PIM 3 predicted mortality compared to the observed mortality rate for patients in the PICU in Universitas Academic Hospital, segregated into four physico-chemical aspects for acid-base disturbances

By

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DEDICATION

This study is dedicated to my wife Adri and my two children Anlea and Liam, who have been by my side during my studies and have supported me in good and difficult times.

I also want to thank our Heavenly Father for giving me this opportunity to work in the field of Medicine and especially to work with our children.

DECLARATION OF AUTHORSHIP

I, John Werner Robbetze, declare that this mini-dissertation titled: '**PIM 3 predicted mortality compared to the observed mortality rate for patients in the PICU in Universitas Academic Hospital, segregated into four physico-chemical aspects for acid-base disturbances',** is my independent work and hereby submit it in a publishable manuscript format for the Master's Paediatrics Degree at the University of the Free State. I also declare that I have not previously submitted it for a qualification at another institution of higher learning.

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ABSTRACT

Background: The PIM 3 score is widely used in PICU's, to monitor the quality of care of patients. The reason for this study is to compare the mortality rate for the PICU at Universitas Academic Hospital with the PIM 3 predicted mortality rate and like previous studies to see if there is any association between mortality and the magnitude or nature of the metabolic acidosis.

Objective: The primary objective is to determine the SMR for the PICU at Universitas Academic Hospital for the period 1 January 2016 to 31 December 2018 and the secondary objective, to determine the association between mortality and the different variable for D.A. Story's four equations for the base excess (BE_{SID}, BE_{Lact}, BE_{Alb} and BE_{OI}).

Method: It was a retrospective cross-sectional chart review of all patients, between 0 and 156 months of age, admitted from 1 January 2016 to 31 December 2018. The data used was obtained from the statistics kept in the PICU, patient's files and NHLS Trackcare system. The data was analysed by the Department of Biostatistics at the University of the Free State and Fisher's Exact Test was applied to the data to determine if there is any statistical significance.

Results: 711 patients were admitted. 12 were excluded due to their ages being more than 156 months. 251 patient files had complete bloodgas information. There were 74 deaths (10.9%) in the PICU during this period. The SMR was calculated as 1.5. Among patients with complete data, an association was noted between mortality and increasing PIM 3 risk score (p-value of 0.0001). Hyperlactataemia (>2 mmol/L) and hyperchloraemia (above 120 mmol/L), had a strong association with mortality with p-values of 0.0041 and 0.013 respectively.

Conclusion: The observed mortality rate was higher than the predicted mortality rate according to the PIM 3 score. The study also concluded that mortality is not associated with the magnitude of the metabolic acidosis, but rather the nature (Hyperlactataemnia and hyperchloraemia) of the acidosis.

LIST OF ABBREVIATIONS

A^-	- Anion
$[A^-]$	- Anion concentration
Alb	- Albumin
BE	- Base excess
BE_{Alb}	- Albumin component of the Base excess
BE_{Lact}	- Lactate component of the Base excess
BE_{SID}	- Strong-ion difference component of Base excess
Cl^-	- Chloride
CO_2	- Carbon dioxide
FiO_2	- Fraction of Inspired Oxygen
g/L	- gram/litre
H^+	- Hydrogen ion / proton
$[H^+]$	- Hydrogen ion concentration
HA	- Acid that dissociates into H^+ and A^-
[HA]	- Concentration of acid HA
Hb	- Blood haemoglobin
HCl	- Hydrochloric acid
HCO_3^-	- Bicarbonate
H_2CO_3	- Carbonic acid
H_2O	- Water
ICU	- Intensive Care Unit
K	- Equilibrium constant

mmol/L - millimol per litre

Na^+ - Sodium

NaOH - Sodium hydroxide

OI - Other ions

PCO_2 - Partial Pressure of Carbon dioxide

PICU - Paediatric Intensive Care Unit

PIM - Paediatric Index of Mortality

pK - Dissociation constant for the acid

PO_2 - Partial Pressure of Oxygen

S_{CO2} - Solubility coefficient for Carbon dioxide

SMR - Standardised mortality risk ratio

SID - String-ion difference

SIG - Strong-ion gap

KEYWORD DEFINITIONS

Acid Arrhenius defined an acid as a substance that forms cations and anions when dissolved in water, thus when dissolved in water produces an increased concentration of hydrogen ions [H^+]. Bronsted and Lowry defined an acid as a substance that can donate a proton (hydrogen ion) [6-7].

Acidosis Condition were the pH in blood is less than 7.35 [6].

Alkalosis Condition were the pH in blood is more than 7.45 [6].

Anion Negatively charged ion

Base According to the Bronsted and Lowry definition is a substance that can bind a proton (hydrogen ion) [6-7].

Cation Positively charged ion

Mortality Rate Number of deaths for a particular population for a defined period of time [4].

pH Dimensionless representation of the hydrogen ion concentration for a solution and it is defined as the negative decimal logarithm of the hydrogen ion concentration [6]. The normal physiologic limits for blood pH is between 7.35 and 7.45 [6].

Strong acid Acid that fully dissociates in water or plasma [6].

Weak acid Acid that only partially dissociates in water or plasma [7].

CHAPTER 1

1.1 Literature Review

Paediatric Index of Mortality

The PIM (Paediatric index of Mortality) 3 score has become widely used in various paediatric intensive care units (PICU's) as a measure for monitoring of the quality of care in these units. The PIM 3 researchers designed this third version of the model to determine the risk of mortality, utilising data gathered within the first hour of contact with the patient at admission to ICU [1].

The first version of the PIM score was based on data that was collected from seven PICU's in Australia and one PICU from the United Kingdom. It consisted of 5695 admissions. The second version included PICU's from Australia, New Zealand and the United Kingdom and included data collected from 20787 patients during a period from 1997 – 1999 [1].

However, for these models to accurately predict possible outcomes of patients, they need to include all the most recent, relevant data based on case-mix and clinical practice. Therefore, these models need regular recalibration. The latest calibration of the PIM 2 score was called the PIM 3 score [1]. Again, data was collected from PICU's in Australia, New Zealand and the

United Kingdom and included 53112 patient admissions. The model was based on several predictor values. PIM 3 has diagnostic categories: very high-risk, high-risk or low-risk. It also included, whether the pupils were fixed in response to light or not, admission status (elective or not) and recovery from post-operative procedure, whether cardiac or not. Continuous variables included, systolic blood pressure, absolute value of base excess, FiO_2 and PO_2 on admission [1].

L.J. Solomon et al. assessed the first two versions of the PIM score for their utility as mortality risk assessment models in a South African PICU. They found that these models do predict the risk for mortality in an ICU very reliably, as well as provide a good benchmark for the quality of care provided. However, these scores do not prognosticate very well when looking at individual patients. For this reason, they should not be used to determine whether a patient requires admission to ICU or not [3].

Mortality Rate

The mortality rate is calculated by taking the number of deaths for a particular population over a defined period. To be able to calculate the mortality rate accurately, the number of recorded deaths and the population's data needs to be accurate and reliable [4].

Acid-Base disturbances in ICU's

Critically ill patients, can have complex acid-base disturbances and electrolyte abnormalities, with one review article stating that up to 64% of critically ill patients can have acute metabolic acidosis. These acid-base disturbances can sometimes be mild and self-limiting, but they can also contribute significantly to morbidity and even mortality of the patient [5]. This is true for any changes in pH in any direction (acidotic or alkalotic) and can lead to severe multiorgan damage and failure [5]. Normal protein structure and enzymatic function needs the pH to be maintained within physiologic limits. These physiologic limits are a blood pH between 7.35 and 7.45. A pH below 7.35 is considered acidotic and above 7.45 as alkalotic [6]. In a study performed by Tang et al., who looked at the impact of modifiable ICU interventions on the outcome of cardio-pulmonary resuscitation in paediatric intensive care units, they found that an arrest that was caused by an acid-base disturbance carried a very poor prognosis [8].

For these reasons, we need to understand how to determine whether the acidosis or alkalosis is of metabolic or respiratory origin. It is also essential to quantify the acid-base disturbance and then correctly interpret it (determine possible causes of the acid-base disturbance present) to correctly manage the acid-base disorder or the cause thereof [6]. All this is required to correct the disturbance and prevent severe morbidity or mortality of the patient.

In this discussion, we will focus on metabolic acid-base disorders as these are the most common that clinicians come across in intensive care units. We will consider a brief historical overview of how acids and bases came to be defined, as well as how the clinical determination of the acid-base status was developed. Finally, we will focus on D.A. Story's bedside approach for calculating the possible cause of the acidosis or alkalosis, which is a simplification of Stewart's physico-chemical analysis of what determined acid-base balance [2].

Definition and history of clinical acid-base

In the 1880s Arrhenius defined an acid as a substance that forms cations (H^+) and anions (A^-), when dissolved in water, thus when dissolved in water produces an increased concentration of hydrogen ions (H^+). Then after World War I, Bronsted and Lowry independently developed an identical definition for acid and base, where acid is a substance that can donate a proton (hydrogen ion) and base a substance that could bind a proton. The equation for the Bronsted-Lowry definition:

$$HA \leftrightarrow H^+ + A^-$$

In this equation HA is the acid that can dissociate into a hydrogen ion (H^+) and base (A^-) [6,7].

$$K = [H^+] \times [A^-] / [HA]$$

In this equation K is the equilibrium constant, indicating the strength (grade of dissociation) of an acid, where a large K, represents a strong acid and a small K, a weak acid [6].

Henderson, a biochemist from Harvard, looked at the relationship between carbon dioxide gas and bicarbonate and its role as a buffer of fixed acids. He then rewrote the law of mass action for an acid and its salts in 1909 and applied it to carbonic acid in the following equilibrium equation:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

Where H_2CO_3 is carbonic acid, CO_2 is carbon dioxide, H_2O is water and HCO_3^- is bicarbonate. The Henderson equation relates the concentrations of carbonic acid, carbon dioxide and hydrogen in the following way:

$$K = [H^+] \times [HCO_3^-] / [H_2CO_3]$$

$$[H^+] = K \times [CO_2] / [HCO_3^-]$$

Sorensen then introduced pH as a dimensionless representation of the hydrogen ion concentration for a solution, in that same year. He defined it as the negative decimal logarithm of the hydrogen ion concentration $[H^+]$ [6].

Then in 1912, Hasselbalch performed the first blood pH measurement with a platinum electrode and then later rearranged the Henderson equation into a logarithmic form and replaced $[CO_2]$ with pCO_2 (partial pressure of carbon dioxide), eventually coming up with the Henderson-Hasselbalch equation:

$$pH = pK + \log([HCO_3^-] / S_{CO2} \times pCO_2)$$

In this equation, S_{CO2} is the solubility coefficient of CO_2 and pK the dissociation constant for the acid [6].

At the Rockefeller University Hospital in New York, Van Slyke developed the Van Slyke apparatus, which he used to measure the total carbon dioxide content in plasma. It is only slightly higher than the bicarbonate content in plasma. This method then became the standard for quantifying acid-base disturbances for the next 40 years. From these experiments, he developed a diagram that relates pH to bicarbonate and bicarbonate was seen as a determinant of the pH [6].

In the 1950s, Siggaard-Andersen, Astrup and Knud Engel embraced the Bronsted-Lowry definition of an acid and from this developed the base excess (BE). They did this by conducting in vitro studies that equilibrated blood with a pCO_2 of 40 mmHg, thus effectively removing any respiratory abnormality. Siggaard-Andersen then calculated the amount of strong (fully dissociated) acid (hydrochloric acid [HCl]) or base (sodium hydroxide [NaOH]) which was required to return 1l of blood back to a pH of 7.4. This is the BE in millimoles per litre and is negative if it is and acidosis (NaOH is required) and positive for an alkalosis (HCl is required) [2,6,7]. Siggaard-Andersen then developed a nomogram so that the BE can be determined in a clinical setting. This nomogram was then mathematically transcribed into the Van Slyke equation that is used by modern bloodgas machines to calculate the base excess,

$$BE = HCO_3^- - 24.4 + (2.3 \times Hb + 7.7) \times (pH - 7.4) \times (1 - (0.023 \times Hb))$$

where Hb is the blood haemoglobin [6].

The normal reference ranges are -3 mmol/L to 3 mmol/L and the more negative the value the more acidotic and vice versa [2].

However, the opinions regarding BE differed between schools in Boston and Copenhagen and thus, the great trans-Atlantic debate began. Schwartz and Relman, from Boston, argued that base excess from blood was an in vitro method and was inaccurate, because it could not replicate the in vivo carbon dioxide titration curve [6]. The reasoning was that only the intravascular compartment was assessed and the interstitial space was excluded. The interstitial space has a much weaker buffering capacity than blood, due to the lower concentration of albumin in the interstitial space and the absence of erythrocytes [6]. Siggaard-Andersen then assumed a haemoglobin concentration of 50 g/L, which reduced the buffering capacity of blood in vitro. In this way, he derived the standard base excess [7]. The Americans continued to argue with this concept and introduced the six Bostonian rules to identify pCO_2-invariant changes in bicarbonate. Due to this, many clinicians continued to use the Henderson-Hasselbalch equation to quantify acid-base disorders by using these six Bostonian rules [6,7].

Table 1 – Six Bostonian Rules [6]

Primary Disorder	Expected HCO_3^- = 24 + …	Expected pCO_2 = …
Acute respiratory acidosis	([pCO_2] - 40)/10	
Chronic respiratory acidosis	([pCO_2] - 40)/3	
Acute respiratory alkalosis	(40 - [pCO_2])/5	
Chronic respiratory alkalosis	(40 - [pCO_2])/2	
Metabolic acidosis		1.5 x [HCO_3] + 8
Metabolic alkalosis		0.7 x [HCO_3] + 21

Peter Stewart, in 1970s to 1980s, suggested that Arrhenius' definition of an acid is more useful than the Bronsted-Lowry definition, when considering acid-base disturbances. Stewart introduced a new approach to acid-base physiology, because he found the bicarbonate centred approach too confusing and inadequate in quantifying an acid-base disorder and determining the possible cause of the disturbance. Stewart used several physico-chemical principles, including conservation of mass; electro-neutrality; and dissociation of electrolytes to come up with this new approach [7]. There are three independent controllers of the acid-base status on body fluids according to Stewart's method: The strong-ion difference (SID), the partial pressure of carbon dioxide and the total weak-acid concentration [2]. Strong-ions are ions that dissociate entirely in plasma and the most important are sodium (Na^+) chloride (Cl^-) and lactate [7]. The SID is the sum of all the cations measured routinely in plasma (sodium, potassium, calcium and magnesium) minus the all the anions that are routinely measured (chloride and lactate) [2]. Weak acids, that are only partially dissociated in plasma, include mostly albumin and to a lesser extent phosphate [7].

Physiologist, James Gamble developed the Gamble-gram which assumes electroneutrality. It illustrates that the anions that make up the SID are mostly bicarbonate and the weak acids of which albumin is the most important [2].

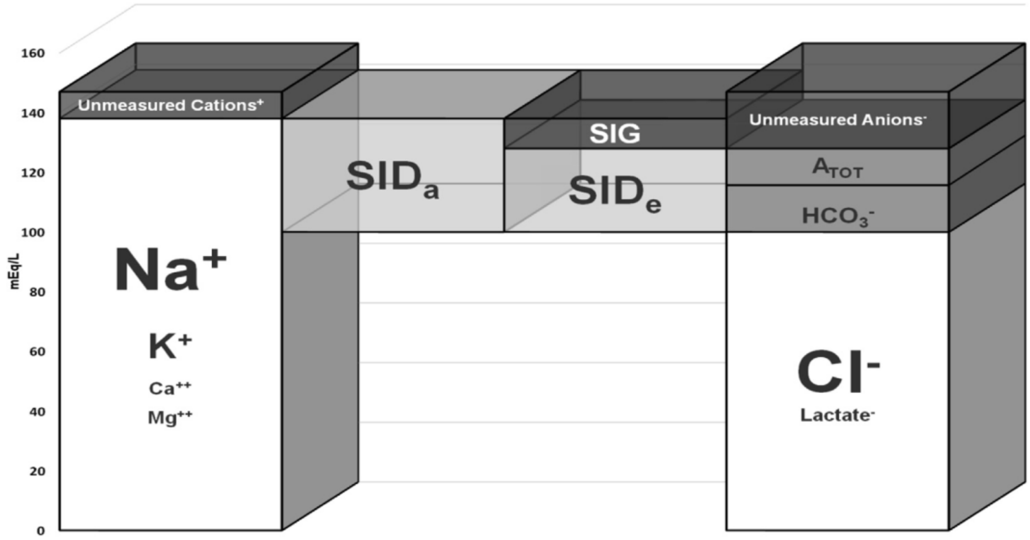

Figure 1 – Graphical representation of the Stewart model [6]

One can deduce from this that a reduced SID, results in a lower bicarbonate level, which indicates the presence of acidosis. Conversely, an increased SID indicates an alkalosis [2]. Weak acids, on the other hand, play an opposite role to SID. An increase in total weak acids will cause an acidosis, whereas a decrease in the total weak acids causes alkalosis and an increase in the SID [2]. Stewart believed that bicarbonate and base excess was useful to determine the extent of the acid-base disorder, but did not indicate the mechanism [7].

Simplified bed-side approach to Stewart's physical-chemical approach

D.A. Story then developed a simplified approach based on the base excess and looking at Stewart's physico-chemical method. Changes in the strong-ion difference (SID) and the total amount of weak acids will cause changes in the base excess [2]. Milliequivalent is a unit of electrical charge and milliequivalent per litre can then be used to unify the concentrations of the chemical constituents that make up the plasma. A milliequivalent is the amount of that substance that is required to combine with one mmol of hydrogen ions [2]. Sodium, potassium, chloride, lactate and bicarbonate are all univalent ions and therefore milliequivalent per litre can be substituted with mmol/L. It is difficult to estimate the electrical charge of albumin, but a good approximation is 0.25 x albumin concentration in g/L. Base excess is derived from mmol/L of HCl (hydrochloric acid) and therefore changes in the determinants of the base excess will lead to changes in the base excess [2].

From this D.A. Story proposed to divide the base excess into four parts:

$$BE_{SID} = \text{measured Na} - \text{measured Cl} - 35$$

$$BE_{Lact} = 1 - \text{measured lactate}$$

$$BE_{Alb} = 0.25 \times (42 - \text{measured albumin})$$

$$BE_{Total} = BE_{SID} + BE_{Lact} + BE_{Alb} + BE_{OI}$$

<u>Strong-ion difference</u>

Sodium and chloride are the major strong-ions apart from lactate and the difference in concentrations make up the SID [2]. If the normal reference values for sodium and chloride are used then:

$$Na^+ - Cl^- = 140 - 105 = 35\text{mmol/l}$$

and therefore, taking into account electrical neutrality:

$$BE_{SID} = \text{measured } Na^+ - \text{measured } Cl^- - 35$$

Thus, hyponatremia or hyperchloremia will lead to a reduced SID and result in metabolic acidosis [2].

<u>Lactate</u>

Lactate is the other strong anion apart from chloride and is therefore important in acid-base disturbances. Sodium is the principal cation in opposition to lactate, but sodium is already accounted for in the SID; thus, the effect of lactate on the base excess taking electroneutrality into account is:

$$BE_{Lact} = 1 - \text{measured lactate}$$

If the lactate increase then the BE becomes more negative indicating to a worsening acidosis [2].

Albumin

As noted, albumin is the most important weak acid. Story calculated the ionic concentration of albumin by 0.25 x albumin concentration in g/L. The normal plasma albumin concentration is 42 g/L, and thus the BE_{Alb} effect is calculated by:

$$BE_{Alb} = 0.25 \times (42 - \text{measured albumin})$$

Therefore, if any patient becomes hypoalbuminaemic, it will become more alkalotic [2].

Other ions and weak acids

Other ions include both measured and unmeasured cations and anions that will also affect the acid-base status. Measured cations include calcium, potassium, magnesium and unmeasured from aluminium, lithium and proteins. Other measured anions include phosphate and those not routinely measured are sulphate and acetate and several others [2].

From this, we see that if the changes in Na-Cl, lactate or the albumin, do not explain the BE, then other ions are playing a significant role in causing the acidosis or alkalosis [2].

Similar research studies

Now, in this study that we propose to compare mortality rates derived from the PIM 3 score with the actual mortality rate in the study PICU. This will determine how accurate the PIM 3 score is in predicting mortality in the study PICU. We also want to test its ability to predict outcomes among sub-categories of the study population, grouped according to the four above equations. We will determine which sub-category will have the most unsatisfactory outcomes. Therefore, we will be looking at the nature of the acid-base disturbance, rather than the magnitude of the metabolic acidosis. Our working hypothesis is that mortality is more closely related to the nature of the metabolic acidosis, rather than the magnitude thereof.

A similar study was performed by Hatherill et al, at the Red Cross War Memorial Children's Hospital in Cape Town and published in 2003 [9]. Their prospective study, examined the relationship between the magnitude of the acid-base disturbance in terms of BE and the nature of the metabolic acidosis (either hyperlactatemia, hyperchloraemia or due to other unmeasured anions) and mortality among children with shock [9]. They defined metabolic acidosis as a BE of less than or equal to -5 mmol/L (more negative than the normal range that was referred to earlier). They recorded the observed ICU mortality and the mortality risk according to the PIM score [9]. The outcome of the study was consistent with their hypothesis, that mortality is more closely related to the nature of the metabolic acidosis rather than the magnitude [9]. They found that hyperlactatemia was associated with a poor outcome in these shocked paediatric patients. However, what was interesting was that an anionaemia (other anions), was not associated with increased mortality and hyperchloraemia showed a trend towards survival [9]. They postulated that the lack of an association between the magnitude of the acidosis and mortality, might have been due to alkalinising factors, such as hypoalbuminaemia, which concealed metabolic acidosis. Another observation that they made was that the admission lactate often failed to discriminate between survivors and non-survivors. However, lactate of >5 mmol/L discriminated well. Lactate in isolation though, is not very useful and that the trend of lactate levels over time are important in predicting mortality versus survival [9].

A similar study by Kwok Ho et al., compared the prognostic significance of the SIG (Strong ion gap) or SID, (the difference between the amount of fully dissociated cations with fully dissociated anions), with other acid-base markers, that included lactate [10]. They found evidence that the SID or SIG are associated with the severity of inflammation [10]. Therefore, they hypothesised that the SIG might be more important in predicting mortality in critically ill patients than other acid-base markers. However, what they found was similar to the previous study that lactate was better at discriminating between survivors and non-survivors, than the SIG [10]. Therefore lactate, according to them is the preferred resuscitation target in critically ill patients [10].

Hyperchloraemic Metabolic Acidosis and hyperchloraemia

Hyperchloraemic metabolic acidosis can result from renal or gastrointestinal losses of sodium or with fluid resuscitation by using 0.9% Saline. Hyperchloraemic metabolic acidosis can lead to hypotension and impaired cardiac contractility. Chloride can also affect the kidneys by reducing renal blood flow and renal cortical perfusion [11]. In the immune system, hyperchloraemic metabolic acidosis induced a pro-inflammatory response via increased interleukin 6 to interleukin 10 ratio. This was shown in animal models and in vitro cell models [11]. Due to all these detrimental effects, there are multiple discussions regarding 0.9% saline as a resuscitation fluid [11]. In an animal study where 0.9% Saline, Ringer's Lactate, Plasmalyte A and Plasmalyte R were compared as resuscitation fluids, it was found that animals resuscitated with Ringer's Lactate had greater 2-week survival rates than those resuscitated with 0.9% Saline and they had better acid-base balance. For this reason, the trend is to move away from using 0.9% Saline as resuscitation fluid [12].

Stenson et al., studied the association between hyperchloraemia and morbidity and mortality in paediatric patients in septic shock. Hyperchloraemia is associated with poor outcomes in critically ill adults [11]. Children in septic shock are aggressively resuscitated with crystalloid solutions and if the solution is 0.9% Saline, it can lead to hyperchloraemia (as stated above). Recently, findings show that resuscitating severely ill children with chloride-rich solutions is associated with poor outcome [11]. They found that if the maximum chloride, during the stay in the PICU was >110 mmol/L, it was usually not associated with a complicated course in the ICU. However, if the minimum chloride was equal to or greater than 110 mmol/L, then there was an increased risk of mortality [11].

This finding is, however, in contrast to that of the study by Hatherill et al. They found a fall in chloride and elevated lactate and unmeasured anions, to preserve electro-neutrality. For this reason, they saw a trend towards hyperchloraemia among survivors [9].

1.2 Research Questions

- How does the mortality rate in the PICU at Universitas Academic Hospital in the Free State, compare to the PIM 3 predicted mortality rate?
- Which of D.A. Story's four equations for the base excess are associated with a poor outcome for patients admitted to the PICU at Universitas Academic Hospital, based on the admission blood analyses?

1.3 Aim of the Study

The study aims to compare the mortality rate predicted by the PIM 3 score with the actual mortality rate for the Paediatric Intensive Care Unit at Universitas Academic Hospital and then to determine, based on the bloodgas and blood chemistry on admission to the PICU, which of to D.A. Story's four equations for the base excess, is associated with poor outcome.

1.4 Objective of the Study

The objective of the study is to determine the actual mortality rate for the Paediatric Intensive Care Unit at Universitas Academic Hospital for the period 1 January 2016 to 31 December 2018 and to compare it with the PIM3 derived expected mortality rate. Following this to determine, according to the bloodgas analyses and blood chemistries, the variables making up the four equations for the base excess, by D.A. Story and then to see which of these physico-chemical variables is associated with poor outcome.

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CHAPTER 2

2.1 Abstract

Background: The PIM 3 score is widely used in PICU's, to monitor the quality of care of patients. The reason for this study is to compare the mortality rate for the PICU at Universitas Academic Hospital with the PIM 3 predicted mortality rate and like previous studies to see if there is any association between mortality and the magnitude or nature of the metabolic acidosis.

Objective: The primary objective is to determine the SMR for the PICU at Universitas Academic Hospital for the period 1 January 2016 to 31 December 2018 and the secondary objective, to determine the association between mortality and the different variable for D.A. Story's four equations for the base excess (BE_{SID}, BE_{Lact}, BE_{Alb} and BE_{OI}).

Method: It was a retrospective cross-sectional chart review of all patients, between 0 and 156 months of age, admitted from 1 January 2016 to 31 December 2018. The data used was obtained from the statistics kept in the PICU, patient's files and NHLS Trackcare system. The data was analysed by the Department of Biostatistics at the University of the Free State and Fisher's Exact Test was applied to the data to determine if there is any statistical significance.

Results: 711 patients were admitted. 12 were excluded due to their ages being more than 156 months. 251 patient files had complete bloodgas information. There were 74 deaths (10.9%) in the PICU during this period. The SMR was calculated as 1.5. Among patients with complete data, an association was noted between mortality and increasing PIM 3 risk score (p-value of 0.0001). Hyperlactataemia (>2 mmol/L) and hyperchloraemia (above 120 mmol/L), had a strong association with mortality with p-values of 0.0041 and 0.013 respectively.

Conclusion: The observed mortality rate was higher than the predicted mortality rate according to the PIM 3 score. The study also concluded that mortality is not associated with the magnitude of the metabolic acidosis, but rather the nature (Hyperlactataemnia and hyperchloraemia) of the acidosis.

2.2 Introduction

The PIM (Paediatric Index of Mortality) 3 score is a mortality risk assessment score, and has become commonly used in various Paediatric Intensive Care Units (PICU) as a measure of the quality of care of these units [1]. PIM 3 is the third version of this model. It was designed to estimate the risk of mortality, by using data gathered within the first hour of contact with the patient during admission to ICU [2]. PIM 3 is based on several different variables. These include whether a diagnosis is of very high-risk, high-risk or low risk, whether the pupils are fixed in response to light or not, systolic blood pressure, absolute base excess, FiO_2 and PO_2 and recovery from a post-operative procedure, whether cardiac or not [2]. From the PIM 3 model, the standardised mortality ratio (SMR) can be calculated, which is the number of deaths in the PICU compared with the expected deaths according to the PIM 3.

The PIM 3 mortality risk assessment score has the absolute base excess as one of the variables which contribute to mortality risk. However, it does not take into account the type of acid-base disturbance, only the magnitude of the change from normal [2].

In the 1970's to 1980's, using a novel approach, Peter Stewart proposed a new approach to acid-base physiology. He used physico-chemical principles like conservation of mass, electroneutrality and dissociation of electrolytes to formulate this new approach [3]. Stuart identified three independent controllers of the acid-base status on body fluids: the strong-ion difference (SID), partial pressure of carbon dioxide and the total weak-acid concentration [3,4]. The most important strong-ions include sodium (Na^+), chloride (Cl^-) and lactate. The most important weak acids include mostly albumin and to a lesser extent phosphate [4]. D.A. Story, later developed a simplified approach based on the base excess (BE) and Stewart's physico-chemical approach. He noted that changes in the strong-ion difference (SID) and the total amount of weak acids would cause changes in the base excess [4]. From this, D.A. Story proposed to divide the base excess into four parts or equations based on the SID, lactate, albumin and then other ions (anions or cations that have a smaller effect on base excess unless present in large concentrations) [4].

From a previous study by Hatherill et al., there is evidence to suggest that the nature of acidosis influences mortality risk. They found that the magnitude of the acidosis as given by the base excess is unrelated to mortality. In contrast, the nature of the metabolic acidosis, according to them hyperlactaemia, is associated with mortality [9]. Stenson et al., found that hyperchloraemia is also associated with mortality as the chloride increased above 110 mmol/L [11].

This study seeks, first to assess how the mortality rate for the PICU at Universitas Academic Hospital, in the Free State compared with the PIM 3 predicted mortality rate. Secondly, whether there is any relationship between the nature of acidosis and mortality risk based on the type of acidosis, which will be determined using the four separate equations by D.A. Story which simplified Stuart's physico-chemical approach to acid-base balance. Therefore, simply put the second objective is to look at the relationship between mortality and the four components of base excess as described by Story. It will try to determine which of these four components is associated with the worst outcome [4].

The reason for this study is due to the limited data available on the evaluation of the PIM 3 mortality risk score in South Africa and the researchers could find no similar research on a PICU in the Free State.

2.3 Methods

Aims of the study

The primary aim of the study was to compare the mortality rate for the Paediatric Intensive Care Unit at Universitas Academic Hospital in the Free State with the PIM 3 predicted mortality score, for the period 1 January 2016 to 31 December 2018, therefore to determine the SMR for this PICU.

The secondary aim was to determine, based on the bloodgas and blood chemistry on admission to the PICU, the association between mortality and D.A. Story's four equations for base excess (BE), which are BE_{SID}, $BE_{Lactate}$, $BE_{Albumin}$ and $BE_{Other\text{-}ions}$.

Study Design

The study was a retrospective cross-sectional study.

Study Population

Universitas Academic Hospital is a tertiary level hospital in the Free State that consists of a five-bed PICU, which cares for all children between the ages of 0 to 156 months (13 years), who require intensive care. The researchers included all the patients between 0 and 156 months that were admitted to the PICU from 1 January 2016 to 31 December 2018. Admission bloodgas parameters (arterial or venous) and blood chemistry, are routinely assessed on all patients admitted to the PICU.

The researchers included all patients for whom PIM 3 data was available in the analysis for the first research question. To answer the second research question, we accessed the patient files from the Records Department to obtain the admission bloodgas information. The researchers measured bloodgasses on a Radiometer ABL90 Flex bloodgas analyser, which is serviced and calibrated by the NHLS. The researchers obtained the rest of the blood results from the NHLS Trackcare web results viewer.

Ethics

The researchers conducted the study with full approval from the Health Science Research Ethics Committee (HSREC) at the University of the Free State, Free State Department of Health and the National Health Laboratory Service (NHLS). As this was a retrospective study and patient files were used, it did not require permission from patients to use patient information in the study however, permission had to be obtained from the authorities mentioned above to make use of the patient files.

Data Collection

The researchers gathered study data from patient admission statistics, patient files and patient laboratory results. The researchers captured the data on a data sheet and transferred it to an Excel spreadsheet, in consultation with the Department of Biostatistics at the University of the Free State.

The Department of Biostatistics did not analyse data from the pilot study that consisted of only five patients, but indicated that all required data variables were available to continue with the research study for complete analysis.

Measurement definitions

The researchers defined mortality as death at any time in the PICU, regardless of the duration of admission.

D.A. Story's four equations for base excess:

$$BE_{SID} = \text{measured Na} - \text{measured Cl} - 35$$

$BE_{Lact} = 1 – \text{measured lactate}$

$BE_{Alb} = 0.25 \times (42 – \text{measured albumin})$

$$BE_{Total} = BE_{SID} + BE_{Lact} + BE_{Alb} + BE_{OI} \quad [4]$$

Statistical analysis

The data was analysed by the Department of Biostatistics, using SAS Software, Version 9.4 (Copyright © 2002-2012 by SAS Institute Inc., Cary, NC, USA). The researchers described the study population in terms of the gender (percentage male to female admissions), the median age at admission to the PICU, length of stay, including the median length of stay and lastly the number of days ventilated, including the median.

The researchers converted the PIM 3 risk for mortality scores to percentages which were divided into three arbitrary categories of low (<10%), medium (10%-50%) and high-risk (>50%) of mortality. The researchers stratified the patient population into these three categories. The researchers determined the actual mortality rate for the whole PICU population and compared it with the expected mortality rate derived from the PIM 3. The researchers also calculated the SMR for this unit.

The researchers divided the pH and Actual BE (BE_{Total}) into three categories; acidosis, normal and alkalosis. BE_{SID}, BE_{Lact}, BE_{Alb} and BE_{OI} were divided into categories; negative values, normal (equal to zero) and positive values. The sodium, chloride and lactate values were also divided into different categories based on the studies performed by Hatherill et al., and Stenson et al. [9,11]. The researchers compared the differences in mortality rates across categories. Fisher's Exact test was applied to these categorical variables to determine the p-value and to see if there is any statistically significant association between these variables and mortality.

2.4 Results

There were 711 patients admitted to the PICU during the study period. The researchers excluded 12 patients due to their ages falling outside the range of 0 months to 156 months. The researchers could not obtain admission bloodgas information for all the patients, as some files were missing and, in some files there was no bloodgas information available. Therefore, only 251 patients with bloodgas information recorded on admission were used to answer the second research question (secondary objective). Figure 1 shows a schematic of the patients included in the study.

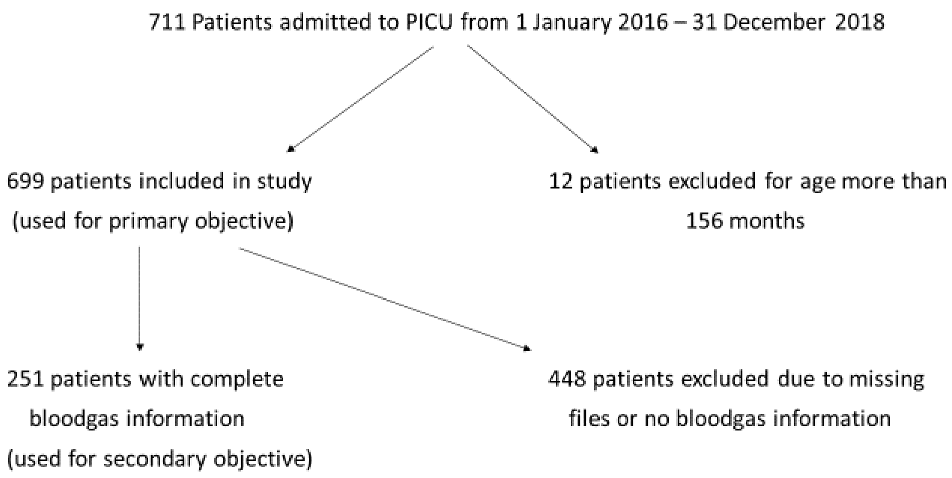

Figure 1 – Schematic of patients included in study

<u>Results for all patients</u>

A total of 699 patients were included in the study. The study population is given in Table 1 and Table 2.

Table 1 – Male vs Female admissions

Gender	**Number of patients**	**Percentages of patients**
Male	430	61.5%
Female	269	38.5%

Table 2 – Study population: Age distribution, length of stay and days ventilated

	Median	**Minimum**	**Maximum**	**Lower**	**Upper**

				Quartile	**Quartile**
Age (months)	19	0.2	156	4	72
Length of stay (days)	4	0	364	2	8
Days ventilated	0	0	114	0	4

One patient was admitted for 364 days and ventilated for 114 days, which were significant outliers. From the table, the researchers noticed that most patients admitted to the PICU are not ventilated or do not require ventilation.

The researchers converted the PIM 3 score to a risk percentage for each patient. The minimum risk for mortality was 0.02% and the maximum was 100%. The median risk for mortality was 1.7%. This percentage indicates that most of the patients admitted to the PICU at UAH have a low risk of mortality. The researchers divided the PIM 3 risk for mortality score percentages into three categories: low, medium and high-risk. A breakdown of the number of patients, expected deaths and actual deaths for each of these categories are showed in Table 3.

Table 3 – PIM 3 risk percentage categories

PIM 3 Risk percentages category	**Number of patients**	**Percentage of patients**	**Predicted number of deaths from PIM 3**	**Percentage of the predicted number of deaths**	**The actual number of deaths**	**Percentage of the actual number of deaths**
Low Risk (<10%)	596	85.3%	12.9	26.4%	36	48.6%
Medium Risk (10% - 50%)	76	10.9%	15.2	31.1%	23	31.1%
High Risk (>50%)	27	3.9%	20.8	42.5%	15	20.3%
Total	699		48.9		74	

If we look at the medium and high-risk categories, then 14.8% of the patients had a more than 10% chance of dying. According to PIM 3, the expected deaths was 48.9 over the study period (expected mortality rate = 7%), giving an SMR of 1.5 for this PICU.

The absolute base excess is one of the variables used to calculate the PIM 3 score. In the study population, the maximum absolute base excess was 30.7 mmol/L, the minimum 0 mmol/L and the median value was 5.5 mmol/L. Therefore, the majority of the base excess values were either within the normal range of -3 mmol/L to 3 mmol/L.

<u>Results of patients with complete bloodgas information</u>

Complete bloodgas information could only be obtained for 251 patients. These 251 patients were categorised according to their bloodgas pH into three groups, normal pH (7.35 – 7.45), acidosis (<7.35) and alkalosis (>7.45). Figure 2 shows the percentages for each category, with 55.9% having an acidosis on admission.

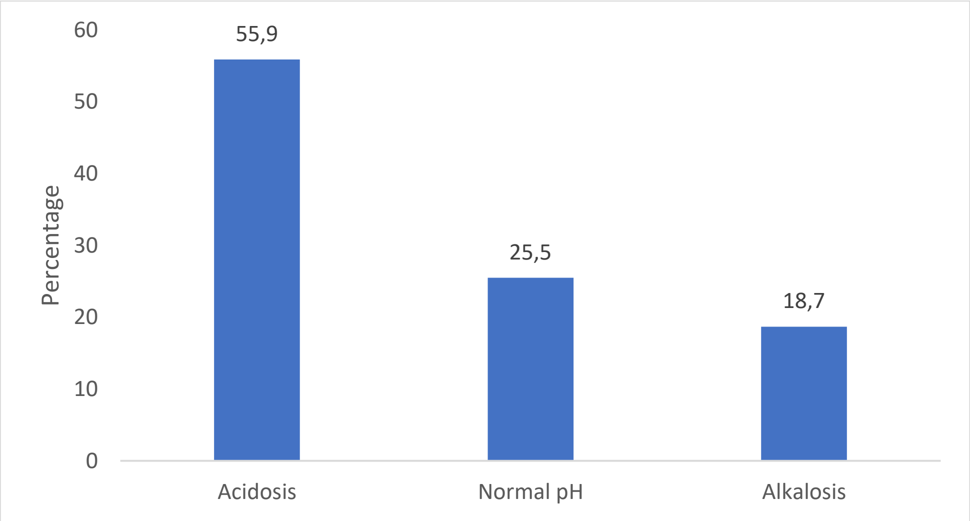

Figure 2 – Acid-base categories

Of the 251 patients with complete data, 228 of the patients were discharged and 23 died. The predicted number of deaths, according to the PIM 3 score was 12.5. This gives an SMR of 1.84 for the group of patients with complete data. Figure 3 shows the comparison in SMR values for all the patients versus the patients with complete data.

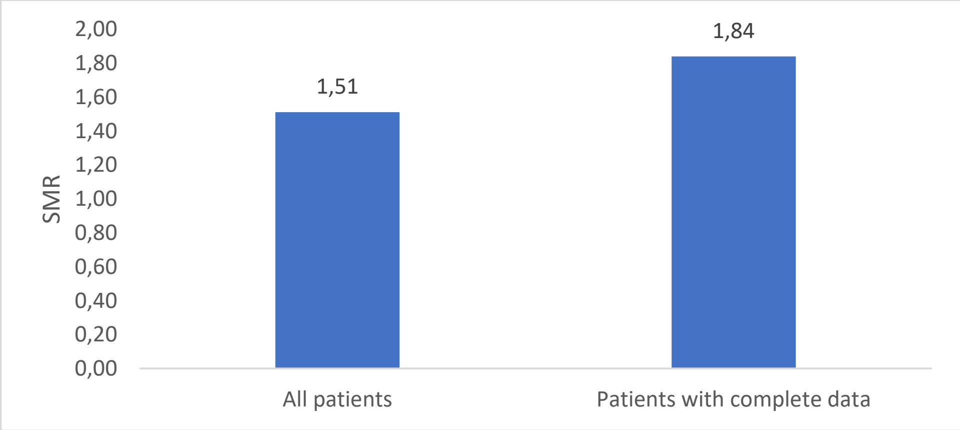

Figure 3 – SMR for all patients vs. patients with complete data

The diagnostic categories for the patients with complete data and the number of patients in each category are showed in Table 4. Table 5 outlines the diagnoses in each category.

Table 4 – Diagnostic categories and number of patients in each category

Diagnostic Category	Number of patients	Diagnostic Category	Number of patients
Central Nervous System	67	Cardiovascular System	39
Respiratory System	55	Haematological System	5
Gastro-intestinal System	47	Nutritional	3
Endocrine System	9	Poisoning	9
Renal System	20	Trauma	12

Table 5 – Diagnoses in each diagnostic category

Diagnostic Category	Diagnoses
Central Nervous System (CNS)	Guillain Barre Syndrome, CNS abscess, transverse sinus thrombosis, stroke, meningitis, seizures/epilepsy, apnoea, encephalitis, hydrocephalus
Post-operative	Subdural empyema drained, temporal lobe resection, craniotomy, endoscopic third

	ventriculostomy, external ventricular drain, ventriculo-peritoneal shunt, encephalocele repair, muscle biopsy, tumour biopsy or resection
Cardiovascular System	Shock (hypovolaemic/cardiogenic/septic), haemangioma, cor-pulmonale, cardiac failure, infective endocarditis, congenital cyanotic and acyanotic heartlesions
Post-operative	Central shunt, transposition of the great arteries repair
Respiratory System	Pneumonia, bronchiolitis, pneumothorax, epiglottitis, croup, tonsillitis, upper airway obstruction, empyema
Post-operative	Tonsillectomy
Gastro-intestinal System	Acute liver failure, acute diarrhoea, cholangitis
Post-operative	Hypertrophic pyloric stenosis, bowel obstruction, inguinal abscess drained, gastrectomy, choledochal cyst, intussusception, inguinal hernia repair, diaphragmatic hernia repair, hepatoblastoma resection, Kasai for biliary atresia, omphalocele repair, appendicectomy, trachea-oesophageal fistula repair
Renal System	Hypertension, urinary tract infection, haemolytic uraemic syndrome, renal abscess, acute kidney injury, nephritis
Post-operative	Nephrectomy for nephroblastoma or other renal tumour
Haematological System	Leukaemia
Endocrine System	Diabetic keto-acidosis
Nutritional	Severe acute malnutrition with and without oedema

Poisoning	Organophosphates, Tegretol, Paraffin, Iron
Trauma	Burns, traumatic brain injury, penetrating abdominal trauma, near drowning
Post-operative	Femur fracture repair, aortic injury repair, skull fracture repair

Tables 6 shows a comparison of the median, lower and upper quartile values for the mortality risk and acid-base variables for the survivor and non-survivor groups.

Table 6 – Survivors vs, non-survivors

	Survivor			**Non-survivor**		
Variables	**Median**	**Lower Quartile**	**Upper Quartile**	**Median**	**Lower Quartile**	**Upper Quartile**
PIM 3 Risk Percentage	1.4	0.4	4.2	6.8	2.2	12.5
pH	7.39	7.33	7.45	7.36	7.25	7.45
Actual Base Excess mmol/L	-4.0	-7.2	0.6	-1.8	-9.3	3.4
Absolute Base Excess mmol/L	5.2	3.1	8.3	5.0	2.2	9.6
Sodium (Na) mmol/L	137.5	135.0	141.0	137.0	132.0	142.0
Chloride (Cl) mmol/L	107.0	103.0	111.0	105.0	99.0	109.0
BE_{SID} mmol/L	-4.0	-7.0	-1.0	-1.0	-5.0	2.0
Lactate mmol/L	1.4	0.9	2.1	2.2	1.4	3.0
BE_{Lact} mmol/L	-0.4	-1.1	0.1	-1.2	-2.0	-0.4
Albumin (Alb) g/L	29.0	25.0	33.0	24.0	22.0	30.0
BE_{Alb} mmol/L	3.3	2.3	4.3	4.5	3.0	5.0
Expected Base Excess mmol/L	-1.8	-5.2	2.2	1.0	-4.0	5.3

BE_{OI} mmol/L	-1.4	-3.8	0.7	-1.6	-5.6	1.0

The median PIM 3 risk for mortality percentage, in the non-survivor group (6.8%) was higher compared to the survivor group (1.4%). We noted that the median actual base excess in the non-survivor group was -1.8 mmol/L, which is within the normal range (-3 to 3 mmol/L), whereas the value for the survivor group (-4 mmol/L) was outside this range. This indicates that the magnitude of the acidosis as given by the base excess is unrelated to mortality.

The median lactate for the non-survivors, was 0.8 mmol/L more than for the survivor group showing that there most likely is an association with high lactate values and mortality. The median BE_{SID} for the survivors was -4 mmol/L, compared to -1 mmol/L in the non-survivor group. The median chloride was higher (107 mmol/L), still normal but trending toward hyperchloraemia in the survivor group compared to the lower median chloride (105 mmol/L) in the non-survivor group.

In Figure 4, the PIM 3 risk percentage categories, were plotted for both the survivors and non-survivors. As can be seen the higher the PIM 3 risk for mortality score the greater the probability of dying. The researchers confirmed this association by Fisher's Exact Test with a statistically significant p-value of 0.0001. There were only four patients in the high-risk group, but 2 (50%) patients died. The proportion of deaths also increases from the low to high-risk groups.

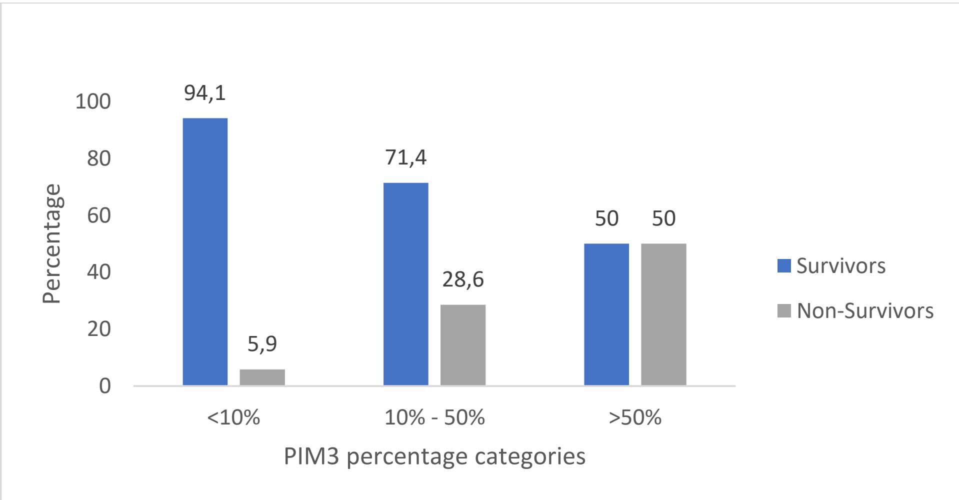

Figure 4 – Comparison of survivors vs. non-survivors for the risk categories (n=251)

As stated previously, we divided the pH into three categories acidosis (<7.35), normal (7.35 to

7.45) and alkalosis (>7.45). We also divided the actual BE into these three categories acidosis (< -3), normal BE (-3 to +3) and alkalosis (> +3). Figure 5 gives a comparison of the deaths in each category based on the pH and the actual BE.

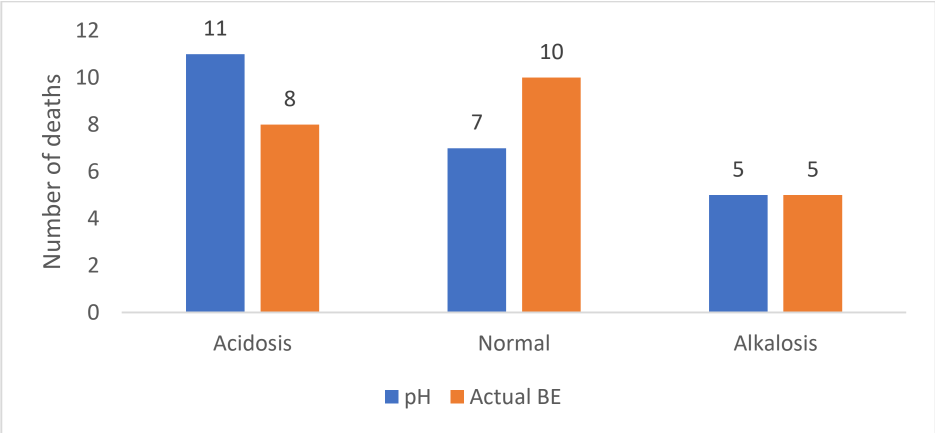

Figure 5 – Comparison of deaths in each acid-base status category based on pH and actual BE

From Figure 5 the researchers noticed there was a difference in the number of deaths in each category, except for the alkalosis category (with 5 deaths), depending on whether we grouped patients according to pH or BE categories.

When looking at the four equations by D.A. Story for BE, each component was divided into categories. BE_{SID}, BE_{Lact} and BE_{Alb} were split into 3 categories: negative values (<0), normal (=0) and positive values (>0) and the BE_{OI} was split into 2 categories negative values (<0) and positive values. Figure 6 shows the percentage of survivors and non-survivors for BE_{SID}.

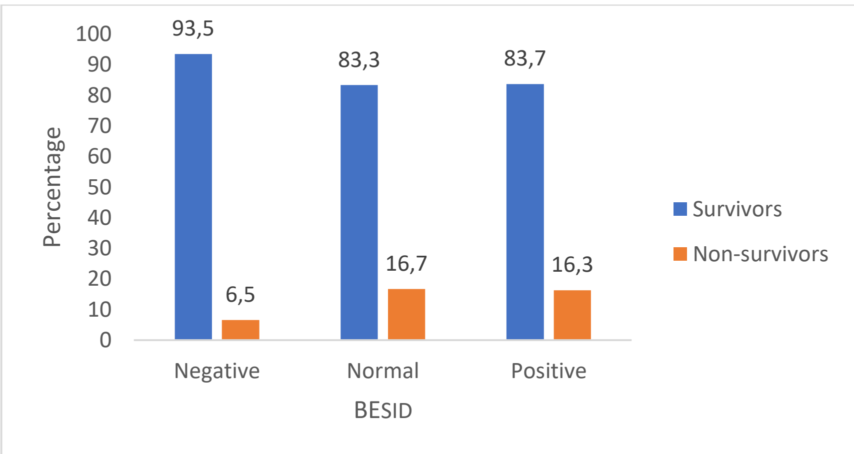

Figure 6 – Percentage of survivors vs. non-survivors in the different BE_{SID} categories

From Figure 6 it was noticed that there was a trend towards survival if the BE_{SID} value was negative, but this may be due to the lack of numbers and most of the patients with complete data having a BE_{SID} that is negative. Fisher's Exact Test was applied to the BE_{SID} categories, which showed that there is an association (although not strong) with increased mortality if the BE_{SID} is abnormal (p-value of 0.0478).

Figure 7 shows the percentage of survivors and non-survivors for BE_{Lact}.

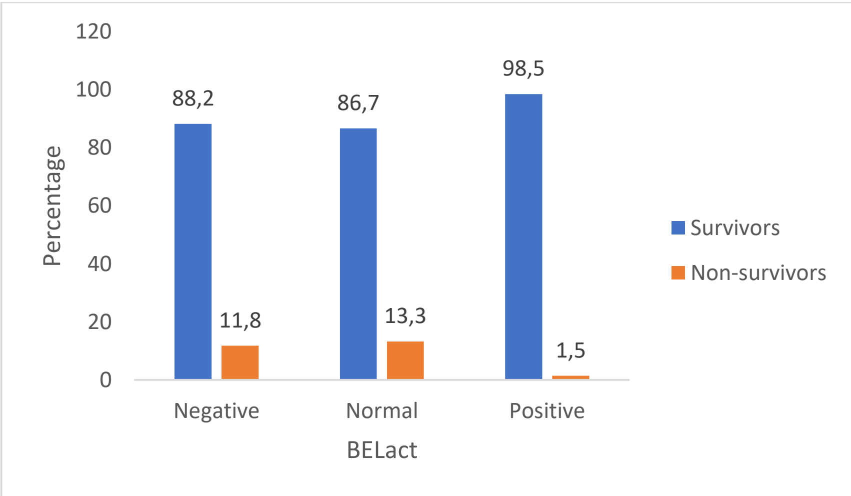

Figure 7 – Percentage of survivors vs. non-survivors for the BE_{Lact} categories

From Figure 7 we notice that the percentage of non-survivors are similar in the negative and normal categories. This may again be due to a lack of numbers in the study. Fisher's Exact Test was applied to the BE_{Lact} categories and it was found to have a strong association with mortality if the BE_{Lact} value was abnormal (p-value of 0.0195).

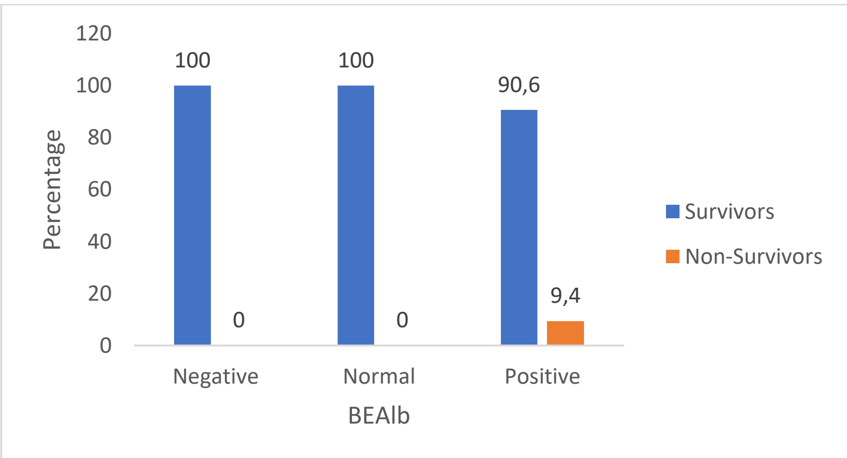

Figure 8 – Percentage of survivors vs. non-survivors for the BE_{Alb} categories

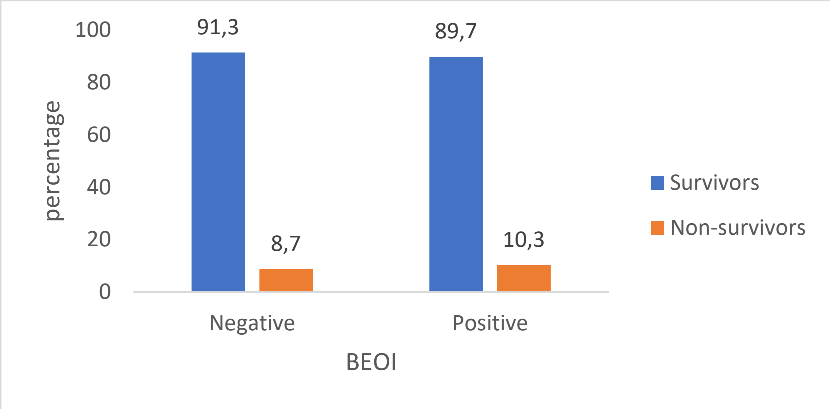

Figure 9 – Percentage of survivors vs. non-survivors for the BE_{OI} categories

Figures 8 and 9 above show the percentages for the survivors and non-survivors in the different categories for BE_{Alb} and BE_{OI}. Fisher's Exact Test was applied to these but showed no association with mortality as the p-values of 1.0 and 0.8134 were not statistically significant.

After noticing the strange results from the 4 D.A. Story equations for BE and the association with mortality, we decided to look at the actual values of sodium, chloride, lactate and albumin, and their association with mortality. Sodium results were divided into 5 categories [13]. The normal range was regarded as 135-146 mmol/L, with critically low values <120 mmol/L and critically high values >150 mmol/L [13]. Figure 10 shows the percentages of survivors and non-survivors for each category. If the sodium was lower than 120 mmol/L; there was an increase in non-survivors. The researchers also observed that the percentage of non-survivors increased as soon as the sodium increased into the hypernatraemic range.

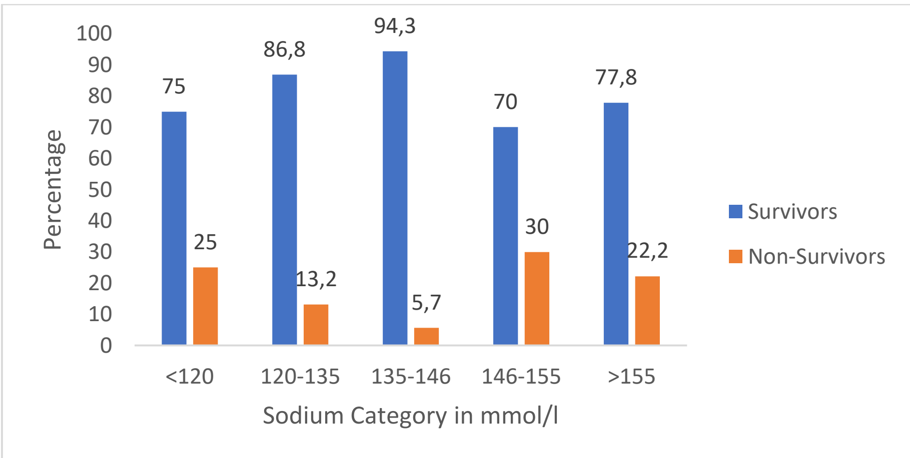

Figure 10 – Percentages of survivors vs. non-survivors in the different sodium categories

Fisher's Exact test was applied to the sodium categories and showed that if the sodium is abnormal (hyponatraemic or hypernatraemic), there is an association with increased mortality (p-value of 0.0092).

Chloride was also divided into 5 categories, with the normal range regarded as 98-110 mmol/L and critically elevated as >120 mmol/L and critically low as <70 mmol/L and the percentages plotted for each category (Figure 11) [11]. Fisher's Exact Test was applied and showed a statistically significant p-value of 0.0132, indicating an association with mortality if the chloride is abnormal. If the chloride was critically elevated (>120 mmol/L), 30% of the patients died, compared to 2.7%, if the elevated chloride is less than 120 mmol/L.

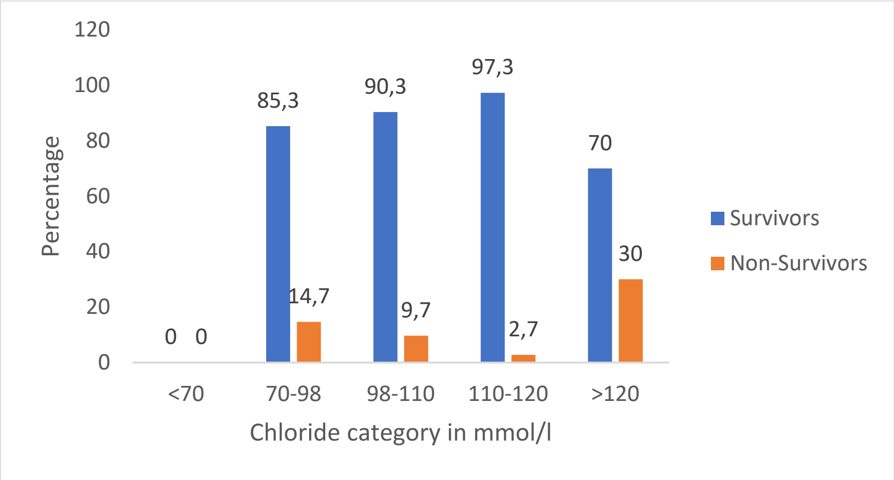

Figure 11 - Percentages of survivors vs non-survivors in the different chloride categories

Lactate was divided into 2 categories with normal <2 mmol/L and elevated >2 mmol/L [9]. The percentages of survivors and non-survivors were plotted in Figure 12. There was a significant increase in mortality, if the lactate was elevated (5.7% deaths in the normal lactate group versus 17.1% in the elevated lactate group). Fisher's Exact Test was applied and it showed a significant association with mortality as the lactate increased (p-value 0.0041).

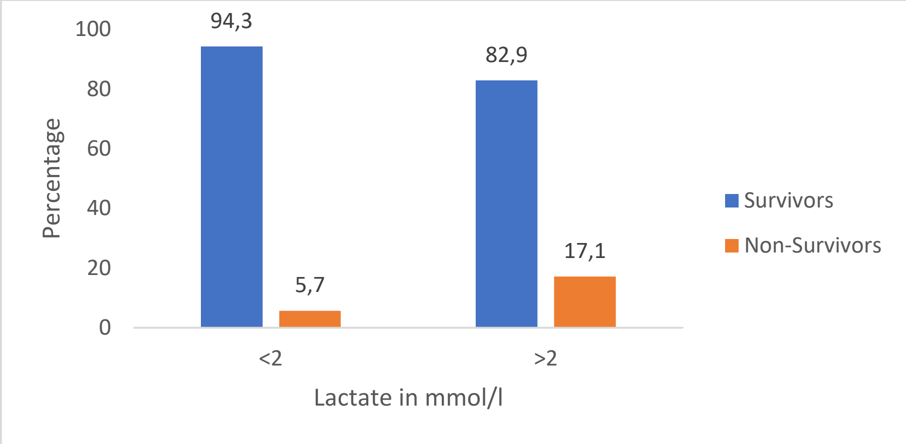

Figure 12 - Percentages for survivors vs non-survivors in the different lactate categories

2.5 Discussion

From the results, the researcher noticed that the majority of patients admitted to this PICU at Universitas Academic hospital were less than 20 months of age. The majority of the patients had a short length of stay, either recovering quickly and getting discharged or dying if severely ill. Possible reasons for the median in days ventilated being so small might be due to patients being admitted post-operatively and not requiring ventilation or the patients were started on non-invasive ventilation like CPAP (continuous positive airway pressure) and then improved clinically; not requiring invasive ventilation.

Looking at the first research question, comparing the PIM 3 predicted mortality with the mortality rate for this PICU, a higher percentage of patients (10.9%) died compared to what was predicted by the PIM 3 score. The predicted mortality rate for this PICU was 48.9 deaths, with the actual mortality rate of 74 deaths. The SMR was 1.5. Therefore, the mortality rate is 50% higher than expected. According to the PIM 3 score only 3.9% of patients had a high risk for mortality and if both the medium and high-risk categories are considered then 14.8% of patients had a more than 10% chance of dying. For the patients with complete data the SMR was 1.84, which is higher than for all the patients. This is due to more deaths occurring in this data set than what was predicted by the PIM 3 score. In the patient group with complete data 23 deaths occurred compared to the 74 for all the patients, this gives 31.1% of the deaths were in the group with complete data. When looking at the predicted mortality according to the PIM 3 score, there was only 12.5 deaths predicted in the group of complete data compared to 48.9 predicted for all patients, which is only 25.6% of the predicted deaths. However, the PIM 3 model was developed on data collected from hospitals in Europe, Australia and other well-resourced countries. It includes multiple variables, among them being certain diagnoses that are classified as low, high and very high-risk [1]. Pneumonia, diarrhoea, meningitis, other common infective illnesses and trauma (not included in the PIM 3 score), occur commonly in South Africa and cause multiple deaths in PICU's. If this was taken into account it may indicate that this PICU is doing relatively well in managing patients requiring intensive care. It is however, advisable to use this mortality risk score, as it relates the quality of care provided in this PICU, to the PICU's from which it was developed.

For the 251 patients with complete data, there was no major difference between the median pH for the survivors and the non-survivors. The median of the actual base excess was more negative in the survivor group compared to the non-survivor group, fitting in with the conclusion from Hathrill et al. that mortality is more closely related to the nature of the metabolic acidosis than the magnitude of the acidosis [9].

The second research question related to which of the variables in the D.A. Story's equations were associated with a poor outcome. The study findings correlated with the study from Hatherill et al. Hyperlactataemia showed an increased risk for mortality compared to other variables with the BE_{Lact} and the lactate showing statistically significant association with mortality. BE_{SID} also showed that there is an association with mortality if the BE_{SID} is abnormal, however what was noticed was that there was a trend towards survival when the BE_{SID} was negative or acidotic, which is not expected. This may be due to the limited number of patients with complete data. A larger data set could show a different outcome. Hyperchloraemia (excluding the critically high values), also showed a trend towards survival together with the BE_{SID}, being more negative in the survivor group than in the non-survivor group. In the non-survivor group, the median for chloride was lower than in the survivor group. This agrees with the statement by Hathrill et al., that to preserve electro-neutrality, the chloride will decrease in response to the increased lactate [9].

The results differed from what was observed in the study by Stenson et al. who found an increased risk for mortality if the chloride increased above 110 mmol/L [11]. In this study the percentage of non-survivors decreased when the chloride increased above 110 mmol/L, but was still less than 120 mmol/L. The percentage of non-survivors, increased after the chloride increased above the critical value of 120 mmol/L. This finding corresponds with Stenson et al, but only at a higher chloride value.

What can be noted is that hyperlactataemia, hyperchloraemia and hypernatraemia were associated with increased mortality rates in the study population.

The BE_{Alb} showed that most of the patients being admitted to the PICU are hypoalbuminaemic. The lower albumin levels, found in the non-survivor group led to a more positive BE_{Alb}. Lower albumin levels, therefore alkalinised the blood. The hypoalbuminaemia counters the acidifying effects of chloride and lactate and pushed the blood pH toward the alkaline range.

For the other-ion group, there was no significant difference between survivors and non-survivors, which indicated that the other cations and anions play a minor role in causing a metabolic acidosis or alkalosis and that these ions need to be quite significantly abnormal to affect the BE and the pH. It may be different for example in the case of a patient with Diabetic Keto-acidosis (DKA). The ketones in the blood will then have a significant acidifying effect on the blood. The BE_{OI} will be elevated, showing the presence of other anions (ketones) causing the metabolic acidosis [14,15].

Although the results agreed with other studies, the patient population was small. This was a limitation to this study as well as the retrospective nature of the study and could lead to bias as many factors could not be controlled to get more accurate data. A recommendation will be to perform a similar, larger prospective study on both PICU's in Bloemfontein over a longer period and with bloodgas information and blood results collected immediately on admission to PICU.

2.6 Conclusion

The percentage of deaths in this PICU at Universitas Academic Hospital was higher than predicted by the PIM 3 score. However, the PIM 3 model does not take into account multiple illnesses (like pneumonia, meningitis and gastro-enteritis etc.) that lead to deaths in counties like South Africa. This could cause the mortality rate to look worse than it might be if these diagnoses were included.

The researchers concluded that mortality is not associated with the magnitude of the metabolic acidosis, but rather the nature of the acidosis. Hyperlactataemia (in particular) and severe hyperchloraemia are associated with an increased risk for mortality. Hypoalbuminaemia counters the acidifying effects of lactate and chloride and other ions have a very small effect on BE, unless present in abundance.

2.7 References

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Appendices

A. Letter of approval from Research Ethics Committee

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

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

[redacted]

Health Sciences Research Ethics Committee

16-Oct-2019

Dear **Dr John Robbetze**

Ethics Clearance: **PIM 3 predicted mortality compared to the observed mortality rate for patients in the PICU in Universitas Academic Hospital, segregated into four physical-chemical aspects for acid-base disturbances**

Principal Investigator: **Dr John Robbetze**

Department: **Paediatrics and Child Health Department (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

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

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2019/0619/2910**

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

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

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

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

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

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

Yours Sincerely

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

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

B. Permission from DOH and NHLS

health
Department of Health
FREE STATE PROVINCE

04 October 2019

Dr J Robbetze
Dept. of Paediatrics and Child Health
UFS

Dear Dr J Robbetze

Subject: PIM 3 predicted mortality compared to the observed mortality rate for patients in the PICU in Universitas Academic Hospital, segregated into four physical-chemical aspects for acid-base disturbances.

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

Trust you find the above in order.

Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 9/10/19

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

health

Department of
Health
FREE STATE PROVINCE

04 October 2019

Dr J Robbetze
Dept. of Paediatrics and Child Health
UFS

Dear Dr J Robbetze

Subject: PIM 3 predicted mortality compared to the observed mortality rate for patients in the PICU in Universitas Academic Hospital, segregated into four physical-chemical aspects for acid-base disturbances.

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

Universitas Academic Hospital	
Name: Dr M Molokomme **Email**: molokommm@fshealth.gov.za **Tel**: 051 405 3557	**PA**: Me M Van Der Berg **Email**: vdbergsu@universitas.fs.gov.za

Trust you find the above in order.

Kind Regards

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

NATIONAL HEALTH LABORATORY SERVICE

Practice No. 5200296

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

REQUEST FOR APPROVAL OF LABORATORY RESOURCES FOR ACADEMIC PURPOSES

Date: 16 May 2019

Requestor: Dr. John Robbetze,

Project Name: "PIM 3 predicted mortality compared to the observed mortality rate for patients in the PICU in Universitas Academic Hospital, segregated into four physical-chemical aspects for acid-base disturbances."

Dear Dr. Robbetze,

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

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

May your project be successful.

NATIONAL HEALTH LABORATORY SERVICE

Regards,

16 MAY 2019

Acting

BUSINESS MANAGER
UNIVERSITAS ACADEMIC
LABORATORIES

Mr. Pakiso Letanta
Acting Business Manager

Prof Eric Buch Dr Karmani Chetty
1 Modderfontein Road, Sandringham, Johannesburg, South Africa
Private Bag X8, Sandringham, 2131, South Africa
+27 (0) 11 386 6000/ 0860 00 NHLS(6457)
5200296

C. Permission from HOD and Universitas Academic Hospital

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA
UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

[redacted]

The Chair: Health Sciences Research Ethics Committee
Dr SM Le Grange
For Attention: Mrs M Marais
Block D, Room 104,
Francois Retief Building
Po Box 339 (G40)
Nelson Mandela Drive
Faculty of Health Sciences
University of the Free State
Bloemfontein
9300

2 April 2019

Dear Dr SM Le Grange

Dr Werner Robbetze (Student number: **2004016578**)
PIM 3 predicted mortality compared to the observed mortality rate for patients in the PICU in Universitas Academic Hospital, segregated into four physical-chemical aspects for acid-base disturbances

I, André Venter, hereby grant Werner Robbetze permission to conduct the above mentioned research project. The research will be completed in accordance with myself as Head of Department of Paediatrics and Child Health and Dr Lincoln Solomon as supervisor of this study.

Yours faithfully

Prof A Venter

2/4/2019.

Date

Department of Paediatrics and Child Health / Departement Pediatrie en Kindergesondheid
205 Nelson Mandela Drive/Rylaan, Park West/Parkwes, Bloemfontein 9301, South Africa/Suid-Afrika
P.O. Box/Posbus 339 (G69), Bloemfontein 9300, South Africa/Suid-Afrika, www.ufs.ac.za, F: +27(0)51 444 3230
Prof A Venter: T: +27 (0)51 405 3181, E: Gnpdav@ufs.ac.za / Prof DK Stones: T: +27 (0)51 405 2820, E: StonesDK@ufs.ac.za

DEPARTMENT: **Paediatrics and Child Health**

This is to certify that the Departmental Evaluation Committee approved of the following MMed research protocol:

CANDIDATE: **Dr John Werner Robbetze (Student nr: 2004016578)**

SUPERVISOR(S): **Dr Lincoln Solomon**

DATE OF THE MEETING: **1 March 2019**

TITLE OF THE RESEARCH PROJECT:

PIM 3 predicted mortality compared to the observed mortality rate for patients in the PICU in Universitas Academic Hospital, segregated into four physical-chemical aspects for acid-base disturbances

RESEARCH CHAMPION — DATE: 2/04/2019

SUPERVISOR(S) — DATE: 2/04/2019

HEAD OF THE DEPARTMENT — DATE: 2/4/2019

health

Department of Health
FREE STATE PROVINCE

24 October 2019

Dr J Robbetze
Department of Paediatrics
Faculty of Health Science
University of the Free State

Dear Robbetze

RESEARCH PROJECT: PIM 3 PREDICTED MORTALITY COMPARED TO THE OBSERVED MORTALITY RATE FOR PATIENTS IN THE PICU IN UNIVERSITAS ACADEMIC HOSPITAL, SEGREGATED INTO FOUR PHYSICAL – CHEMICAL ASPECTS FOR ACID – BASE DISTURBANCES

Herewith permission for the mentioned project to be done at Universitas Academic Hospital on the following condition:

1. The researcher/s should comply with all the conditions referred to in the approval letter obtained from the HOD's Office: Dr D Motau on 9 October 2019.
2. Your research should not interfere with or disrupt the day to day running of the Departments at UAH.
3. The Researcher shall be held personally liable for any additional costs that are incurred by this research and that are not a part of the day to day running of the Departments where the research is conducted.
4. A progress report must be submitted to HOCD: Clinical Services every 3 months.
5. A copy of the results must be submitted to HOCD: Clinical Services once your research is completed.
6. Briefing sessions should be conducted with all stakeholders prior to commencement and at the end of the study to provide feedback where appropriate.

The Chief Executive Officer and HOCD: Clinical Services must be notified of the findings of the project upon completion.

Yours sincerely,

DR RITA NATHAN
B.MedSc, MBCHB, M.MedComm Health, FCPHM(SA), MBA
HOCD: CLINICAL SERVICES
UNIVERSITAS ACADEMIC HOSPITAL

HOCD: CLINICAL SERVICES: DR RITA NATHAN
Private Bag X20660, Bloemfontein, 9300. Tel. No.: 051-4053496,
Fax: 051-4053500, Room 1077, First Floor, Universitas Academic Hospital
Email: nathanr@fshealth.gov.za

www.fs.gov.za

D. <u>Copy of research protocol approved by the HSREC</u>

RESEARCH PROTOCOL

PIM 3 predicted mortality compared to the observed mortality rate for patients in the PICU in Universitas Academic Hospital, segregated into four physical-chemical aspects for acid-base disturbances

By

Dr John Werner Robbetze, MBChB

Protocol for a mini-dissertation submitted in fulfilment of the requirements for the degree:
Master of Medicine in Paediatrics
in the
Department of Paediatrics and Child Health
Faculty of Health Sciences at the University of the Free State

CANDIDATE

Dr John Werner Robbetze, MBChB (UFS)
Registrar: Department of Paediatrics and Child Health
Faculty of Health Sciences
University of the Free State
Student Number: 2004016578

STUDY LEADER

Dr LJ Solomon, MBChB (UCT), MMed (Ped) (UFS), Cert. Critical Care (SA) Paed.
Consultant: Department of Paediatrics and Child Health
Faculty of Health Sciences
University of the Free State

Table of Contents

List of Acronyms

A^- - Anion

$[A^-]$ - Anion concentration

Alb - Albumin

BE - Base excess

BE_{Alb} - Albumin component of the Base excess

BE_{Lact} - Lactate component of the Base excess

BE_{SID} - Strong-ion difference component of Base excess

Cl^- - Chloride

CO_2 - Carbon dioxide

FiO_2 - Fraction of Inspired Oxygen

g/l - gram/litre

H^+ - Hydrogen ion / proton

$[H^+]$ - Hydrogen ion concentration

HA - Acid that dissociates into H^+ and A^-

[HA] - Concentration of acid HA

Hb - Blood haemoglobin

HCl - Hydrochloric acid

HCO_3^- - Bicarbonate

H_2CO_3 - Carbonic acid

H_2O - Water

ICU - Intensive Care Unit

K - Equilibrium constant

mmol/l - millimol per litre

Na^+ - Sodium

NaOH - Sodium hydroxide

OI - Other ions

PCO_2 - Partial Pressure of Carbon dioxide

PICU - Paediatric Intensive Care Unit

PIM - Paediatric Index of Mortality

pK - Dissociation constant for the acid

PO_2 - Partial Pressure of Oxygen

S_{CO2} - Solubility coefficient for Carbon dioxide

SID - String-ion difference

SIG - Strong-ion gap

Selected Definitions of Terms

Acid	Arrhenius defined an acid as a substance that forms cations and anions when dissolved in water, thus when dissolved in water produces an increased concentration of hydrogen ions [H^+]. Bronsted and Lowry defined an acid as a substance that can donate a proton (hydrogen ion). [6-7]
Acidosis	Condition were the pH in blood is less than 7.35. [6]
Alkalosis	Condition were the pH in blood is more than 7.45. [6]
Anion	Negatively charged ion
Base	According to the Bronsted and Lowry definition is a substance that can bind a proton (hydrogen ion). [6-7]
Cation	Positively charged ion
Mortality Rate	Number of deaths for a particular population for a defined period of time. [4]
pH	Dimensionless representation of the hydrogen ion concentration for a solution and it is defined as the negative decimal logarithm of the hydrogen ion concentration. [6] The normal physiologic limits for blood pH is between 7.35 and 7.45. [6]
Strong acid	Acid that fully dissociates in water or plasma. [6]
Weak acid	Acid that only partially dissociates in water or plasma. [7]

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1. Introduction

The PIM 3 mortality risk assessment score has absolute Base excess as one of the variables which contribute to mortality risk. It does not take into account, however, the type of acid-base disturbance, only the magnitude of the change from normal.

There is evidence to suggest that the nature of acidosis influences mortality risk as found in a similar study by Hatherill et al. They found that the magnitude of the acidosis as given by the base excess is unrelated to mortality, whereas the nature of the metabolic acidosis, according to them hyperlactaemia, is associated with mortality. [9]

This study seeks to assess whether there is any relationship between nature of acidosis and mortality risk based on the initial bloodgas for admission to the Paediatric Intensive Care Unit. The type of acidosis will be determined using Stuart's physical-chemical approach to acid-base balance which has been simplified into four separate equations by D.A. Story. This depends on the strong-ion difference between sodium and chloride, lactate, plasma albumin and other ions that in abundance may lead to an acidosis or alkalosis. It will try to determine which of these four components is associated with worst outcome. [2]

2. Literature Review

2.1. Paediatric Index of Mortality

The PIM (Paediatric index of Mortality) 3 score has become widely used in various paediatric intensive care units (PICUs) as a measure for monitoring of the quality of care in these units. It is the third version of this model that has been designed with the intension of looking at the risk of mortality, utilising data gathered within the first hour of contact with the patient at admission to ICU. [1]

The first version of the PIM score was based on data that was collected from seven PICUs in Australia and one PICU from the United Kingdom. It consisted of 5695 admissions. The second version included PICUs from Australia, New Zealand and the United Kingdom and consisted of data collected from 20787 patients that were admitted during a period from 1997 – 1999. [1]

However, for these models to still predict the possible outcome of the patients, it needs to include all the most recent, relevant data based on case-mix and clinical practice. Therefore these models need to be recalibrated regularly to include this relevant data and the new version was then called the PIM 3 score. [1] Again data was collected from PICUs in Australia, New Zealand and the United Kingdom and included 35701 patients. The model was based on several different predictor values, which include whether a diagnosis is of very high-risk, high-risk or low-risk, whether the pupils were fixed in response to light or not, elective admission, systolic blood pressure, absolute value of the base excess, the FiO_2 and the PO_2 on admission and recovery from post-operative procedure, whether cardiac or not. [1]

In a study by L.J. Solomon et al where the first two versions of the PIM score were assessed for their utility as mortality risk assessment models in a South African PICU, it was found that these models do predict the risk for mortality in an ICU very reliably, as well as provide a good benchmark for the quality of care provided, however they do not prognosticate very well when looking at a patient individually and for this reason should not be used as an indication of whether a patient requires admission to ICU or not. [3]

2.2. Mortality Rate

The mortality rate can be calculated by taking the number of deaths for a particular population over a defined period of time. To be able to calculate the mortality rate, the number of deaths and the population's data needs to be accurate and reliable. [4]

2.3. Acid-Base disturbances in ICUs

Critically ill patients, like most of the patients admitted in intensive care units, can have complex acid-base disturbances and electrolyte abnormalities, with one review article stating that up to 64% of critically ill patients can have acute metabolic acidosis. These acid-base disturbances can sometimes be mild and self-limiting, but they can also contribute significantly to morbidity and even mortality of the patient. [5] This is true for any pH changes in any direction (acidotic or alkalotic) and can lead to severe multiorgan damage and failure. [5] The pH needs to be maintained within physiologic limits in order to maintain normal protein structure and enzymatic function. These physiologic limits are a blood pH between 7.35 and 7.45. Below 7.35 is considered acidotic and above 7.45 as alkalotic. [6] In a study performed by Tang et al, who looked at the impact of modifiable ICU interventions on the outcome of cardio-pulmonary resuscitation in paediatric intensive care units, they found that an arrest that was caused by an acid-base disturbance has got a very poor prognosis. [8]

For these reasons we need to understand how to calculate the acidosis or alkalosis by a certain means in order to decide if metabolic or respiratory of origin. From there to quantify the acid-base disturbance and then correctly interpret it (look into possible causes of the acid-base disturbance present) in order to correctly manage the acid-base disturbance or the cause thereof. [6] All this is required to correct the disturbance and prevent severe morbidity or mortality of the patient.

In this discussion we will focus on metabolic acid-base disorders as these are the most common that clinicians come across in the intensive care units. For more clarity we need to look at the definitions of an acid and base, a brief history on how these definitions came to pass as well as a brief history on the development of clinical acid-base (all the different methods used to calculate the acid-base disturbance). In the end we will focus on D.A. Story's simplified bedside approach for calculating the possible cause of the acidosis or alkalosis, which is a simplification of Stewart's physical-chemical approach. [2]

2.3.1. Definition and history of clinical acid-base

In the 1880s Arrhenius defined an acid as a substance that forms cations(H^+) and anions (A^-), when dissolved in water, thus when dissolved in water produces an increased concentration of hydrogen ions (H^+). Then after World War I, Bronsted and Lowry independently developed an identical definition for an acid and a base, where an acid is a substance that can donate a proton (hydrogen ion) and a base a substance that could bind a proton. The equation for the Bronsted-Lowry definition:

$$HA \leftrightarrow H^+ + A^-$$

In this equation HA is the acid that can dissociate into a hydrogen ion (H^+) and a base (A^-). [6-7]

$$K = [H^+] \times [A^-] / [HA]$$

In this equation K is the equilibrium constant, indicating the strength (grade of dissociation) of an acid, where a large K, is a strong acid and a small K, a weak acid. [6]

Henderson, a biochemist from Harvard, looked at the relationship between carbon dioxide gas and bicarbonate and its role as a buffer of fixed acids. He then rewrote the law of mass action for an acid and its salts in 1909 and applied it to carbonic acid in the following equilibrium equation:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

Where H_2CO_3 is carbonic acid, $CO_2$is carbon dioxide, H_2O is water and HCO_3^- is bicarbonate. This leads to the following equation, the Henderson equation:

$$K = [H^+] \times [HCO_3^-] / [H_2CO_3]$$

$$[H^+] = K \times [CO_2] / [HCO_3^-]$$

Sorensen then introduced pH as a dimensionless representation of the hydrogen ion concentration for a solution, in that same year. He defined it as the negative decimal logarithm of the hydrogen ion concentration [H^+]. [6]

Then in 1912, Hasselbalch performed the first blood pH measurement with a platinum electrode and then later rearranged the Henderson equation into a logarithmic form and replaced [CO_2] with pCO_2 (partial pressure of carbon dioxide), eventually coming up with the Henderson-Hasselbalch equation:

$$pH = pK + \log([HCO_3^-] / S_{CO2} \times pCO_2)$$

In this equation S_{CO2} is the solubility coefficient of CO_2 and pK the dissociation constant for the acid. [6]

At the Rockefeller University Hospital in New York, Van Slyke developed the Van Slyke apparatus, which he used to measure the total carbon dioxide content in plasma. It is only slightly higher than the bicarbonate content in plasma. This method then became the standard for quantifying acid-base disturbances for the next 40 years. From these experiments he developed a diagram that related pH to bicarbonate and bicarbonate was seen as a determinant of the pH. [6]

In the 1950s, Siggaard-Andersen, Astrup and Knud Engel embraced the Bronsted-Lowry definition of an acid and from this developed the base excess (BE). They did this by conducting in vitro studies that equilibrated blood with a pCO_2 of 40mmHg, thus effectively removing any respiratory abnormality. Siggaard-Andersen then calculated the amount of strong (fully dissociated) acid (hydrochloric acid [HCl]) or base (sodium hydroxide [NaOH]) which was required to return 1l of blood back to a pH of 7.4. This is the BE in millimoles per litre and is negative if it is and acidosis (NaOH is required) and positive for an alkalosis (HCl is required). [2,6,7] Siggaard-Andersen then developed a nomogram so that the BE can be determined in a clinical setting. This nomogram was then mathematically transcribed into the Van Slyke equation that is being used these days by bloodgas machines to calculate the base excess.

$$BE = HCO_3^- - 24.4 + (2.3 \times Hb + 7.7) \times (pH - 7.4) \times (1 - (0.023 \times Hb))$$

Where Hb is the blood haemoglobin. [6]

The normal reference ranges are -3mmol/l to 3mmol/l and the more negative the value the more acidotic and visa versa. [2]

However the opinions regarding BE differed between schools in Boston and Copenhagen and thus the great transatlantic debate began. Schwartz and Relman, from Boston, argued that base excess from blood was an in vitro method and was inaccurate, because it could not replicate the in vivo carbon dioxide titration curve. [6] The reasoning was that only the intravascular compartment was assessed and the interstitial space was excluded. The interstitial space has a much weaker buffering capacity than blood, due to the lower concentration of albumin in the interstitial space and the absence of erythrocytes. [6] Siggaard-Andersen then assumed a haemoglobin concentration of 50g/l. This reduced the buffering capacity of blood in vitro. This is known as the standard base excess. [7] The Americans continued to argue with this concept and introduced the six Bostonian rules to identify pCO_2-invariant changes in bicarbonate. Due to this many clinicians continued to use the Henderson-Hasselbalch equation to quantify acid-base disorders by using these six Bostonian rules. [6-7]

Primary Disorder	Expected HCO_3^- = 24 + …	Expected pCO_2 = …
Acute respiratory acidosis	$([pCO_2] - 40)/10$	
Chronic respiratory acidosis	$([pCO_2] - 40)/3$	
Acute respiratory alkalosis	$(40 - [pCO_2])/5$	
Chronic respiratory alkalosis	$(40 - [pCO_2])/2$	

Metabolic acidosis		1.5 x [HCO_3] + 8
Metabolic alkalosis		0.7 x [HCO_3] + 21

Table 1 – Six Bostonian Rules [6]

Peter Stewart, in 1970s to 1980s, suggested that Arrhenius' definition of an acid is more useful than the Bronsted-Lowry definition, when considering acid-base disturbances. Stewart introduced a new approach to acid-base physiology, because he found the bicarbonate centred approach too confusing and inadequate in quantifying an acid-base disturbance and determining the possible cause of the disturbance. Stewart used several physical chemistry principles including: conservation of mass; electro-neutrality; and dissociation of electrolytes to come up with this new approach. [7] There are three independent controllers of the acid-base status on body fluids according to Stewart's approach: The strong-ion difference (SID), partial pressure of carbon dioxide and the total weak-acid concentration. [2] Strong-ions are ions that are completely dissociated in plasma and the most important are sodium (Na^+) chloride (Cl^-) and lactate. [7] The SID is the sum of all the cations measured routinely in plasma (sodium, potassium, calcium and magnesium) minus the all the anions that are routinely measured (chloride and lactate). [2] Weak acids, that are only partly dissociated in plasma, include mostly albumin and to a lesser extent phosphate. [7]

A Gamble gram, developed by a physiologist James Gamble, illustrates that, assuming electroneutrality, the ions that fill the SID between the cations and the anions is made up of, mostly, bicarbonate and the weak acids of which albumin is the most important. [2]

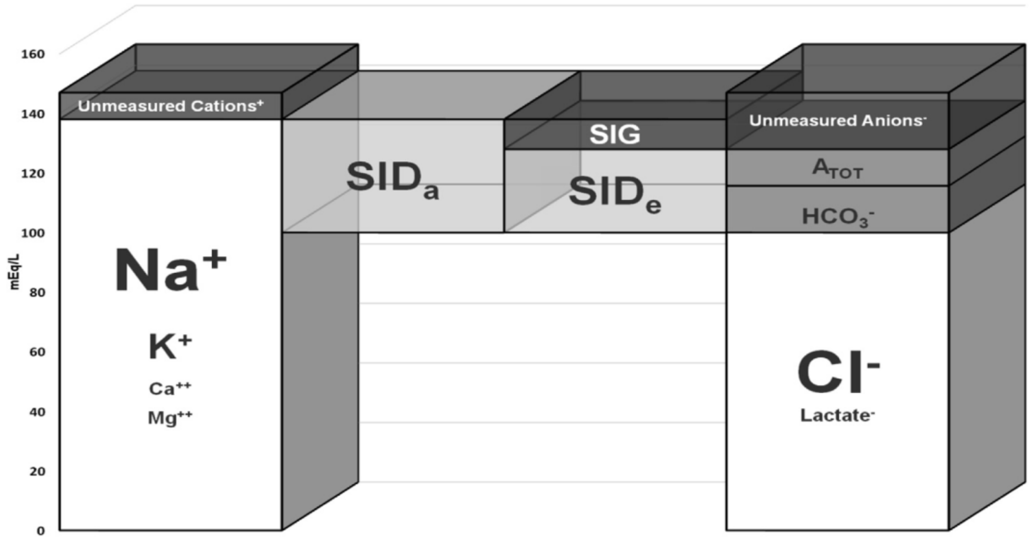

Figure 1 – Graphical representation of the Stewart model [6]

From this it can be deduced that a reduced SID, indicates to a lower bicarbonate level, which indicates the presence of an acidosis. When the SID is however increased, the bicarbonate level is also increased, indicating to an alkalosis. [2] Weak acids on the other hand play an opposite role to SID. An increase in total weak acids will cause an acidosis, whereas stated earlier a decrease in the SID will cause an acidosis. For an alkalosis it is a decrease in the total weak acids and an increase in the SID. [2] Stewart was of the opinion that bicarbonate and base excess was good to determine the extent of the acid-base disorder, but did not indicate the mechanism. [7]

2.3.2. Simplified bed-side approach to Stewart's physical-chemical approach

D.A. Story, then developed a simplified approach based on the base excess and looking at Stewart's physical-chemical approach. Changes in the strong-ion difference (SID) and total amount of weak acids will cause changes in the base excess. [2] Milliequivalent is a unit of electrical charge and milliequivalent per litre can then be used to unify the concentrations of the chemical constituents that make up the plasma. A milliequivalent is the amount of that substance that is required to combine with 1mmol of hydrogen ions. [2] Sodium, potassium, chloride, lactate and bicarbonate are all univalent ions and therefore milliequivalent per litre can be substituted with mmol/l. It is difficult to estimate the electrical charge of albumin, but a good approximation is 0.25 x albumin concentration in g/l. Base excess is derived from mmol/l of HCl (hydrochloric acid) and therefore changes in the determinants of the base excess will lead to changes in the base excess. [2]

From this D.A. Story proposed to divide the base excess into 4 parts:

$$BE_{SID} = \text{measured Na} - \text{measured Cl} - 35$$

$$BE_{Lact} = 1 - \text{measured lactate}$$

$$BE_{Alb} = 0.25 \times (42 - \text{measured albumin})$$

$$BE = BE_{SID} + BE_{Lact} + BE_{Alb} + OI$$

2.3.3. Strong-ion difference

Sodium and chloride are the major strong-ions apart from lactate and the difference in concentrations make up the SID. [2] If the normal reference values for sodium and chloride are used then:

$$Na^+ - Cl^- = 140 - 105 = 35\text{mmol/l}$$

and therefore taking into account electrical neutrality:

$$BE_{SID} = \text{measured } Na^+ - \text{measured } Cl^- - 35$$

From this it can be seen that hyponatremia or hyperchloremia will lead to a smaller SID and this results in a metabolic acidosis. [2]

2.3.4. Lactate

Lactate is the other strong anion apart from chloride and is therefore important in acid-base disturbances. Sodium is the principle cation in opposition to lactate, but is already accounted for in the SID, thus the effect of lactate on the base excess taking electroneutrality into account is:

$$BE_{Lact} = 1 – \text{measured lactate}$$

If the lactate increase then the BE becomes more negative indicating to a worsening acidosis. [2]

2.3.5. Albumin

As previously stated albumin is the most important weak acid and it was shown that to calculate the ionic concentration of albumin is 0.25 x albumin concentration in g/l. The normal plasma albumin concentration is 42g/l and thus the BE_{Alb} effect is calculated by:

$$BE_{Alb} = 0.25 \times (42 – \text{measured albumin})$$

If the patient becomes hypoalbuminaemic, the patient will become more alkalotic. [2]

2.3.6. Other ions and weak acids

Other ions include both measured and unmeasured cations and anions that will also have an effect on the acid-base status. Measured cations include calcium, potassium, magnesium and unmeasured from aluminium, lithium and proteins. Other measured anions include phosphate and those not routinely measured are sulphate and acetate and multiple others. [2]

From this it can be seen that if the changes in the BE is not explained by Na-Cl, lactate or the albumin, then other ions are playing a major role in causing the acidosis or alkalosis. [2]

2.3.7. Similar research studies

Now to consider the study that we are proposing to perform, where the PIM 3 score will be compared with the actual mortality rate to determine how accurate the PIM 3 score is in predicting mortality in the PICUs and to discriminate according to the four above equations, making up the BE, which will have the poorest prognosis according to the admission bloodgas. Therefore looking at the nature of the acid-base disturbance, rather than the magnitude of the metabolic acidosis and going in with the hypothesis that mortality is more closely related to the nature of the metabolic acidosis, rather than the magnitude.

A similar study was performed by Hatherill et al, at the Red Cross War Memorial Children's Hospital in Cape Town and published in 2003. [9] Their study was a prospective study that examined the relationship between the magnitude of the acid-base disturbance in terms of BE and the nature of the metabolic acidosis (either hyperlactataemia, hyperchloraemia or due to other unmeasured anions) and mortality in children with shock. [9] In their study they stated that a metabolic acidosis was a BE of less than or equal to -5mmol/l (more negative than the normal range that was referred to earlier. They recorded the observed ICU mortality and the mortality risk according to the PIM score. [9] The outcome of the study was consistent with their hypothesis, that mortality is more closely related to the nature of the metabolic acidosis rather than the magnitude. [9] It was found that hyperlactataemia was related to a poor outcome in these shocked paediatric patients. However what was interesting was that an anionaemia (other anions), was not associated with an increased mortality and hyperchloraemia was actually showing a trend towards survival. [9] They postulated that the lack of an association between the magnitude of the acidosis and mortality, might be due to alkalinising factors, such as hypoalbuminaemia, actually concealing the metabolic acidosis. Another observation that was made was that the admission lactate often failed to discriminate between survivors and non-survivors, however a lactate of >5mmol/l discriminated well on the other hand. Lactate in isolation though is not very useful and that the lactate levels over time are important in predicting mortality versus survival. [9]

A similar study by Kwok Ho et al, compared the prognostic significance of the SIG (Strong ion gap) or SID, (the difference between the amount of fully dissociated cations with fully dissociated anions), with other acid-base markers, that included lactate. [10] They found evidence that the SID or SIG are associated with the severity of inflammation. [10] Therefore they hypothesised that the SIG might be more important in predicting mortality in critically ill patients than other acid-base markers. However what they found was similar to the previous study that lactate was better in discriminating between survivors and non-survivors, than the SIG. [10] Therefore lactate, according to them is the preferred resuscitation target in critically ill patients. [10]

2.3.8. Hyperchloraemic Metabolic Acidosis and hyperchloraemia

Hyperchloraemic metabolic acidosis can result from renal or gastrointestinal losses of sodium and with fluid resuscitation by using 0.9% Saline. Hyperchloraemic metabolic acidosis can lead to hypotension and impaired cardiac contractility. Chloride can also affect the kidneys by reducing renal blood flow and the renal cortical perfusion. [11] In the immune system, hyperchloraemic metabolic acidosis induced an proinflammatory response via an increased interleukin 6 to interleukin 10 ratio. This was shown in animal models and in vitro cell models. [11] Due to all these detrimental effects, there are multiple discussions regarding 0.9% saline as a resuscitation fluid. [11] This was seen in a study on pigs where 0.9% saline, Ringer's lactate, Plasmalyte A and Plasmalyte R were compared as resuscitation fluids. In that study it found that Ringer's lactate had a better 2-week survival rate than those resuscitated with 0.9% saline and had a better acid-base balance. For this reason the trend is to move away from using 0.9%saline as resuscitation fluid. [12]

In a study performed by Stenson et al, they wanted to see if hyperchloraemia is associated with increased morbidity and mortality in paediatric patients in septic shock, as it is well known that hyperchloraemia is associated with a poor prognosis in critically ill adults. [11] Children in septic shock are exposed to aggressive resuscitation with crystalloid solutions and if the solution is 0.9% saline it can lead to hyperchloraemia (as stated above) and it was also recently found that resuscitating children with chloride-rich solutions such as 0.9% saline is actually associated with a poor outcome in the ill paediatric patient. [11] What they found in the study was that if the maximum chloride, during the stay in the PICU was >110mmol/l, it was usually not associated with a complicated course in the ICU. However if the minimum chloride was equal to or greater than 110mmol/l, then there was an increased risk of mortality. [11]

This is however slightly in contrast to the study performed by Hatherill et al. They found that in order to preserve electro-neutrality, there was a fall in the chloride (hypochloraemia) when the lactate and the unmeasured anions were elevated. For this reason they actually saw a trend towards hyperchloraemia in survivors. [9]

3. Aim of the study

The aim of the study is to compare the PIM 3 predicted mortality score with the actual mortality rate for the Paediatric Intensive Care Unit at Universitas Academic Hospital and then to see based on the bloodgas and bloods on admission to the PICU, according to D.A. Story's four equations for the base excess, which has the worst prognosis.

4. Objective of the study

The objective of the study is to compare the PIM 3 predicted mortality score with the actual mortality rate for the Paediatric Intensive Care Unit at Universitas Academic Hospital for the period 1 January 2016 to 31 December 2018 and to see based on the bloodgas and bloods on admission to the PICU, according to D.A. Story's four equations for the base excess, which has the worst prognosis in terms of mortality, length of stay in the PICU and number of days ventilated.

5. Methodology

5.1. Study Design

The study will be a retrospective cross-sectional study.

5.2. Study Population

The study population will include all patients admitted to the PICU at Universitas Academic Hospital during the period 1 January 2016 to 31 December 2018, as a bloodgas and admission bloods, whether arterial or venous, are done on each patient on admission the PICU.

5.3. Sample Size

The estimated number of patients that will be included in the study will be about 600 – 711 patients, ranging from the ages 0 to 156 months (13years).

5.4. Inclusion Criteria

- All patients between the ages of 0 to 156 months admitted to the PICU at Universitas Academic Hospital during the period 1 January 2016 to 31 December.

- Patients will be included in the study regardless if the bloodgas iis arterial or venous in origin.
- Patients where the bloodgas information is lost will still be included into the study as the primary research question can still be answered with the PIM 3 score information, the secondary question on which has the worst prognosis will then be excluded for that patient.

5.5. Exclusion Criteria

- Patients where the file is lost.

6. Measurement

The candidate will identify all the admissions during the period 1 January 2016 to 31 December from the admission statistics that are kept on the computer in the Paediatric Intensive Care Unit at Universitas Academic Hospital. From this the PIM 3 score information will be obtained and all the patient files will be drawn to obtain the bloodgas information. The bloodgasses in the PICU at Universitas Academic Hospital is done on the Radiometer ABL90 Flex bloodgas machine and is serviced and calibrated by the National Health Laboratory Service (NHLS). The rest of the laboratory results will be obtained from the NHLS Trackcare web results viewer, following permission from the head of the NHLS from Universitas Academic Hospital. The information gathered from the statistics, patient files and patient laboratory results will then be captured on a data capturing sheet for further processing.

The researcher will be the one to collect and enter all the data on the data capturing sheet, for proper documentation and accuracy purposes and then transfer it to the Excel spreadsheet.

The data capture sheet (Appendix A), pre-designed by the researcher, based on the information gathered during the literature review, will be used for this study to ensure that all the relevant data required for the research is captured.

The data collected will then be entered into an Excel spreadsheet, as discussed with the Department of Biostatistics during the planning phase, to ensure that all the data is captured correctly and that the data is analysable.

7. Ethics

The research protocol will be submitted to the Ethics Committee of the Faculty of Health Sciences at the University of the Free State for ethical consideration. Approval to conduct the research will be obtained from the Free State Department of Health after the preliminary ethical approval, as an ethics number is required for this application. After approval has been obtained, approval to use patient laboratory results during the research will then be obtained from the head of the NHLS laboratory at Universitas Academic Hospital. The approval letter from the Free State Department of Health will then be handed in to the Ethics Committee of the Faculty of Health Sciences of the University of the Free State for final ethical approval.

Patient consent will not be required as this is a retrospective study and no active participation by any patient will take place.

All data gathered will be anonymised, to ensure patient confidentiality. A number coding system will be used to ensure the patient confidentiality and therefore no names or hospital numbers will appear on any data sheet that is sent for statistical analysis.

8. Statistics

8.1. Pilot study

A pilot study will be conducted as soon as approval, to perform the research study, has been obtained from the Ethics Committee. A pilot study will be performed on 5 participants to determine the feasibility of the study, to see if the measurement instruments are adequate and to get an idea of possible results. Any short falls will then be detected and the necessary changes will be made before the research commences.

8.2. Data Capturing and Analysis

All data that will be collected, from the data capturing sheet (Appendix A) will be sent to the Department of Biostatistics at the University of the Free State for further analysis. Continuous variables will be summarised by means, standard deviations or medians and percentiles, whereas categorical variables will be summarised by frequencies and percentages. Differences between groups will be evaluated using appropriate statistical tests and confidence interval for unpaired data.

9. Value of this Study

There is no published data regarding the accuracy of the PIM 3 score for predicting mortality in the Free State and no study performed to determine the risk for mortality based on the nature of the metabolic acidosis, as both the studies mentioned during the literature review were performed at the Red Cross War Memorial Children's Hospital in Cape Town.

This study will firstly give an estimation regarding the accuracy of the PIM 3 score in determining the risk for mortality, for the patient demographic in Universitas Academic Hospital in the Free State. It will also give an indication based on the initial bloodgas and nature of the acid-base disturbance, what the probable prognosis will be in terms of length of stay in the PICU, number of days ventilated and risk of mortality.

10. Limitations of the Study

As the PIM 3 score has only been implemented recently in the PICU at Universitas Academic Hospital and his PICU is only a five bed ICU, the sample size will be small compared to similar studies performed at Hospitals that have a larger PICU and where the PIM 3 score has been implemented for a longer period.

The sample size can be increased for more accurate information by including the PICU at Pelonomi Hospital, as this ICU also makes use of the PIM 3 score. However due to the limited period for data collection and analysis, this researcher decided only to include Universitas Academic Hospital in the study and stating that a similar study can be performed at a later stage by another researcher including both PICUs to increase the sample size and thereby get more accurate information for the Free State.

In this study the researcher will also just look at the four simplified equations of acid-base analysis according to D.A. Story. In the case of the other ions the researcher will not go further to see what led to the other ions contributing to the BE. For this reason another researcher can do a follow-up study to further examine the possible ions contributing to these acid-base disturbances that fall under the other ion category.

11. Time schedule for execution of the study

Preliminary literature study	October – November 2018
Write protocol	December 2018 – March 2019
Submit to study leader/Evaluation Committee	February - March 2019
Submit final protocol to Biostatistics	February 2019
Submit to Ethics Committee	April 2019
Submit to Dept. of Health	May 2019 – Adjusted September 2019
Data Collection	June – August 2019 – Adjusted October – November 2019
Submit Data to Biostatistics	August - September 2019 – Adjusted November 2019
Write thesis	October 2019 – Adjusted December 2019

Revise thesis	November 2019 – Adjusted January 2019
Printing, binding and submission of final thesis	December 2019 – January 2020

12. Budget

The budget of the study will be approximately R800. The budget will cover all the stationaries, printing and binding required during the research and completion of the thesis.

The cost will be split as follows:

Stationary	R 300
Printing and Binding	R 500
Total	R 800

13. References

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E. Data capturing form

Case Number

Age		Months
Gender		Female = 0 Male = 1
Date of Admission		
Length of Stay		Days
Mortality		No = 0 Yes = 1
PIM 3 Mortality Risk		
Days Ventilated		Days
pH		
Actual Base Excess		
Absolute Base Excess		
Nature of acid-base disturbance		Alkalosis = 0 Acidosis = 1
Na		
Cl		
BE_{SID} = Na – Cl - 35		

Lactate

BE_{Lact} = 1 - Lactate

Albumin

BE_{Alb} = (42 – Albumin)/4

Other Ions BE = BE - BE_{SID} - BE_{Lact} - BE_{Alb}

F. Instructions to authors of the named peer reviewed journal: SAMJ (South African Medical Journal)

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

- Research
- Editorials
- CME
- In Practice and Case reports
- Reviews
- Clinical trials
- Correspondence
- Obituaries
- Book reviews
- Guidelines

Research

Guideline word limit: 4 000 words

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

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.

- **Objectives:** what the study intends to find out
- **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
- **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
- **Conclusion:** must be supported by the data, include recommendations for further study/actions.

- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

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

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

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

G. Summary report compiled in the Turnitin Plagiarism Search Engine

PIM 3 predicted mortality compared to the observed mortality rate for patients in the PICU in Universitas Academic Hospital, segregated into four physical-chemical aspects for acid-base disturbances

by John Robbetze

Submission date: 01-Jul-2020 08:40PM (UTC+0200)

Submission ID: 1352298538

File name: Final_Manuscript.docx (269.52K)

Word count: 9514

Character count: 49767

PIM 3 predicted mortality compared to the observed mortality rate for patients in the PICU in Universitas Academic Hospital, segregated into four physical-chemical aspects for acid-base disturbances

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