

**Point-of-Care Testing and The Predictive Value of Serum Myoglobin as a Prognostic
Marker for Acute Kidney Injury Requiring Dialysis in Rhabdomyolysis Caused by
Sjambok and/or Community Assault Blunt Injuries**

Dr Cynthia T.Y CHEUNG



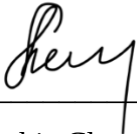
UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

A Research Report submitted to the Faculty of Health Science, University of Witwatersrand,
in fulfilment of the requirements for the degree of Masters in Surgery
MMed (Surg)

Johannesburg 2022

DECLARATION

I, Dr Cynthia Cheung, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the Department of Surgery at University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



Dr Cynthia Cheung

FCS(SA), MBChB (UCT)

DEDICATION

To my late parents, KS Cheung and LF Leung

ACKNOWLEDGEMENT

My supervisors Professor G Candy, Professor F Plani, and Dr V Jennings, for all the support and advice throughout this research project.

Professor M Smith, Head of Department of Surgery, for believing in me and for all the teaching, support, and guidance throughout my surgical career.

Dr Q Isaacs who assisted with some of the data collection.

Lastly, to the patients who participated in the study, for contributing to the knowledge and advancement of science.

ABSTRACT

Background:

Rhabdomyolysis and crush syndrome were initially described where patients were trapped under buildings and rubble for an extended period following disasters such as earthquakes and bombings. Clinical management has been guided from data based on these patients' injuries and many predictors have been proposed to predict prognosis, but there is no gold standard. In South Africa, crush injuries arising from community assault (CA) and sjambok injuries have a different profile to those from disaster crush injuries. This study determined the prognostic value of different predictive markers including serum myoglobin for the development of Acute Kidney Injury (AKI) due to rhabdomyolysis caused by sjambok and/or CA blunt injuries.

Methods:

Prospective observational study of all sjambok and/or CA injury patients admitted for in-patient management at Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto – Gauteng, South Africa over 6 months from May to November 2018.

Results:

The mean patient age was 29 years and 95% were male. The total length of hospital stay ranged 1-27 days (mean 5.1), with median length of stay of 1 day longer in the group with elevated creatinine. Creatinine on admission and the worst creatinine correlated with pH, bicarbonate, lactate, and myoglobin ($p < 0.001$); with the best measure being myoglobin ($r = +0.61$ on admission and $r = +0.41$ with worst creatinine, $p < 0.001$).

Conclusions:

Our study suggested that venous bicarbonate and serum myoglobin should be used as predictors of AKI and risk of Acute Renal Failure (ARF) in crush injuries due to community assault and sjambok injuries. A larger-scale study would be necessary to validate these markers and to guide clinical practice.

TABLE OF CONTENTS

<i>Declaration.....</i>	<i>ii</i>
<i>Dedication</i>	<i>iii</i>
<i>Acknowledgement.....</i>	<i>iv</i>
<i>Abstract</i>	<i>v</i>
<i>Table of Contents.....</i>	<i>vi</i>
<i>List of Abbreviations</i>	<i>viii</i>
<i>List of Tables, Graph, and Figure</i>	<i>ix</i>
<i>Research Report</i>	<i>1</i>
<i>Introduction</i>	<i>2</i>
Crush Injury.....	2
Crush Injury Markers	3
Crush Injury Management.....	5
South African Burden of Trauma	6
Acute Kidney Injury.....	7
Study Aims and Objectives	7
<i>Methods.....</i>	<i>7</i>
Study design	7
Ethics.....	8
Setting.....	8
Data Collection	8
Data Analysis.....	9
<i>Results.....</i>	<i>9</i>
<i>Discussion.....</i>	<i>10</i>
<i>Limitations.....</i>	<i>11</i>
<i>Conclusion</i>	<i>12</i>
<i>Conflict of Interest</i>	<i>12</i>

Funding	12
<i>Tables, Graph, and Figure</i>	<i>12</i>
<i>Reference List</i>	<i>17</i>
<i>Appendix A: Protocol</i>	<i>20</i>
<i>Appendix B: Protocol Assessment Form.....</i>	<i>32</i>
<i>Appendix C: Ethics Clearance</i>	<i>35</i>
<i>Appendix D: Supervisor Declaration</i>	<i>36</i>
<i>Appendix E: Data Collection Sheet.....</i>	<i>38</i>
<i>Appendix F: Turnitin Report</i>	<i>39</i>

LIST OF ABBREVIATIONS

AKI = Acute kidney injury

ARF = Acute renal failure

CA = community assault

CHBAH = Chris Hani Baragwanath Academic Hospital

CK = serum creatine kinase

GCS = Glasgow Coma Scale

s-Cr = serum creatinine

s-Mgb = serum myoglobin

v-HCO₃ = venous bicarbonate

TBSA = Total Body Surface Area

LIST OF TABLES, GRAPH, AND FIGURE

Table 1: Patient demographics and injury pattern upon admission.

Table 2: Biochemical results at admission and after 24 hours

Table 3: Patient demographics and biochemical results dichotomized by creatinine concentration

Table 4: Correlation of creatinine measure with different predictors on admission

Graph 1: Correlation of admission creatinine with admission myoglobin

Figure 1: RIFLE Criteria

RESEARCH REPORT

This research report is written in the submission format for the South African Journal of Surgery.

POINT-OF-CARE TESTING AND THE PREDICTIVE VALUE OF SERUM MYOGLOBIN AS A PROGNOSTIC MARKER FOR ACUTE KIDNEY INJURY REQUIRING DIALYSIS IN RHABDOMYOLYSIS CAUSED BY SJAMBOK AND/OR COMMUNITY ASSAULT BLUNT INJURIES

Cynthia T.Y Cheung, Geoffrey P Candy, Frank Plani, Vicky Jennings

Correspondence: CTY Cheung – cheung.cty@gmail.com

MMed(Surg) – student number: 0500196D, Department of General Surgery

Background:

Rhabdomyolysis and crush syndrome were initially described where patients were trapped under buildings and rubble for an extended period following disasters such as earthquakes and bombings. Clinical management has been guided from data based on these patients' injuries and many predictors have been proposed to predict prognosis, but there is no gold standard. In South Africa, crush injuries arising from community assault (CA) and sjambok injuries have a different profile to those from disaster crush injuries. This study determined the prognostic value of different predictive markers including serum myoglobin for the development of Acute Kidney Injury (AKI) due to rhabdomyolysis caused by sjambok and/or CA blunt injuries.

Methods:

Prospective observational study of all sjambok and/or CA injury patients admitted for in-patient management at Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto – Gauteng, South Africa over 6 months from May to November 2018.

Results:

The mean patient age was 29 years and 95% were male. The total length of hospital stay ranged 1-27 days (mean 5.1), with median length of stay of 1 day longer in the group with elevated

creatinine. Creatinine on admission and the worst creatinine correlated with pH, bicarbonate, lactate, and myoglobin ($p < 0.001$); with the best measure being myoglobin ($r = +0.61$ on admission and $r = +0.41$ with worst creatinine, $p < 0.001$).

Conclusions:

Our study suggested that venous bicarbonate and serum myoglobin should be used as predictors of AKI and risk of Acute Renal Failure (ARF) in crush injuries due to community assault and sjambok injuries. A larger-scale study would be necessary to validate these markers and to guide clinical practice.

INTRODUCTION

Crush Injury

The Royal College of Surgeons of Edinburgh defines crush injury as ‘...a direct injury resulting from crush. Crush syndrome is the systemic manifestation of muscle cell damage resulting from pressure or crushing’.¹

Rhabdomyolysis and crush syndrome were initially described following disasters such as earthquakes and bombings, where patients were trapped under buildings and rubble for an extended period. Rhabdomyolysis results from the traumatic breakdown of skeletal muscle following muscle compression and ischaemia with leakage from sarcolemmal membrane and the release of the muscle contents into the circulation.¹⁻² This causes various metabolic and electrolyte derangements.³ Myoglobin released into the circulation concentrates in the glomeruli and precipitates in an acidic environment to form renal casts. These casts obstruct the renal glomeruli resulting in acute tubular necrosis and the consequent acute kidney injury (AKI).³⁻⁵ Rhabdomyolysis may also be the result of non-traumatic causes such as seizures, metabolic disorders, infections and toxins.

Data from earthquake and bombing crush injuries appear different to the profile of injury seen in South Africa where the majority are caused by sjamboks and community assaults (CA). A sjambok is defined as ‘a long, stiff whip made of leather, originally carved from dried elephant or rhinoceros hides’.⁶ Injuries are caused when the victim is whipped with a sjambok. CA is a

form of severe beating by the community towards an individual by punching or kicking and using objects such as sticks, bricks, and stones.

Crush Injury Markers

Rhabdomyolysis has no universal definition, however, it is often defined as creatine kinase (CK) level that is 5 times the upper limit of normal.⁷ Many markers have been evaluated for predicting AKI caused by rhabdomyolysis but there is no consensus on which may be regarded as the gold standard. Many studies also included a heterogeneous group of patients, which may introduce selection bias.

Vanmassenhove et al.⁸ reviewed the literature of markers for AKI following crush injury and showed improved prognostic value when the timing and cause of injury were known.⁸ However, in South Africa many crush injury victims have a delayed presentation to the hospital and often the time of injury is not known. Furthermore, many markers are elevated in both AKI and other comorbid or concurrent illnesses which diminish the specificity of these markers. Finally, heterogeneity of a study population would further limit the value of the marker in predicting AKI.⁸

CK has been used as a surrogate marker of myoglobin, which is regarded as the causative agent in rhabdomyolysis. CK above 500 u/l was significant for rhabdomyolysis,⁹ with levels above 5 000 u/l being associated with an increased risk of renal dysfunction¹⁰ and above 10 000 u/l being a significant predictor of acute renal failure¹¹(ARF). Fernandez et al.¹² suggested a cut-off CK above 1 000 u/l may be associated with missed cases of rhabdomyolysis, without major complications.¹²

In rhabdomyolysis, myoglobin is released from damaged muscles resulting in tubular damage. Serum myoglobin (s-Mgb) peaks on average 16 hours earlier, and is eliminated faster than s-CK. S-Mgb elimination is not dependent on glomerular filtration rate.¹³⁻¹⁵ At 90% sensitivity, elevated s-Mgb and CK have a 62% and 24% specificity in the development of ARF respectively.¹⁵ CK correlated with the severity of rhabdomyolysis, but serum creatinine (s-Cr) correlated better with s-Mgb when compared to s-CK. S-Mgb therefore better predicted AKI and the need for dialysis.¹⁶ S-Mgb level has been proposed as being more accurate for

rhabdomyolysis and the development of AKI^{14,17} and s-Mgb level above 5 254 µg/l is suggestive of an increased risk of AKI.¹³ Kasaoka et al.¹⁸ showed that the peak value of s-Mgb on day two was superior in prognosticating ARF from rhabdomyolysis, compared to s-CK.¹⁸ Furthermore, Mikkelsen and Toft showed CK above 100 000 u/l or myoglobin above 61 000 µg/L were associated with 100% development of ARF from rhabdomyolysis of various causes including trauma, coma, seizures, arterial occlusion, and sepsis.¹⁵

Fernandez et al.¹² determined causes of rhabdomyolysis and predictors of ARF in emergency department patients and concluded that initial s-Cr was the only significant predictor of ARF.¹² However, a similar study of an ICU population with CK levels above 10 000 u/l, concluded that initial s-Cr did not predict ARF.¹¹ Serum urea and creatinine measures of renal function cannot be used to predict renal failure as these are often abnormal for reasons other than crush injury.¹⁹

In a prospective study from KwaZulu Natal (KZN), South Africa, Muckart et al.¹⁹, suggested a venous bicarbonate level (v-HCO₃) below 17mmol/L, together with an admission urine dipstick positive for haemoglobin, was indicative of severe injury and identified patients at risk of renal failure.¹⁹ Skinner et al.²⁰ at Edendale Hospital (KZN) hypothesized that following CA crush injuries: 1) damaged muscle undergo reperfusion and release lactate; 2) delay in obtaining treatment results in sequestration of fluid in the damaged muscles with relative hypovolaemia and hyperlactatemia; 3) intra-renal compartment syndrome then results from decreased renal blood flow and reduced glomerular filtration and peritubular vascular supply; and finally 4) the increased metabolic demands of the kidneys reduces renal clearance of lactate. The research showed that patients with AKI had lower pH, lower base excess, and higher lactate levels on presentation. However, the correlation of hyperlactataemia and incidence of AKI was not statistically significant, as was the relationship between the delay in presentation and the development of AKI.²⁰

CK, v-HCO₃, s-Cr, and total body surface area (TBSA) of injury have previously been shown to be good prognostic markers of AKI in rhabdomyolysis. Furthermore, s-Mgb appears to be a promising biomarker.^{13,15,18}

Crush Injury Management

Crush injury results in rhabdomyolysis and causes AKI by several mechanisms. The aim of standard of care management is to increase renal blood flow, increase urine output, and prevent any ongoing skeletal muscle damage. The mainstay of treatment is thus intravenous fluid to restore renal perfusion and increase urine output.²¹

A systematic review of studies conducted between 1946 and 2020 determining fluids used in crush injury management was limited by the 1) few studies available; 2) low numbers of patients in the studies; 3) inconsistency in patient management; and 4) observational nature of most studies. The management guideline for resuscitation of rhabdomyolysis recommended the aggressive use of intravenous fluid but recommended against the use of bicarbonate and mannitol. There was no recommendation on the volume of fluid to be administered but rather fluid therapy to achieve a urine output of 2-3 ml/kg/hr was recommended. Fluids were to be continued until CK level decreased below 5 000-10 000 u/l or urine was cleared of myoglobin.⁷

Dialysis was to be considered if fluid therapy was ineffective. Myoglobin is a large non-spherical molecule with electrical charges, which makes it difficult to be filtered by conventional dialysis techniques.²² It has been recommended that the dialysis mode in rhabdomyolysis be continuous venovenous haemofiltration, continuous venovenous haemodiafiltrations, or super-high flux membrane dialysis. Extended dialysis with a high molecular weight cut-off membrane was most effective in removing myoglobin.²³ Premru et al.¹⁶ recommended that dialysis should be considered in patients with s-Mgb above 15 000-20 000 µg/l.¹⁶ In a resource limited setting such as South Africa the indication and selection criteria for offering dialysis needs to be carefully analysed. A retrospective review of patients receiving acute dialysis at Chris Hani Baragwanath Academic Hospital (CHBAH) over a 2-year period showed that only 3% of the dialysed patients were due to rhabdomyolysis complicated with AKI. In agreement with the literature, the study also showed that a lower serum urea at time of dialysis initiation correlated with a lower 60-day mortality rate.²⁴ Skinner et al.²⁵, in KZN found a surprisingly high 38% of AKI in trauma patients received dialysis due to the readily availability of a protocol and dialysis for their crush injury patients.²⁵

South African Burden of Trauma

Sjambok and CA injuries are frequently observed in South Africa, and especially in the Trauma Unit of Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto – Johannesburg, Gauteng. Sjambok and CA injuries are usually a result of the community assaulting the alleged criminals either as punishment or as a warning to other criminals.²⁶ There is limited data on crush injury caused by sjambok and CA injuries alone.

South African statistics show that interpersonal violence contributes to a significant burden of hospital admissions and these numbers are increasing. In a KZN study, interpersonal violence accounted for 65% of trauma admissions, of which 8% were due to CA.²⁷ A tertiary hospital in Pretoria found 12% of trauma admissions were CA cases.²⁸ CA victims were usually young, with average age 25-31 years, 95-97% males, and 99% black Africans.²⁷⁻²⁸ Ninety-two percent of injuries arising from CAs were blunt force trauma, and 8% mixed blunt and penetrating injuries. In 50% of cases the weapons could be identified, and multiple weapons were identified in 3% of cases.²⁷

In South Africa, it has been observed that treatment may be delayed as the injured patients often hide for many hours²⁶ before presenting for medical treatment or may be found unconscious and are brought to hospital. Early aggressive fluid therapy has been shown to reduce the incidence of ARF and therefore morbidity and mortality.^{10,19,26} It is therefore necessary for the clinician to have a high index of suspicion¹⁹ and make use of markers to identify patients at risk of developing ARF so that they can be appropriately managed.^{3,10,19,26}

CA cases have a higher mortality rate than non-CA interpersonal violence cases (17.3% vs 3%).²⁸ CA does not increase the mortality risk, however, it increases the morbidity rate due to AKI.²⁷ CA victims are more likely to suffer significant musculocutaneous injury with rhabdomyolysis and thus at higher risk of AKI compared to non-CA victims (9% vs 1%).²⁷ However, renal failure due to traumatic rhabdomyolysis only accounted for 7% of trauma deaths.²⁸

Acute Kidney Injury

The RIFLE classification and criteria (Figure 1), based on s-Cr and urine output, has good prognostic value of AKI.²⁹ It classifies the severity of AKI into 3 classes of i) Risk; ii) Kidney Injury and iii) Kidney Failure, and on outcome i) Loss of kidney function, and ii) End-stage kidney disease.

Skinner et al.²⁵, determined the development of AKI in a Trauma Intensive Care Unit in KZN. Fifteen percent of the trauma patients developed AKI, with 57% of the 15% AKI patients having ARF. Patient with AKI had a 57% mortality rate with 79% of these patients being in the renal injury group as per the RIFLE category. In patients with ARF, those due to sjambok injury had a lower mortality than those without sjambok injury. The rate of renal recovery was high following AKI in trauma.²⁵

Study Aims and Objectives

Our study aimed to determine different markers in predicting AKI in patients with blunt crush injuries/syndrome resulting from only sjambok or CA. The study was done at the Trauma Unit of the Chris Hani-Baragwanath Academic Hospital in Soweto, Johannesburg in the Gauteng Province of South Africa.

The objectives were to

- 1) determine which serum markers better predicted AKI in patients following blunt injuries arising after sjambok or CA;
- 2) determine the added predictive value of s-Mgb in identifying such AKI in the South African setting;

A secondary objective was to evaluate the type of fluids used in resuscitation and its relationship to the development of AKI.

METHODS

Study design

A prospective observational study was done over a six-month period from May to November 2018. Twenty more patients were screened and included in the study for a 1 month period in 2019 to achieve a sample size of 100 patients. This was because some enrolled patients had

incomplete data or had been excluded later for incorrect inclusion following subsequent investigations and review of their data. Trauma patients over 18 years old with only sjambok injury or CA who had sustained blunt injuries only were screened for enrolment.

Inclusion criteria: All patients requiring admission for hospital management were included in the study. This was based on their clinical condition. Inclusion criteria for hospital admission included a) CK above 5 000 u/l; b) v-HCO₃ less than 17 mmol/l; c) TBSA above 15%; d) renal impairment based on the RIFLE criteria as evident from initial blood test; and e) any clinical evidence of rhabdomyolysis such as ‘coca-cola’ colour urine, oliguria or anuria.

Exclusion criteria: Patients younger than 18 years old. Rhabdomyolysis due to entrapment. penetrating injuries, motor vehicle accidents, pedestrian vehicle accidents, and previous cerebral vascular accidents were excluded, as were patients with pre-existing paralysis, cardiac disease, ischaemic heart disease, renal disease, or liver disease.

Ethics

Ethics clearance was obtained from the Medical Human Research Ethics Committee of the University of Witwatersrand – Johannesburg, South Africa. Clearance certificate number M170429.

Setting

The study was done at the Trauma Unit of CHBAH in Soweto, Johannesburg. CHBAH is the third largest hospital in the World, spanning across a 233 795m² land, with approximately 3 200 beds and 6 760 staff.³⁰ It is the largest teaching hospital of the University of Witwatersrand.

Data Collection

Data were prospectively collected from admitted patients for admission day and day one post-admission, as well as the outcome of their hospital stay. Collected data included basic demographics, time of the injury, injury type, laboratory and point-of-care test results, and basic patient management questions such as fluids used and the outcome of the patient. Data were collected in the form of a datasheet consisting of tick-boxes, and single or short-answer questions.

Data Analysis

Data was recorded in Microsoft Excel (Microsoft Corporation) and presented in tables and figures. Normally distributed data was presented as mean $\pm$ std or as median and range, or as a log when these data were not normally distributed. Comparisons between groups were made by importing the data into Statistica V13.6. A Student's t-test was used to compare normally distributed data (age, biochemical parameters) with Wilcoxon sign-test used for non-normally distributed data (s-Mgb and CK) with repeated measures to compare variables at admission and on day 1. Data was dichotomised by s-Cr concentrations with s-Cr $\leq$ 114.9 μ mol/L in males and $\leq$ 97.2 μ mol/L in females taken to be normal and above these values to be elevated.³¹ A Pearson's correlation was used to determine association between variables.

RESULTS

One-hundred and twenty-five patients were screened. A total of 105 patients were recruited into the study during the study period, however 7 patients were excluded for data analysis due to incorrect inclusion as per our inclusion criteria. The mean age of our study population was 29 years, of which 95% were male patients. The total length of hospital stay ranged from 1 to 27 days with a mean of 5.1 days (Table 1). The median length of hospital stay was 1 day longer in the group with elevated s-Cr upon admission (Table 3).

The cause of injury was known by 92 patients, 48 being assaulted with various weapons, 13 beaten with only sjamboks, and 31 being both assaulted and beaten with sjamboks. Twenty-eight patients were injured with a single weapon and 49 patients by multiple weapons (Table 1).

Admission and day 1 parameters show improvement in most values suggesting patient recovery. S-Mgb decreased from admission to day 1 confirming that the marker appeared to peak early, while s-CK continued to increase (Table 2).

Dichotomised by admission s-Cr (text and Table 3), patients with elevated s-Cr were older ($p=0.0052$), had lower pH ($p<0.0001$), lower v-HCO₃ ($p=0.0002$), a near 3-fold higher lactate,

increased potassium ($p<0.05$) and a median s-Mgb concentration that was more than 4 times that of patients with normal s-Cr concentrations ($p<0.0001$; Table 3).

Using s-Cr as a measure of renal function during the patients' hospital stay suggested that majority of patients recovered, with a few patients ($n=8$) worsening ($> 20 \mu\text{mol/L}$; median[range] $145.5 [26 - 300 \mu\text{mol/L}]$). S-Cr on admission and the worst s-Cr correlated with pH, bicarbonate, lactate ($p<0.001$), and most significantly with s-Mgb ($r=+0.61$, $p<0.001$; Graph 1). However, when comparing the change of renal functions as an indication of renal injury and risk of renal failure, none of the markers reached statistical significance (Table 4).

Intravenous fluid resuscitation administered were at the discretion of the treating doctor. Types of fluid used for resuscitation were 72% (71 patients) ringers lactate, 10% combination of different fluids, and 9% fluid type were not recorded. Other fluids used included Balsol, 0.9% sodium chloride, Plasmalyte, and Hartman's solution which were given to 3, 3, 1, 1 patients respectively. All patients in the study received high volume fluid resuscitation as per unit protocol under the guidance of the treating doctor. The volume of fluid administered, and urine output were not well recorded, hence analysis of fluids could not be carried out. Sodium bicarbonate and mannitol were administered to a few patients ($n=8$ & 1 respectively) despite the lack of evidence for their use.

Renal dialysis was only offered to 3 patients (3%). Mortality rate in our study population was 5% ($n=5$). Two of the five patients who died had received dialysis. All 5 of the mortalities had elevated s-Cr, markedly elevated s-Mgb, and reduced $v\text{-HCO}_3$. The small number of dialysis and mortality patients in our study prevents any further analysis.

DISCUSSION

The aim of this study was to determine which markers predict the development of AKI in patients with blunt crush injuries/syndrome resulting from only sjambok or CA. Patients were mainly young male patients with no comorbidities, similar to the demographic data of other studies done in South Africa.²⁷⁻²⁸ The overall mean length of hospital stay was 5.1 days and the mortality rate was low, suggesting that the prognosis in this young fit population was good, with majority of patients making a full recovery. This confirms that fluid resuscitation is highly

effective in the management of crush injury.²¹ However, in the patients who had an elevated s-Cr on admission the median length of stay was increased by 1 day.

We assessed multiple potential predictors of AKI in this population. S-Cr although significantly elevated in our population and validated as a general predictor of AKI should not be used due to its non-specificity for crush injury.¹⁹ S-Cr used as a predictor in multiple previous studies⁹⁻¹² was a poor predictor of AKI in our population. Although s-Cr remains elevated for longer, there was no difference in the s-Cr values between patients with normal s-Cr and elevated s-Cr. S-Cr also had no statistically significant correlation with admission or worst s-Cr.

Admission v-HCO₃ levels were lower in patients with an elevated s-Cr compared to patients with normal s-Cr (mean 17.4 vs 21.3; p 0.0002). Furthermore, admission v-HCO₃ showed an inverse correlation with the worst s-Cr during the patients' hospital stay. Admission v-HCO₃ was shown to be a good time-independent prognostic marker for AKI in CA and/or sjambok crush injury in this study. Our study is consistent with the previous study by Muckart et al.¹⁹ that v-HCO₃ can be used to identify patients at risk for AKI.¹⁹

Hyperlactataemia was previously found by Skinner et al.²⁰ not to be a predictor of AKI.²⁰ Our study reached a similar conclusion.

S-Mgb on the other hand appeared to rise early and decline early. It was significantly elevated in patients with elevated s-Cr on admission compared to patients with normal s-Cr (6726 vs 2855, p<0.0001). It correlated better with admission s-Cr than worst s-Cr during the patients' hospital stay. S-Mgb thus may be a good all-time predictor of AKI in CA or sjambok crush injury, and appear to have a better correlation than v-HCO₃.

LIMITATIONS

The concentration of many measured markers is dependent on how long after the injury the marker is measured. However, when presenting at the hospital the patient may not have recalled the time of injury, or was unknown to the person accompanying the patient. As noted, patients may have presented to hospital long after sustaining injury as they hide, fearing further beatings

or may have been unconscious and only found later. In contrast, other patients may have been brought to hospital immediately post-injury by assisting individuals.

The CHBAH Trauma unit is busy and incomplete documentation of clinical records and point-of-care test results affected the quality of the study data recorded. Therefore, the study was conducted prospectively with most data recorded by the investigator upon patient admission to minimise data errors. Management of patients depended upon the treating doctor, which led to variance with respect to the type and volume of fluids administered.

Although our study only included crush injury from CA and/or sjambok injuries, there could have still been other variables such as head injury and long bone fractures that may have affected the predictive serum markers.

CONCLUSION

This study concluded that admission venous bicarbonate and serum myoglobin may predict AKI and risk of ARF in crush injuries from community assault and sjambok injuries. A larger-scale study would validate these markers and may guide clinical practice.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING

No funding source to be declared.

TABLES, GRAPH, AND FIGURE

Table 1: Patient demographics and injury pattern upon admission. Data as numbers (frequency) and mean $\pm$ standard deviation or as median [range]

Parameter	Admission (n)
Age	29.3 $\pm$ 10.7 (98)
Sex M/F (% male)	93/5 (95)
Length of Hospital stay	5.1 $\pm$ 4.2; 4 [1-27]
<u>Mechanism of injury</u>	
- Assault	48
- Sjambok	13
- Assault and Sjambok	31
- Unknown	6
<u>Weapons type</u>	(n=98)
- Single weapon	28
- Multiple weapons	49
- Unknown weapons	21
<u>Weapons used</u>	(n=98)
- Bricks	15
- Stones	13
- Sticks	37
- Punched/Kicked	29
- Sjambok	34
- Others	33
- Unknown	18

Table 2: Biochemical results at admission and after 24 hours. Data as mean±standard deviation or as median [range]

Parameter	Admission (n)	Day 1 (n)	Change: Admission – day1	Difference (p)
pH (units)	7.3±0.2 (94)	7.4±0.1 (63)	0.14±0.17 (62) 0.09 [-0.19-+0.83]	<0.0001
Bicarbonate	19.9±5.0 (94) [6.4-31.4]	25.1±4.1 (63)	5.89±5.92 (62) 4.75 [-5.10-+20.0]	<0.0001
Lactate	4.9±4.4 (90)	2.8±8.6 (61)	-2.27±8.76 (58) -1.85 [-18.2-+55.8]	0.052
Haemoglobin	13.5±2.2 (93)	12.4±11.6 (63)	-2.33±2.15 (60) -2.40 [-6.6-+4.6]	<0.0001
Potassium	4.0±0.7 (95)	4.1±0.7 (80)	0.12±0.99 (79) 0 [-3.6-+3.7]	0.32
Calcium	1.1±0.4 (60)	3.6±15.8 (n=40)	0.04±0.35 (29) -0.02 [-0.61-+1.08]	0.67
Creatinine	106.6±41.6 (98) [49-293]	104.9±83.0 (86) [46-577]	-3.47±63.03 (86) -14.5 [-124.0-+300]	0.86
Myoglobin	4262±4652 (66) 2331 [121-	1764±3214 (32) 380 [61-12814]	-1548±2508 (18) -1391 [-6758-+5254]	0.0005
Creatine kinase	19891] 3640±2766 (89) 2933 [62-11743]	5792±4299 (22) 2539 [140-15015]	1733±3733 (20) 1075 [-3787-+12731]	0.08

Table 3: Patient demographics and biochemical results dichotomized by creatinine concentration normal creatinine $\leq 114.9 \mu\text{mol/L}$ in males and $\leq 97.2 \mu\text{mol/L}$ in females or greater than these values respectively. Data as mean $\pm$ standard deviation or as median [range]

	Admission			Day 1		
Parameter	Normal Cr (n)	Elevated Cr (n)	p	Normal Cr (n)	Elevated Cr (n)	p
Age	27.1 $\pm$ 7.2 (64)	33.4 $\pm$ 14.6 (34)	0.0052	-	-	-
Sex (m/f)	61/3 (64)	32/2 (34)	0.57	-	-	-
LoS (days)	4.3 $\pm$ 3.4 (63)	6.9 $\pm$ 5.1 (29)	0.0002	-	-	-
	4 [1-23]	5 [1-27]				
pH (units)	7.4 $\pm$ 0.1 (61)	7.2 $\pm$ 0.2 (33)	<0.0001	7.4 $\pm$ 0.1 (38)	7.4 $\pm$ 0.1 (25)	0.0397
Bicarbonate	21.3 $\pm$ 4.3 (61)	17.4 $\pm$ 5.2 (33)	0.0002	25.9 $\pm$ 3.3 (38)	23.8 $\pm$ 4.8 (25)	0.0390
Lactate	3.3 $\pm$ 2.5 (35)	8.1 $\pm$ 5.5 (31)	<0.0001	1.5 $\pm$ 0.7 (38)	5.0 $\pm$ 13.7 (23)	0.12
Haemoglobin	13.6 $\pm$ 2.3 (60)	13.5 $\pm$ 2.0 (33)	0.84	11.8 $\pm$ 2.2 (37)	9.8 $\pm$ 2.2 (25)	0.0008
Potassium	3.9 $\pm$ 0.6 (61)	4.2 $\pm$ 0.8 (34)	0.0294	3.9 $\pm$ 0.4 (50)	4.4 $\pm$ 1.0 (30)	0.0016
Calcium	1.1 $\pm$ 0.4 (39)	1.1 $\pm$ 0.4 (n=21)	0.71	1.1 $\pm$ 0.1 (23)	1.2 $\pm$ 0.5 (16)	0.67
Creatinine	84.3 $\pm$ 17.2 (64)	148.5 $\pm$ 42.0 (34)	<0.0001	74.1 $\pm$ 13.2 (54)	156.9 $\pm$ 118.9 (32)	0.0001
Myoglobin	2855 $\pm$ 3754 (42)	6726 $\pm$ 5108 (24)	<0.0001	407 $\pm$ 383 (21)	4356 $\pm$ 4525 (11)	0.0010
	1202 [121-13977]	5183 [548-19891]		327 [61-1658]	3844 [217-12814]	
Creatine kinase	3565 $\pm$ 2827 (59)	3789 $\pm$ 2685 (30)	0.51	4573 $\pm$ 3262 (15)	8405 $\pm$ 5307 (7)	0.10
	2792 [62-11743]	3822 [156-10330]		4386 [957-11262]	9400 [140-15015]	

*Cr = Creatinine; CI = confidence interval; LoS = Length of Stay;

Table 4: Correlation of creatinine with different markers on admission (r-value, p-value, and number)

Admission markers	Admission creatinine	Worst creatinine	Change in creatinine
TBSA	+0.07 (ns; 84)	+0.08 (ns; 82)	+0.06 (ns; 75)
pH	-0.4094 (p<0.001; 94)	-0.4722 (p<0.001; 92)	-0.13 (ns; 92)
Bicarbonate	-0.3262 (p=0.001; 94)	-0.3845 (p<0.001; 92)	-0.08 (ns; 84)
Lactate	+0.4720 (p<0.001; 90)	+0.4332 (p<0.001; 88)	+0.01 (ns; 80)
Haemoglobin	-0.13 (p=0.21; 93)	-0.19 (p=0.068; 91)	-0.2302 (p=0.036; 83)
Potassium	+0.19 (p=0.061; 95)	0.02 (p=0.85; 93)	-0.20 (p=0.068; 84)
Myoglobin	+0.6101 (p<0.001; 66)	+0.41 (p=0.001; 64)	+0.23 (p=0.092; 57)
Creatine kinase	+0.05; p=0.66; 89)	0.09 (p=0.38; 87)	-0.17 (p=0.50; 19)

Graph 1: Correlation of admission creatinine with admission myoglobin

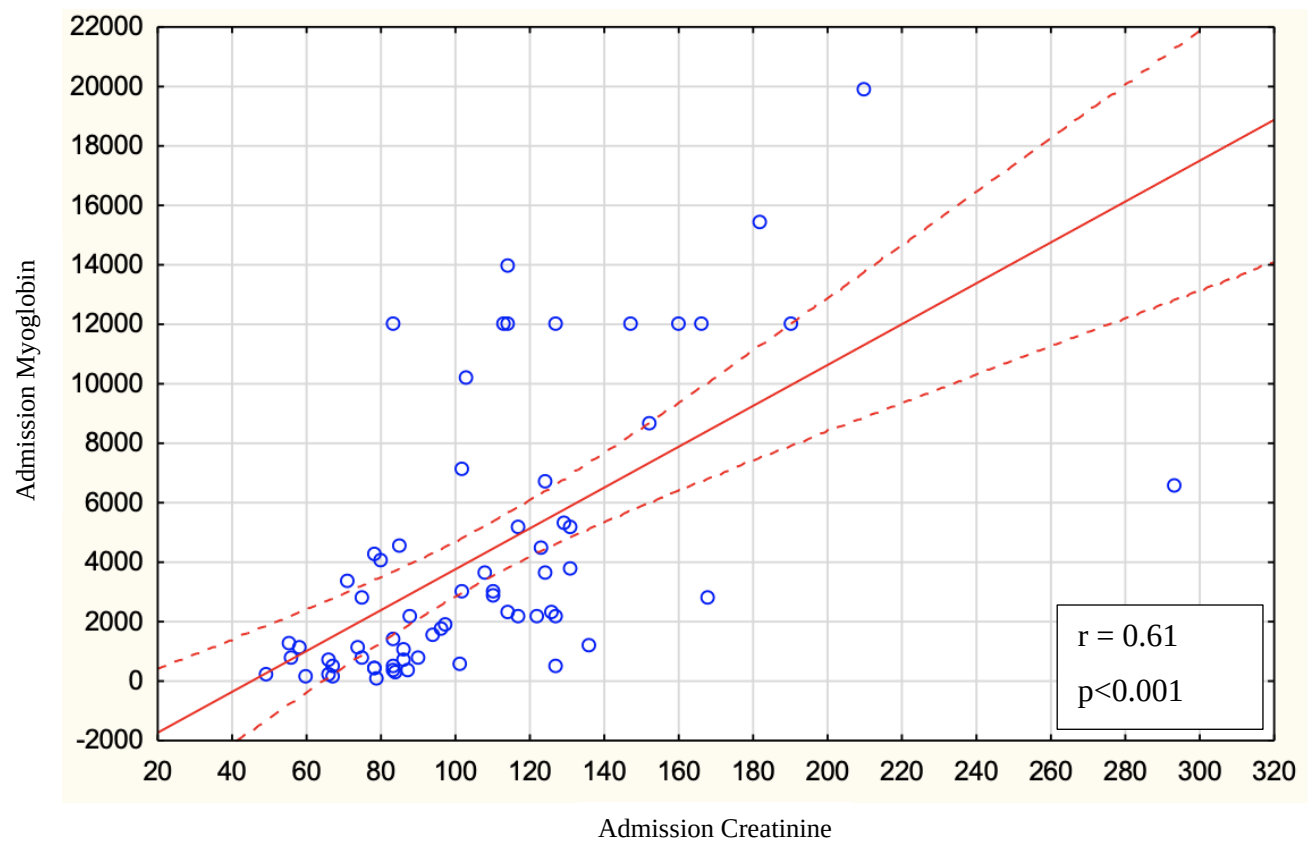
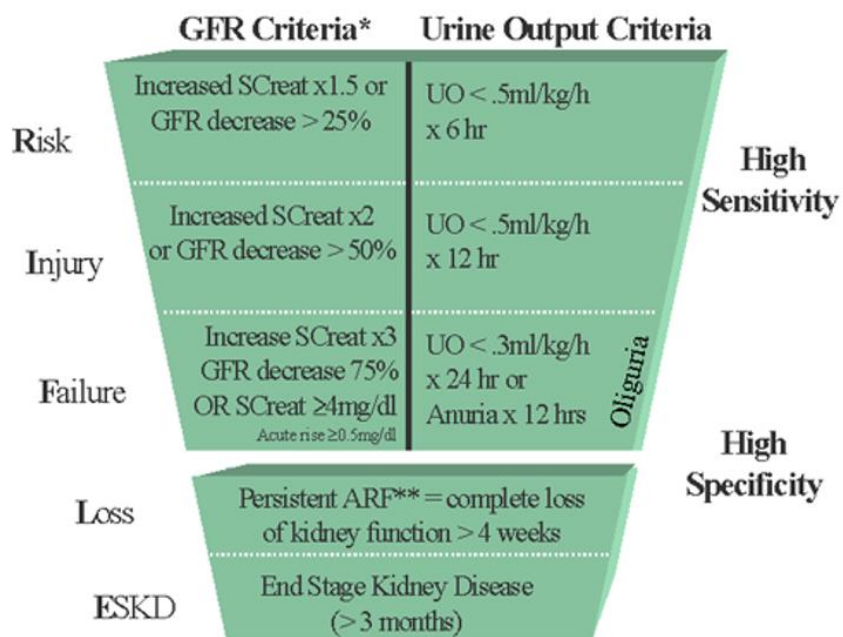


Figure 1: RIFLE Criteria³²



REFERENCE LIST *

1. Greaves I, Porter K, Smith JE. Consensus statement on the early management of crush injury and prevention of crush syndrome. J R Army Medical Corps. 2003;149(4):255-259. DOI:10.1136/jramc-149-04-02
2. Bosch X, Poch E, Frau JM. Rhabdomyolysis and Acute Kidney Injury. NEJM. 2009;361(1):62-72. DOI:10.1056/NEJMra0801327
3. Lovallo E, Koyfman A, Foran M. Crush Syndrome. African Journal of Emergency Medicine. 2012;2:117-123. DOI:10.1016/j.afjem.2012.05.005
4. Cote DR, Fuentes E, Elsayes AH, Ross JJ, Quraishi SA. A "crush" course on rhabdomyolysis: risk stratification and clinical management update for the perioperative clinician. Journal of Anesthesia, 2020. DOI:10.1007/s00540-020-02792-w
5. Smith J, Greaves I. Crush Injury and Crush Syndrome: A Review. Journal of Trauma. 2003;54: 226-230. DOI:10.1097/01.TA.0000047203.00084.94
6. Oxford Advanced Learner's Dictionary. [Online] Oxford University Press. [Cited: 2022 February 28.] <https://www.oxfordlearnersdictionaries.com/definition/english/sjambok>.
7. Sawhney JS, Kasotakis G, Goldenberg A, Abramson S, Dodgion C, Patel N, Khan M, Como JJ. Management of rhabdomyolysis: A practice management guideline from the Eastern Association for the Surgery of Trauma. American Journal of Surgery. In press 2021. DOI:10.1016/j.amjsurg.2021.11.022
8. Vanmassenhove J, Vanholder R, Nagler E, van Biesen W. Urinary and serum biomarkers for the diagnosis of acute kidney injury: an in-depth review of the literature. Nephrology Dialysis Transplantation. 2013;28:254-273. DOI:10.1093/ndt/gfs380
9. Brown CVR, Rhee P, Chan L, Evans K, Demetriades D, Velmahos GC. Preventing renal failure in patients with rhabdomyolysis: do bicarbonate and mannitol make a difference? J Trauma. 2004;56:1191-1196. DOI:10.1097/01.TA.0000130761.78627.10
10. Smith WA, Hardcastle TC. A crushing experience: The spectrum and outcome of soft tissue injury and myonephropathic syndrome at an urban South African University Hospital. African Journal of Emergency Medicine. 2011;1:17-24. DOI:10.1016/j.afjem.2011.04.002
11. de Meijer AR, Fikkers BG, de Keijzer MH, van Engelen BGM, Drenth JPH. Serum creatine kinase as predictor of clinical course in rhabdomyolysis: a 5 year intensive care survey. Intensive Care Med. 2003;29:1121-1125. DOI:10.1007/s00134-003-1800-5

12. Fernandez WG, Hung O, Bruno R, Galea S, Chiang WK. Factors predictive of acute renal failure and need for hemodialysis among ED patients with rhabdomyolysis. *American Journal of Emergency Medicine*. 2005;23:1-7. DOI:10.1016/j.ajem.2004.09.025
13. Lappalainen H, Tiula E, Uotila L, Manttari M. Elimination kinetics of myoglobin and creatine kinase in rhabdomyolysis: Implication for follow-up. *Crit Care Med*. 2002;30(10):2212-2215.
14. El-Abdellati E, Eyselbergs M, Sirimsi H, van Hoof V, Wouters K, Verbrughe W, Jorens PG. An observational study on rhabdomyolysis in the intensive care unit - exploring its risk factors and main complication: acute kidney injury. *Annals of Intensive Care*. 2013;3:1-8. DOI:10.1186/2110-5820-3-8
15. Mikkelsen, TS and Toft, P. Prognostic value, kinetics and effect of CVVHDF on serum of the myoglobin and creatine kinase in critically ill patient with rhabdomyolysis. *ACTA Anaesthesiologica Scandinavica*. 2005;49:859-864. DOI:10.1111/j.1399-6576.2005.00577.x
16. Premru V, Kovač J, Ponikvar R. Use of Myoglobin as a Marker and Predictor in Myoglobinuric Acute Kidney Injury. *Therapeutic Apheresis and Dialysis*. 2013;17(4):391-395. DOI:10.1111/1744-9987.12084
17. Oda Y, Shindoh M, Yukioka H, Nishi S, Fujimori M, Asada A. Crush syndrome sustained in the 1995 Kobe, Japan, earthquake: treatment and outcome. *Ann Emerg Med*. 1997;30:507-512.
18. Kasaoka S, Todani M, Kaneko T, Kawamura Y, Oda Y, Tsuruta R, Maekawa T. Peak value of blood myoglobin predicts acute renal failure induced by rhabdomyolysis. *Journal of Critical Care*. 2010;25:601-604. DOI:10.1016/j.jcrc.2010.04.002
19. Muckart DJJ, Moodley M, Naidu AG, Redding ADR, Meineke KR. Prediction of acute renal failure following soft-tissue injury using the venous bicarbonate concentration. *The Journal of Trauma*. 1992;33(6):813-817.
20. Skinner DL, Lewis C, de Vasconcellos K, Bruce J, Laing G, Clarke D, Muckart D. Hyperlactataemia with acute kidney injury following community assault: casue or effect? *SAJS*. 2019;57(2):63-67. DOI:10.17159/2078-5151/2019/v57n2a2779
21. Zimmerman JL, Shen MC. Rhabdomyolysis. *Chest*. 2013;144(3):1058-1065. DOI:10.1378/chest.12-2016
22. Ronco C. Extracorporeal therapies in acute rhabdomyolysis and myoglobin clearance. *Critical Care*. 2005;9:141-142. DOI:10.1186/cc3055

23. Sorrentino SA, Kielstein JT, Lukasz A, Sorrentino JN, Gohrbandt B, Haller H, Schmidt BMW. High permeability dialysis membrane allows effective removal of myoglobin in acute kidney injury resulting from rhabdomyolysis. *Critical Care Medicine*, 2011;39(1):184-186. DOI:10.1097/CCM.0b013e3181feb7f0
24. Variava M. A retrospective review of the profile and clinical course of patients requiring acute dialysis at Chris Hani Baragwanath Academic Hospital over a 2-year period. [MMed research report] Johannesburg: University of Witwatersrand, 2014.
25. Skinner DL, Hardcastle TC, Rodseth RN, Muckart DJJ. The incidence and outcomes of acute kidney injury amongst patients admitted to a level I trauma unit. *Injury*. 2014;45:259-264. DOI:10.1016/j.injury.2013.07.013
26. Proctor M, Carter N, Barker P. Community assault - the cost of rough justice. *SAMJ*. 2009;99(3):160-161.
27. Traynor Jr MD, Laing GL, Bruce JL, Hernandez MC, Kong VY, Rivera M, Zielinski MD, Clarke DL. Mob Justice in South Africa: A comparison of blunt trauma secondary to community and non-community assaults. *Injury*. 2020;51:1791-1797. DOI:10.1016/j.injury.2020.04.014
28. Human R, Geyser M. Major interpersonal violence cases seen in a Pretoria academic hospital over a one-year period, with emphasis on community assault cases. *African Journal of Emergency Medicine*. 2020;10:81-83. DOI:10.1016/j.afjem.2020.01.006
29. Lopes JA, Jorge S. The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review. *Clinical Kidney Journal*. 2013;6:8-14. DOI:10.1093/ckj/sfs160
30. Chris Hani Baragwanath Hospital. [Online] [Cited: 22 February 2022.] <https://www.chrishanibaragwanathhospital.co.za>
31. Group, Mount Sinai Hospital. [Online] [Cited: 21 March 2022.] <https://www.mountsinai.org/health-library/tests/creatinine-blood-test>
32. Bellomo R, Ronco C, Kellum JA, Mehta RL, Ralevsky P, ADQI workgroup. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Critical Care*. 2004;8:R204-R212. DOI:10.1186/cc2872

*Vancouver referencing style

APPENDIX A: PROTOCOL

Point-of-care testing and the predictive value of serum myoglobin as a prognostic marker for acute kidney injury requiring dialysis in rhabdomyolysis caused by sjambok and/or community assault blunt injuries

By: Dr Cynthia Cheung – Student number: 0500196D, MMed, University of Witwatersrand

Supervisors:

- Dr Vicky Jennings – MBChB (Pret), FCS (SA), Certificate of Trauma Surgery (CMSA) – Trauma Consultant, Chris Hani Baragwanath Academic Hospital
- Prof Frank Plani – LMC (Trieste), FCS (SA), FRACS, Sub-specialty in Trauma Surgery – Trauma Consultant and Head of Trauma Unit, Chris Hani Baragwanath Academic Hospital
- Prof Geoffrey Candy – PhD, MSc – MMed Research Manager, University of Witwatersrand

List of Abbreviations

AKI = Acute kidney injury

ARF = Acute renal failure

CK = Creatine kinase

GCS = Glasgow Coma Scale

s-Cr = serum creatinine

s-Mb = serum myoglobin

v-HCO₃ = venous bicarbonate

TBSA = Total Body Surface Area

ABSTRACT

Introduction: Rhabdomyolysis and crush syndrome was initially described following disasters such as earthquakes and bombings, where patients were trapped under buildings and rubble for an extended period of time. The majority of the available data for crush injury management is derived from earthquakes and bombings which is a different profile to the sjambok and community assault blunt injuries that are prevalent in South Africa. In this study we aim to

determine the prognostic value of different biomarkers for the development of acute kidney injury due to rhabdomyolysis caused by sjambok and/or community assault blunt injuries. We also aim to evaluate the value of point-of-care testing in sjambok and community assault blunt injuries.

Method: A prospective observational study will be done. All patients with sjambok and/or community assault blunt injuries who are admitted for hospital management will be included. Patients will have data collected from admission and day one of admission. Data will be obtained from clinical notes, laboratory results, and nursing charts.

Results: We will evaluate pH and venous bicarbonate levels from blood gases. Serum creatine kinase will be obtained from laboratory results, while serum potassium, creatinine, myoglobin, and calcium will be tested with point-of-care test. Total body surface area, fluids and the amount of fluids used will be obtained from clinical notes. The outcome of the patient will be recorded as whether the patient required dialysis or not, as well as whether the patient was discharged from the hospital or demised.

Conclusion: We propose that serum myoglobin tested at the point-of-care can be used to identify the patients who are at risk of acute kidney injury. We also aim to determine whether serum myoglobin tested at the point-of-care is a better prognostic marker than other previously studied biomarkers in determining acute kidney injury caused by rhabdomyolysis due to sjambok and/or community assault blunt injuries.

INTRODUCTION / BACKGROUND

Rhabdomyolysis is the breakdown of skeletal muscles which results in the release of muscle contents into the circulating blood. (1) Rhabdomyolysis and crush syndrome was initially described following disasters such as earthquakes and bombings, where patients were trapped under buildings and rubble for an extended period of time. Muscle compression and ischaemia

result in acute kidney injury caused by muscle damage, leading to the release of intracellular contents and resulting in various metabolic derangements. (2) The majority of the data for crush syndrome have been derived from earthquakes and bombings which are different to the profile of crush injury/syndrome seen in South Africa where the majority are caused by sjambok and community assault injuries.

Sjambok and community assault injuries are frequently observed in South Africa, and especially in the trauma unit of Baragwanath Hospital in Soweto – Johannesburg, Gauteng. Sjambok and community assault injuries are usually a result of the community punishing the alleged criminals either as a punishment to them or a warning to other criminals. (3) There is very limited data on crush injury caused by sjambok and community assault injuries alone.

It has been observed that the injured patients often hide in the bush for many hours (3) before they present for medical treatment or is found unconscious and brought to hospital for further management. Early aggressive fluid therapy has been shown to reduce the incidence of acute renal failure and therefore mortality. (3) (4) (5) It is therefore necessary for the clinician to have a high index of suspicion (4) and make use of biomarkers to identify patients who are at high risk of developing renal failure so that they can be appropriately managed. (2) (3) (4) (5)

Many of the available data for crush injury induced by rhabdomyolysis included study samples from blunt forces such as motor vehicle accidents, entrapments, blunt force assaults, burns, etc. Some studies also included rhabdomyolysis due to non-traumatic causes such as seizures, metabolic disorders, infections, toxins, etc. Vanmassenhove et al (6) reviewed the literature on biomarkers for acute kidney injury (AKI) and showed that biomarkers yield better results when the timing and cause of injury is known. Many biomarkers are elevated not only in AKI but

with other conditions which may be present as a comorbid or concurrent illness, thereby impacting on the specificity of the biomarker. Heterogeneity of the study population will limit the value of the biomarker in predicting AKI. (6)

Many studies have used creatine kinase (CK) as a surrogate marker of myoglobin which is believed to be the causative agent in rhabdomyolysis. CK level above 500u/L is significant for rhabdomyolysis, (7) while a CK level above 5000u/L is associated with an increased risk of renal dysfunction, (5) and CK above 10 000u/L is significant for acute renal failure (ARF). (8) Fernandez et al on the other hand suggested that by having a higher cut off of CK level above 1000u/L there may be missed cases of rhabdomyolysis, though these would probably have been insignificant for major complications. (9)

Fernandez et al evaluated various causes of rhabdomyolysis and predictors of acute renal failure due to rhabdomyolysis in patients from the emergency department. They used a cut-off CK value above 1000u/L and concluded that initial serum creatinine (s-Cr) was the only significant predictor of ARF. (9) However de Meijer et al in a similar study of ICU population with a CK cut-off value above 10 000u/L concluded that initial s-Cr did not show statistical significance in predicting ARF. (8) Renal function with measurements of serum urea and creatinine should not be used as a predictor of renal failure as this is often abnormal due to other causes other than crush injury, thus having many confounding factors. (4)

Muckart et al in a prospective study suggested that a venous bicarbonate level ($v\text{-HCO}_3$) below 17mmol/L together with a urine dipstick positive for haemoglobin on admission is indicative of severe injury, thereby identifying patients who are at risk of renal failure. (4) Total body

surface area (TBSA) involvement of above 18% in blunt force trauma has also been shown to be associated with an increased risk of renal dysfunction. (5)

In rhabdomyolysis, myoglobin is released from damaged muscles resulting in tubular damage. Serum myoglobin (s-Mb) is therefore the actual causative agent as compared to CK which has been used in previous studies as a surrogate marker for s-Mb. S-Mb peaks earlier than s-CK and its elimination is not dependent on glomerular filtration rate. (10) ⁽¹¹⁾ S-Mb level has been proposed as being more accurate for rhabdomyolysis and the development of AKI ⁽¹¹⁾ (12) and a s-Mb level above 300nmol/L is suggestive of an increased risk of AKI. (10) Kasaoka et al showed that the peak value of serum myoglobin on day two is superior to serum CK in prognosticating renal failure due to rhabdomyolysis. (13)

The measurements of CK, v-HCO₃, s-Cr, and TBSA have previously been studied and have shown to be a good prognostic marker of AKI in rhabdomyolysis. S-Mb is a biomarker which has previously been studied in the studies by Kasaoka et al (13) and Lappalainen et al (10) which have both shown to produce promising results. It is therefore our aim to include s-Mb as a new addition to the evaluation of sjambok and community assault blunt injuries in the South African setting.

STUDY OBJECTIVES

Many biomarkers have been evaluated for the prediction of AKI caused by rhabdomyolysis, however, there has been no consensus as to which is the gold standard. Many studies also included a heterogeneous group of patients which may introduce selection bias. Our study is aimed at evaluating different biomarkers in predicting the development of AKI caused only by sjambok or community assault blunt crush injuries/syndrome in the South African setting.

The objectives will be:

- To evaluate the predictive value of different previously studied biomarkers in prognosticating acute kidney injury specifically for sjambok and community assault blunt injuries.
- To evaluate the predictive value of serum myoglobin in prognosticating acute kidney injury in sjambok and community assault blunt injuries as compared to other previously studied biomarkers.
- To determine the value of point-of-care testing in sjambok and community assault blunt injuries.
- Secondary objective is to evaluate the type of fluids used in resuscitation and its relationship to the development of acute kidney injury.

METHODS

- 1) Design: Prospective observational study
- 2) Site of Study: Chris Hani Baragwanath Academic Hospital – Trauma Unit.
- 3) Study Duration: Six months
- 4) Study Population: Trauma patients above the age of 18, with sjambok injury or community assault who sustained blunt injuries only will be screened. All patients who require admission for hospital management will be included in the study. Patients are admitted for hospital treatment on the bases of their clinical condition and at the discretion of the treating doctor.

5) Sampling: Patients must be above the age of 18 to be considered for inclusion into the study. All patients who are victims of sjambok or community assault blunt injuries will be screened. Patients who are admitted will have data collected for admission and day one post-admission, as well as the outcome of their hospital stay.

a. Inclusion criteria for hospital admission are: Patients who have a CK value above 500, $v\text{-HCO}_3$ of less than 17mmol/l, TBSA above 15%, renal impairment based on the RIFLE criteria as evident from initial blood test, and any clinical evidence of rhabdomyolysis such as coca-cola colour urine, oliguria or anuria, etc.

b. Exclusion criteria are: rhabdomyolysis due to entrapment, penetrating injuries, motor vehicle accidents, pedestrian vehicle accidents, and previous cerebral vascular accidents. Patients who have pre-existing paralysis, cardiac disease, renal disease, or liver diseases will also be excluded.

6) Estimated Sample Size: Approximately 180 patients (Estimated on one patient recruited to the study per day over a six month period)

7) Measuring Tools/Instruments: Data will be collected in the form of a datasheet which consist of tick boxes, single and short answers, laboratory results, and point-of-care test results. The date and time of injury, as well as date and time of presentation will be recorded to account for the biomarker changes during the time interval of injury to biomarker measurements. Biomarkers that will be measured are venous pH, $v\text{-HCO}_3$, venous lactate, potassium, haemoglobin level, calcium level, CK, s-Cr, and s-Mb. Other measurement will include TBSA, and urine output. S-Cr and urine output has been

evaluated for use as a marker of AKI in the RIFLE criteria and is therefore included in our study as a standard of evaluating the degree of AKI.

The outcomes that will be measured are the worst s-Cr measured during the patient's hospital stay and the need for dialysis, and whether the patient was eventually discharged or that he/she died. These will be used to evaluate the degree of renal impairment or failure based on the RIFLE criteria, and also give an idea of the morbidity and mortality of crush injury/syndrome in our setting.

- 8) Data Collection: The usual management of patients with crush injury at Chris Hani Baragwanath Academic Hospital Trauma Unit involves taking blood for blood gas analysis, laboratory CK level, and point-of-care test of renal functions including chemistry and myoglobin testing. Blood tests will be done on patients' first presentation and during the patients hospital stay to evaluate the patients' trend of disease progression or improvement.

The information for our study will be collected from admission clinical assessment, admission blood gas and point-of-care test results, hospital records, and nursing records of volume of fluid administered and urine output from the patient files. Laboratory blood results will be retrieved from the National Health Laboratory Service (NHLS).

9) Study Limitations:

- a. Time interval between injury to hospital presentation: We know from previous studies that patients may present to hospital late post injury as they go into hiding to avoid further beatings or is unconscious and only found later. Others may be brought

to hospital immediately post-injury by bystanders, family, or emergency medical personnel. This time difference will affect the level of biomarkers, therefore affecting the significance of our results.

- b. TBSA: TBSA is assessed by the treating doctor therefore it is observer dependent. It may be overestimated as sjambok and community assault injuries do not create well define large areas for body surface area assessment. It may also be underestimated as the degree of bruising and muscle injury may not be apparent on presentation if it is soon after the injury.
- c. Quality of data: Our study is dependent on the blood tests done by the treating doctor. As there will be many different doctors collecting blood samples on the study subjects, the quality of our samples may be affected.
- d. Incomplete data: In a busy casualty such as Chris Hani Baragwanath Academic Hospital Trauma unit, there is the potential for incomplete clinical records or misplaced point-of-care test results.

DATA ANALYSIS

Data will be recorded in EXCEL and summarized in Tables and Graphs. Different statistical tests will be used to evaluate our data. Mechanism of injury and weapons used will be calculated by percentages. Differences between patients in renal failure and without renal failure will be determined using Statistica using a t-test or Mann-Whitney test for continuous variables. Differences in non-continuous variables would be calculated using a Chi-squared Wilcoxon test. Logistic regression would be used to determine variables predicting renal failure.

In addition time to discharge would be determined as Kaplan-Meier survival curves in patients who had compromised renal function. Factors affecting time to discharge in these patients would be determined using a Cox regression analysis.

ETHICS

Informed consent will be obtained from all participating patients with a Glasgow coma scale (GCS) of 15. Patients with a GCS below 15 will have forms completed by their family for unconscious patients, or consent will be obtained when the patient regains their full level of consciousness.

A submission to the ethics committee for ethics clearance will be made in April 2017.

TIMING

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb
Literature Review														
Preparing Protocol														
Protocol Assessment														
Ethics Application														
Collecting Data														
Data Analysis														
Write up – thesis														
Write up – paper														

FUNDING

All the documentation and investigation results required for this study are part of the routine management for patients presenting to Chris Hani Baragwanath Academic Hospital following crush injury. There is therefore no added cost requiring funding.

The Investigator's own resources will be used for administrative work – such as laptop, internet data, printing and photocopying, etc.

REFERENCES

- 1) Bosch X, Poch E, Frau JM. Rhabdomyolysis and Acute Kidney Injury. NEJM. 2009; 361(1): 62-72.
- 2) Lovallo E, Koyfman A, Foran M. Crush syndrome. African Journal of Emergency Medicine. 2012; 2: 117-123.
- 3) Proctor M, Carter N, Barker P. Community assault - the cost of rough justice. SAMJ. 2009; 99(3): 160-161.
- 4) Muckart DJJ, Moodley M, Naidu AG, Redding ADR, Meineke KR. Prediction of acute renal failure following soft-tissue injury using the venous bicarbonate concentration. The Journal of Trauma. 1992; 33(6): 813-817.
- 5) Smith WA, Hardcastle TC. A crushing experience: The spectrum and outcome of soft tissue injury and myonephropathic syndrome at an urban South African University Hospital. African Journal of Emergency Medicine. 2011; 1: 17-24.
- 6) Vanmassenhove J, Vanholder R, Nagler E, van Biesen W. Urinary and serum biomarkers for the diagnosis of acute kidney injury: an in-depth review of the literature. Nephrology Dialysis Transplantation. 2013; 28: 254-273.
- 7) Brown CVR, Rhee P, Chan L, et al. Preventing renal failure in patients with rhabdomyolysis: do bicarbonate and mannitol make a difference? J Trauma. 2004; 56: 1191-1196.
- 8) de Meijer AR, Fikkers BG, de Keijzer MH, van Engelen BGM, Drenth JPH. Serum creatine kinase as predictor of clinical course in rhabdomyolysis: a 5 year intensive care survey. Intensive Care Med. 2003; 29: 1121-1125.
- 9) Fernandez WG, Hung O, Bruno R, Galea S, Chiang WK. Factors predictive of acute renal failure and need for hemodialysis among ED patients with rhabdomyolysis. American Journal of Emergency Medicine. 2005; 23: 1-7.

- 10) Lappalainen H, Tiula E, Uotila L, Manttari M. Elimination kinetics of myoglobin and creatine kinase in rhabdomyolysis: Implication for follow-up. *Crit Care Med.* 2002; 30(10): 2212-2215.
- 11) El-Abdellati E, Eyselbergs M, Sirimsi H, van Hoof V, Wouters K, Verbrughe W, Jorens PG. An observational study on rhabdomyolysis in the intensive care unit. Exploring its risk factors and main complication: acute kidney injury. *Annals of Intensive Care.* 2013; 3: 1-8.
- 12) Oda Y, Shindoh M, Yukioka H, Nishi S, Fujimori M, Asada A. Crush syndrome sustained in the 1995 Kobe, Japan, earthquake: treatment and outcome. *Ann Emerg Med.* 1997; 30: 507-512.
- 13) Kasaoka S, Todani M, Kaneko T, Kawamura Y, Oda Y, Tsuruta R, Maekawa T. Peak value of blood myoglobin predicts acute renal failure induced by rhabdomyolysis. *Journal of Critical Care.* 2010; 25: 601-604.

APPENDIX B: PROTOCOL ASSESSMENT FORM

Faculty of Health Sciences, Postgraduate Office
 Phillip V Tobias Building, 2nd Floor
 Cnr York & Princes of Wales Terrace, Parktown 2193
 Tel: (011) 717 2463/2125 | Fax: (011) 717 2119
 Email: pulesa.khumalo@wits.ac.za; thando.mbockwa@wits.ac.za



ASSESSOR GROUP COMMENT FORM

Student Full name(s) & Surname		Cynthia CHEUNG	
Student Number		0500196D	
Degree	MMed	Department	Department of Surgery
Title <i>To evaluate the value of point-of-care testing and the predictive value of serum myoglobin as a prognostic marker for acute kidney injury in rhabdomyolysis caused by sjambok and/or community assault blunt injuries in the South African setting.</i>			
Date of Assessor Group Meeting: 12 th April 2017		School / Department / Division: GENERAL SURGERY	

Yes

☒

Is the research question clearly identified and described?

Comments: *Define rhabdomyolysis*

pg. 5: List specific objectives, 1st paragraph under "Study Obj" is not an objectives.

Yes

No

☒ Not entirely

Is the design of the study and methods used appropriate for the research question being asked?

Comments: *hurry-to-presentation delay and correct; for this (Stats)*

Add duration of study & proposed sample size

Add Budget for measurements not done routinely.

Clarify inclusion criteria → established vs non-established renal failure.

Specify primary outcome → Urinary renal failure?

Add Statistical Analysis → univariate, multivariate

Update datasheet to be more clear as per supervisor's suggestion.

Update title to better reflect outcome (form required).

Student: Cynthia CHEUNG

Is the study feasible within: _____

- i. the applicant's resources? ☒ Yes ☐ No
- ii. the department's resources? ☒ Yes ☐ No
- iii. the time frame? ☒ Yes ☐ No

Please add budget to reflect this.

Do you recommend:

- i. shortening / lengthening of the protocol? Please specify and explain.

Please incorporate changes/suggestions above.

- ii. the appointment of a co-supervisor?

☐ Yes ☒ No

Nominee/s : _____

Overall recommendation regarding the protocol :

- i. revision of the protocol to the Supervisor (if HOD approval is also required, please specify):
(Candidates: One copy, list of corrections with page numbers, supervisor approval letter – submit to PG Office) ☒ Yes ☐ No
- ii. revision of the protocol to the satisfaction of the Assessor Group:
(Candidates: One copy, list of corrections with page number, supervisor approval letter – submit to PG Office)
(PG Office to forward to the Assessor Group Chair) ☐ Yes ☐ No
- iii. revision of the protocol and resubmission of the revised protocol to the next Assessor Group Meeting:
(Candidates: six copies, list of corrections with page numbers, supervisor approval Letter - submit one copy to PG Office / 5 to school assessor group administrator/ for PhD all six copies to be submitted to the PG Office) ☐ Yes ☐ No
- iv. candidate goes ahead: ☐ Yes ☐ No

Student: Cynthia CHEUNG

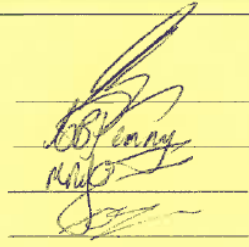
Assessor Names, and Signatures Email :

Prof Damon Bizos

Dr Claire Penny

Dr Marietha Nel

Dr Deirdré Kruger





Assessor Group Chair: Dr D Kruger

12th April 2017

Date

Student: Cynthia **CHEUNG**

APPENDIX C: ETHICS CLEARANCE

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG



R14/49 Dr Cynthia Tsz Ying Cheung

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170429

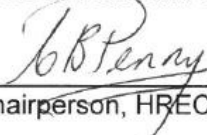
NAME: Dr Cynthia Tsz Ying Cheung
(Principal Investigator)
DEPARTMENT: General Surgery
Chris Hani Baragwanath Academic Hospital
Trauma Unit

PROJECT TITLE: To Evaluate the Value of Point-of-Care Testing and the Predictive Value of Serum Myoglobin as a Prognostic Marker for Acute Kidney Injury in Rhabdomyolysis Caused by Sjambok and/or Community Assault Injuries in the South African Setting

DATE CONSIDERED: 05/05/2017
DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Dr V. Jennings, Prof F. Plani and Prof G. Candy

APPROVED BY: 
Prof C Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL: 30/04/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in April and will therefore be due in the month of April each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX D: SUPERVISOR DECLARATION

Ni

Tē

Si

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG



FACULTY OF
HEALTH SCIENCES

CERTIFICATE OF SUBMISSION FOR EXAMINATION SIGNED BY SUPERVISORS OF HIGHER DEGREES

Ni

CANDIDATES

Tē

Full name	Cynthia Tsz Ying CHEUNG
Student number	0500196D

Si

Candidate for the degree of: MMed(Surg)
has submitted his/her thesis/dissertation/research report

Ni

Entitled: Point-of-Care Testing and The Predictive Value of Serum Myoglobin as a Prognostic Marker for Acute Kidney Injury Requiring Dialysis in Rhabdomyolysis Caused by Sjabok and/or Community Assault Blunt Injuries

Si

==

IM

Contact no	+27 82 592 6345	E-mail	cheung.cty@gmail.com
------------	-----------------	--------	----------------------

A.

Mark with an X on appropriate box		Yes	No
If I for Gr ex the	Has this thesis/dissertation/research report been submitted with the acquiescence of the supervisor?	x	
	To the best of your knowledge are you able to verify that this is the candidate's work, except as otherwise stated by the candidate?	x	
	The substance (nor any part of it) has not been submitted in the past nor is being submitted for a degree in any other university?	x	
A.	The candidate has acknowledged wherever any information used in the thesis, dissertation or other work has been obtained by him/her while employed by, or working under the aegis of, any person or organization other than the University or its associated institutions?	x	
	Have examiners been nominated and approved?	x	

A.

Th

ac

I certify that this thesis/dissertation/research report has the approval of the Animal Ethics Committee / Committee for Research on Human Subjects and the Number of the Certificate of Approval is:

M170429

List all publications, which your student has published in peer-reviewed journals from his/her postgraduate research report/dissertation/thesis during the course of his/her studies in the Faculty of Health Sciences (Include authors, year, title of paper, name of journal, volume number and page numbers). This information is mandatory.

Nil

APPENDIX E: DATA COLLECTION SHEET

Study subject number: _____

Crush Injury Datasheet

PRESENTATION: DATE _____ TIME _____

INJURY: DATE _____ TIME _____

AGE OF PATIENT: _____

GENDER: ☐ Male ☐ Female

COMORBIDITIES: ☐ IHD ☐ prev. CVA ☐ Established renal failure ☐ Liver disease

☐ Others: _____

MECHANISM OF INJURY:

☐ Community assault ☐ Sjambok Injury

WEAPONS USED:

☐ Bricks ☐ Stones ☐ Sticks ☐ Punch/Kicked ☐ Others: _____

% TBSA INVOLVED: _____

BLOOD RESULTS:

	ON PRESENTATION	DAY 1
Venous Blood Gas (VBG)	pH	pH
	HCO ₃	HCO ₃
	Lactate	Lactate
	Hb	Hb
Point-of-Care Potassium		
Point-of-Care Calcium		
Serum Creatinine		
Serum Myoglobin		
Formal CK level		

FLUID THERAPY:

	ON ADMISSION	DAY 1
Type of fluid		
Volume of fluid		
Urine output		
Mannitol/SodaBic used		

OUTCOME:

Worst Creatinine results: _____

Dialysis: ☐ Yes ☐ No

End Results: ☐ Patient Died ☐ Discharged - Duration of hospital stay: _____

APPENDIX F: TURNITIN REPORT

ORIGINALITY REPORT

5%

SIMILARITY INDEX

3%

INTERNET SOURCES

4%

PUBLICATIONS

1%

STUDENT PAPERS

PRIMARY SOURCES

1

David Lee Skinner, Carolyn Lewis, Kim de Vasconcellos, John Bruce, Grant Laing, Damian Clarke, David Muckart.

"Hyperlactataemia with acute kidney injury following community assault: cause or effect?", South African Journal of Surgery, 2019

Publication

1%

2

"Abstracts", HPB, 9/1/2006

Publication

1%

3

Submitted to University of Bristol

Student Paper

1%

4

W.A. Smith, T.C. Hardcastle. "A crushing experience: The spectrum and outcome of soft tissue injury and myonephropathic syndrome at an Urban South African University Hospital", African Journal of Emergency Medicine, 2011

Publication

<1%

5

cyberleninka.org

Internet Source

<1%

6	s22e0fc21194cb415.jimcontent.com Internet Source	<1 %
7	Submitted to University of Johannesburg Student Paper	<1 %
8	Marta Nunes, Sthembile Sibanda, Vicky Baillie, Gaurav Kwatra, Ricardo Aguas, Shabir Madhi. "SARS-CoV-2 Omicron symptomatic infections in previously infected or vaccinated South African healthcare workers", Cold Spring Harbor Laboratory, 2022 Publication	<1 %
9	Christina W. Lee, Henry A. Pitt, Taylor S. Riall, Sean S. Ronnekleiv-Kelly et al. "Low Drain Fluid Amylase Predicts Absence of Pancreatic Fistula Following Pancreatectomy", Journal of Gastrointestinal Surgery, 2014 Publication	<1 %
10	bio-protocol.org Internet Source	<1 %
11	traumainternational.co.in Internet Source	<1 %
12	N/A. "Abciximab and eptifibatide 'safe' for use in octogenarians", Reactions Weekly, 10/2003 Publication	<1 %
13	Nirav Patel, I. Khofi-Phiri, L. R. Mathiva, A. Grieve, J. Loveland, G. D. Nethathe. "Trauma	<1 %

related admissions to the PICU at Chris Hani Baragwanath Academic Hospital, Johannesburg", Pediatric Surgery International, 2017

Publication

14

Premru, Vladimir, Janko Kovač, and Rafael Ponikvar. "Use of Myoglobin as a Marker and Predictor in Myoglobinuric Acute Kidney Injury : Myoglobin as a Marker in Myoglobinuric AKI", Therapeutic Apheresis and Dialysis, 2013.

Publication

<1 %

15

pubmed.ncbi.nlm.nih.gov

Internet Source

<1 %

16

www.researchsquare.com

Internet Source

<1 %

Exclude quotes On
Exclude bibliography On

Exclude matches < 5 words



Ekene Nweke

RE: MMed for Turnitin submission
To: Cynthia Cheung

16:59



Dear Dr Cheung,

Herewith your MMed plagiarism report is attached. Your overall similarity index is 5% with a maximum single match of 1% which is from generic terms. All other matches are ≤ 1%. Therefore, your similarity index is **ACCEPTABLE** within our Department.

For PG submissions - Please only submit the Turnitin report PDF pages in the attached report showing the similarity index (Page 19-21), as well as this email stating that your plagiarism report is **ACCEPTABLE** within the Department of Surgery.

Kind regards
Emmanuel