuscript.

Ethics approval and consent to participate

Ethical clearance was obtained from the University of the Free State Health Science Research Ethics Committee (HSREC) UFS-HSD2019/0018/2506.

Consent for publication

Not applicable.

Background

Annually over 4 million people are affected by peptic ulcer disease worldwide [1]. Peptic ulcer disease is complicated by bleeding, obstruction and perforation [2]. Perforation is after bleeding the second most common complication [3].

The incidence of perforation is 4-10/ 100 000 population per annum and can be the first hospital presentation of patients with peptic ulcer disease [4, 5]. Endoscopic management and modern interventional radiology techniques have improved outcomes for bleeding ulcers, but outcomes for perforation have remained mostly unchanged [6, 7].

Perforation is the cause of more than 70% of deaths associated with peptic ulcer disease [8]. Sepsis and septic shock are common and a frequent ultimate cause of mortality [9–11]. Perforated peptic ulcer carries a mortality of 1.3% to 40% [2, 3, 16–21, 7, 9–15].

Admission status has been described as a significant prognostic indicator in patients with peptic ulcer perforation [13]. The diagnosis must be made early, resuscitation efforts initiated swiftly and rapid surgical intervention initiated to improve patient outcome [12, 22].

In a condition such as perforated peptic ulcer disease, electrolyte disturbances, anaemia, hypoalbuminaemia, renal failure and leucocytosis can all be described as part of the sepsis syndrome [3]. The diagnosis of a perforated peptic ulcer cannot be made by using laboratory values in isolation and these values are non-specific [12]. Laboratory values are however good indicators of organ dysfunction, local and systemic inflammation. They are also used to exclude other pathologies, like acute pancreatitis [8, 18, 22]. The biggest advantage for the use of laboratory values in risk stratification is that they are objective in nature, routinely done and readily available [6].

Table 1: Laboratory values that form part of scoring systems used for prediction models in patients with perforated peptic ulcers [3,23]

Scoring system used for outcome prediction	**Target population**	**Outcome measured**	**Laboratory values used as part of scoring system**
Hacettepe score [16]	Patients with perforated peptic ulcer	30-day mortality	Acute renal failure, White blood cell count
Jabalpur score [24]	Patients with perforated peptic ulcer	30-day mortality	Serum creatinine
PULP (Peptic ulcer perforation score) [15]	Patients with perforated peptic ulcer	30-day mortality	Liver failure, serum-creatinine
POMPP (Prediction of mortality in perforated peptic ulcer) score [25]	Patients with perforated peptic ulcer	30-day mortality	Albumin, urea

Mannheim Peritonitis index	General peritonitis	Preoperative prediction of outcome	Organ failure
APACHE II (Acute physiology and chronic health evaluation II) [26]	Critically ill patients	Prediction of outcome in ICU patients	White blood cell count, creatinine, Potassium, Sodium
SAPS II (Simplified acute physiology score II) [27]	Critically ill patients	Prediction of outcome in ICU patients	White blood cell count, Bilirubin, Urea, Potassium, Sodium
MPM II (Mortality Probability Models) [28]	Critically ill patients	Prediction of outcome for ICU patients	Liver failure, Renal insufficiency
POSSUM (Physiological and operative severity score for the enumeration of mortality and morbidity score) [29]	Surgical patients	Prediction of mortality	White blood cell count, Haemoglobin, Urea, Potassium, Sodium
CORES (Calculation of post-operative risk in emergency surgery) [30]	Patients who underwent emergency surgery	In hospital mortality	White blood cell count, urea, platelet count
Multiple organ dysfunction score (MODS) [31]	Critically ill patients	Prediction of mortality and outcome for ICU patients	Serum creatinine, platelet count

Scoring systems are used to provide an objective description of the patient's condition at a specific stage in the disease process to try and assist the physician with the diagnosis, give guidance in the course that the disease is taking in the specific patient and help the surgeon to follow the appropriate management and treatment algorithm [2]. These scoring systems use different subsets of available laboratory values in an attempt to predict mortality. Our question was whether admission laboratory findings are of any value in isolation, and could they be used as a reliable indicator of prognosis.

The objective of the study was to calculate the predictive value in terms of surgical outcome (in-hospital mortality as well as ICU admission, length of stay in ICU and length of stay in hospital) of different routine admission laboratory values in patients with perforated peptic ulcers.

Methods

A retrospective, cohort analytical, observational study was performed. All consecutive patients from July 2014-June 2019 with surgically confirmed (during laparotomy) perforated peptic ulcer (gastric or duodenal) disease and available demographic and admission laboratory data were enrolled. Pelonomi Tertiary Hospital provides the bulk of the acute care surgical and trauma services for the Free State Province in South Africa.

Exclusion criteria were:

- Histological confirmed malignant perforations
- Traumatic or iatrogenic perforations
- Perforations due to caustic ingestion or foreign bodies
- Perforations found during autopsy
- Patients managed conservatively without surgical intervention
- Patients who had surgery but no confirmation of perforated ulcer
- Patients younger than 13 years

In-hospital mortality was defined as any death occurring during or after surgical intervention before hospital discharge.

Data was collected for all patients who met the inclusion criteria. Demographic data was collected from Pelonomi Hospital's electronic database (Meditech) and matched to National Health Laboratory Service database (Labtrak). The University of the Free State Department of Surgery Statistical Database and Pelonomi Hospital theatre record books were used to verify concordance of collected data.

Demographic data included age and sex.

The following laboratory values on admission were collected from the NHLS database (Labtrak):

- Full blood count (Haemoglobin, Haematocrit, White cell count, Platelets)
- Renal function (Urea and Creatinine)
- Electrolytes (Sodium and Potassium)
- Inflammatory markers (C-reactive Protein- CRP)
- Albumin

The reference range for normal laboratory values used by the South African NHLS (see additional file 1, Appendix F) was applied to the laboratory values with values outside normal range categorised as abnormal low or abnormal high.

Data captured was recorded on the approved data sheet by the researcher and onto an Excel sheet that served as a second copy of all data.

Analysis was done by the Department of Biostatistics University of Free State. Numerical variables were summarised by medians and interquartile ranges (IQR) due to skew distributions and categorical variables by frequencies and percentages. Chi-square and Fisher's exact tests were used to assess the significance of associations of categorical variables with categorical outcomes. Logistic regression analysis with backward elimination was performed using variables identified as statistically significant on univariate analyses. Risk was presented as an odds ratio (OR) with 95% CI. A p-value of < 0.05 was considered statistically significant. Calculation of sensitivity, specificity, positive and negative predictive values were done.

Results

Over the 5-year study period, we identified 194 patients of whom 188 met the inclusion criteria. Three patients were excluded due to missing admission laboratory values, two due to confirmed malignancy and one due to surgery for suspicion of PPU without confirmation of perforation. Demographic characteristics showed our patient cohort had a median age of 46 years with a range between 15 and 87 years. The gender distribution showed a male predominance of 134 (71.3%) versus 54 (28.7%) female patients.

The median values and interquartile ranges (IQR) of laboratory variables on admission as well as cases with in-hospital mortality and ICU admission are shown in Table 2.

Table 2: Admission laboratory values

Laboratory variable	Median (N)	Median: In-hospital mortality (N)	Median: ICU admission (N)
Hemoglobin (g/dL)	14.30 (N=188)	12.60 (N=47)	12.60 (N=59)
	IQR: 12.10-16.15	IQR: 10.90-15.20	IQR: 10.80-15.60
Haematocrit (L/L)	0.44 (N=184)	0.41 (N=47)	0.41 (N=59)
	IQR: 0.38-0.50	IQR: 0.34-0.48	IQR: 0.34-0.48
WCC ($x10^9$/L)	10.96 (N=188)	9.72 (N=47)	9.26 (N=59)
	IQR: 7.17-15.33	IQR: 6.43-14.02	IQR: 5.82-15.25
Platelet count ($x10^9$/L)	324 (N=188)	341 (N=47)	332 (N=59)
	IQR: 231.50-408.50	IQR: 227.00-452.00	IQR: 234.00-457.00
Urea (mmol/L)	8 (N=187)	13 (N=47)	12.6 (N=58)
	IQR: 4.90-12.70	IQR: 9.10-20.70	IQR: 8.00-20.00
Creatinine (umol/L)	95 (N=177)	181 (N=47)	176.50 (N=58)
	IQR: 71.00-162.00	IQR: 118.00-293.00	IQR: 118.00-293.00
Sodium (mmol/L)	137 (N=188)	137 (N=47)	137 (N=59)
	IQR: 133.00-141.50	IQR: 133.00-142.00	IQR: 133.00-143.00
Potassium (mmol/L)	4.30 (N=186)	4.90 (N=47)	4.90 (N=59)
	IQR: 3.90-5.00	IQR: 4.00-5.40	IQR: 4.00-5.40
C-reactive protein (mg/L)	170 (N=150)	246 (N=35)	246 (N=45)
	IQR: 63.00-280.00	IQR: 136.00-305.00	IQR: 181.00-302.00
Albumin (g/L)	25.0 (N=119)	20.0 (N=43)	19.0 (N=58)
	IQR: 17.00-32.00	IQR: 14.00-29.00	IQR: 14.00-26.00

The median length of hospital stay was 7 days (range 1-94) and 59 (31.4%) patients were admitted to the Intensive Care Unit. Operative in-hospital mortality was found to be 25.0% (N=47). Age, mortality and ICU admission distribution are illustrated in Chart 1. The mortality for patients admitted to the Intensive Care Unit was 64.4% (N=38).

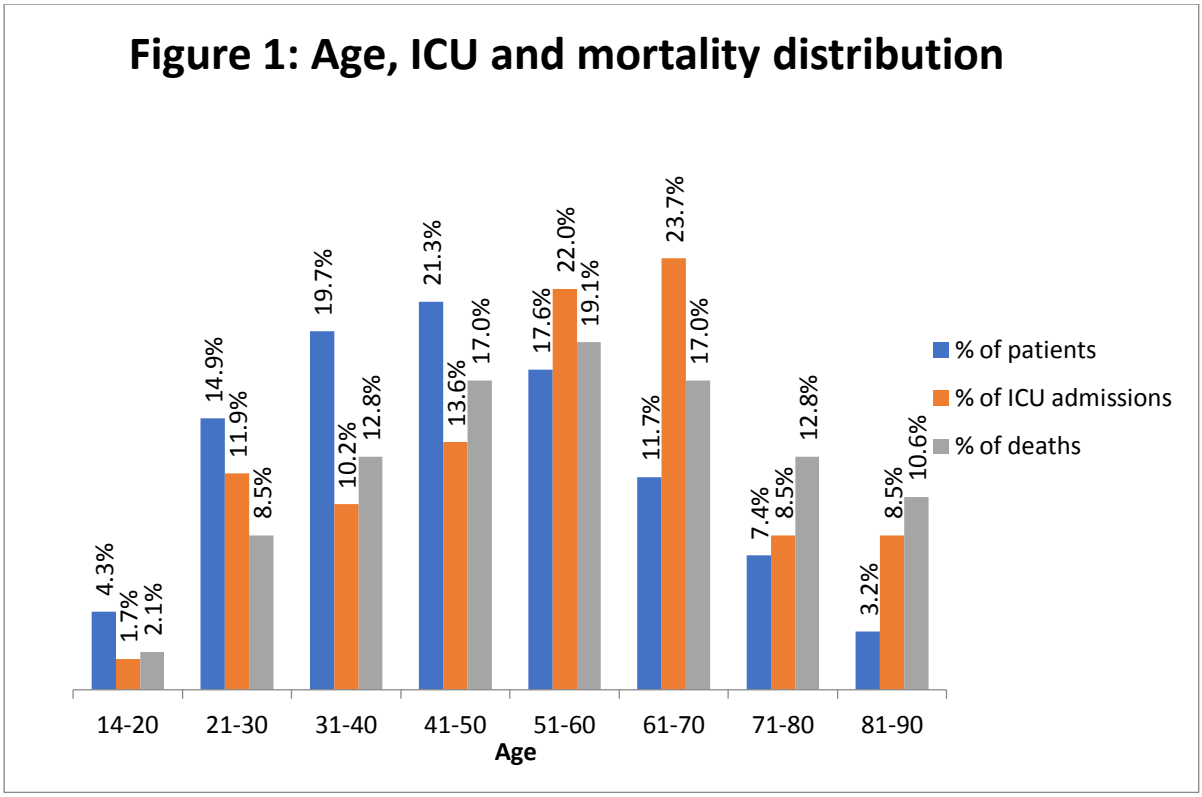

Figure 1:

In terms of predicting the two categorical outcomes of in-hospital mortality and ICU admission abnormal haemoglobin, platelet count, urea, creatinine and potassium were all found to be statistically significant in univariate analysis. Abnormal albumin showed a statistical significance in predicting ICU admission but not in-hospital mortality. The different P-values as well as percentage of patients according to outcome categories of in-hospital mortality and ICU admission are shown in Table 3 and 4.

Table 3: P-values calculated for prediction of in-hospital mortality by categorised laboratory values

Laboratory variable		*% Low (N)*	*% Normal (N)*	*% High (N)*	*p value*
Haemoglobin	Mortality	68.1% (32)	19.2 % (9)	12.8% (6)	0.0016
	Survived	43.3% (61)	48.9% (69)	7.8% (11)	
Haematocrit	Mortality	57.5% (27)	31.9% (15)	10.6% (5)	0.0996
	Survived	40.9% (56)	49.6% (68)	9.5% (13)	
WCC	Mortality	14.9% (7)	38.3% (18)	46.8% (22)	0.2169
	Survived	7.1% (10)	36.2% (51)	56.7% (80)	
Platelets	Mortality	14.9% (7)	48.9% (23)	36.2% (17)	0.0067
	Survived	4.3% (6)	70.9% 100)	24.8% (35)	
Urea	Mortality	2.1% (1)	12.8% (6)	85.1% (40)	<.0001*
	Survived	0% (0)	54.3% (76)	45.7% (64)	
Creatinine	Mortality	4.3% (2)	12.8% (6)	83.0% (39)	<.0001
	Survived	18.5% (24)	48.5% (63)	33.1% (43)	
Sodium	Mortality	40.4% (19)	51.1% (24)	8.5% (4)	0.8207

	Survived	35.5% (50)	56.0% (79)	8.5% (12)	
Potassium	Mortality	6.4% (3)	53.2% (25)	40.4% (19)	0.0008
	Survived	10.1% (14)	75.5% (105)	14.4% (20)	
C reactive peptide	Mortality	-	5.7 % (2)	94.3% (33)	0.7331*
	Survived	-	8.7% (10)	91.3% (105)	
Albumin	Mortality	90.7% (39)	9.3% (4)	-	0.0996
	Survived	79.0% (60)	21.1% (16)	-	

* P-value derived from Fisher's Exact Test all others derived from Chi-square

Table 4: P-values calculated for prediction of ICU admission by categorised laboratory values

Laboratory variable		*% Low (N)*	*% Normal (N)*	*% High (N)*	*p-value*
Haemoglobin	ICU	64.4% (38)	27.1 %(16)	8.5% (5)	0.0167
	No ICU	42.6% (55)	48.1% (62)	9.3% (12)	
Haematocrit	ICU	55.9% (33)	33.9% (20)	10.2% (6)	0.0959
	No ICU	40.00%(50)	50.4% (63)	9.6% (12)	
WCC	ICU	15.3% (9)	40.7% (24)	44.1% (26)	0.0583
	No ICU	6.2% (8)	34.9% (45)	58.9% (76)	
Platelets	ICU	11.9% (7)	49.2% (29)	39.0% (23)	0.0052
	No ICU	4.7% (6)	72.9% (94)	22.5% (29)	
Urea	ICU	0% (0)	17.2% (10)	82.8% (48)	<.0001 *
	No ICU	0.8% (1)	55.8% (72)	43.4% (56)	
Creatinine	ICU	3.5% (2)	17.2 (10)	79.3% (46)	<.0001
	No ICU	20.2% (24)	49.6% (59)	30.3% (36)	
Sodium	ICU	35.6% (21)	54.2% (32)	10.2% (6)	0.8557
	No ICU	37.2% (48)	55.0% (71)	7.8% (10)	
Potassium	ICU	6.8% (4)	54.2% (32)	39.0% (23)	0.0002
	No ICU	10.2%(13)	77.2% (98)	12.6% (16)	
C reactive peptide	ICU	-	6.7 % (3)	93.3% (42)	1.0000 *
	No ICU	-	8.6% (9)	91.4% (96)	
Albumin	ICU	93.1% (54)	6.9% (4)	-	0.0048
	No ICU	73.8% (45)	26.2% (16)	-	

* P-value derived from Fisher's Exact Test all others derived from Chi-square

Logistic regression analysis was applied to the above mentioned statistically significant outcomes using age and gender as confounders. P-values, estimated Odds Ratios and 95% Confidence Intervals of logistic regression analysis for in-hospital mortality and ICU admission are shown in Tables 5 and 6.

For in-hospital mortality age ($p = 0.0091$) haemoglobin ($p = 0.0432$) and creatinine ($p < .0001$) were significant in multivariate analysis. For ICU admission albumin was excluded from the model due to a large number of missing values and there was no clear independent relation to outcome. Multivariate analysis significant parameters for ICU admission were age, gender, platelet count and creatinine.

Table 5: Logistic regression analysis using age and gender as confounders for in-hospital mortality

Variable	Odds Ratio	95% CI for OR	*p* value
Age	1.03	1.01-1.06	0.0091
Abnormal low Hemoglobin	2.88	1.15-7.20	0.0432
Abnormal high Hemoglobin	4.36	0.98-19.39	
Abnormal high Creatinine	7.76	2.90- 20.74	<.0001

Table 6: Logistic regression analysis using age and gender as confounders for ICU admission

Variable	Odds Ratio	95% CI for OR	*p* value
Age	1.03	1.00-1.05	0.0441
Gender male vs. female	0.37	0.15-0.93	0.0352
Abnormal low Platelet count	2.21	0.58-8.43	0.0409
Abnormal high Platelet count	2.94	1.24-7.01	
Abnormal high Creatinine	6.90	2.87-16.61	<.0001

The sensitivity, specificity and predictive values of different cut off values of the laboratory variables were calculated for predicting in-hospital mortality and ICU admission. Values with highest success in prediction are demonstrated in Tables 7 and 8.

Table 7: Success in predicting in-hospital mortality of a value greater or equal to mentioned value for Urea and Creatinine

Variable	Value	PPV	NPV	Sensitivity	Specificity	AUC
Urea	10.9mmol/L	56.9%	89.2%	70.2%	82.1%	0.79
Creatinine	109umol/L	47.5%	90.7%	80.9%	67.7%	0.80

PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under the ROC curve

Table 8: Success in predicting ICU admission of a value greater or equal to mentioned value for Urea and Creatinine and a value smaller or equal for Albumin

Variable	Value	PPV	NPV	Sensitivity	Specificity	AUC
Urea	8.9mmol/L	55.3%	85.6%	72.4%	73.6%	0.74
Creatinine	136umol/L	66.2%	86.7%	74.1%	81.5%	0.82
Albumin	30g/L	61.7%	78.9%	86.2%	49.2%	0.78

PPV: positive predictive value; NPV: Negative predictive value; AUC: Area under the ROC curve

Secondary outcome analyses for length of hospital and ICU stay showed urea (p=0.0048), creatinine (p=0.0055) and albumin (p=0.0416) to be statistically significant in predicting length of ICU stay. Although all subgroups for these three variables had median ICU stay of 0 days, some differences were observed regarding 75th percentiles and differences were due to differences in ICU admission (as shown in Table 4). Potassium (p=0.0167) and Albumin (p=0.213) were statistically significant in predicting length of hospital stay. Patients

with low potassium had median hospital stay of 8 days (IQR 6 to 11 days), those with high potassium levels median stay of 8.5 days (IQR 6 to 11 days) and those with normal potassium levels median hospital stay of 6 days (IQR 5 to 9 days). Patients with low albumin levels had median stay of 8 days (IQR 6 to 15 days) compared to patients with a normal albumin level who had median stay of 7 days (IQR 4 to 8 days). These were calculated for patients who did not die in hospital.

Discussion

The diagnosis of perforated peptic ulcer disease is made using a combination of history, clinical and radiological findings. Surgical intervention with explorative laparotomy, ulcer biopsy, primary repair and omentoplasty is the preferred surgical management of perforated peptic ulcers in our institution. This is followed by post-operative Proton Pump Inhibitor and Helicobacter Pylori eradication therapy in all patients.

Our study included all presenting patients in the defined population with no selection in referral; therefore we expected our mortality rate (25%) to be similar to mortality reported in the literature (1.3-40%) [2, 3, 16–21, 7, 9–15].

Investigations into risk factors for perforation are complicated by the wide variation in demographics, socioeconomic status, Helicobacter pylori prevalence as well as medication and substance use in different population groups [18]. Cohorts from other African countries shows a male predominance of 6-13:1 to females [18]. In developing countries young (predominantly male) smokers make up the biggest patient group whereas in the developed world elderly patients (increase in females) with other co-morbidities and associated use of NSAIDs are more commonly found [8, 13, 22]. Significant inequality in South Africa leads to a wide spectrum of socio-economic circumstances in our study population and both these population groups might have been included [32]. Our age distribution, with median of 46 years (range 15-87), was similar to other South African study demographics as compared to an older age distribution found in most literature [21]. We had a male predominance (2.48:1) but it was not as high as similar patient groups in South African and other African series and closer to distribution in the rest of the literature [18, 21]. Our median length of hospital stay of 7 days (range 1-94) was similar to other studies [33, 34].

Perforated peptic ulcer is multifactorial and multiple scoring systems have been suggested and used as outcome predictors thereof [3]. Scoring systems range from simple to complex (combining demographical data, history, vital signs and clinical findings, chosen surgical intervention and management options as criteria) sometimes making practical implementation thereof more difficult [2, 35]. The ASA (American Society of Anaesthesiologist physical status classification system) and Boey score are the most commonly used validated scores for patients with perforated peptic ulcers [22]. ICU and other standard surgical scores have also been evaluated in patients with perforated peptic ulcers [18]. Replication of original high positive predictive values of used scores has not always been shown in other study populations and there is a lack of external cohort validation [2, 18, 35]. There is still no agreed standard scoring system and investigation towards an optimal prediction model in terms of outcome for patients with perforated peptic ulcers in today's setting is still not saturated [6, 18]. The reason for none of the multiple scoring systems being widely accepted in clinical practice can be due to the complexity, non-specificity or subjective points of these scoring systems [25]. The goals of being easy to calculate, accurate in predicting outcome and being reproducible across different populations have not been comprehensively satisfied by any score [23].

Due to the wide rural drainage area of our hospital, a large number of our patients have a late presentation that already falls outside the 24 hour window period at time of theatre. Literature from South Africa demonstrates a late presentation in patients with perforated peptic ulcers, outside of the 24h window from onset of symptoms [21]. Record bias in terms of pre-hospital data plays a part in retrospective studies. Patient recall bias in terms of

medical and complaint history can also be possible and patients with pre-existing peptic ulcer disease might experience pain or symptoms for some time and are therefore unable to pinpoint exactly when pain was exacerbated [36]. Accurate patient history might not be possible due to the clinical condition of the patient (e.g. Decrease in level of consciousness, elderly patients). This will influence patient medical history in terms of other co morbidities and medication-use at the time of admission [25]. All these risk factors have been questioned due to lack of objectivity and have been reported to lack sensitivity and specificity [36]. However, these risk factors still form part of scoring systems (PULP score, Mannheim Peritonitis score, Hacettepe score) previously described in the prediction of patient outcome [15, 16].

The POMPP score was developed in 2015 as a practical scoring system to assist in calculating mortality risk in patients with perforated peptic ulcers. It indicated age, albumin and urea levels to be three variables that are statistically relevant in multivariate analysis. This new scoring system compared well to ASA, PULP and Boey scoring systems but was found less complex as it only made use of age and two admission laboratory values (albumin and urea).[25] We found urea ($p < 0.0001$) to be significant in predicting mortality and ICU admission and albumin ($p = 0.0048$) to predict ICU admission in univariate analysis. Due to a large number of missing albumin values (n=69) in our study it could unfortunately not be included in the multivariate analysis.

A model to calculate postoperative risk specifically for emergency surgery (CORES) was developed in Japan in 2012. It uses five preoperative variables which include white blood cell count (WCC), platelet count and blood urea nitrogen as laboratory values and were able to reproducibly predict postoperative mortality in the validation and multicentre subgroups. It was postulated that the better prediction in the General Surgery patient subset compared to the P-POSSUM score can be due to the inclusion of platelet count, as thrombocytopenia has been shown as a risk factor for mortality in ICU patients and is the most commonly cited manifestation of haematological dysfunction [30, 31]. Patients with a high platelet count (>300,000) interestingly also had higher mortality rates demonstrated in the study used to develop the CORES model [30]. We found thrombocytopenia (OR 2.212 [95% CI 0.581-8.427]) and thrombocytosis (OR 2.942 [95% CI 1.235-7.009]) both to be significant variables after multivariate analysis in predicting ICU admission.

A contemporary study done among an African population in Côte d'Ivoire who had operative interventions for perforated peptic ulcer disease, showed a high median value WCC ($p < 0.0001$), low level of natraemia (134 vs. 137, $p = 0.02$) and low potassium (3.6 vs. 3.7, $p = 0.01$) in patients that had postoperative complications or mortality compared to those without. We did not find WCC or sodium to be significant variables in our patient group, but did find abnormal potassium ($p = 0.0008$) to be significant in predicting mortality in univariate analysis.

Development of CORES, Hacettepe, PULP and Jabalpur scores all demonstrated elevated creatinine as a significant risk factor [15, 16, 24, 30]. We found abnormal high creatinine to be the strongest single predictor of outcome in patients with perforated peptic ulcers. It demonstrated an OR of 7.755 [95% CI 2.899-20.740; $p < 0.0001$] in predicting in-hospital mortality and an OR of 6.900 [95% CI 2.866-16.609; $p < .0001$] in predicting ICU admission. This is much higher than the odds ratios demonstrated in developing the PULP score (OR 2.25 [95% CI 1.78-2.84]) [15].

Our study demonstrated urea ≥ 10.9mmol/L had a sensitivity of 70.21% and specificity of 82.14% (AUC 0.79) and creatinine ≥ 109umol/L a sensitivity of 80.85% and specificity of 67.69% (AUC 0.80) in predicting in-hospital mortality.

The PULP score demonstrated an OR of 1.13 [95% CI 0.80-1.61] for a haemoglobin < 6 mmol/L in predicting mortality [15]. Our study demonstrated abnormal low (OR 2.877 [95% CI 1.149-7.201]) and high (OR 4.363 [95% CI 0.982-19.386]) haemoglobin levels both to be significant in predicting in-hospital mortality.

Our study also validated age as a significant prognosticator. It showed an OR of 1.034[95% CI 1.008-1.061]; p = 0.0091 for predicting in-hospital mortality and an OR of 1.025 [95% CI 1.001-1.051]; p = 0.0441 for predicting ICU admission. The importance of advanced age as an independent risk factor remains as valid as in literature [3, 7, 9, 25, 33].

A large part of our study validated previously identified outcome predictors found in literature in our specific patient cohort. Discrepancies can most likely be accounted for by differences in demographical factors and mortality in other settings. These research findings will assist in the practical usage of easily available laboratory values in predicting outcomes in patients with perforated peptic ulcers. It can lead to better clinical decisions and cost-benefit strategies. This will promote optimal management as well as facilitate better assignment of resources such as theatre space and consultant coverage. Limited ICU bed availability in most health care settings emphasizes the importance of individual risk stratification. Scoring systems should be easy to calculate and have a high degree of accuracy in predicting adverse outcomes, which have been proven difficult to materialise in this patient group as seen in the literature. Patients identified as higher risk could have earlier access to organ support, intensive care and more aggressive resuscitation. Outcomes can then be improved based on individual risk stratification. It has been proven that extra perioperative care and management protocols for high risk patients improve in-hospital mortality [10, 25]. Knowledge of significant independent risk factors by the surgeon will assist in confident judgement about operative planning and appropriateness [16]. This awareness will also improve patient counselling in terms of risks, possible complications and outcome expectations. Naturally, an individual predictor can't be ascribed to a single patient, but the presence of a significant or more than one risk factor presents a much higher mortality risk in contrast to patients with none [6].

These findings can also be used in combination with other preoperative information or in further prospective studies to develop appropriate prediction and scoring systems for this health care setting or used in different populations as a comparison. Most of the studies available in the literature were done mainly in western and Asian countries [17]. In the era of hand-held devices and smartphones more complex scoring systems might be easier to calculate at the bedside than before [23]. It might be difficult to develop a universally reproducible scoring system due to geographical variation in age, gender and patterns of presentation [18]. Laboratory values however have the advantage of being an objective variable not influenced by subjective interpretation and therefore ideal for validation between different patient cohorts and demographic regions [6].

Although the study involved a consecutive cohort a limitation of this study is that it is a retrospective, single centre study. An additional limitation was that both gastric and duodenal ulcers have been grouped under the umbrella of peptic ulcer disease, as information with regards to anatomical location during surgery of these

ulcers was not available, even though etiological factors and pathophysiological processes may differ. An advantage is that we had minimal missing data due to consistent laboratory records. This might be more of a problem in future studies using other perioperative variables depending on pre hospital and hospital records. Laboratory values might just be indicators for other underlying factors like chronic disease. Further investigation into causality from the findings in the study might therefore be warranted at a later stage. The long term outcome after hospital discharge for our patient group was also not assessed. Logical regression was used to minimise confounding variables. Some of the calculated 95% Confidence intervals are wide, which indicates low statistical precision. Other reference ranges for abnormal values and definitions or categorizations of demographic variables might have produced different results.

Conclusion

All laboratory values might not be exact in predicting mortality but we found that routine admission laboratory values does most certainly contribute to building a risk stratification model for this patient group in our health care setting. A local risk prediction model should be developed and validated in future prospective studies with inclusion of other risk factors. This study simply questioned whether admission laboratory values in isolation can be trusted to assist with predicting outcomes. Admission laboratory values are valuable in predicting surgical outcomes and they play a crucial role in our approach and management of the patient from the time of admission.

List of abbreviations

ASA	American Society of Anaesthesiologist physical status classification system
CI	Confidence interval
CORES score	Calculation of post-operative risk in emergency surgery
HSREC	Health Science Research Ethics Committee
ICU	Intensive Care Unit
IQR	Interquartile range
Meditech	Medical technology system data storage
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds Ratio
POMPP score	Prediction of mortality in perforated peptic ulcer
PPI	Proton Pump Inhibitor
P-POSSUM score	Portsmouth Physiological and operative severity score for the enumeration of mortality and morbidity (Portsmouth modification of the original POSSUM score)
PPU	Perforated peptic ulcer
PULP score	Peptic Ulcer Perforation score
UFS	University of the Free State
WCC	White Blood Cell Count

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Appendix A – HSREC Letter of Approval

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

05-Jun-2019

Dear **Dr Wikus Mulder**

Ethics Clearance: **Are admission laboratory values in isolation valuable in predicting surgical outcome in patients with perforated peptic ulcers?**

Principal Investigator: **Dr Wikus Mulder**

Department: **Surgery Department (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is: **UFS-HSD2019/0018/2506**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00006240; REC 230408-011; IORG0005187; FWA00012784
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa

Appendix B – FSDoH Letter of Approval

health
Department of Health
FREE STATE PROVINCE

06 May 2019

Dr W Mulder
Dept. of Surgery
UFS

Dear Dr W Mulder

Subject: Are admission laboratory values in isolation valuable in predicting surgical outcome in patients with perforated peptic ulcers?

- Please ensure that you read the whole document, Permission is hereby granted for the above – mentioned research on the following conditions:
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of **Pelonomi Hospital** nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** sebeelats@fshealth.gov.za / lithekom@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- **Please discuss your study with Pelonomi Hospital CEO's on commencement for logistical arrangements see 2nd page for contact details.**
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see http://nhrd.hst.org.za

Trust you find the above in order.

Kind Regards

Dr D Motala
HEAD: HEALTH
Date: 7/5/19

Head : Health
PO Box 227, Bloemfotein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and, Harvey Road, Bloemfotein
Tel: (051) 408 1646 Fax: (051) 408 1556 e-mail:khusemj@fshealth.gov.za@fshealth.gov.za/chikobvup@fshealth.gov.za

health
Department of
Health
FREE STATE PROVINCE

07 May 2019

Dr. W Mulder
Dep. Of Surgery
UFS
BFN

Dear Dr. W Mulder

Subject: Are admission laboratory values in isolation valuable in predicting surgical outcome in patients with perforated peptic ulcers?

Please find below the contact details of Pelonomi Hospital CEO for logistical arrangements.

Pelonomi Hospital CEO

Name: Ms BS Ramodula
Email: ramodulabs@fshealth.gov.za
Tel: 051 405 1026

PA: Caroline
Email: Ntlhokc@fshealth.gov.za

Trust you find the above in order.

Kind Regards

Head : Health
PO Box 227, Bloemfotein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and, Harvey Road, Bloemfotein
Tel: (051) 408 1646 Fax: (051) 408 1556 e-mail:khusemj@fshealth.gov.za@fshealth.gov.za/chikobvup@fshealth.gov.za

Appendix C – NHLS Approval Letter

NATIONAL HEALTH LABORATORY SERVICE

Practice No. 5200296

Office of the Business Manager
UNIVERSITAS ACADEMIC LABORATORIES
PO BOX 339(G3)
C/O: CHEMICAL PATHOLOGY
1st FLOOR
BLOCK C
FACULTY OF HEALTH SCIENCES
UNIVERSITY OF FREE STATE
BLOEMFONTEIN
9301

REQUEST FOR APPROVAL OF LABORATORY RESOURCES FOR ACADEMIC PURPOSES

Date: 11 April 2019

Requestor: Dr Wikus W Mulder

Project Name: "Are admission laboratory values in isolation valuable in predicting surgical outcome in patients with perforated peptic ulcers?"

Dear Dr Mulder,

Your request for use of laboratory facilities / data is hereby granted under following conditions:

1) That University Ethical Committee approval and approval from the Universitas Hospital management is obtained
2) All laboratory data remain confidential to the patient and doctor (anonymity is maintained)
3) This Office must be notified before any publication of any results / findings are made.
4) NHLS is recognised in all publications
5) That a successful K-Project application be made and relevant NHLS project cost centre be created to utilise testing at NHLS as per your protocol.

May your project be successful.

Regards

NATIONAL HEALTH LABORATORY SERVICE
11 APR 2019
BUSINESS MANAGER
UNIVERSITAS ACADEMIC LABORATORIES

Mr. Pakiso Letanta
Acting Business Manager

Appendix D – Head of Department of Surgery and Supervisor Letter of Approval

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

MASTER OF MEDICINE

This is to certify that the Departmental Research Meeting approved of the following MMed research protocol:

DATE OF MEETING	22-02-2019

DEPARTMENT	Surgery
STUDENT NUMBER	2007016583
INITIALS AND SURNAME OF CANDIDATE	Dr W Mulder
NAME OF DEGREE	M Med
SUPERVISOR	Dr Dr E Arko-Cobbah
CO-SUPERVISOR	

TITLE OF THE RESEARCH PROJECT
Are admission laboratory values in isolation valuable in predicting surgical outcome in patients with perforated peptic ulcers?

RESEARCH CHAMPION — DATE: 05/03/2019

SUPERVISOR(S) — DATE: 05/03/2019

HEAD OF THE DEPARTMENT — DATE: 05/03/2019

Are admission laboratory values in isolation valuable in predicting surgical outcome in patients with perforated peptic ulcers?

INDEX

1. RESEARCHERS

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2. INTRODUCTION

Peptic ulcer disease results from an imbalance between pepsin and acid in the stomach and defensive barriers of stomach mucosa[1]. Annually over 4 million people are affected by peptic ulcer disease worldwide [2]. Peptic ulcer disease is complicated by bleeding, obstruction and perforation [3]. The incidence of perforation is 4-10/ 100 000 population per annum and the most common operation is simple closure [4]. Even though the surgical therapy has not changed much over the last few decades, perforated peptic ulcer disease remains a dangerous surgical condition with a morbidity and mortality not to be underestimated[5]. More than 70% of deaths associated with peptic ulcer disease are due to perforation [5]. Perforated peptic ulcer carries a mortality of 1.3% to 30% [6-8]. A classic triad of tachycardia, sudden onset abdominal pain and abdominal rigidity has been described, but patients can present with a wide array of gastrointestinal or systemic symptoms[1 6]. Admission status has been described as a significant prognostic factor in patients with peptic ulcer perforation [8].

Perforated peptic ulcer is a multifactor disease and multiple scoring systems have been suggested and used as outcome predictors thereof [9]. Investigations into risk factors for perforation are complicated by the wide variation in demographics, socioeconomic status, prevalence of Helicobacter pylori as well as medication and substance use in different population groups [6]. Scoring systems range from simple to complex (combining demographical data, history, vital signs and clinical findings, chosen surgical intervention and management options as criteria) sometimes making practical implementation thereof more difficult. Replication of original high positive predictive values of some scores has also not always been shown in other study populations[3 10]. There is still no agreed standard and investigation towards an optimal prediction model in terms of outcome for patients with perforated peptic ulcers in today's setting is still not saturated [6 11]. The reason for none of the multiple scoring systems being widely accepted in clinical practise can be due to the complexity, non-specificity or subjective points of these scoring systems [12]. None have been able to comprehensively satisfy goals of being easy to calculate, accurate in predicting outcome and being reproducible across different populations.[13]

The time period from ulcer perforation until surgical intervention is one of the criteria used in the Boey score[7]. It has been described as a significant predictor of mortality in some

studies [8 14], but found not to be significant in others [15 16]. Due to the wide rural drainage area of our hospital, a large number of our patients have a late presentation that already falls outside the 24 hour window by time of theatre. Use of alternative medication according to cultural beliefs and symptomatic treatment at primary care centres also contribute to late presentation in an African healthcare setting [17]. Record bias in terms of pre hospital data plays a part in retrospective studies. Patient recall bias in terms of medical and complaint history can also be possible and patients with pre-existing peptic ulcer disease might experience pain or symptoms for some time and are therefore unable to pinpoint exactly when pain exacerbated [16]. Accurate patient history might not be possible due to the clinical condition of the patient (e.g. Decrease in level of consciousness, elderly patients). This will influence patient medical history in terms of other co morbidities and medication- use at the time of admission[12]. All these risk factors have been questioned due to lack of objectivity and have been reported to lack sensitivity and specificity [16]. However, these risk factors still form part of scoring systems (PULP score, Mannheim Peritonitis score, Hacettepe score) previously described in the prediction of the patient's outcome [15 18].

Acute renal failure and a white blood cell count (WCC) of more than 20 x 10^9/l have been shown to be significant factors influencing mortality in perforated peptic ulcers. With male sex they contribute 3 out of the 4 scoring points used in the Hacettepe Score which showed a predictive accuracy of 93% [15]. A study in Japan found a low white blood cell count to be a significant risk indicator, and it was dependant on age [19].

A practical scoring system of mortality in patients with perforated peptic ulcer (POMPP) was developed in 2015, indicating age, albumin and urea levels to be three variables that are statistically relevant in multivariate analysis. This new scoring system compared well to ASA (American Society of Anaesthesiologist physical status classification system), PULP (Peptic Ulcer Perforation score) and Boey scoring systems but was found less complex as it only made use of age and two admission laboratory values (albumin and urea) [12].

A contemporary study done among an African population in Côte d'Ivoire who had surgery for perforated peptic ulcer disease, showed a high median value of WCC ($P < 0.0001$) and low level of natraemia (134 vs 137, $P = 0.02$) in patients that had post operative

complications or mortality compared to those without. Patients with hyponatremia had a twofold increase in the risk of complications or death in this study population [17].

Elevated serum creatinine levels can be due to untreated peritonitis or pre existing renal disease (known or unknown before diagnosis). Together with elevated urea level and metabolic acidosis it can be indicative of prerenal injury and SIRS (Systemic inflammatory Response Syndrome) [1].With delay in medical attention there is deficit in total body water which leads to hypotension. Uninterrupted hypotension can then also progress to acute kidney injury [1]. Acute kidney injury can be a reflection of dehydration, shock or sepsis and loss of renal function is a poor prognostic sign [11 20]. In the development of the Mortality Probability Models (MPM II) patients who were admitted to ICU with acute renal failure were 4.4 times more likely to die in the hospital (OR 4.4 [95% CI 3.7-5.2]) [21]. In the era before Proton Pump Inhibitor (PPI) therapy, pre operative serum creatinine has already been shown to be the single most important predictor of survival, with patients with a normal serum creatinine 25.5 times more likely to survive [16]. It has been shown that ICU mortality rate increases with increasing serum creatinine concentration [22]. Elevated serum creatinine was also associated with mortality during development of the Jabalpur prognostic scoring system and forms one of its criteria [23]. Another multivariable regression analysis found hypoalbuminaemia, hyperbilirubinaemia and increase creatinine all to be predictive of 30-day post-operative mortality [11]. During development of the Peptic Ulcer Perforation (PULP) score, which had a better prediction of 30 day mortality than the ASA score and Boey score in the same population group, elevated serum creatinine was also one of the factors with the highest prognostic impact [18]. Elevated serum creatinine in itself may therefore be an indicator for other underlying factors like pre- existing disease or the state of the acute disease [11]. A mortality of 75% has been demonstrated in patients with perforated gastroduodenal ulcer and renal failure [19].

A model to calculate post-operative risk in emergency surgery (CORES) was developed in Japan in 2012. It uses five preoperative variables which include WCC, platelet count and blood urea nitrogen and were able to reproducibly predict post-operative mortality in the validation and multicentre subsets. It was postulated that the better prediction in the General Surgery patient group compared to the P-POSSUM score (Physiological and operative severity score for the enumeration of mortality and morbidity) might be due to

the inclusion of platelet count, since thrombocytopenia has been reported as a risk factor for mortality in ICU patients and is the most commonly cited manifestation of haematological dysfunction [22 24].

In a condition such as perforated peptic ulcer disease, electrolyte disturbances, anaemia, hypoalbuminaemia, renal failure and leucocytosis can all be seen as part of the sepsis syndrome [9].

The diagnosis of a perforated peptic ulcer cannot be made by using laboratory values in isolation. Laboratory values are however good indicators of organ dysfunction and inflammation. They are also used to rule out other pathologies on the differential diagnosis, like pancreatitis [1 5 6]. Laboratory values form part of most perforated ulcer and other prognostic scoring systems used currently (Table 1) [9 13]:

Table 1:

Scoring system used for outcome prediction	**Target population**	**Outcome measured**	**Laboratory values used as part of scoring system**
Hacettepe score[15]	Patients with perforated peptic ulcer	30 day mortality	Acute renal failure, White blood cell count
Jabalpur score[23]	Patients with perforated peptic ulcer	30 day mortality	Serum creatinine
PULP (Peptic ulcer perforation score)[18]	Patients with perforated peptic ulcer	30 day mortality	Liver failure, serum-creatinine
Mannheim Peritonitis index	General peritonitis	Preoperative prediction of outcome	Organ failure
APACHE II *(Acute physiology and chronic health evaluation II)[20]	Critically ill patients	Prediction of outcome in ICU patients	White blood cell count, creatinine, Potassium, Sodium
SAPS II (Simplified acute physiology score II)[25]	Critically ill patients	Prediction of outcome in ICU patients	White blood cell count, Bilirubin, Urea, Potassium, Sodium
MPM II (Mortality Probability	Critically ill patients	Prediction of	Liver failure, Renal

Models)[21]		outcome for ICU patients	insufficiency
POSSUM (Physiological and operative severity score for the enumeration of mortality and morbidity score)[26]	Surgical patients	Prediction of mortality	White blood cell count, Haemoglobin, Urea, Potassium, Sodium
CORES (Calculation of post operative risk in emergency surgery) [24]	Patients who underwent emergency surgery	In hospital mortality	White blood cell count, urea, platelet count
Multiple organ dysfunction score [22]	Critically ill patients	Prediction of mortality and outcome for ICU patients	Serum creatinine, platelet count

As described all these scoring systems uses a different subset of available laboratory values in an attempt to predict mortality. The question remains whether admission laboratory findings are of any value in isolation, and can they be used as a reliable indicator of prognosis?

The diagnosis of perforated peptic ulcer disease is made using a combination of history, clinical and radiological findings. Surgical intervention with laparotomy, biopsy, primary repair and omentoplasty is the preferred surgical management of perforated peptic ulcers in our institution. This is followed by post operative Proton Pump Inhibitor and eradication therapy.

3. RESEARCH QUESTIONS, AIMS AND OBJECTIVES

To calculate the predictive value in terms of surgical outcome of different admission laboratory values in patients with perforated peptic ulcers.

4. METHODOLOGY

4.1 Study design

This is a retrospective, cohort analytical, observational study. All patients with confirmed peptic ulcers which were surgically treated will be considered for the study

Predictive value in terms of outcome will be assessed and compared.

4.2 Sample/ study participants

A mortality figure similar to the mortality reported in our literature review (1-30%) is expected in our study population. We anticipate approximately 150-250 patients to meet our inclusion criteria over the five year period.

Inclusion criteria:

- All consecutive patients at Pelonomi Regional Hospital from July 2014- June 2019 in both sexes with surgically confirmed (during laparotomy) perforated peptic ulcer (gastric or duodenal) disease and available demographic and admission laboratory data. Pelonomi Regional Hospital provides the bulk of the acute care surgical and trauma services for the Free State province in South Africa

Exclusion criteria:

- Histological confirmed malignant perforations
- Traumatic or iatrogenic perforations
- Perforations due to caustic ingestion or foreign bodies
- Perforations found during autopsy
- Patients managed conservatively without surgical intervention
- Patients who had surgery but no confirmation of perforated ulcer
- Patients younger than 13 years

4.3 Measurement

Data will be collected for patients who meet the inclusion criteria

Demographic data will be collected from Pelonomi hospital's electronic database (Meditech) and matched to NHLS database (Labtrak). Department of Surgery statistics database and theatre record books will be used as backup measure to ensure no patient that meets inclusion criteria is excluded from data collection.

Demographic data will include age and sex.

Laboratory values will be values collected from National Health Laboratory Service database (Labtrak). The following values on admission will be used:

- Full blood count (Haemoglobin, Haematocrit, White cell count, Platelets)
- Renal function (Urea and Creatinine)
- Electrolytes (Sodium and Potassium)
- Inflammatory markers (C-reactive Protein- CRP)
- Albumin

All data will be captured on a data sheet (See appendix)

Patient endpoint:

Primary comparative outcome measure: In hospital mortality- all deaths during stay of admission

Secondary endpoints:

ICU admission

Time of stay in ICU

Time of stay in hospital

Study outcome:

1. Accurate predictive value of laboratory values
2. Secondary outcomes:

- Predictive value of demographic data
- Comparison of predictive value between laboratory results
- Prediction of ICU or hospital stay

4.4 Methodology and measurement errors

Due to the fact that this is a retrospective study, incomplete or missing records from the National Health Laboratory Service (labtrak) or the hospitals electronic database (Meditech) may be problematic and lead to bias. Incomplete records will need to be evaluated carefully

and compared to information in the Department of Surgery's statistical data base as control measure.

As stated in the introduction, laboratory values might just be indicators for other underlying factors like chronic disease. Further investigation into causality from the findings in the study might therefore be warranted at a later stage.

In order to minimise bias in terms of our literature review we tried to include and evaluate all the recognised scoring systems and included up to date as well as older studies of proposed outcome predictors that were still used popularly or acknowledged in high regard.

Multivariate techniques will be used to minimise confounding variables as far as possible

5. DATA CAPTURING AND ANALYSIS

Data will be captured on an Excel spreadsheet from the data sheets. Captured data will be analysed by researchers and the department of Bio-statistics at the University of the Free State.

Logistic regression analysis will be used to assess the significance of the risk factors. P values, odds ratios, predictive value, sensitivity and specificity will be calculated with a P-value of <0,05 considered significant. Receiver operating characteristic (ROC) curve will be created and Area under ROC curve (AUC) will be calculated.

6. IMPLEMENTATION OF FINDINGS

This study will be used as part of the MMed curriculum and handed in to be marked as a MMed dissertation.

The findings will assist in the practical usage of easily available laboratory values in predicting outcome in patients with perforated peptic ulcers. It can lead to better clinical decisions and cost-benefit strategies. This will promote optimal management as well as facilitate better assignment of resources. Patients identified as higher risk could have earlier access to organ support, intensive care and more aggressive resuscitation. Outcome can then be improved based on individual risk stratification. It will also improve patient counselling and operative planning.

These findings can also be used in combination with other preoperative information or in further prospective studies to develop appropriate prediction and scoring systems for this health care setting or used in different populations as comparison.

7. PROPOSED TIME SCHEDULE

Writing of Protocol	October- December 2018
Submission to ethics committee	January 2019
Data capturing	November 2019- April 2020
Submission of data for analysis	May 2020
Submission of completed article	November 2020

8. BUDGET

Travel and stationary costs to be covered by researchers (< R1000)
No sponsors will be used in this study
No other expenses are budgeted for

9. ETHICAL ASPECTS

The study protocol will be submitted to the Health Sciences Research Ethics Committee of the University of the Free State.

Permission for the study will be obtained from Dr N Pearce, Head of department of General Surgery, University of the Free State as well as the Free State Department of Health. Permission from the National Health Laboratory Service for use of their database will also be obtained.

Study will only commence once ethical approval has been obtained as well as permission from other relevant parties as mentioned above.

All retrospectively collected patient data will be treated as confidential. Patient names and hospital numbers will be changed to new study numbers to insure confidentiality. Patient identifier-depleted data will be stored on a password controlled computer on a secure server. Only the researchers will have access to the patient records.

10. REFERENCES/ BIBLIOGRAPHY

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11. APPENDICES

DATA CAPTURE SHEET:

DEMOGRAPHIC DATA		
Study number		1
Gender	M 1 F 2	2
Age	years	3
LABORATORY VALUES		
FULL BLOOD COUNT		
Hb	,	4 ,
Haematocrit	,	5 ,
WCC	,	6 ,
Plt		7
RENAL FUNCTION		
Urea	,	8 ,
Creat		9
ELECTROLYTES		
Sodium(Na)		10
Potassium (K)	,	11 ,
INFECTIVE MARKERS		
Crp		12
OTHER		
Albumin		13
OUTCOME		
In Hospital Mortality	Y 1 N 2	14
ICU admission	Y 1 N 2	15
Days in ICU	days	16
Days in Hospital	days	17

Appendix F – South African National Health Laboratory Service (NHLS) Reference Ranges for Laboratory Values

Hemoglobin	14.3-18.3 g/dL
Haematocrit	0.43-0.55 L/L
WCC	4.0-10.0 x 109 /L
Platelet count	171-388 x 109/L
Urea	2.1-7.1 mmol/L
Creatinine	64-104 umol/L
Sodium	136-145 mmol/L
Potassium	3.5-5.1 mmol/L
C-reactive protein	0-5 mg/L
Albumin	35-52 g/L

Appendix G – Instructions to Authors of the European Journal of

European Journal of Trauma and Emergency Surgery

Official Publication of the European Society for Trauma and Emergency Surgery

- Journal home
- Submission guidelines

Submission guidelines

Contents

Instructions for Authors

Types of Papers

- Accepted article types: Original Articles, Reviews, and Letters to the Editors.
- Declaration of Conflict of Interest is mandatory for all submissions. Please refer to the section "Integrity of research and reporting" in the Instructions for Authors.
- Case Reports will not be considered for publication.
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Back to top ↑

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Manuscript Submission

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Back to top ↑

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- The name(s) of the author(s)
- The affiliation(s) of the author(s), i.e. institution, (department), city, (state), country
- A clear indication and an active e-mail address of the corresponding author
- If available, the 16-digit ORCID of the author(s)

If address information is provided with the affiliation(s) it will also be published.

For authors that are (temporarily) unaffiliated we will only capture their city and country of residence, not their e-mail address unless specifically requested.

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Please provide a structured abstract of 150 to 250 words which should be divided into the following sections:

- Purpose (stating the main purposes and research question)
- Methods
- Results
- Conclusion

For life science journals only (when applicable)

Trial registration number and date of registration

Trial registration number, date of registration followed by “retrospectively registered”

Keywords

Please provide 4 to 6 keywords which can be used for indexing purposes.

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All manuscripts must contain the following sections under the heading 'Declarations'.

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To be used for all articles, including articles with biological applications

Funding (information that explains whether and by whom the research was supported)

Conflicts of interest/Competing interests (include appropriate disclosures)

Availability of data and material (data transparency)

Code availability (software application or custom code)

Authors' contributions (optional: please review the submission guidelines from the journal whether statements are mandatory)

Additional declarations for articles in life science journals that report the results of studies involving humans and/or animals

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Consent to participate (include appropriate statements)

Consent for publication (include appropriate statements)

Please see the relevant sections in the submission guidelines for further information as well as various examples of wording. Please revise/customize the sample statements according to your own needs.

Back to top ↑

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- Use the table function, not spreadsheets, to make tables.
- Use the equation editor or MathType for equations.
- Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

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LaTeX macro package (Download zip, 188 kB) ⬇

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Abbreviations should be defined at first mention and used consistently thereafter.

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Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

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Always use footnotes instead of endnotes.

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Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

Back to top ↑

References

Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:

1. Negotiation research spans many disciplines [3].

2. This result was later contradicted by Becker and Seligman [5].

3. This effect has been widely studied [1-3, 7].

Reference list

The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text.

The entries in the list should be numbered consecutively.

If available, please always include DOIs as full DOI links in your reference list (e.g. “https://doi.org/abc”).

- Journal article

  Smith JJ. The world of science. Am J Sci. 1999;36:234–5.

- Article by DOI

  Slifka MK, Whitton JL. Clinical implications of dysregulated cytokine production. J Mol Med. 2000; https://doi.org/10.1007/s001090000086

- Book

  Blenkinsopp A, Paxton P. Symptoms in the pharmacy: a guide to the management of common illness. 3rd ed. Oxford: Blackwell Science; 1998.

- Book chapter

  Wyllie AH, Kerr JFR, Currie AR. Cell death: the significance of apoptosis. In: Bourne GH, Danielli JF, Jeon KW, editors. International review of cytology. London: Academic; 1980. pp. 251–306.

- Online document

Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. 1999. http://www.rsc.org/dose/title of subordinate document. Accessed 15 Jan 1999.

Always use the standard abbreviation of a journal's name according to the ISSN List of Title Word Abbreviations, see

ISSN.org LTWA

If you are unsure, please use the full journal title.

Back to top

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- All tables are to be numbered using Arabic numerals.
- Tables should always be cited in text in consecutive numerical order.
- For each table, please supply a table caption (title) explaining the components of the table.
- Identify any previously published material by giving the original source in the form of a reference at the end of the table caption.
- Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

Back to top

Artwork and Illustrations Guidelines

Electronic Figure Submission

- Supply all figures electronically.
- Indicate what graphics program was used to create the artwork.
- For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MSOffice files are also acceptable.
- Vector graphics containing fonts must have the fonts embedded in the files.
- Name your figure files with "Fig" and the figure number, e.g., Fig1.eps.

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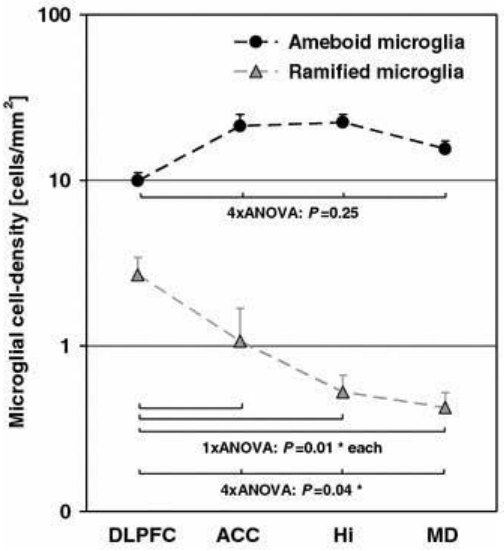

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- Vector graphics containing fonts must have the fonts embedded in the files.

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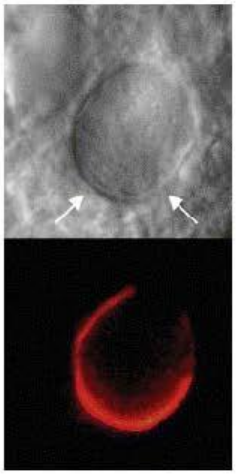

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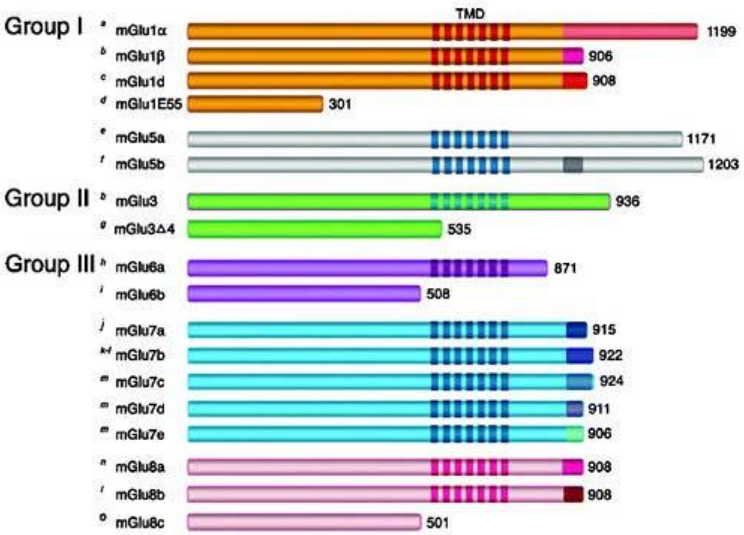

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- Color art is free of charge for online publication.
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- Avoid effects such as shading, outline letters, etc.
- Do not include titles or captions within your illustrations.

Figure Numbering

- All figures are to be numbered using Arabic numerals.
- Figures should always be cited in text in consecutive numerical order.
- Figure parts should be denoted by lowercase letters (a, b, c, etc.).
- If an appendix appears in your article and it contains one or more figures, continue the consecutive numbering of the main text. Do not number the appendix figures,"A1, A2, A3, etc." Figures in online appendices [Supplementary Information (SI)] should, however, be numbered separately.

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Back to top ↑

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Back to top ↑

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Back to top ↑

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Back to top ↑

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Back to top ↑

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Suggesting / excluding reviewers

Authors are welcome to suggest suitable reviewers and/or request the exclusion of certain individuals when they submit their manuscripts. When suggesting reviewers, authors should make sure they are totally independent and not connected to the work in any way. It is strongly recommended to suggest a mix of reviewers from different

countries and different institutions. When suggesting reviewers, the Corresponding Author must provide an institutional email address for each suggested reviewer, or, if this is not possible to include other means of verifying the identity such as a link to a personal homepage, a link to the publication record or a researcher or author ID in the submission letter. Please note that the Journal may not use the suggestions, but suggestions are appreciated and may help facilitate the peer review process.

Back to top ↑

Research involving human participants, their data or biological material

Ethics approval

When reporting a study that involved human participants, their data or biological material, authors should include a statement that confirms that the study was approved (or granted exemption) by the appropriate institutional and/or national research ethics committee (including the name of the ethics committee) and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. If doubt exists whether the research was conducted in accordance with the 1964 Helsinki Declaration or comparable standards, the authors must explain the reasons for their approach, and demonstrate that an independent ethics committee or institutional review board explicitly approved the doubtful aspects of the study. If a study was granted exemption from requiring ethics approval, this should also be detailed in the manuscript (including the reasons for the exemption).

Retrospective ethics approval

If a study has not been granted ethics committee approval prior to commencing, retrospective ethics approval usually cannot be obtained and it may not be possible to consider the manuscript for peer review. The decision on whether to proceed to peer review in such cases is at the Editor's discretion.

Ethics approval for retrospective studies

Although retrospective studies are conducted on already available data or biological material (for which formal consent may not be needed or is difficult to obtain) ethics approval may be required dependent on the law and the national ethical guidelines of a country. Authors should check with their institution to make sure they are complying with the specific requirements of their country.

Ethics approval for case studies

Case reports require ethics approval. Most institutions will have specific policies on this subject. Authors should check with their institution to make sure they are complying with the specific requirements of their institution and seek ethics approval where needed. Authors should be aware to secure informed consent from the individual (or parent or guardian if the participant is a minor or incapable) See also section on **Informed Consent**.

Cell lines

If human cells are used, authors must declare in the manuscript: what cell lines were used by describing the source of the cell line, including when and from where it was obtained, whether the cell line has recently been authenticated and by what method. If cells were bought from a life science company the following need to be given in the manuscript: name of company (that provided the cells), cell type, number of cell line, and batch of cells.

It is recommended that authors check the NCBI database for misidentification and contamination of human cell lines. This step will alert authors to possible problems with the cell line and may save considerable time and effort.

Further information is available from the International Cell Line Authentication Committee (ICLAC).

Authors should include a statement that confirms that an institutional or independent ethics committee (including the name of the ethics committee) approved the study and that informed consent was obtained from the donor or next of kin.

Research Resource Identifiers (RRID)

Research Resource Identifiers (RRID) are persistent unique identifiers (effectively similar to a DOI) for research resources. This journal encourages authors to adopt RRIDs when reporting key biological resources (antibodies, cell lines, model organisms and tools) in their manuscripts.

Examples:

Organism: *Filip1*$^{tm1a(KOMP)Wtsi}$ **RRID:MMRRC_055641-UCD**

Cell Line: RST307 cell line **RRID:CVCL_C321**

Antibody: Luciferase antibody DSHB Cat# LUC-3, **RRID:AB_2722109**

Plasmid: mRuby3 plasmid **RRID:Addgene_104005**

Software: ImageJ Version 1.2.4 **RRID:SCR_003070**

RRIDs are provided by the Resource Identification Portal. Many commonly used research resources already have designated RRIDs. The portal also provides authors links so that they can quickly register a new resource and obtain an RRID.

Clinical Trial Registration

The World Health Organization (WHO) definition of a clinical trial is "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes". The WHO defines health interventions as “A health intervention is an act performed for, with or on behalf of a person or population whose purpose is to assess, improve, maintain, promote or modify health, functioning or health conditions” and a health-related outcome is generally defined as a change in the health of a person or population as a result of an intervention.

To ensure the integrity of the reporting of patient-centered trials, authors must register prospective clinical trials (phase II to IV trials) in suitable publicly available repositories. For example www.clinicaltrials.gov or any of the primary registries that participate in the WHO International Clinical Trials Registry Platform.

The trial registration number (TRN) and date of registration should be included as the last line of the manuscript abstract.

For clinical trials that have not been registered prospectively, authors are encouraged to register retrospectively to ensure the complete publication of all results. The trial registration number (TRN), date of registration and the words 'retrospectively registered’ should be included as the last line of the manuscript abstract.

Standards of reporting

Springer Nature advocates complete and transparent reporting of biomedical and biological research and research with biological applications. Authors are recommended to adhere to the minimum reporting guidelines hosted by the EQUATOR Network when preparing their manuscript.

Exact requirements may vary depending on the journal; please refer to the journal’s Instructions for Authors.

Checklists are available for a number of study designs, including:

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Case reports (CARE)

Clinical practice guidelines (AGREE) and (RIGHT)

Qualitative research (SRQR) and (COREQ)

Animal pre-clinical studies (ARRIVE)

Quality improvement studies (SQUIRE)

Economic evaluations (CHEERS)

Summary of requirements

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Ethics approval'.

Examples of statements to be used when ethics approval has been obtained:

• All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Medical University of A (No. ...).

• This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University B (Date.../No. ...).

• Approval was obtained from the ethics committee of University C. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

• The questionnaire and methodology for this study was approved by the Human Research Ethics committee of the University of D (Ethics approval number: ...).

Examples of statements to be used for a retrospective study:

• Ethical approval was waived by the local Ethics Committee of University A in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

• This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the IRB of XYZ who determined that our study did not need ethical approval. An IRB official waiver of ethical approval was granted from the IRB of XYZ.

• This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of University B approved this study.

Examples of statements to be used when no ethical approval is required/exemption granted:

• This is an observational study. The XYZ Research Ethics Committee has confirmed that no ethical approval is required.

• The data reproduced from Article X utilized human tissue that was procured via our Biobank AB, which provides de-identified samples. This study was reviewed and deemed exempt by our XYZ Institutional Review Board. The BioBank protocols are in accordance with the ethical standards of our institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Authors are responsible for correctness of the statements provided in the manuscript. See also Authorship Principles. The Editor-in-Chief reserves the right to reject submissions that do not meet the guidelines described in this section.

Back to top ↑

Informed consent

All individuals have individual rights that are not to be infringed. Individual participants in studies have, for example, the right to decide what happens to the (identifiable) personal data gathered, to what they have said during a study or an interview, as well as to any photograph that was taken. This is especially true concerning images of vulnerable people (e.g. minors, patients, refugees, etc) or the use of images in sensitive contexts. In many instances authors will need to secure written consent before including images.

Identifying details (names, dates of birth, identity numbers, biometrical characteristics (such as facial features, fingerprint, writing style, voice pattern, DNA or other distinguishing characteristic) and other information) of the participants that were studied should not be published in written descriptions, photographs, and genetic profiles unless the information is essential for scholarly purposes and the participant (or parent/guardian if the participant is a minor or incapable or legal representative) gave written informed consent for publication. Complete anonymity is difficult to achieve in some cases. Detailed descriptions of individual participants, whether of their whole bodies or of body sections, may lead to disclosure of their identity. Under certain circumstances consent is not required as long as information is anonymized and the submission does not include images that may identify the person.

Informed consent for publication should be obtained if there is any doubt. For example, masking the eye region in photographs of participants is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic profiles, authors should provide assurance that alterations do not distort meaning.

Exceptions where it is not necessary to obtain consent:

• Images such as x rays, laparoscopic images, ultrasound images, brain scans, pathology slides unless there is a concern about identifying information in which case, authors should ensure that consent is obtained.

• Reuse of images: If images are being reused from prior publications, the Publisher will assume that the prior publication obtained the relevant information regarding consent. Authors should provide the appropriate attribution for republished images.

Consent and already available data and/or biologic material

Regardless of whether material is collected from living or dead patients, they (family or guardian if the deceased has not made a pre-mortem decision) must have given prior written consent. The aspect of confidentiality as well as any wishes from the deceased should be respected.

Data protection, confidentiality and privacy

When biological material is donated for or data is generated as part of a research project authors should ensure, as part of the informed consent procedure, that the participants are made aware what kind of (personal) data will be processed, how it will be used and for what purpose. In case of data acquired via a biobank/biorepository, it is possible they apply a broad consent which allows research participants to consent to a broad range of uses of their data and samples which is regarded by research ethics committees as specific enough to be considered "informed". However, authors should always check the specific biobank/biorepository policies or any other type of data provider policies (in case of non-bio research) to be sure that this is the case.

Consent to Participate

For all research involving human subjects, freely-given, informed consent to participate in the study must be obtained from participants (or their parent or legal guardian in the case of children under 16) and a statement to this effect should appear in the manuscript. In the case of articles describing human transplantation studies,

authors must include a statement declaring that no organs/tissues were obtained from prisoners and must also name the institution(s)/clinic(s)/department(s) via which organs/tissues were obtained. For manuscripts reporting studies involving vulnerable groups where there is the potential for coercion or where consent may not have been fully informed, extra care will be taken by the editor and may be referred to the Springer Nature Research Integrity Group.

Consent to Publish

Individuals may consent to participate in a study, but object to having their data published in a journal article. Authors should make sure to also seek consent from individuals to publish their data prior to submitting their paper to a journal. This is in particular applicable to case studies. A consent to publish form can be found

here. (Download docx, 36 kB)

Summary of requirements

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Consent to participate' and/or 'Consent to publish'. Other declarations include Funding, Conflicts of interest/competing interests, Ethics approval, Consent, Data and/or Code availability and Authors' contribution statements.

Please see the various examples of wording below and revise/customize the sample statements according to your own needs.

Sample statements for **"Consent to participate"**:

Informed consent was obtained from all individual participants included in the study.

Informed consent was obtained from legal guardians.

Written informed consent was obtained from the parents.

Verbal informed consent was obtained prior to the interview.

Sample statements for **"Consent to publish"**:

The authors affirm that human research participants provided informed consent for publication of the images in Figure(s) 1a, 1b and 1c.

The participant has consented to the submission of the case report to the journal.

Patients signed informed consent regarding publishing their data and photographs.

Sample statements if identifying information about participants is available in the article:

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Authors are responsible for correctness of the statements provided in the manuscript. See also Authorship Principles. The Editor-in-Chief reserves the right to reject submissions that do not meet the guidelines described in this section.

Images will be removed from publication if authors have not obtained informed consent or the paper may be removed and replaced with a notice explaining the reason for removal.

Back to top

Authorship principles

These guidelines describe authorship principles and good authorship practices to which prospective authors should adhere to.

Authorship clarified

The Journal and Publisher assume all authors agreed with the content and that all gave explicit consent to submit and that they obtained consent from the responsible authorities at the institute/organization where the work has been carried out, **before** the work is submitted.

The Publisher does not prescribe the kinds of contributions that warrant authorship. It is recommended that authors adhere to the guidelines for authorship that are applicable in their specific research field. In absence of specific guidelines it is recommended to adhere to the following guidelines*:

All authors whose names appear on the submission

1) made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work;

2) drafted the work or revised it critically for important intellectual content;

3) approved the version to be published; and

4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

* Based on/adapted from:

ICMJE, Defining the Role of Authors and Contributors.

Transparency in authors' contributions and responsibilities to promote integrity in scientific publication, McNutt at all, PNAS February 27, 2018

Disclosures and declarations

All authors are requested to include information regarding sources of funding, financial or non-financial interests, study-specific approval by the appropriate ethics committee for research involving humans and/or animals, informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals (as appropriate).

The decision whether such information should be included is not only dependent on the scope of the journal, but also the scope of the article. Work submitted for publication may have implications for public health or general welfare and in those cases it is the responsibility of all authors to include the appropriate disclosures and declarations.

Data transparency

All authors are requested to make sure that all data and materials as well as software application or custom code support their published claims and comply with field standards. Please note that journals may have individual policies on (sharing) research data in concordance with disciplinary norms and expectations.

Role of the Corresponding Author

One author is assigned as Corresponding Author and acts on behalf of all co-authors and ensures that questions related to the accuracy or integrity of any part of the work are appropriately addressed.

The Corresponding Author is responsible for the following requirements:

- ensuring that all listed authors have approved the manuscript before submission, including the names and order of authors;
- managing all communication between the Journal and all co-authors, before and after publication;*
- providing transparency on re-use of material and mention any unpublished material (for example manuscripts in press) included in the manuscript in a cover letter to the Editor;
- making sure disclosures, declarations and transparency on data statements from all authors are included in the manuscript as appropriate (see above).

* The requirement of managing all communication between the journal and all co-authors during submission and proofing may be delegated to a Contact or Submitting Author. In this case please make sure the Corresponding Author is clearly indicated in the manuscript.

Author contributions

In absence of specific instructions and in research fields where it is possible to describe discrete efforts, the Publisher recommends authors to include contribution statements in the work that specifies the contribution of every author in order to promote transparency. These contributions should be listed at the separate title page.

Examples of such statement(s) are shown below:

• Free text:

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [full name], [full name] and [full name]. The first draft of the manuscript was written by [full name] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Example: CRediT taxonomy:

• Conceptualization: [full name], …; Methodology: [full name], …; Formal analysis and investigation: [full name], …; Writing - original draft preparation: [full name, …]; Writing - review and editing: [full name], …; Funding acquisition: [full name], …; Resources: [full name], …; Supervision: [full name],….

For **review articles** where discrete statements are less applicable a statement should be included who had the idea for the article, who performed the literature search and data analysis, and who drafted and/or critically revised the work.

For articles that are based primarily on the **student's dissertation or thesis**, it is recommended that the student is usually listed as principal author:

A Graduate Student's Guide to Determining Authorship Credit and Authorship Order, APA Science Student Council 2006

Affiliation

The primary affiliation for each author should be the institution where the majority of their work was done. If an author has subsequently moved, the current address may additionally be stated. Addresses will not be updated or changed after publication of the article.

Changes to authorship

Authors are strongly advised to ensure the correct author group, the Corresponding Author, and the order of authors at submission. Changes of authorship by adding or deleting authors, and/or changes in Corresponding Author, and/or changes in the sequence of authors are **not** accepted **after acceptance** of a manuscript.

- **Please note that author names will be published exactly as they appear on the accepted submission!**

Please make sure that the names of all authors are present and correctly spelled, and that addresses and affiliations are current.

Adding and/or deleting authors at revision stage are generally not permitted, but in some cases it may be warranted. Reasons for these changes in authorship should be explained. Approval of the change during revision is at the discretion of the Editor-in-Chief. Please note that journals may have individual policies on adding and/or deleting authors during revision stage.

Author identification

Authors are recommended to use their ORCID ID when submitting an article for consideration or acquire an ORCID ID via the submission process.

Deceased or incapacitated authors

For cases in which a co-author dies or is incapacitated during the writing, submission, or peer-review process, and the co-authors feel it is appropriate to include the author, co-authors should obtain approval from a (legal) representative which could be a direct relative.

Authorship issues or disputes

In the case of an authorship dispute during peer review or after acceptance and publication, the Journal will not be in a position to investigate or adjudicate. Authors will be asked to resolve the dispute themselves. If they are unable the Journal reserves the right to withdraw a manuscript from the editorial process or in case of a published paper raise the issue with the authors' institution(s) and abide by its guidelines.

Confidentiality

Authors should treat all communication with the Journal as confidential which includes correspondence with direct representatives from the Journal such as Editors-in-Chief and/or Handling Editors and reviewers' reports unless explicit consent has been received to share information.

Back to top ↑

Compliance with Ethical Standards

To ensure objectivity and transparency in research and to ensure that accepted principles of ethical and professional conduct have been followed, authors should include information regarding sources of funding, potential conflicts of interest (financial or non-financial), informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals.

Authors should include the following statements (if applicable) in a separate section entitled "Compliance with Ethical Standards" when submitting a paper:

- Disclosure of potential conflicts of interest
- Research involving Human Participants and/or Animals
- Informed consent

Please note that standards could vary slightly per journal dependent on their peer review policies (i.e. single or double blind peer review) as well as per journal subject discipline. Before submitting your article check the instructions following this section carefully.

The corresponding author should be prepared to collect documentation of compliance with ethical standards and send if requested during peer review or after publication.

The Editors reserve the right to reject manuscripts that do not comply with the above-mentioned guidelines. The author will be held responsible for false statements or failure to fulfill the above-mentioned guidelines.

Back to top ↑

Conflicts of Interest / Competing Interests

Authors are requested to disclose interests *that are directly or indirectly related to the work submitted for publication.* Interests within the last 3 years of beginning the work (conducting the research and preparing the work for submission) should be reported. Interests outside the 3-year time frame must be disclosed if they could reasonably be perceived as influencing the submitted work. Disclosure of interests provides a complete and transparent process and helps readers form their own judgments of potential bias. This is not meant to imply that a financial relationship with an organization that sponsored the research or compensation received for consultancy work is inappropriate.

Interests that should be considered and disclosed but are not limited to the following:

Funding: Research grants from funding agencies (please give the research funder and the grant number) and/or research support (including salaries, equipment, supplies, reimbursement for attending symposia, and other expenses) by organizations that may gain or lose financially through publication of this manuscript.

Employment: Recent (while engaged in the research project), present or anticipated employment by any organization that may gain or lose financially through publication of this manuscript. This includes multiple affiliations (if applicable).

Financial interests: Stocks or shares in companies (including holdings of spouse and/or children) that may gain or lose financially through publication of this manuscript; consultation fees or other forms of remuneration from organizations that may gain or lose financially; patents or patent applications whose value may be affected by publication of this manuscript.

It is difficult to specify a threshold at which a financial interest becomes significant, any such figure is necessarily arbitrary, so one possible practical guideline is the following: "Any undeclared financial interest that could embarrass the author were it to become publicly known after the work was published."

Non-financial interests: In addition, authors are requested to disclose interests that go beyond financial interests that could impart bias on the work submitted for publication such as professional interests, personal relationships or personal beliefs (amongst others). Examples include, but are not limited to: position on editorial board, advisory board or board of directors or other type of management relationships; writing and/or consulting for educational purposes; expert witness; mentoring relations; and so forth.

Primary research articles require a disclosure statement. Review articles present an expert synthesis of evidence and may be treated as an authoritative work on a subject. Review articles therefore require a disclosure statement.Other article types such as editorials, book reviews, comments (amongst others) may, dependent on their content, require a disclosure statement. If you are unclear whether your article type requires a disclosure statement, please contact the Editor-in-Chief.

Please note that, in addition to the above requirements, funding information (given that funding is a potential conflict of interest (as mentioned above)) needs to be disclosed upon submission of the manuscript in the peer review system. This information will automatically be added to the Record of CrossMark, however it is **not added** to the manuscript itself. Under 'summary of requirements' (see below) funding information should be included in the '**Declarations**' section.

Summary of requirements

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Funding' and/or 'Conflicts of interests'/'Competing interests'. Other declarations include Ethics approval, Consent, Data, Material and/or Code availability and Authors' contribution statements.

Please see the various examples of wording below and revise/customize the sample statements according to your own needs.

When all authors have the same (or no) conflicts and/or funding it is sufficient to use one blanket statement.

Examples of statements to be used when funding has been received:

- Partial financial support was received from [...]
- The research leading to these results received funding from […] under Grant Agreement No[…].
- This study was funded by […]
- This work was supported by […] (Grant numbers […] and […]

Examples of statements to be used when there is no funding:

- The authors did not receive support from any organization for the submitted work.
- No funding was received to assist with the preparation of this manuscript.
- No funding was received for conducting this study.
- No funds, grants, or other support was received.

Examples of statements to be used when there are interests to declare:

- **Financial interests:** Author A has received research support from Company A. Author B has received a speaker honorarium from Company Wand owns stock in Company X. Author C is consultant to company Y.

  Non-financial interests: Author C is an unpaid member of committee Z.

- **Financial interests:** The authors declare they have no financial interests.

  Non-financial interests: Author A is on the board of directors of Y and receives no compensation as member of the board of directors.

- **Financial interests:** Author A received a speaking fee from Y for Z. Author B receives a salary from association X. X where s/he is the Executive Director.

  Non-financial interests: none.

- **Financial interests:** Author A and B declare they have no financial interests. Author C has received speaker and consultant honoraria from Company M and Company N. Dr. C has received speaker honorarium and research funding from Company M and Company O. Author D has received travel support from Company O.

  Non-financial interests: Author D has served on advisory boards for Company M, Company N and Company O.

Examples of statements to be used when authors have nothing to declare:

- The authors have no relevant financial or non-financial interests to disclose.
- The authors have no conflicts of interest to declare that are relevant to the content of this article.
- All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.
- The authors have no financial or proprietary interests in any material discussed in this article.

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Back to top ↑

Research involving human participants, their data or biological material

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Case reports require ethics approval. Most institutions will have specific policies on this subject. Authors should check with their institution to make sure they are complying with the specific requirements of their institution and seek ethics approval where needed. Authors should be aware to secure informed consent from the individual (or parent or guardian if the participant is a minor or incapable) See also section on **Informed Consent**.

Cell lines

If human cells are used, authors must declare in the manuscript: what cell lines were used by describing the source of the cell line, including when and from where it was obtained, whether the cell line has recently been authenticated and by what method. If cells were bought from a life science company the following need to be given in the manuscript: name of company (that provided the cells), cell type, number of cell line, and batch of cells.

It is recommended that authors check the NCBI database for misidentification and contamination of human cell lines. This step will alert authors to possible problems with the cell line and may save considerable time and effort.

Further information is available from the International Cell Line Authentication Committee (ICLAC).

Authors should include a statement that confirms that an institutional or independent ethics committee (including the name of the ethics committee) approved the study and that informed consent was obtained from the donor or next of kin.

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Examples:

Organism: *Filip1*$^{tm1a(KOMP)Wtsi}$ **RRID:MMRRC_055641-UCD**

Cell Line: RST307 cell line **RRID:CVCL_C321**

Antibody: Luciferase antibody DSHB Cat# LUC-3, **RRID:AB_2722109**

Plasmid: mRuby3 plasmid **RRID:Addgene_104005**

Software: ImageJ Version 1.2.4 **RRID:SCR_003070**

RRIDs are provided by the Resource Identification Portal. Many commonly used research resources already have designated RRIDs. The portal also provides authors links so that they can quickly register a new resource and obtain an RRID.

Clinical Trial Registration

The World Health Organization (WHO) definition of a clinical trial is "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes". The WHO defines health interventions as “A health intervention is an act performed for, with or on behalf of a person or population whose purpose is to assess, improve, maintain, promote or modify health, functioning or health conditions” and a health-related outcome is generally defined as a change in the health of a person or population as a result of an intervention.

To ensure the integrity of the reporting of patient-centered trials, authors must register prospective clinical trials (phase II to IV trials) in suitable publicly available repositories. For example www.clinicaltrials.gov or any of the primary registries that participate in the WHO International Clinical Trials Registry Platform.

The trial registration number (TRN) and date of registration should be included as the last line of the manuscript abstract.

For clinical trials that have not been registered prospectively, authors are encouraged to register retrospectively to ensure the complete publication of all results. The trial registration number (TRN), date of registration and the words 'retrospectively registered’ should be included as the last line of the manuscript abstract.

Standards of reporting

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Diagnostic/prognostic studies (STARD) and (TRIPOD)

Case reports (CARE)

Clinical practice guidelines (AGREE) and (RIGHT)

Qualitative research (SRQR) and (COREQ)

Animal pre-clinical studies (ARRIVE)

Quality improvement studies (SQUIRE)

Economic evaluations (CHEERS)

Summary of requirements

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Ethics approval'.

Examples of statements to be used when ethics approval has been obtained:

• All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Medical University of A (No. ...).

• This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University B (Date.../No. ...).

• Approval was obtained from the ethics committee of University C. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

• The questionnaire and methodology for this study was approved by the Human Research Ethics committee of the University of D (Ethics approval number: ...).

Examples of statements to be used for a retrospective study:

• Ethical approval was waived by the local Ethics Committee of University A in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

• This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the IRB of XYZ who determined that our study did not need ethical approval. An IRB official waiver of ethical approval was granted from the IRB of XYZ.

• This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of University B approved this study.

Examples of statements to be used when no ethical approval is required/exemption granted:

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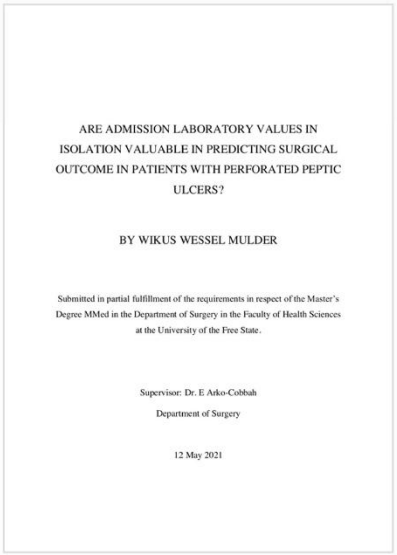

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BY WIKUS WESSEL MULDER

Submitted in partial fulfillment of the requirements in respect of the Master's Degree MMed in the Department of Surgery in the Faculty of Health Sciences at the University of the Free State.

Supervisor: Dr. E Arko-Cobbah

Department of Surgery

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