dfAugmented renal clearance in critically ill trauma patients admitted to Chris Hani Baragwanath Academic Hospital Intensive Care Unit: a retrospective review of data.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg in fulfillment of the requirements for the degree

Of

Master of Medicine in the branch of Internal Medicine

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DECLARATION

I, Zoleka Mafuya, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine (in submissible format with protocol and an extended literature review) in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg. This research report has not been submitted before for any degree or examination at this or any other university.

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Signed

On this 04th day of August 2020

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My heartfelt gratitude goes to my two supervisors and mentors:

Dr Gladness Nethathe, many thanks for suggesting such a great topic and affording me an opportunity to be part of an amazing project. I am truly grateful for the guidance and patience in helping me to achieve this.

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Prof Colin Menezes, you have been an amazing mentor and a phenomenal leader and for that I am sincerely grateful.

DEDICATION

This work is dedicated to my daughter Mbali Mafuya for her love and unwavering support.

PRESENTATION ARISING FROM THIS PROJECT

Poster presentation

Augmented renal clearance in critically ill trauma patients admitted to Chris Hani Baragwanath Academic Hospital Intensive Care Unit: a retrospective review of data. Poster Presentation, South African Renal Society (SARS) Congress, Johannesburg 11-14 October 2018.

ABSTRACT

Background

Augmented renal clearance (ARC) is enhanced elimination of solutes by the kidneys. Patients with ARC have normal plasma creatinine concentrations and typically display a hyperdynamic circulation, with increased cardiac output, resulting in renal hyper-perfusion and increased creatinine clearance (CrCl). The resultant enhanced elimination of renally cleared agents may be associated with sub-therapeutic drug levels and lower minimum inhibitory concentration of antibiotics. There is a paucity of studies describing the occurrence and features of ARC in a South African population.

Methods

We conducted a retrospective review of data of all trauma patients admitted to the Intensive Care Unit (ICU) at Chris Hani Baragwanath Academic Hospital (CHBAH) during a one-year period to identify those with features of ARC.

Results

Of the 96 trauma patients admitted to CHBAH ICU over the study period, 38 met inclusion criteria. Of these, 29 showed features of ARC (CrCl > (130mL/min/1.73 m^2). Most patients with ARC were male 75.9% (n=22/29), with a mean age of 32.7 years (SD 11.3 years) and mean weight of 75.7 kg (SD 14.0). Overall, 76.3% (n=29/38) of patients had at least 1 episode of ARC during the first 7 days of ICU admission. CrCl was highest on day 4 occurring in 77.8% (n=14/18) of patients with an average CrCl of 180 ml/min/1.73m^2 and again at day 7 in 77.8% of patients with an average CrCl of 163 ml/min/1.73m^2 The majority of those with ARC 86.2% (n=31) had undergone emergency surgery on admission, and 25% (n=9) had required inotropic support during their ICU stay. There was no significant difference in modified Sequential Organ Failure Assessment (p=0.836), Acute Physiology and Chronic Health Evaluation (p=0.081), or Injury Severity Scores (p=0.422) between patients with ARC and those with no features of ARC.

Conclusion

A high prevalence of ARC was detected in our South African ICU population. As this was a single centre, retrospective audit, with a limited sample size, further studies

exploring the presence and clinical impact of ARC in the South African trauma population and in other populations are still needed.

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LIST OF ACRONYMS

ADH	Antidiuretic Hormone
AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
APACHE	Acute Physiology and Chronic Health Evaluation
ARC	Augmented Renal Clearance
BSA	Body Surface Area
CHBAH	Chris Hani Baragwanath Academic Hospital
CKD	Chronic Kidney Disease
CrCl	Creatinine Clearance
eGFR	Estimated Glomerular Filtration Rate
GFR	Glomerular Filtration Rate
ICU	Intensive Care Unit
ISS	Injury Severity Score
LOS	Length of Stay
MDRD	Modification of Diet in Renal Disease
MIC	Minimum Inhibitory Concentration
P	Probability value
PAH	Para aminohippurate
RIFLE	Risk Injury Failure Loss End Stage Kidney disease
SCr	Serum Creatinine
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Function Assessment

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CHAPTER ONE: PROTOCOL AND EXTENDED LITERATURE REVIEW

1.1 Introduction

The occurrence of acute kidney injury (AKI) is common among the critically ill and is associated with worse outcomes.(1) The RIFLE (Risk Injury Failure Loss of renal function and End-stage kidney disease) and later AKIN (Acute Kidney Injury Network) classifications, formulated by the Acute Dialysis Quality Initiative allows for a standardised definition of AKI.(2) Acute kidney injury complicates the presentation of 1% to 25% of all critically ill patients in developing countries.(1) Of these, up to 4% require renal replacement therapy (RRT) with an overall hospital mortality of 60% within the first month following Intensive Care Unit (ICU) admission.(3) Acute kidney injury occurs at a lower incidence in trauma patients and at higher rates among patients presenting with severe sepsis.(4) Renal injury in the intensive care setting is thought to involve multiple different mechanisms including hypotension, renal hypoperfusion, drugs, and the release of endogenous nephrotoxins in the presence of sepsis.(5) The result is endothelial damage, vasoconstriction and activation of inflammatory processes.(6) Renal function may worsen with consequent accumulation of renally excreted solutes, metabolites and drugs.(7)

On the other end of the spectrum is augmented renal clearance (ARC), which refers to enhanced elimination of circulating solutes such as waste products and pharmaceutical products by the kidneys. It is defined as a creatinine clearance (CrCl) of more than or equal to 130 ml/min/1.73m^2, however some studies have used 120 ml/min/1.73m^2.(8-10) The prevalence of ARC in another study varies and has been reported to range from 28 to 65%.(11,12) In one study 17,9% of patients had evidence of hyperfiltration (CrCl >120ml/min/1.73m^2) on day 1 of ICU admission.(10) The prevalence was shown to be highest on day 5 post ICU admission.(13) Augmented renal clearance has been shown to be more common in young patients.(14) Male gender and polytrauma have been identified as additional risk factors for its development.(9,15,16)

1.2 Determining Renal Function

In clinical practice, glomerular filtration rate (GFR) is utilised to assess renal function, to help determine medication dosing in renal failure for renally excreted drugs, to monitor chronic renal disease progression, to assess the need for renal replacement therapy and to determine response to intervention.(18) The normal GFR is estimated at 90-120ml/min per 1.73m^2 of body surface area (BSA) and is the sum amount of filtered plasma by each functioning nephron in the glomerulus per minute.(8) It can be used indirectly to assess the number of functional nephrons in the kidney and varies depending on age, gender, muscle mass and an individual's BSA.(20) The most accurate methods for measuring GFR require the measurement of exogenous substances which are not metabolised in the body, are freely filtered with no tubular absorption or secretion. Examples of these include inulin, iohexol and para aminohippurate (PAH). Limitations for the use of these include availability, cost and the fact that the tests do not provide information on the cause of renal failure.(21-23) Endogenous markers such as serum creatinine concentration and cystatin C have also been used to measure GFR.(23) Cystatin C is not affected by age, race, gender or muscle mass however price and availability still limit its routine use. (21-23)

Glomerular Filtration Rate, in CKD, is estimated using the Cockcroft Gault and Modification of Diet in Renal Disease (MDRD) tools. These tools use measured serum creatinine and take into account age and weight when estimating GFR. MDRD also considers race in the estimate of GFR.(20,24) The use of MDRD is validated for stable adult populations of Caucasian and African American descent and has not been adequately validated in other population groups or at the extremes of age.(25)

Traditionally, renal function has also been determined through the measurement of CrCl using a 24-hour urine collection. A 24-hour collection has several limitations such as collection errors and delayed availability of results. An 8-hour urine collection has been found to be as accurate as the standard 24-hour collection and is thus the currently preferred method.(23,25)

1.3 Augmented Renal Clearance

1.3.1 Definition

In ARC a phenomenon of enhanced elimination of solutes, waste and pharmaceutical products by the kidney occurs and is defined as a CrCl greater than or equal to 130 ml/min/1.73m^2.(8,14)

1.3.2 Epidemiology of ARC

Recent data suggest ARC has been observed in about 17 to 60% of critically ill patients in ICU. This proportion can be as high as 80% in critically ill trauma and septic patients.(13,26,27) The subset of critically ill patients who are at risk of developing ARC tends to be younger, less than 50 years of age, and male. Trauma patients with low illness severity scores (ISS) using the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores are also more likely to be affected; as well as patients with good diastolic blood pressures and good urine outputs on ICU admission.(28) Other at-risk populations include patients with traumatic brain injury, post-surgical recovery, burns, sepsis and ventilator associated lung injury.(29) An increased incidence of ARC in patients with severe head injury who received hypertonic saline, with or without vasopressors, to maintain cerebral perfusion has also been demonstrated.(30) There is a suggestion that ARC also occurs in other patient populations outside the ICU setting.(30)

1.3.3 Mechanisms of ARC

The pathophysiological changes promoting ARC are not well understood. Important factors that are thought to be contributory include haemodynamic instability, inotropic support, sepsis, aggressive fluid resuscitation, an increase in major organ perfusion and low systemic vascular resistance.(14,18) Mechanisms postulated to be implicated are cytokine release from acute injury with associated inflammatory and immune responses which then enhance organ perfusion and therefore augmented handling of renally cleared substances.(11,15) Vasodilation and increased cardiac output together increase renal blood flow, renal perfusion and GFR.(28) Affected patients have creatinine levels within normal range and typically exhibit signs of a hyperdynamic circulatory status with a high cardiac output, resulting in high renal

perfusion and increased CrCl.(8) The result is enhanced elimination of all renally cleared agents.(15)

Another mechanism thought to contribute to the development of ARC is systemic inflammatory response syndrome (SIRS), a state of physiological and biochemical abnormalities common in critical illness regardless of the underlying cause. Common causes include sepsis, ischaemia, autoimmune conditions, burns, trauma, and major surgery. Haemodynamic changes associated with SIRS are a low systemic vascular resistance and a high cardiac output.

A flow diagram is presented in Figure 1 showing a summary of postulated mechanisms underlying ARC.(27, 28)

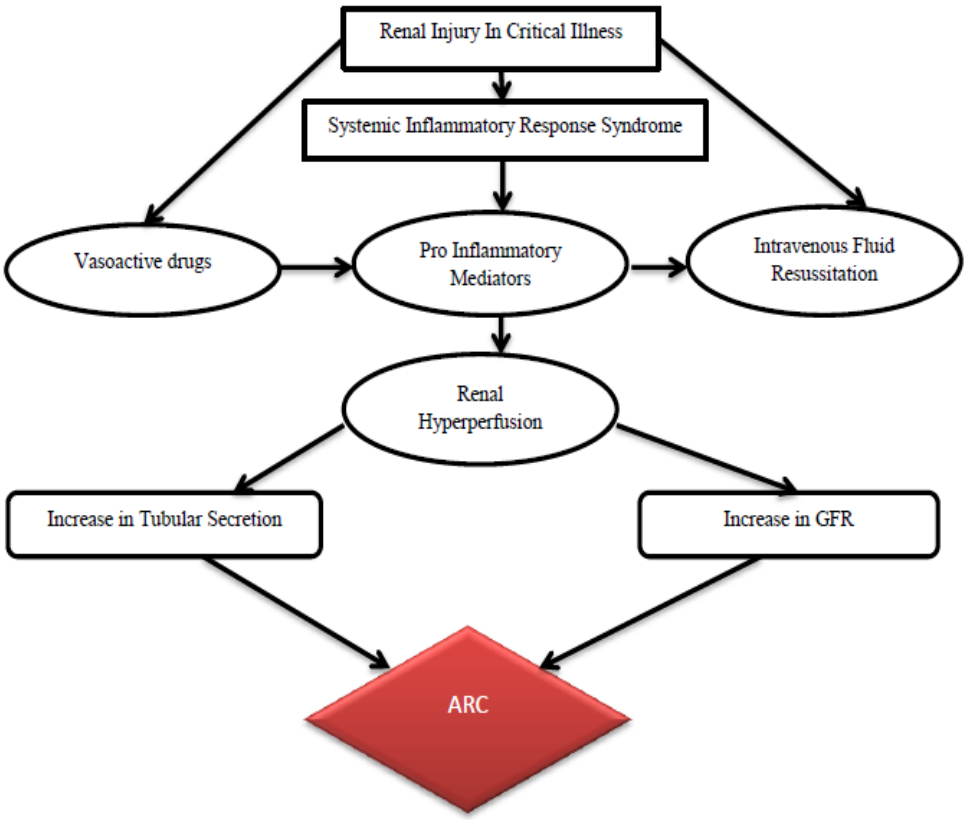

Figure 1: Causes of ARC

1.3.4 Diagnosis and evolution of ARC

The diagnosis of ARC is defined as a CrCl greater than or equal to 130 ml/min/1.73m^2 with some studies using 120 ml/min/1.73m^2.(8,14,30,31)

The timing of the development of ARC during the course of ICU admission likely varies between patients depending on the underlying disease process, surgical procedures and medical interventions.(32) A recent study by Fuster et al demonstrated a peak CrCl on day 5 of ICU admission.(13) A mean of 4.7 days of treatment before the development of ARC was demonstrated in patients with traumatic brain injury who developed ARC.(9,32) There is an increase in cases of ARC of up to 30% during the first week of ICU admission.(9,15)

1.3.5 Consequences of ARC

Renal excretion of medications such as antibiotics and low molecular weight heparin (LMWH) can be significantly increased in patients who exhibit ARC.(13,15) Of interest are beta-lactam antibiotics. These include penicillins, cephalosporins, carbapenems and monobactams.(28,29) Beta lactams have time dependent pharmacokinetic properties. Thus the time for which the drug concentration is persistently above minimum inhibitory concentration (MIC) is essential for bactericidal activity.(28,30) Drug dosing should focus on maintaining plasma concentrations above MIC for 90-100% of dosing intervals, with concentrations of at least 4 to 5 times the MIC for maximal bactericidal effect.(28) Considering the time dependent bactericidal properties, higher doses with a more frequent or continuous drug dosing would be ideal in maintaining therapeutic drug concentrations in patients with ARC.(27)

Aminoglycosides have concentration dependent bactericidal properties and their effect is determined by the ratio of maximum plasma drug concentration to MIC.(12,29) They are excreted almost unchanged by the kidney. Once daily dosing has been shown to be superior to multiple divided doses. A more frequent dosing to at least 18 hourly has been advised where ARC is suspected as well as therapeutic drug monitoring (TDM) where available.(32) In clinical practice, TDM for aminoglycosides is routinely measured because of their narrow therapeutic index for toxicity but is also useful in monitoring efficacy.(34)

Plasma concentrations of vancomycin have been shown to be lower in patients with ARC during the first days of treatment. This persists despite increasing doses of vancomycin.(17,30) Monitoring and the maintenance of a steady state of trough levels is associated with good clinical outcomes.(35) With regards to

fluoroquinolones, dosing depends on the area under the time curve for a 24-hour period.(26,29) It has been suggested that more repeated frequent dosing would be beneficial in patients with ARC.(26)

Anticoagulation is commonly employed in critical care and is often achieved with the use of LMWH. It cannot be directly measured in plasma and thus a surrogate marker, anti-factor Xa is used to measure its biological effect. The presence of ARC has been associated with shortened activity of enoxaparin and therefore the recommendation is to dose adjust and monitor the biological effect using a surrogate marker such as anti-factor Xa activity as it correlated well with clinical effect.(33)

1.4 Conclusion

Renal function monitoring is of paramount importance in the critically ill. Assessment is most commonly achieved through the measurement and monitoring of serum creatinine concentrations. Alterations in CrCl may require adjustments to drug dosing. Augmented renal clearance is a common phenomenon, which should be considered by clinicians in the management of critically ill patients.(21)

2.1 Study Aims and Objectives

2.1.1 Aims

The aim of this study was to describe the prevalence and implications of ARC among critically ill, adult trauma patients admitted to CHBAH ICU.

2.1.2 Objectives

1. To retrospectively identify patients admitted to CHBAH ICU during a 12-month period from 1 January 1999 to 31 December 1999 with features of ARC.

2. To describe the clinical characteristics of trauma patients with ARC admitted to CHBAH ICU during a 12-month period from 1 January 1999 to 31 December 1999

3. To determine and compare the outcomes, as indicated by length of ICU stay and ICU mortality, of critically ill trauma patients admitted to CHBAH ICU identified retrospectively to have had ARC with critically ill trauma patients admitted to CHBAH ICU identified retrospectively to not have had ARC.

2.2 Research Assumptions

Definitions: ARC was defined by a creatinine clearance measurement of more than or equal to 130 ml/min/1.73m^2.

2.3. Methods

2.3.1. Study Design

This was a retrospective review of data of all trauma admissions to CHBAH ICU from 1 January 1999 to 31 December 1999.

2.3.2. Study Population

2.3.2.1 Site of Study

Chris Hani Baragwanath Academic Hospital Intensive Care Unit

2.3.2.2 Sample Size

The sample size consisted of data of all consecutive trauma admissions to ICU between 1 January 1999 to 31 December 1999.

2.3.2.3 Sampling Procedures

Consecutive patients admitted to CHBAH ICU during the study period.

2.3.2.4 Selection Criteria

Inclusion criteria:

1. ICU length of stay of more than 24 hours.

2. Admission plasma creatinine less than 120 micromol/L.

3. No history of prior renal replacement therapy or chronic kidney disease.

Exclusion criteria:

1. Age less than 18 years.

2. Rhabdomyolysis clinically suspected or admission creatinine kinase more than 5000 IU/L where such data was available.

3. Known pregnancy.

4. Acute kidney injury as defined by features of RIFLE/AKIN criteria.

The data collection process and tools:

The ICU ledger was used to identify trauma admissions during the study period. Names and file numbers collected from the ledger were used to identify appropriate patient files from our records room. The files that were not obtained were excluded from the results. Subject records that were analysed include referring unit's admissions records and notes and ICU data collected during the admission. Data was recorded and stored using a numerical system in a password protected excel data sheet. Data of all trauma admissions during the study period was analysed to obtain data relating to ICU length of stay and ICU mortality.

The following data was collected:

1. Total number of admissions and deaths during the study period.

2. Indication for admission/ admission diagnosis.

3. Demographic and anthropometric data as follows:

a) Age in years (yrs).

b) Gender (Male or Female).

c) Weight in kilogram (kg).

d) Height in meters (m).

e) Body mass index (kg/m^2).

f) Body surface area (m^2).

4. Acute Physiology and Chronic Health Evaluation II score.

5. Sequential Organ Failure Assessment score.

6. Injury severity score.

7. Data describing interventions in ICU.

a) Mechanical ventilation required at any point (documented as Yes or No).

b) Vasopressor/inotropes required at any point (documented as Yes or No).

c) Plasma creatinine concentration on day 1 (µmol).

d) Creatinine clearance on day 1 (ml/min/1.73m^2).

8. Length of ICU stay (days).

9. Mortality in ICU during study period.

Measuring ARC:

An 8-hour urinary creatinine clearance collection was the primary method of measuring creatinine clearance during the study period. Urine was collected via the urinary catheter for a period of 8 hours daily. Urinary volume was documented, concurrent urine and plasma creatinine concentrations were obtained. This was used to calculate creatinine clearance using the standard formula:

$$CrCl = \frac{Urine\ creatinine}{Plasma\ creatinine}\ x\ \frac{Urine\ volume\ (ml)}{Time\ (minutes)} x\ \frac{1.73m^2}{BSA}$$

Body surface area is estimated by the equation of DuBois and DuBois (1916) using the following formula:

$$BSA(m^2) = 0.007184 + 0.425Wt + 0.725Ht$$

Values were subsequently normalized to a BSA of 1.73m^2.

2.4 Data Analysis

Data was collected onto an Excel spreadsheet and was analysed with the assistance of a statistician using STATA version 14.0 (Stata Corp, Collage Station, TX). Categorical data was expressed using percentages (%) and frequencies. Continuous data was expressed using mean, range and percentages. Non-paired analysis of continuous data was done using an independent student t-test. A Mann-Whitney U test was used for non-nominal data. Paired comparison was done using a paired student t-test. A p value of less than 0.05 was considered as statistically significant.

2.5. Significance of the Study

Augmented renal clearance has clinical implications relating to appropriate dosing of renally cleared therapeutic agents such as antibiotics and anticoagulants. Results of this study will help inform current prescribing practices in our setting as well as generate interest in future clinical research.

2.6. Ethics

The study was granted ethics clearance by University of the Witwatersrand Human Research Ethics Committee (M180721). Hospital approval to retrieve and analyse data was obtained.

2.7. Confidentiality

Subject anonymity was maintained at all times. A study number was assigned to each patient after data collection was complete to protect patient confidentiality. All data was kept in a secure location with the names and file numbers kept on a password-restricted excel document.

2.8. Project Outline

This is a MMed project which was planned to be completed over a 2-year period. The date for submission of protocol to the Post Graduate Committee Meeting was on 7th May 2016. The date for submission to the Ethics committee was on 7th June 2018. Data collection started on the 10th July of 2018.

Table 1: Study Timeline Chart

	2016			2018							
Activity	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Literature Review											
Preparing Protocol											
Protocol Assessment											
Ethics application											
Data collection											
Data analysis											
Write-up report											
Write-up article											

2.9. Funding

This is was low cost study. In-kind costs were for photocopying and for data collection. No costs were incurred by participants or by the Hospital.

2.10. Limitations

This was a retrospective study with a small sample size. Limitations of the study pertain to retrospective designs such as missing data.

The results of this study are contextual and may not be applicable to patients in all ICUs.

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CHAPTER TWO: SUBMISSIBLE ARTICLE

Title: Augmented Renal Clearance in Critically Ill Trauma Patients admitted to a Tertiary Intensive Care Unit: A retrospective review of data

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Short Title: Augmented Renal Clearance in Critically Ill Trauma Patients

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KEYWORDS: Augmented renal clearance, intensive care unit, trauma, renal function.

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ABSTRACT

Background

Augmented renal clearance (ARC) is enhanced elimination of solutes by the kidneys. Patients with ARC have normal plasma creatinine concentrations and typically display a hyperdynamic circulation, with increased cardiac output, resulting in renal hyper-perfusion and increased creatinine clearance (CrCl). The resultant enhanced elimination of renally cleared agents may be associated with sub-therapeutic drug levels and lower minimum inhibitory concentration of antibiotics. There is a paucity of studies describing the occurrence and features of ARC in a South African population.

Methods

We conducted a retrospective review of data of all trauma patients admitted to the Intensive Care Unit (ICU) at Chris Hani Baragwanath Academic Hospital (CHBAH) during a one-year period to identify those with features of ARC.

Results

Of the 96 trauma patients admitted to CHBAH ICU over the study period, 38 met inclusion criteria. Of these, 29 showed features of ARC (CrCl > (130mL/min/1.73 m^2). Most patients with ARC were male 75.9% (n=22/29), with a mean age of 32.7 years (SD 11.3 years) and mean weight of 75.7 kg (SD 14.0). Overall, 76.3% (n=29/38) of patients had at least 1 episode of ARC during the first 7 days of ICU admission. CrCl was highest on day 4 occurring in 77.8% (n=14/18) of patients with an average CrCl of 180 ml/min/1.73m^2, and again at day 7 when 77.8% of patients demonstrated ARC with an average CrCl of 163 ml/min/1.73m^2. The majority of those with ARC 86.2% (n=31/36) had undergone emergency surgery on admission and 25% (n=9/36) had required inotropic support. There was no significant difference in modified Sequential Organ Failure Assessment (mSOFA) (p=0.836), Acute Physiology and Chronic Health Evaluation (APACHE) (p=0.081), or Injury Severity Scores (ISS) (p=0.422) between patients with ARC and those with no features of ARC.

Conclusion

A high prevalence of ARC was detected in our South African ICU population. As this was a single centre, retrospective audit, further studies exploring the presence and clinical impact of ARC in the South African trauma population and in other populations are still needed.

Introduction

Acute kidney injury (AKI) is common in critically ill patients and is associated with worse outcomes.(1) The RIFLE (Risk Injury Failure Loss of renal function and End-stage kidney disease) and later AKIN (Acute Kidney Injury Network) classifications, formulated by the Acute Dialysis Quality Initiative allows for the standardised definition of AKI.(2) Acute kidney injury complicates the presentation of 1 to 25% of all critically ill patients in developing countries.(1) Of these, up to 4% require renal replacement therapy (RRT) with an overall hospital mortality of 60% within the first month following Intensive Care Unit (ICU) admission.(3) Acute kidney injury occurs at a lower incidence in trauma patients and at higher rates in patients presenting with severe sepsis.(4) Renal injury in the intensive care setting is thought to involve multiple different mechanisms including hypotension, renal hypoperfusion, drug toxicity, and the release of endogenous nephrotoxins in the presence of sepsis.(5) The result is endothelial damage, vasoconstriction and activation of inflammatory processes.(6) Renal function may worsen with the consequent accumulation of renally excreted solutes, metabolites and drugs.(7)

On the other end of the spectrum is augmented renal clearance (ARC), a phenomenon that refers to enhanced renal elimination of circulating solutes such as waste products and pharmaceutical products. Augmented renal clearance is defined as a creatinine clearance (CrCl) of greater than or equal to 130 ml/min/1.73m^2. Some studies have used 120 ml/min/1.73m^2.(8-10) The prevalence of ARC has been reported to range from 28 to 65%,(11,12) but the proportion can be as high as 80% in trauma and septic patients admitted to ICU.(13,14) In one study 17.9% of patients had evidence of hyperfiltration defined as a CrCl >120ml/min/1.73m^2 on day 1 of ICU admission.(10) The prevalence of ARC in another study was shown study to be highest on day 5 post ICU admission.(11) There is a documented increase in cases of ARC of up to 30% during the first week of ICU admission.(9,15)

The subset of critically ill patients who are at risk of developing ARC tend to be male and less than 50 years of age. In a study conducted in 2013, a higher prevalence (85.7%) of ARC was noted in those with polytrauma.(11,16) Polytrauma patients with

low illness severity scores using the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores are also more likely to be affected; as well as patients with good diastolic blood pressures and good urine outputs on admission to ICU.(9,11,15,16) Other at-risk populations include patients with burns, sepsis and ventilator associated lung injury.(17) Recent studies have also demonstrated an increased incidence of ARC in patients with severe head injury who received hypertonic saline, with or without vasopressors to maintain cerebral perfusion.(18)

Pathophysiological factors that are thought to be contributory include haemodynamic instability, inotropic support, sepsis, aggressive fluid resuscitation, an increase in major organ perfusion and low systemic vascular resistance.(11,19,20) Affected patients have plasma creatinine levels within normal ranges and typically exhibit signs of a hyperdynamic circulatory status, with a high cardiac output, resulting in high renal perfusion and increased CrCl.(8)

Augmented renal clearance is associated with sub-therapeutic drug concentrations particularly in critically ill patients which may have therapeutic and prognostic implications and should therefore be recognized in ICU settings.(16) Clinically relevant therapeutic implications include effects on renally cleared drugs, such as sub-therapeutic drug levels of antibiotics and efficacy of thromboprophylaxis with low molecular weight heparin (LMWH).(15,21)

Of interest are beta-lactam antibiotics. These include penicillins, cephalosporins, carbapenems and monobactams.(34,17) Beta lactams have time dependent pharmacokinetic properties. Therefore, , the time for which the drug concentration is persistently above minimum inhibitory concentration (MIC) is essential for bactericidal activity.(34,18) Drug dosing should focus on maintaining plasma concentrations above MIC for 90-100% of dosing intervals, with concentrations of at least 4 to 5 times the MIC for maximal bactericidal effect.(34) Considering the time dependent bactericidal properties, higher doses with a more frequent or continuous drug dosing would be ideal in maintaining therapeutic drug concentrations in patients with ARC.(14)

Aminoglycosides have concentration dependent bactericidal properties and their effect is determined by the ratio of maximum plasma drug concentration to MIC.(12,17) They are excreted almost unchanged by the kidney. Once daily dosing

has been shown to be superior to multiple divided doses. A more frequent dosing to at least 18 hourly has been advised where ARC is suspected and should be implemented together with therapeutic drug monitoring (TDM) where available.(36) In clinical practice, TDM for aminoglycosides is routinely measured because of their narrow therapeutic index to reduce risk of toxicity and is also useful in monitoring efficacy.(23)

Plasma concentrations of vancomycin have been shown to be lower in patients with ARC during the first days of treatment, despite adequate dosing.(18,22) Monitoring and the maintenance of a steady state of trough levels is associated with good clinical outcomes.(36)

With regards to fluoroquinolones dosing depends on the area under the time curve for a 24-hour period.(19,29) It has been suggested that more frequent dosing would be beneficial in patients with ARC.(19)

Anticoagulation in critical care is often achieved with the use of LMWH. Levels cannot be directly measured in plasma and thus a surrogate marker, anti-factor Xa is used to measure its biological effect. The presence of ARC has been associated with shortened activity of enoxaparin and therefore the recommendation is to dose adjust and monitor the biological effect using anti-factor Xa activity which correlates well with clinical effect.(21)

Little is known about the prevalence of ARC in the South African critically ill population. We aimed to determine the prevalence of ARC among critically ill trauma patients admitted to a tertiary ICU and to identify risk factors associated with its occurrence.

Methods

Study population

This was a single centre, retrospective cohort study of data of all trauma patients admitted to CHBAH ICU from January 1999 to December 1999.

Data Collection

Permission to conduct this study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (M180721). The ICU ledger was used to identify trauma admissions during the study period. This study period was a time when creatinine clearance was routinely measured in our unit. The names and file numbers collected from the ledger were used to identify appropriate records from the records room. Subject records that were analysed include referring unit's ICU admissions records, and notes and ICU data collected during the admission. Data was recorded and stored using a numerical system in a password protected Excel data sheet. Two files were missing and were thus excluded from the results.

Definitions

Augmented renal clearance was defined as a creatinine clearance of greater than or equal to 130ml/min/1.73 m^2. An episode of ARC was defined as a single event or measurement of creatinine clearance of greater than or equal to 130ml/min/1.73 m^2.

Data of patients were included if the patients had had an ICU length of stay of more than 24 hours, had an admission plasma creatinine of < 120 micromol/L and no history of prior renal replacement therapy or chronic kidney disease. Data was excluded if the patient was under 18 years of age. Pregnant patients, patients suspected clinically to have rhabdomyolysis or those with admission creatinine kinase more than 5000 IU/L (where such data was available), and those with AKI as defined by features of RIFLE/AKIN criteria were also excluded.

Assays

An 8-hour creatinine clearance collection was the primary method of measuring creatinine clearance during the study period. Urine was collected via the urinary catheter for a period of 8 hours daily. Urine volume was documented, and concurrent urine and plasma creatinine concentrations were obtained. This was used to calculate creatinine clearance using the standard formula:

$$CrCl = \frac{Urine\ creatinine}{Plasma\ creatinine}\ x\ \frac{Urine\ volume\ (ml)}{Time\ (minutes)} x \frac{1.73m^2}{BSA}$$

Body surface area (BSA) was estimated by the equation of DuBois and DuBois (1916) using the following formula:

$$BSA(m^2) = 0.007184 + 0.425Wt + 0.725Ht \quad . (30)$$

Values were subsequently normalized to a BSA of 1.73m^2.

Statistical Analysis

Data was collected into an Excel spreadsheet and exported to STATA v14 (Stata Corp, College Station, TX) for analysis.

Categorical data was summarized using frequencies and percentages (%) whereas continuous data was summarized using means and standard deviations (where normally distributed). The Pearson's chi-square test (and Fischer's exact test if cell frequencies <5) were used to compare categorical variables and the independent student's t-test was used to compare continuous variables. Prevalence of ARC was computed as the percentage of patients with at least one ARC episode among the total study patients admitted to the CHBAH ICU over the 7-day study period.

Bivariate and multivariate modified-Poisson regression models were used to examine predictors of ARC occurrence and mortality. Modified-Poisson regression is the preferred approach to binary logistic regression as the main study outcome occurred commonly (>10%). For inclusion into multivariate models we considered variables that were a *priori* and were significant at 20% in the bivariate analysis. All p-values of less than 0.05 were considered as statistically significant.

Results

Study participant selection and characteristics at baseline.

Of the 96 trauma patients admitted to ICU over the study period, 38 met inclusion criteria and were included in the study. The following patients were excluded from the study: 25 patients had abnormal renal function (creatinine >120 µmol/L) on admission, of these which 2 patients also had rhabdomyolysis, 18 patients were less

than 18 years of age, one patient was pregnant and 14 patient files were excluded due to insufficient data, including 2 files which could not be located. The selection of the final study participants is presented in Figure 2 below.

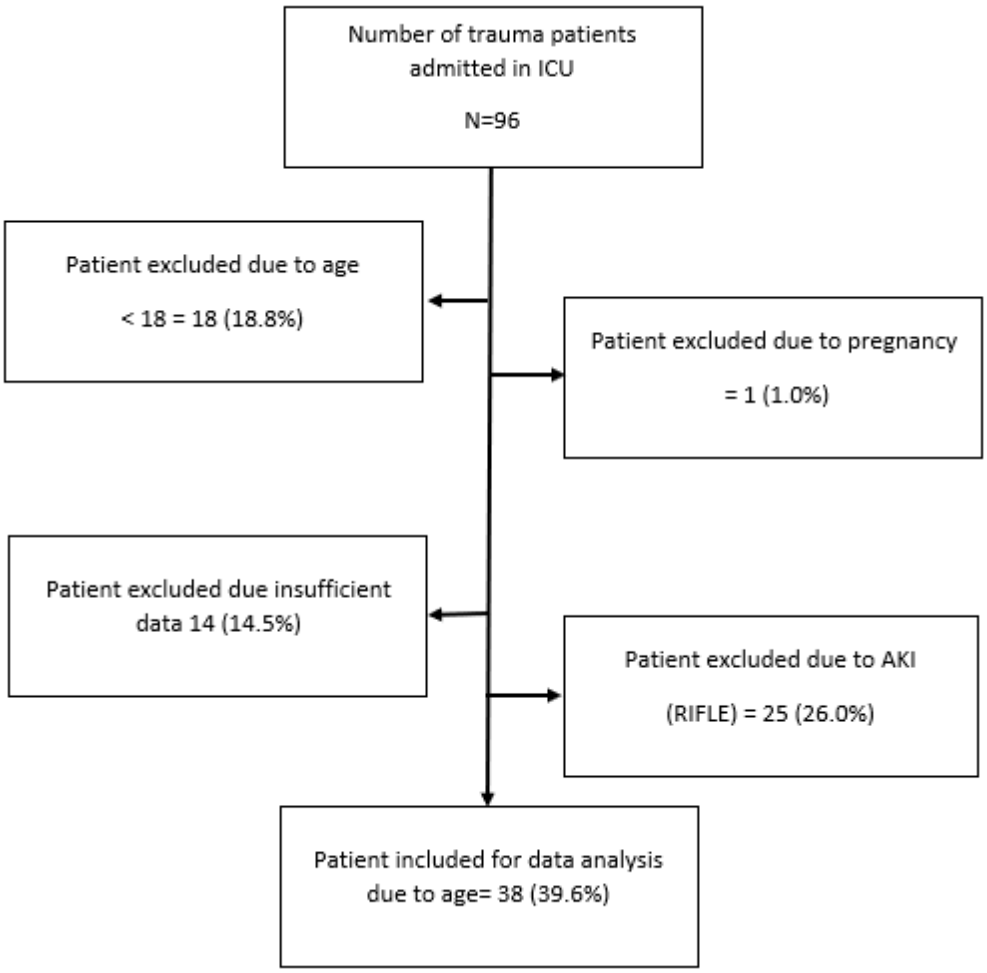

Figure 2: Selection of the final study sample of patients

Prevalence of ARC

Twenty-nine (76.3%) patients had ARC (CrCl > 130 mL/min/1.73 m^2) during the first 7 days of ICU admission. Of those included in the study, the prevalence of ARC on the day of admission was 35.1% (n=13). The prevalence of ARC increased to 53.6% on day 1 post ICU admission. Day 4 of ICU admission had the highest ARC prevalence of 77.8% (n=14) of the 18 patients remaining in ICU. (Figure 3). Prevalence continued to increase until day 4 from 35.1% to 77.8%. The prevalence

of ARC in those remaining in ICU until day 7 remained between 55.6% to 77.8% (Figure 3).

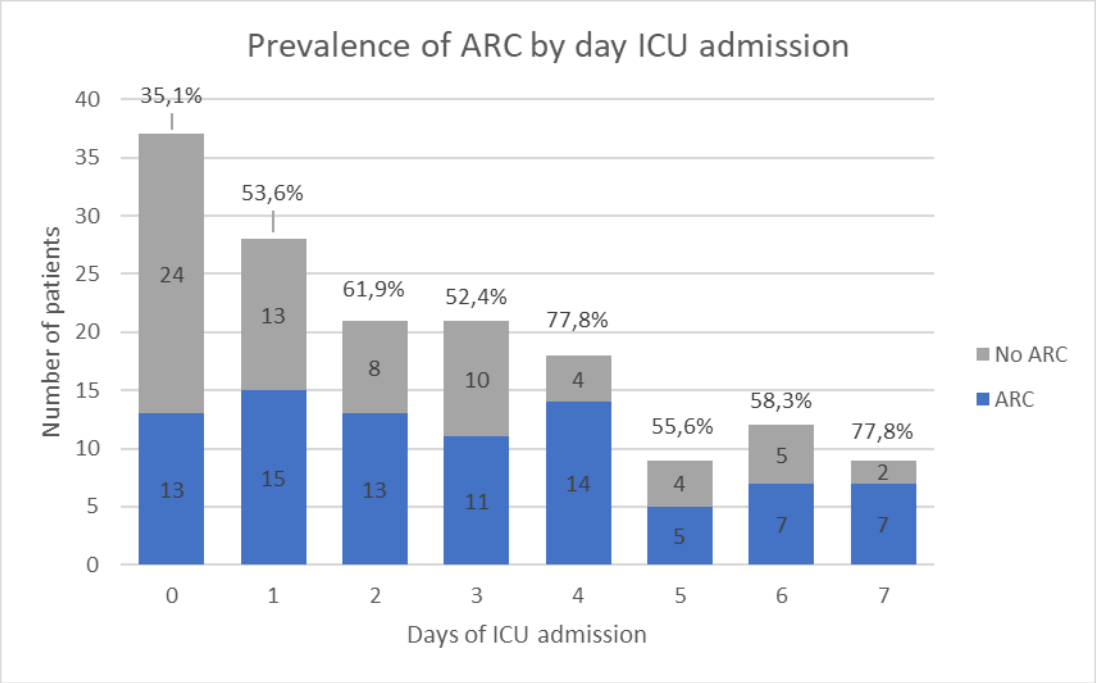

Figure 3: Prevalence of ARC by day of ICU admission

All patients had serum creatinine and urine collection collected as part of their routine management. Baseline demographic and clinical characteristics of the study patients are shown in Table 2.

Demographics

Of the 38 patients included in the study, the majority were male (76.3%, n=29), the mean age was 32.7 years (SD 11.3 years) and mean weight was 75.7 kg (SD 14.0 years).

Table 2: Characteristics of the study patients at admission

Characteristic	Total	No ARC	ARC	p-value
Total, n (%)	38 (100)	9 (100%)	29 (100%)	
Sex, n (%) Male	29 (76.3%)	8 (88.9%)	21 (72.4%)	0.310
Age (years), mean (SD)	32.7 (11.3)	31.7 (9.8)	33.0 (11.8)	0.760
Weight (kg), mean (SD)	75.7 (14.0)	74.3 (13.1)	76.1 (14.5)	0.745
Ventilation - Yes, n (%)	34 (94.4%)	7 (87.5%)	27 (96.4%)	0.331
Inotropes - Yes, n (%)	9 (25%)	2 (25.0%)	7 (25.0%)	1.000
Surgery - Yes, n (%)	31 (81.6%)	6 (66.7%)	25 (86.2%)	0.186
APACHE score, mean (SD)	12 (4.4)	14 (4.8)	11 (4.1)	0.081
SOFA score, mean (SD)	11.8 (3.4)	12.0 (3.6)	11.7 (3.4)	0.836
ISS score, mean (SD)	24.5 (9.1)	22.3 (7.4)	25.2(9.6)	0.422
Creatinine, mean (SD)	84.8 (19.9)	79.9 (19.8)	100.0 (9.5)	0.005

SD – standard deviation

Clinical Characteristics

On admission, 94.4% (n=34) received mechanical ventilation, 25% (n=9) received inotropic support and 81.6% (n=31) had antecedent emergency surgery. The proportion of these interventions by ARC status are shown in Figure 4 below.

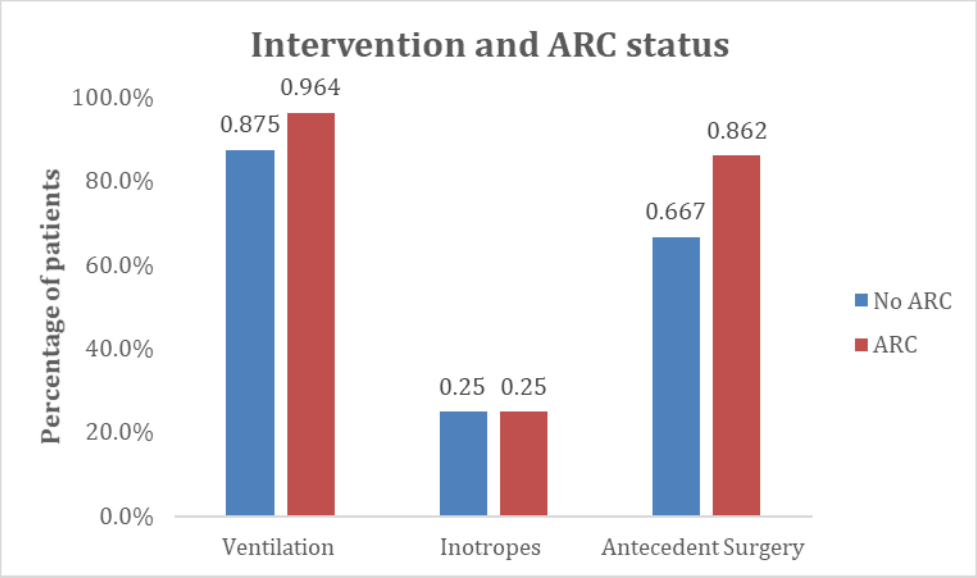

Figure 4: Interventions by ARC status

Patients in our study, those with ARC as well as those without ARC, had higher illness severity scores (APACHE, modified SOFA and ISS scores) compared to patients in previously published studies, with similar illness severity scores being found in both groups. (3,13) The mean creatinine level on admission was 84.8 µmol/L (SD 19.9) in the total sample of 38 patients. As expected, patients who exhibited ARC had a lower mean creatinine level 79.9 µmol/L (SD 19.8) compared to those without ARC, 100 µmol/L (SD 9.5 p=0.005).

Natural history of ARC

Figure 5 illustrates mean CrCl by day of ICU admission. There was a steady increase in CrCl from day of admission (120ml/min/1.73m^2), which peaked to 180ml/min/1.73m^2 on day 4 among patients with ARC. At the end of the study period (day 7), the mean CrCl was 163ml/min/1.73m^2.

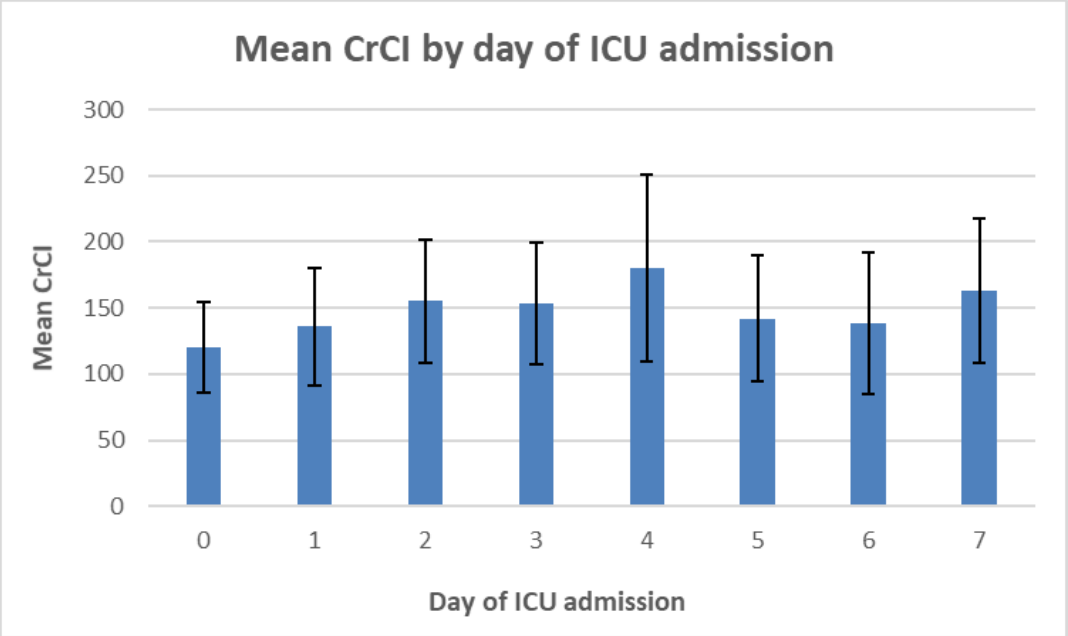

Figure 5: Mean creatinine clearance by day of ICU admission

Mortality

By day 7, a large proportion of the patients had been discharged, and five patients had died during the seven-day study period (13.2%). The ARC cohort had a lower mortality at 10.3% (n=2/29) compared to 22.2% (n=3/29) of those without ARC as demonstrated in Figure 6 below. There was, however, no statistically significant difference in mortality between the 2 groups (p =0.848).

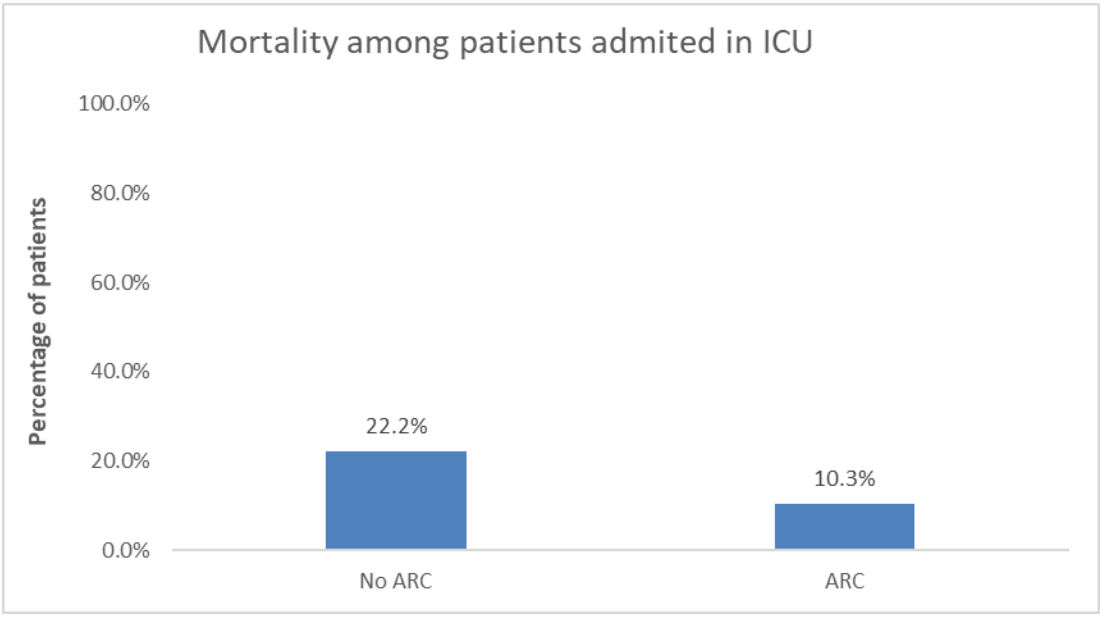

Figure 6: Mortality by ARC status

Predictors of ARC occurrence and mortality

In multivariate analysis, a statistically significant predictor of ARC was a lower APACHE score (adjusted relative risk (aRR) 0.96, 95% CI 0.93-1.00, p=0.050). Estimates for male sex and increase in age failed to reach statistical significance. For mortality, reduced mSOFA score seemed the only significant predictor (aRR 1.54, 95% CI 1.14-2.08, p=0.005). Reduced number of ARC episodes and lower creatinine levels on admission were not statistically significant. These findings should however be interpreted cautiously due to the low sample size and small number of events. See Table 3 below.

Table 3: Multivariate estimates of predictors of ARC occurrence and mortality

	ARC occurrence				Mortality		
Predictor	aRR*	95% CI	p-value		aRR*	95% CI	p-value
Male sex	1.04	0.78-1.40	0.792				
Age	1.03	0.99-1.02	0.644				
APACHE score	0.96	0.93-1.00	0.050				

Creatinine	0.99	0.98-1.00	0.016		1.04	1.00-1.08	0.075
ARC episodes					1.13	0.79-1.60	0.507
mSOFA score					1.54	1.14-2.08	0.005

*aRR – adjusted relative risk.

Discussion

We examined the prevalence of ARC in trauma patients in the ICU of the largest referral hospital in South Africa. The finding of a high prevalence of ARC (76.3%) in this study population is similar to previous studies conducted in high income countries showing a high prevalence of ARC in ICU trauma patients.(8,9,10,12,33) The prevalence of ARC has been reported to range from 28% to as high as 65.1%.(8,10,23). A younger trauma population in our region with a higher renal mass, and fewer comorbidities than in many other settings are likely contributing factors.

The majority of patients with ARC were male (75.9%). This is in line with previous studies that identified male gender as a risk factor for ARC.(14) Postulated reasons why ARC occurs more commonly in males include a higher renal mass in males compared to females.(24) In addition, in our study, the male preponderance could possibly be a reflection of the high male trauma related admissions in our setting. Analysis showed that 78% (n =75) of all ICU trauma admissions in the year studied were male, which did not differ significantly from the male preponderance of 76.3% (n=29) included in the study group.

The mean age of patients (years) with ARC in this study was 33.0. This is similar to previous studies that have found ARC to be more common in the younger population.(9,11,14,16) Age less than 50 has previously been identified as an independent risk factor for the occurrence of ARC.(9,11,20) The non-ARC population in this study was on average slightly younger than the patients with ARC with a mean age of 31.7 years, however this was not statistically significant. Our low sample size may explain this observation.

There was no significant difference in mSOFA (p = 0.836), APACHE (p = 0.081), or ISS (p = 0.422) scores between patients with ARC and those without ARC. Illness severity scores in this study population were relatively higher compared to previous studies, the mSOFA score in one such study was below 4 compared to a mean SOFA of 12 in this study.(3,13) This finding differs from previous studies that suggested ARC was associated with lower illness severity scores.(25,27) The higher severity scores noted in both those patients with ARC and those who did not develop ARC in our study may be a reflection of strict admission criteria in a resource limited ICU, where only the sickest qualified to be admitted with 86% of patients in this study having antecedent operation and over 94% received mechanical ventilation. APACHE and mSOFA scores in one study by Udy et al were lower in the ARC group at 16 and 3 respectively compared to 12 and 11.8 in our study. (11)The reason for the higher APACHE scores notable in the study by Udy and colleagues is unclear and may be a result of a younger trauma population in our study and variations in pattern of injury such as fewer head injuries in our population. Unit sedation practices may also result in a lower GCS in the first 24 hours and thus higher APACHE scores. Multi-organ dysfunction seen in sepsis and septic shock may account for the higher mSOFA score, seen in our population.

Patients that had undergone emergency surgery prior to ICU admission had a higher incidence of ARC (86.2%). This is compared to the 66.7% of the non-ARC patients who had antecedent surgery. We did not observe any statistical significance (p=0.186) between the two groups, likely related to the small sample sizes. The observed trend of higher ARC following emergency surgery is thought to be a reflection of the underlying inflammatory processes related to the pathology and to the surgery, and to the aggressive fluid resuscitation patients may have received in theatre prior to ICU admission.(8)

Ventilated patients were more likely to develop ARC in our study. Ninety seven percent of ventilated patients had ARC. This was an interesting trend but was not statistically significant. Similar trends have been found by other authors, suggesting an effect of mechanical ventilation on cardiac output resulting in increased renal perfusion, hyperfiltration and subsequent increased tubular secretion. (8,9,11)

Only 25% of patients demonstrating ARC had received inotropes, which was lower than the cohort of patients who did not develop ARC but was not statistically

significant (p= 1.000), likely due to the small sample size. Nevertheless, an interesting finding as the use of vasoactive drugs has been associated with altered vascular tone and cardiac output resulting in renal hyperfiltration and subsequent ARC in other studies. (9,11,19)

A study of the onset and duration of ARC suggested that a high creatinine clearance was present in 35.1% of patients on day 0 of ICU admission. This continued to rise during ICU stay and was highest on day 4 of ICU admission at 77.8% (n=14). This is in line with earlier studies that observed that a marked rise in creatinine clearance on day 1 post ICU admission predicts a sustained increase in CrCl over the next 7 days.(16) Fuster-Lluch and colleagues found 17.9% of critically ill patients had evidence of hyperfiltration (CrCl >120ml/min/1.73m^2) on day 1 of ICU admission and this is thought to be related to the aggressive fluid resuscitation and use of inotropic agents prior to ICU admission, which increased renal blood flow and subsequently GFR.*(*3,13) This was also noted in our study but with an even higher incidence on day 1 of 35.1%. Consistent with previous studies, CrCl was highest on day 4 of ICU admission, likely a result of therapeutic interventions in ICU such as inotropic support and pathophysiological events like the SIRS response that can increase cardiac output and subsequent GFR. (3,31)

The onset and duration of ARC may be linked to the acute insult caused by the underlying pathological process.(8) Aggressive fluid resuscitation, inotropes and vasoactive drugs are thought to contribute to the development of ARC.(9,11) The improvement by day 7 could be related to the improvement in haemodynamic parameters due to the mobilisation of excess fluid as well as renal recovery with return to baseline function. (6,24)

Mortality was lower in the ARC cohort (10.3%) compared to the non-ARC population (22.2%) and this is because patients with ARC compared to non-ARC improved, maintained their renal function and were discharged from ICU. There was, however, no statistically significant difference in mortality between the 2 groups (p =0.848).

Limitations

This was a retrospective study with a small sample size and has limitations that pertain to retrospective designs such as missing data to calculate creatinine

clearance. The results of this study population are contextual and may not be applicable to patients in all ICUs.

Recommendations

Future prospective studies should consider the impact of confounding factors on ARC for example sepsis, types of inotropes used and injury patterns.

Conclusions

A high prevalence of ARC was detected in our South African ICU population. A majority of patients were male which we attribute in part, to the demographics of trauma patients we admit to ICU. Although not statistically significant, 97% of ventilated patients and 86% of those that had antecedent surgery in our study developed ARC. There was no significant difference in illness severity scores or in mortality outcomes between patients with ARC and those without ARC.

Measurements of creatinine clearance in critically ill patients may help identify ARC early, allow for early drug dosing modification and the avoidance of treatment failure.

As this was a single centre retrospective audit, with a limited sample size, further studies exploring the presence and clinical impact of ARC in the South African population and in other populations including paediatrics are still needed.

Disclosure statement

The authors have no conflict of interest to declare

Conflict of interest

Nil

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APPENDICES

APPENDIX A: Permission from Ethics Committee

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Zoleka Mafuya

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180721

NAME: (Principal Investigator)	Dr Zoleka Mafuya
DEPARTMENT:	Internal Medicine Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Augmented renal clearance in critically ill trauma patients admited to Chris Hani Baragwanath Academic Hospital Intensive Care: a restrospective review of data
DATE CONSIDERED:	27/07/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Gladness Nethathe and Gloria Teckie
APPROVED BY:	Prof C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	07/08/2018

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 July and will therefore be due in the month of July 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 B: Approval letter from Head of Department of ICU at CHBAH

health and social development
Department: Health and Social Development
GAUTENG PROVINCE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL
Intensive Care unit

Dr JM Brown
Jacqui.Brown@wits.ac.za
Tel: 0119381596
Fax:0119381595

6th September 2016

To whom it may concern

Re: Permission to conduct research for MMed in Chris Hani Baragwanath Hospital Intensive Care unit

Title of research project:
Augmented Renal Clearence in Critically ill Trauma Patients Admitted to Chris Hani Baragwanath Academic Hospital Intensive Care Unit: A retrospective review of data.

Investigator: Zoleka Mafuya

Permission is hereby granted for Zoleka Mafuya to access ICU files for the purpose of her data collection. The data collected will be used for her MMed.

Regards

Dr JM Brown
Deputy Head: Intensive Care Unit
Chris Hani Baragwanath Hospital
Soweto
Affiliated to University of the Witwatersrand

APPENDIX C: Data collection sheet

Indication for admission	Admission diagnosis	
Antecedent operation (pre-admission surgery)	Yes =1 /No= 2	
Admission date (ccmmdd) and time (hour: min)		
Discharge date (ccmmdd) and time (hour: min)		
ISS Score		
APACHE II score (24 hours)		
Modified Sequential Organ Failure Assessment score (max), median (IQR)		
Age (years)		
Gender		
Height (m)		
Weight (kg)		
Body mass index, kg/m2		
Body surface area, m2		
Interventions in the unit: Arterial line inserted? Yes =1 /No=2		
Organs support required during ICU stay: Ventilation: Yes = 1 /No = 2		
Inotropic support at any point during ICU stay:		

Yes =1 /No=2	
Laboratory investigations Plasma creatinine (admission), µmol/L	
Creatinine excretion rate, mg/kg/d, (day 1)	
Creatinine Clearance measurements mL/min/1.73 m2 taken during the first 7 days of ICU stay 1. 2. 3. 4. 5. 6. 7.	
Outcome at ICU discharge: alive/dead	