The Association between Serum Procalcitonin Levels and Outcomes of Patients Admitted to Two Tertiary Paediatric Intensive Care Units in the Bloemfontein Academic Complex: A Retrospective Analytical Study

By:

Dr Augusto Martin Luyo Sanchez

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Candidate:

Dr A.M. Luyo Sanchez, MBChB(UKZN)

Registrar, Department of Paediatrics and Child Health

Faculty of Health Sciences

University of the Free State

Student number:2017498169

E-mail: 2017498169@ufs4life.ac.za

Supervisor:

Dr M.A. Pienaar, MBChB, MMed (UFS), FC Paed (CMSA)

Consultant, Department of Paediatrics and Child Health

Faculty of Health Sciences

University of the Free State

E-mail:PienaarMA1@ufs.ac.za

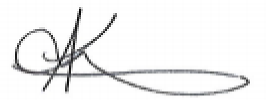
DEDICATION

This study is dedicated, with much love and appreciation, to my dear wife Syona, as well as Joey and Chandler, who are my pillars of strength and always provide me with amazing love and support.

I also dedicate this study to my father, Roberto, my siblings, Carol and Robert, and my late mother, Delfina - all of whom guided me to where I am today.

DECLARATION OF AUTHORSHIP

I, Augusto Martin Luyo Sanchez, declare that this mini-dissertation titled: 'The Association between Serum Procalcitonin Levels and Outcomes of Patients Admitted to Two Tertiary Paediatric Intensive Care Units in the Bloemfontein Academic Complex: A Retrospective Analytical Study', 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.



Dr Augusto Martin Luyo Sanchez
UFS Student number:
E-mail:

AUTHOR'S CONTRIBUTIONS

Author	Role in study
Dr A.M. Luyo Sanchez	Study concept and design, data collection and interpretation and drafting of the article.
Dr M.A. Pienaar	Supervision, study concept and design, revising critically for clinical content, final approval of the manuscript to be submitted.
Prof G. Joubert	Statistical supervision, data analysis.

There is no conflict of interest to be declared by any of the authors. No other situation of real, potential or apparent conflict of interest is known to them. The university will be informed should there be any change in these circumstances.

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ABSTRACT

Background: The risk of mortality should be assessed in all patients admitted to the Paediatric Intensive Care Unit (PICU). Procalcitonin (PCT) is a valuable biomarker in the diagnosis of sepsis in the PICU. Its use as a prognostic marker has been widely investigated with conflicting results. This study was done to assess the association between PCT and outcomes in the PICU in our setting thereby investigating its prognostic capabilities.

Objectives: The primary objectives were to determine the admission PCT, the PCT between 48 – 72 hours of admission, and the PCT change within this time frame, of patients admitted to the PICU at two tertiary hospitals within the Bloemfontein academic complex as well as their primary (PICU mortality) and secondary (length of PICU stay, number of ventilatory days) outcomes. The secondary objectives were to compare these PCT trends with the primary and secondary outcomes.

Methods: The study was a retrospective analytical cross-sectional medical record review of patients, between 1 to 60 months of age, who were admitted to the PICU within the Bloemfontein academic hospital complex from 01 January 2017 to 31 December 2018. Admission PCT and trends within 72 hours of admission were compared to the participant outcomes (PICU mortality, length of PICU stay and number of ventilator days). Data was obtained from the participants electronic and paper medical records and the National Health Laboratory Services database. De-identified data was submitted for analysis by the Department of Biostatistics, University of Free State.

Results: 381 participants were included in the study. 55 participants died. 220 required mechanical ventilation. The median length of PICU stay was 6 days. Non-survivors had a higher median admission PCT (13.94ng/ml, IQR 1.0 – 100.0) than survivors (1.45ng/ml, IQR 0.36 – 13.08) ($p<0.0001$, 95% CI 1.28 – 15.12). Non-survivors had a higher median PCT at 48-72(12.79ng/ml, IQR 2.08 – 100.00) hours than survivors (1.31ng/ml, IQR 0.29 – 7.15) ($p<0.0001$, 95% CI 2.50 – 21.72). Non-survivors had less of a median decrease in PCT (-0.12ng/ml, IQR -3.68 to +4.125) than survivors (-0.40ng/ml, IQR -4.88 to +0.05) ($p=0.22$, 95% CI -0.59 - 4.72). The area under the receiver operating characteristics curve (AUROCC) for admission PCT to discriminate for mortality was 0.6702 and for the 48-72-hour PCT it was 0.7369. The strongest profile for PCT to discriminate for mortality was found at the 48-72hour PCT at a threshold of 3.16ng/ml (sensitivity 73.3%; specificity 64.5%). The median PCT change in participants requiring ventilation (-0.23ng/ml, IQR -2.72 to +0.52) was less than for those not requiring ventilation (-0.76ng/ml, IQR -6.34 to -0.05) ($p= 0.0044$, 95% CI -1.67 - -0.16). There was a positive correlation between PCT and number of ventilator days (spearman correlation co-efficient =0.1477, $p=0.0138$). There was no significant correlation between the length of PICU stay and admission PCT($p=0.7579$), the PCT change ($p=0.2034$) or the percentage PCT change ($p=0.2625$).

Conclusion: PCT displays some ability to discriminate for PICU mortality. Serial PCT measurements provide greater prognostic information. Non-survivors had a significantly greater median admission PCT, median PCT at 48-72 hours and a lower median PCT decrease than survivors. PCT above 3.16ng/ml at 48-72 hours had the strongest profile to discriminate for mortality.

LIST OF ABBREVIATIONS

AUC – Area Under the Curve

CALC1 – Calcitonin-1

CRP – C-reactive protein

ICU – Intensive Care Unit (usually in reference to an adult ward)

IL-6 – Interleukin 6

IL1B – Interleukin 1 beta

ng/ml – Nanograms per millilitre

NHLS – National Health Laboratory Services

PCT – Procalcitonin

PH – Pelonomi Hospital

PICU – Paediatric Intensive Care Unit

ROC – Receiver Operating Characteristics

TNFα – Tumour necrosis factor alpha

UAH – Universitas Academic Hospital

UFS – University of Free State

μg/L – Microgram per litre

KEYWORDS AND DEFINITIONS

Biomarker – a detectable cellular or molecular indicator of exposure, health effects or susceptibility, which can be used to measure the absorbed, metabolised, or biologically effective dose of a substance, the response to the substance including susceptibility and resistance, idiosyncratic reactions, and other factors or conditions. [1]

Critical care - the specialized management of patients who require comprehensive care and constant monitoring usually done within the hospital ward known as the intensive care unit. [1]

Endogenous peptide – a compound originating within an organism or one of its parts [1]

Inotropes – a specific class of drugs that influence the contractility of muscular tissue. [1]

Length of stay – recorded commonly in hospital notes as the number of days the patient was admitted to a specific ward or hospital.

Mechanical ventilation – the use of an automatic mechanical device to perform all or part of the work of breathing [1]

Mortality – a fatal outcome [1]

Nanograms per millilitre – a conventional unit of measurement for procalcitonin (1ng/ml=1µg/L).

Procalcitonin – an endogenous peptide widely used as an established biomarker in the diagnosis of bacterial sepsis[2]

Prognosis – a forecast of the probable course and/or outcome of a disease [1]

Sepsis – SIRS in the presence of or as a result of suspected or proven infection. [3]

Septic shock – patients with defined sepsis leading to cardiovascular dysfunction. [3]

Serum – The fluid portion of blood obtained after removal of the fibrin clot and blood cells, distinguished from plasma in circulating blood. [1]

SIRS – The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:

● Core temperature of 38.5°C or 36°C.

● Tachycardia, defined as a mean heart rate 2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or
otherwise unexplained persistent elevation over a 0.5- to 4-hr time period OR for children <1 yr old: bradycardia, defined as a mean heart rate
<10th percentile for age in the absence of external vagal stimulus, B-blocker drugs, or congenital heart disease; or otherwise unexplained
persistent depression over a 0.5-hr time period.

● Mean respiratory rate _2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular
disease or the receipt of general anesthesia.

● Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or _10% immature neutrophils. [3]

Ventilation days – recorded in hospital notes as the number of days which a patient required invasive mechanical ventilation

CHAPTER 1

1.1 LITERATURE REVIEW

The severity of disease and risk of mortality should be assessed in all patients admitted to the paediatric intensive care unit (PICU) in order to provide effective and timely treatment [4–7]. Independent risk factors for mortality in patients admitted to the PICU include mechanical ventilation frequency, length of hospital-stay and the presence of sepsis. Sepsis remains a major cause of mortality and morbidity in the paediatric population both in and out of the PICU setting [8]. Extensive research has been done to identify biomarkers to aid in the management of sepsis. The ideal sepsis biomarker should allow for early diagnosis, risk stratification and an improvement in antibiotic stewardship. An early diagnosis of sepsis is crucial in children as urgent appropriate intervention is required to adequately treat the infection and prevent complications and death [2,4–9]. Biomarkers such as C-reactive protein (CRP) and Procalcitonin (PCT) have been used to aid in the management of sepsis. PCT has been established as a superior diagnostic biomarker of bacterial sepsis in comparison to CRP [2,4,9–19]. Several studies in the South African paediatric population have validated the use of PCT in the diagnosis of bacterial sepsis, particularly in the critical care setting [10,16,18]. The role of PCT in antimicrobial stewardship appears valuable, various studies in the adult population have reported the successful use of PCT-guided antibiotic protocols to decrease the duration of antibiotics. Similar studies in the paediatric population have displayed promising results [2,10,17,20–23]. The use of PCT in risk stratification as well as its ability to predict mortality has also been extensively investigated, the results of which have been conflicting in both the adult and paediatric populations [2,4,5,7,11,13,15,24–27].

Procalcitonin

Procalcitonin (PCT) is an endogenous peptide primarily secreted by the parafollicular C cells of the thyroid gland and has been described as a precursor to the hormone calcitonin [2,4,5,7,9–12,18,19,26]. Other suggested sites of origin include the lung, liver and kidneys [10,19]. PCT levels are generally undetectable or low (<0.1ng/ml) in healthy individuals, however a range up to 2.0ng/ml may be considered normal [4,12,19,26]. In 1993 *Assicot et al.* described PCT in the context of sepsis and demonstrated a rise in response to certain pro-inflammatory stimuli and various bacterial endotoxins. CALC1 is described as the gene responsible for PCT production. Pro-inflammatory cytokines, TNFα, IL1B, and IL6, produced in the presence of bacterial infections trigger CALC1 expression in various cells throughout the body, ultimately resulting in the rise of PCT. Importantly, cytokines that attenuate the upregulation of CALC1 are selectively produced in viral infections and therefore the same degrees of PCT elevation is not induced. Subsequently, PCT has been accepted as a reliable biomarker in the early diagnosis of bacterial sepsis [2,4,5,9–11,19,24,26]. Although other inflammatory conditions, such as burns, surgeries and bowel wall ischaemia, may cause a transient rise in PCT levels, the elevations are substantially lower than those caused by bacterial infections. In bacterial infections levels may go beyond >100 000 times the normal value. The physiological role of PCT in bacterial sepsis is not fully understood [2,4,19]. Theoretically, PCT, due to its similarity with calcitonin, plays a role in calcium metabolism in patients with bacterial sepsis as they frequently develop hypocalcaemia. However, a correlation between an increase in PCT levels and a subsequent rise in calcitonin levels has not been demonstrated. In bacterial sepsis there appears to be no considerable correlation between PCT and calcium metabolism. In contrast, a rise in PCT levels from neuroendocrine tumours and small cell carcinomas of the lung is associated with an increase in calcitonin [4,19].

In the context of bacterial sepsis PCT rises more rapidly than C-reactive protein(CRP) [4]. The rise in PCT can be detected as early as 2 hours after exposure to a bacterial endotoxin. It rises significantly after 3-4 hours, plateaus by 8-12 hours and has a half-life of 25 – 30 hours [9,19]. In the last decade several investigators have investigated the role of PCT in the context of bacterial sepsis with regards to diagnostic capabilities, disease monitoring and stratification, antimicrobial stewardship and prognostic value [2,4,5,7,9–12,16,18,19,21,22,24,26–28]. Due to gaps in the available literature, findings from studies in adult populations are not uncommonly extrapolated for application in the paediatric setting [2,9].

Procalcitonin in the Diagnosis of Bacterial Sepsis

Procalcitonin is a well-established biomarker for bacterial infections in the adult population [9,12,24,26]. A systematic review of studies across Europe and North America by *Hoeboer et al.* reported a sensitivity of 76% and specificity of 69% at a low PCT cut-off of 0.5ng/ml. In South Africa, a cut off-off of 2.0ng/ml is used as a threshold to alert physicians to potential underlying sepsis. A study by *Ramasawmy et al.* conducted at a level 1 trauma centre investigated the accuracy of PCT in identifying bacteremia, which was defined as a confirmed positive blood culture. Despite a good sensitivity of 86%, using a cut-off of 2.0ng/ml, the investigators also reported a significantly low specificity of 29% and positive predictive value of 28%. The study supported an overall accuracy of PCT in detecting bacteremia, however, the high false positive rate highlighted the possible shortcomings of using a single PCT value and low cut-off value, potentially resulting in an overdiagnosis of bacteremia and subsequently unnecessary use of antimicrobials. Due to the study having a relatively small sample size, the investigators acknowledged that larger multi-centre studies should be done to validate their results [12].

Table 1: The use of PCT in the Diagnosis of Bacterial Sepsis in Children

	Author	Age of Participants	Results/ Findings
PCT in Pyrexia without a clinical source	*Luaces-Cubell et al.*	1 – 36 months	PCT at cut-off 0.9ng/ml to detect bacterial infections has a sensitivity of 86.7% and specificity of 90%[9]
	Mahajan et al.	</= 36 Months	PCT at cut-off 0.6ng/ml to detect bacterial infections has a sensitivity of 51% and specificity of 93%[9]
PCT in Urinary Tract Infections	*Liao et al.*	Meta-analysis </= 2 years	In children with urinary tract infections, PCT levels >0.5ng/ml strongly predicted the presence of renal parenchymal involvement[9,19]
PCT in LRTI	*Zhu et al.*	10 months - 16 years	PCT is a sensitive marker in distinguishing bacterial and non-bacterial aetiology of pneumonia[9,19]
	Toikka et al.	1 month - 17 years	In children with pneumonia, PCT above 2ng/ml suggests bacterial aetiology. However, PCT below this optimum cut-off does not exclude bacterial infection[9,19]
PCT in Meningitis	*Dubos et al.*	1 month -16 years	PCT above an optimum cut-off value of 0.3ng/ml had a 99% sensitivity and 83% specificity for bacterial meningitis[19]
	Henry et al	Meta-analysis	PCT is a reliable serum biomarker to rapidly differentiate viral and bacterial meningitis[19]
PCT in Neonatal Sepsis	*Bobillo-Perez et al.*	Systematic review	Multiple factors may affect procalcitonin levels in neonates: physiological rise, gestation, perinatal conditions such as respiratory distress syndrome. Appropriate reference ranges for PCT levels in neonates are not well established[9]
	White et al.	Newborn, suspected sepsis within 24 hours of life	PCT at a cut-off of 0.5ng/ml had a sensitivity of 48 % and specificity of 74%. At a higher cut-off of 10ng/ml, to account for physiological rise, improved PCT specificity to 98% but worsened sensitivity to 22%[10]

In the paediatric population, PCT has similarly been recognised as a valuable biomarker in the diagnosis of bacterial sepsis (Table 1), predominantly in the context of the critical care setting [2,4,5,9,10,13,15–19]. Several studies have concluded the ability of PCT to reliably aid in the diagnosis of urinary tract infections, bacterial meningitis and bacterial sepsis in children with fever without a known clinical source. However, there are conflicting reports on the ability of PCT to help differentiate bacterial and non-bacterial pneumonia. While some studies report PCT levels above an optimum cut-off may help in the diagnosis of bacterial pneumonia, many investigators conclude that PCT levels below an optimum cut-off does not reliably exclude bacterial aetiology. As a single biomarker, PCT is frequently reported to have a better sensitivity and specificity than CRP in the diagnosis of bacterial sepsis. A systematic review by *Downes et al.* highlighted that the use of both biomarkers significantly improved overall diagnostic accuracy, particularly in the exclusion of bacterial infections. Although the results of the studies quoted had statistically significant results, the study sample sizes were relatively small. Further larger centre studies are required to advocate the use of two biomarkers concurrently, ideally with a cost-effectiveness analysis [2]. The role of PCT in the neonatal population remains largely debated. In neonates, many factors may affect PCT levels, including non-infectious pathologies. Several investigators suggest further studies are required to establish appropriate reference ranges in this population group [2,9,10,19]. In recent years, there has been a growing interest in point-of-care procalcitonin(POCP). POCP requires a small blood sample of 0.5ml and results are generally available within 20 minutes. A study by *Waterfield et al.* assessed the diagnostic accuracy of POCP in the emergency department setting. In this study, at a low cut-off of 1.0ng/ml, POCP had a sensitivity of 100% and specificity of 92%. Although the results were promising, the study had several limitations. It was a single centre with a small sample size and participants were included at the discretion of the treating clinician, potentially allowing for selection bias [28].

Diagnostic value of Procalcitonin in Haemato-Oncology Patients

In haemato-oncology patients, diagnosing bacterial infections remains challenging. PCT induction may be reduced in patients with neutropaenia or those undergoing chemotherapy. Despite immunosuppressed states, PCT levels still increase in response to a pro-inflammatory stimulus [2,9,15,19]. A debate remains with regards to an appropriate PCT cut-off to detect bacterial infections. In neutropenic patients, the cut-off may lie low between 0.1 to 1.5ng/ml. *Gunasekaran et al.* identified a possible optimal cut-off of 0.7ng/ml, which despite its poor sensitivity of 45-55% had a specificity of 70-83%. Most researchers agree further studies are required to establish an appropriate PCT cut-off [9,15,19].

Diagnostic value of Procalcitonin in Surgical and Trauma Patients

Surgery induces an inflammatory response [9,18]. Identifying a biomarker which could differentiate between non-infective and infective related inflammation is crucial in the management of these patients. In children and adults, the response of PCT is dependent on the characteristics of the surgery. In abdominal surgery, PCT may rise to 2ng/ml and return to normal within 24-36 hours post-surgery. Patients undergoing cardio-pulmonary bypass may show PCT levels elevated as high as 10ng/ml without the presence of sepsis. Patients after a liver transplant may have PCT levels elevated for up to a week before returning to normal. Therefore, serial PCT measurements, as oppose to single specific cut-offs, is more useful in alerting the clinician to the possibility of septic complications [9].

Similarly, inflammation after a traumatic injury may mask underlying sepsis [9,18]. Due to lack of research done, findings from studies in the adult population has been extrapolated to paediatric patients. The rise in PCT depends on the severity and type of trauma. In peripheral isolated injuries, PCT rise may be mild. Patients with abdominal trauma may show PCT increase within the range seen in patients after abdominal surgery. Burn injuries induce a severe inflammatory response as well as a degree of immuno-paresis. Due to nature of the injury, burn wound infections are difficult to identify and subsequently manage. In South Africa, *Martinez et al.* reported on the use of PCT in detecting sepsis in burn victims in their burn unit. Patients with culture confirmed sepsis had an average PCT value of 39.4ng/ml. However, studies suggest PCT levels as low as 0.5ng/ml as an early indication of sepsis. This burn unit used a cut-off of 2.0ng/ml, in combination with the American Burn Association SIRS/sepsis criteria, as an indication to start antibiotic therapy. Further studies are required to evaluate the efficacy of this protocol in reducing mortality and morbidity from sepsis [18].

Procalcitonin in Antimicrobial Stewardship Programmes

Clinicians appear to unnecessarily lengthen antibiotic therapy due to non-reassuring clinical and laboratory findings. Antibiotic overuse may have serious adverse effects [2,5,9,10,14–21,23,26]. Evidence based protocols are required to safely guide antibiotic duration without compromising clinical outcome [2,9,14,17,20,21,23]. The PRORATA trial, by *Bouadma et al.*, is a case-control multi-centre study that analysed the effect of a PCT based algorithm in reducing antibiotic exposure in adult non-surgical patients in the critical care setting. The results reported a successful reduction in duration of antibiotic therapy without any significant difference in mortality resulting from sepsis [9,20].

The implementation of antimicrobial stewardship programmes in paediatrics has been successful in some countries [21]. However, the inclusion of PCT in an antimicrobial protocol is still being evaluated [2,7,8,14,17]. In the PRORANI study by *Launes et al.*, the implementation of a PCT-guided protocol at single centre in Spain resulted in a 2-day reduction in antibiotic exposure after its introduction [9,17]. The OASIS II study, conducted by *Downes et al.*, evaluated the ability of a biomarker-based algorithm in reducing antibiotic exposure in patients with systemic inflammatory response syndrome, without confirmed bacterial infections, and concluded no overall reduction in antibiotic duration in the participants [9,14,16,18]. In the ProPICU study, a randomised control study conducted by *Katz et al.*, the implementation of a PCT-guided antibiotic protocol resulted in the reduction in the duration of antibiotics for patients with pneumonia in the intervention group. However, the study included patients with various other diagnoses, and overall, there was no reduction in duration of antibiotics between the control and intervention groups. This possibly suggests a PCT guided algorithm may help reduce antiobiotic duration in only a specific set of patients in the PICU. The conflicting results of these three studies highlighted the need for further research in this area [22].

Prognostic Value of Procalcitonin

It is important to assess the risk of mortality in patients admitted to an intensive care unit [4,5,11,25]. In the adult population, elevated procalcitonin (PCT) levels, above 10ng/ml, is associated with the increased need for mechanical ventilation, inotropic support and blood transfusions. Investigators identify these interventions as independent risk factors for mortality, thereby hypothesised that PCT may be a marker of mortality [4,11]. Various studies have been done to assess the association between PCT levels and the risk of mortality. *Seong Mok Ryoo et al.* reported that PCT or CRP done at admission were not strong predictors of mortality [24]. In contrast, *Meng et al.* reported that a PCT >10ng/ml at the time of admission to ICU was a strong predictor of short-term mortality, better than both CRP and the APACHEII score [4,5,25]. Monitoring and comparing serial PCT measurements appear to provide better prognostic information than interpreting just a single admission value. A study by *Poddar et al* evaluated the prognostic value of the change in serum PCT levels in adults admitted to the ICU with a diagnosis of sepsis or septic shock. The investigators concluded that a single value at the time of admission could not aid in predicting the prognosis of a patient. However, a decrease in serum PCT levels within 4 days of admission was associated with survival. The study reported a median decrease of 9.73ng/ml in the survivor group, whilst the non-survivor group had median increase of 5.95ng/ml [11]. Similarly, the MOSES study, by *Scheutz et al.*, reported a higher risk of mortality in patients whose PCT levels did not decrease by at least 80% from their baseline within 4 days of admission to the intensive care unit [2]. In South Africa, a study conducted by *Naidoo et al.* reported that the admission PCT level is an inferior predictor of mortality in comparison to the PCT level at 48 hours of admission. The study results showed the risk of mortality was increased in patients whose PCT levels increased or remained above 10ng/ml at 48 hours. A rise or no change in PCT levels during the first few days of ICU admission may therefore serve as a potential marker of poor prognosis [26].

The prognostic value of PCT in the paediatric population is still being evaluated. Outside of the critical care setting, *Gunasekaran et al.* reported that a PCT level >5ng/ml on admission was associated with a 7-fold increase of mortality in haemato-oncology patients admitted with suspected bacterial infection [15]. In the critical care setting, many investigators report that a low admission PCT, below a critical threshold of 1.0ng/ml, had a high negative predictive value for mortality. The prognostic value of an elevated admission PCT is still largely inconclusive [2]. In a study by *Aygun et al.* the investigators evaluated the association between PCT and CRP levels on admission and clinical outcomes of patients in the PICU. The investigators concluded that both elevated CRP and PCT levels are associated with the need for mechanical ventilation, inotropic support, development of acute kidney injury and an increased risk of mortality. PCT elevation above 10ng/ml was associated with 2-fold increase in risk of mortality. This finding is supported by similar findings in adult patient studies. The investigators acknowledged that value of the study is limited by its sample size, but suggested it provided some information in the apparent gap in data in the paediatric population [2,4,5]. *Siddiqui et al.* conducted a retrospective analysis to evaluate the prognostic value of PCT, CRP and lactic acid levels in the critical care setting. They reported lactic acid levels were the more reliable biomarker among the three to predict multi-organ dysfunction and mortality. No statistically significant association between increased PCT and risk of mortality was established. The study had some recognised limitations such as a limited sample size and that it was done in a single centre. Importantly, the retrospective analysis meant only patients who had PCT levels done were included in the study. In this unit PCT is only done when there is clinical suspicion of infection, therefore selection bias could not be ruled out [5]. Various investigators suggest serial PCT measurements provide more reliable prognostic information than single PCT measurements [2,7,11,27]. A prospective study by *Baranwal et al.* reported that the trend of serial PCT measurements within the first 10 days of PICU admission correlated better with organ dysfunction scores than CRP measurements did. Furthermore, the trend of PCT levels decreased faster in the surviving participants than non-surviving participants [27]. *Hatherill et al.* reported that the absence of a decline in PCT within the first 24 hours of starting treatment for patients with septic shock was associated with an increased risk for mortality. The RESOLVE study (REsearching severe Sepsis and Organ dysfunction in children: a gLobal pErspective) reported a greater decline in PCT over 6 days in patients who survived sepsis than non-survivors [2]. *Poddar et al*, who also investigated PCT kinetics in the adult population, conducted a pilot study in the paediatric setting to investigate if PCT reduction could predict 28-day mortality. The study included 25 participants, 14 survivors and 11 non-survivors. The median reduction of PCT 17.3ng/ml in the survivor group, whilst in the non-survivor group there was a median increase of 1.1ng/ml. Expressed as a percentage change from the admission PCT, the survivor group had on overall reduction of 75.5% whilst the non-survivor group had an overall increase of 200.3% which was deemed statistically significant. This small pilot study concluded children admitted with sepsis or septic shock are less likely to die if the PCT decreased by >4ng/ml or >50% from the baseline and suggested a percent reduction as better prognostic marker than absolute values [2,7].

In South Africa, the prognostic value of procalcitonin (PCT) has not thoroughly been evaluated. Most studies, conducted out of the critical setting, were focused on the diagnostic value of PCT. In many instances, obtaining PCT levels is usually limited to critically ill children requiring admission to PICU. This selection bias makes assessing the prognostic value of serum PCT levels difficult [10,16]. No study has been conducted in South Africa with the aim to evaluate the prognostic value of PCT in the paediatric critical care setting.

In conclusion, the risk of mortality should be assessed in all patients admitted to the PICU to deliver efficient critical care services [4–7]. This has prompted researchers to identify a biomarker that may aid in this assessment. PCT is a biomarker that is frequently used in the PICU[2,9,19] for diagnosis and management of bacterial sepsis. Emerging literature suggests potentially valuable prognostic capabilities of PCT. Low admission PCT values appear to indicate a favourable prognosis, whilst elevated admission PCT levels are associated with unfavourable outcomes such as increased number of ventilator days, increased length of PICU-stay and an overall increased risk of mortality [2,4,13]. The trend of serial serum PCT measurements may provide more valuable prognostic information. The absence, or slow decline, of PCT levels within the first few days of admission to the PICU is associated with an increased risk of mortality [2,7,11,27]. In South Africa, evaluation of PCT trends and outcomes in the critical care setting has been undertaken in the adult population[26] but not in the paediatric population.

1.2 PROBLEM STATEMENT

Investigators have reported an association between elevated serum PCT levels and an increased risk of PICU mortality, length of PICU stay and number of ventilator days. A rise or no change in PCT levels during the first few days of ICU admission may also serve as a potential marker of poor prognosis [2,4,7,27] This potentially can guide clinicians in making critical decisions in the management of these patients. This includes escalation or limitation of care decisions. Such decisions are crucial in resource limited settings.

The problem identified pertains to the lack of a South African based study that investigates the association between serum PCT levels and PICU mortality, length of PICU stay and number of ventilator days. In the context of an upper-middle income setting, an understanding of its clinical utility in this setting is crucial in guiding its use.

1.3 RESEARCH QUESTION

What is the association between serum PCT levels (taken on admission and the change in PCT levels within 48 - 72 hours of admission) and the outcomes (mortality or survival at discharge from PICU, length of PICU stay and the number of ventilator days) of patients admitted to a PICU at two tertiary hospitals in the Bloemfontein Academic Complex over a two-year period from January 2017 to December 2018?

1.4 AIM OF THE STUDY

To investigate the association between serum PCT levels (taken on admission and the change in PCT levels within 48 - 72 hours of admission) and the outcomes (mortality or survival at discharge from PICU, length of PICU stay and the number of ventilator days) of patients admitted to a PICU at two tertiary hospitals in the Bloemfontein Academic Complex over a two-year period from January 2017 to December 2018.

1.5 OBJECTIVES

Primary Objectives

1) To determine admission serum PCT levels and the serum PCT levels between 48 – 72 hours of admission in patients admitted to a PICU at two tertiary hospitals in the Bloemfontein Academic Complex over a two-year period from January 2017 to December 2018.

2) To calculate the change from serum PCT levels obtained at admission to PCT levels obtained between 48 - 72 hours of admission in patients admitted to the PICU at two tertiary hospitals in the Bloemfontein

Academic Complex over a two-year period from January 2017 to December 2018.

3) To determine the primary outcomes of patients (mortality or survival at discharge from PICU) admitted to the PICU at two tertiary hospitals in the Bloemfontein Academic Complex over a two-year period from January 2017 to December 2018.

4) To determine the secondary outcomes of patients (length of PICU stay and the number of ventilator days) admitted to the PICU at two tertiary hospitals in the Bloemfontein Academic Complex over a two-year period from January 2017 to December 2018.

Secondary Objectives

1) To compare the admission serum PCT levels to the primary outcomes (mortality or survival at discharge from PICU) of patients admitted to the PICU at two tertiary hospitals in the Bloemfontein Academic Complex over a two-year period from January 2017 to December 2018.

2) To compare the change from serum PCT levels obtained at admission to PCT levels obtained between 48 - 72 hours of admission to the primary outcome (mortality or survival at discharge from PICU) of patients admitted to the PICU at two tertiary hospitals in the Bloemfontein Academic Complex over a two-year period from January 2017 to December 2018.

3) To compare the admission serum PCT levels to the secondary outcomes (length of PICU stay and the number of ventilator days) of patients admitted to the PICU at two tertiary hospitals in the Bloemfontein Academic Complex over a two-year period from January 2017 to December 2018.

4) To compare the change from serum PCT levels obtained at admission to PCT levels obtained between 48 - 72 hours of admission to the secondary outcomes (length of PICU stay and the number of ventilator days) of patients admitted to the PICU at two tertiary hospitals in the Bloemfontein Academic Complex over a two-year period from January 2017 to December 2018.

1.6 REFERENCES

1. Stedman TL. Stedman's Medical Dictionary for the Health Professions and Nursing. 7th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012.

2. Downes KJ, Fitzgerald JC, Weiss SL. Utility of Procalcitonin as a Biomarker for Sepsis in Children. J Clin Microbiol. 2020;58(7).

3. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. In: Pediatric Critical Care Medicine.

2005.

4. Aygun F. Procalcitonin Value Is an Early Prognostic Factor Related to Mortality in Admission to Pediatric Intensive Care Unit. Crit Care Res Pract. 2018;2018.

5. Siddiqui I, Jafri L, Abbas Q, Raheem A, Haque AU. Relationship of serum procalcitonin, c-reactive protein, and lactic acid to organ failure and outcome in critically ill pediatric population. Indian J Crit Care Med. 2018;22(2):91–5.

6. Pudjiadi AH, Yanti M, Tumbelaka AR. Prognostic factors of death in children admitted to pediatric intensive care unit, Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Paediatr Indones [Internet]. 2002 [cited 2019 Jun 25];42(11):254–60. Available from: https://paediatricaindonesiana.org/index.php/paediatrica-indonesiana/article/view/1035

7. Poddar B, Gurjar M, Singh S, Aggarwal A, Baronia A. Reduction in procalcitonin level and outcome in critically ill children with severe sepsis/septic shock—A pilot study. J Crit Care. 2016;36:230–3.

8. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Pediatr Crit Care Med. 2020;

9. Bobillo-Perez S, Rodríguez-Fanjul J, Jordan Garcia I. Is Procalcitonin Useful in Pediatric Critical Care Patients? Vol. 13, Biomarker Insights. 2018.

10. White D. Can a negative procalcitonin level guide antibiotic therapy in early-onset neonatal sepsis? South African J Child Heal [Internet]. 2007 Jan 23 [cited 2019 Jun 25];1(4):146–50. Available from: http://www.sajch.org.za/index.php/SAJCH/article/view/33

11. Poddar B, Gurjar M, Singh S, Aggarwal A, Singh R, Azim A, et al. Procalcitonin kinetics as a prognostic marker in severe sepsis/septic shock. Indian J Crit Care Med. 2015;19(3):140–6.

12. Ramasawmy D, Pillay M, Hardcastle TC. Correlation of procalcitonin to positive blood culture results in a sample of South African trauma ICU patients between 2016 and 2017. Eur J Trauma Emerg Surg. 2020;

13. Achra A, Narsaria P, Lodha R, Kabra SK, Kapil A. Procalcitonin in pediatric intensive care unit of a tertiary care hospital. Clin Epidemiol Glob Heal. 2016;4(2):80–2.

14. Downes KJ, Weiss SL, Gerber JS, Klieger SB, Fitzgerald JC, Balamuth F, et al. A pragmatic biomarker-driven algorithm to guide antibiotic use in the pediatric intensive care unit: The optimizing antibiotic strategies in sepsis (OASIS) study. J Pediatric Infect Dis Soc. 2017;6(2):134–41.

15. Gunasekaran V, Radhakrishnan N, Dinand V, Sachdeva A. Serum Procalcitonin for Predicting

Significant Infections and Mortality in Pediatric Oncology. Indian Pediatr. 2016;53(12):1075–8.

16. Karsas M, Becker PJ, Green RJ. Serious bacterial infections in febrile young children: Lack of value of biomarkers. SAJCH South African J Child Heal. 2016;10(1):33–6.

17. Launes C, Esteban E, Balaguer M, Alsina M, Cambra FJ, Jordan I. Procalcitonin-guidance reduces antibiotic exposure in children with nosocomial infection (PRORANI). Vol. 72, Journal of Infection. 2016. p. 250–3.

18. Martinez R, Rode H. Role of procalcitonin in paediatric burn wound sepsis. South African Med J. 2018;108(10):793–4.

19. Memar MY, Varshochi M, Shokouhi B, Asgharzadeh M, Kafil HS. Procalcitonin: The marker of pediatric bacterial infection. Biomed Pharmacother. 2017;96:936–43.

20. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet. 2010;375(9713):463–74.

21. Donà D, Barbieri E, Daverio M, Lundin R, Giaquinto C, Zaoutis T, et al. Implementation and impact of pediatric antimicrobial stewardship programs: a systematic scoping review. Vol. 9, Antimicrobial Resistance and Infection Control. 2020.

22. Katz S, Crook J, Gillon J, Szeles A, Stanford JE, Wang L, et al. 2239. Randomized Controlled Trial of a PROcalcitonin-Guided Antibiotic Treatment Algorithm Plus Antibiotic Stewardship the Pediatric Intensive Care Unit (ProPICU). Open Forum Infect Dis. 2019;6(Supplement_2):S765–6.

23. Chiotos K, Gerber JS, Himebauch AS. How Can We Optimize Antibiotic Use in the PICU?*. Pediatr Crit Care Med. 2017;18(9):903–4.

24. Ryoo SM, Han KS, Ahn S, Shin TG, Hwang SY, Chung SP, et al. The usefulness of C-reactive protein and procalcitonin to predict prognosis in septic shock patients: A multicenter prospective registry-based observational study. Sci Rep. 2019;9(1).

25. Meng FS, Su L, Tang YQ, Wen Q, Liu YS, Liu ZF. Serum procalcitonin at the time of admission to the ICU as a predictor of short-term mortality. Clin Biochem. 2009;42(10–11):1025–31.

26. Naidoo K, De Vasconcellos K, Skinner DL. Procalcitonin kinetics in the first 48 hours of ICU admission is associated with higher mortality in critically ill patients with community-acquired pneumonia in a setting of high HIV prevalence. South African J Anaesth Analg. 2018;24(5):128–34.

27. Baranwal A, Singh V, Muralidharan J, Sachdeva N. Serial Procalcitonin Correlated well with Organ Dysfunction and outcome of Pediatric Septic Shock. Crit Care Med [Internet]. 2019

Jan;47:809. Available from: http://journals.lww.com/00003246-201901001-01620

28. Waterfield T, Maney JA, Hanna M, Fairley D, Shields MD. Point-of-care testing for procalcitonin in identifying bacterial infections in young infants: A diagnostic accuracy study. BMC Pediatr. 2018;18(1).

CHAPTER 2

2.1 ABSTRACT

Background: Procalcitonin (PCT) is used in the diagnosis of sepsis. Its capability as a prognostic marker is unclear. The association between PCT and PICU outcomes has not been investigated in the South African setting.

Objectives: To determine the association between admission PCT, and trends within 72 hours of admission, and outcomes of patients admitted to the PICU at two tertiary academic hospitals.

Methods: The study was a 2-year, double centre, retrospective, analytical cross-sectional medical record review.

Results: A total of 381 participants were included in the study - 55 died, 220 required mechanical ventilation. Non-survivors had a higher median admission PCT than survivors (p <0.0001, 95% CI 1.28 – 15.12). Non-survivors had a higher median PCT at 48-72 hours than survivors (p <0.0001, 95% CI 2.50 – 21.72). Non-survivors had less of a median decrease in PCT than survivors (p= 0.22, 95% CI -0.59 - 4.72). The area under the receiver operating characteristics curve (AUROCC) for admission PCT to discriminate for mortality was 0.6702 and for the 48-72 hour PCT it was 0.7369. There was a positive correlation between PCT trend and number of ventilator days (Spearman correlation co-efficient =0.1477, p=0.0138). There was no correlation between the length of PICU stay and admission PCT(p=0.7579) or PCT change (p=0.2034).

Conclusion: PCT displays some ability to discriminate for PICU mortality. Serial PCT measurements provide greater prognostic information than single measurements.

2.2 MANUSCRIPT

Introduction

The risk of mortality should be assessed in all patients admitted to the Paediatric Intensive Care Unit (PICU) to deliver effective critical care services.[1–4] Various independent risk factors for PICU mortality have been described in the literature such as mechanical ventilation frequency, length of stay and presence of sepsis. Bacterial sepsis remains a major risk factor for mortality and morbidity in the paediatric population both in out of the PICU setting. [1–3,5–7] Procalcitonin (PCT) and C-reactive protein (CRP) have been identified as important biomarkers in the management of sepsis.[1,2,5,6,8] PCT is an endogenous peptide primarily secreted by the parafollicular C cells of the thyroid gland. It rises in response to certain pro-inflammatory stimuli and various bacterial endotoxins. Its efficiency in the early diagnosis of bacterial sepsis in paediatric patients has been widely reported.[5,6,8] However, there is conflicting data regarding appropriate cut-off values in the neonatal period, partly due to the physiological increase in PCT after birth.[5] Other inflammatory conditions such as burns, surgeries and bowel wall ischaemia, may cause a rise in PCT levels, however in the absence of infection there is subsequent decrease. PCT values for the diagnosis of sepsis in these patients also vary substantially within the literature. [5,6,9] Other uses of PCT are frequently being investigated including its use in guiding antimicrobial duration and its prognostic capabilities.[1,2,4–6,10–15] The prognostic capability of PCT in the paediatric setting is unclear.[1,4,6,12,14] In South Africa, the prognostic capability of PCT in the critical care setting has been evaluates in the adult population. Naidoo et al reported an increased risk of mortality in patients who had an increasing PCT trend or a PCT that remained above 10ng/ml within 48 hours of admission to the ICU.[11] Therefore, evaluating the trend of PCT at 48 hours of admission to the ICU may assist in assessing the prognosis of patients. Considering this evidence, the evaluation of PCT trends in the PICU setting may similarly provide insight into the prognostic capability of PCT. This study therefore aims to investigate the association between PCT on admission and the trend within the first 48-72 hours of admission, and outcomes in the PICU thereby further evaluating alternative uses of PCT in this setting.

Methods

This study was a retrospective analytical cross-sectional medical record review of consecutive patients admitted to the PICU in the Bloemfontein academic hospital complex in the Free State, consisting of Universitas Academic Hospital and Pelonomi Hospital, over the period 01 January 2017 to 31 December 2018. Participants were identified from the electronic admissions registry available at each PICU. All patients between the ages of 1 month (30.44 days) and 60 months were assessed for eligibility. Patients who did not have a PCT done on admission, patients who were elective post-surgery PICU admissions, patients who were admitted due to trauma or burn injuries and patients who had missing critical information were excluded from the study. Data collected included demographic characteristics, laboratory results and outcomes. Study data were collected and managed using REDCap® electronic data capture tools hosted at the University of Free State. REDCap® (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.[16,17] Demographic characteristics included age on admission, sex, HIV status and primary diagnosis on admission. Laboratory results included the participant's PCT value on admission and the PCT value within 48 to 72 hours of admission. These hospitals made use of the National Health Laboratory Services (NHLS), where quantitative serum PCT levels are determined using the Elecsys® BRAHMS PCT assay in the Cobas® e immunoassay analyser (Roche Diagnostics GmbH, Mannheim, Germany). PCT values on admission included the first PCT value recorded within 24 hours of admission. PCT values within 48 to 72 hours of admission included the first recorded PCT within this time frame. The difference in PCT from admission to 48 to 72 hours of admission was calculated and recorded as an integer rounded to 2 decimal points (PCT change). The difference was also calculated as a percentage change from the admission value (PCT percentage change). Outcome data included PICU outcome at discharge, duration of mechanical ventilation and length of PICU stay.

De-identified data from the registered RedCap® secure database was exported to a Microsoft Excel® spreadsheet and submitted to the Department of Biostatistics, University of Free State, for statistical analysis using SAS Software, Version 9.4 (Copyright © 2002-2012 by SAS Institute Inc., Cary, NC, USA). The J-statistic was thereafter calculated by the investigator to evaluate the performance of PCT to discriminate for mortality at various PCT cut-off points.

The research was approved by the Human Research Ethics Committee of the Faculty of Health Science of the University of the Free State. (UFS-HSD2019/2251/203)

Results

A total of 953 patients were admitted to the PICU from 01 January 2017 to 31 December 2018. 650 patients fell within the age range 1 month to 60 months. 216 were excluded due to a diagnosis of either trauma, burns or elective post-surgery admission. 51 patients were excluded due to no admission PCT being done. 2 patients were excluded due to missing information. A total of 381 participants were eligible to be included in the study.

Table 1: Demographic Characteristics

Demographics		(n=381)
Age (months)		median=7.1 (IQR 3.0-18.0)
Sex	Male	216 (56.7%)
	Female	165 (43.3%)
HIV Status	Negative	348 (91.3%)
	Positive	32 (8.4%)
	Unknown	1 (0.3%)
Primary diagnosis		
	Sepsis	144 (37.8%)
	Respiratory tract disease	131 (34.4%)
	Intoxications	31 (8.1%)
	Neurological disease	25 (6.6%)
	Cardiovascular disease	24 (6.3%)
	Other	20 (5.3%)
	Haematology Oncology	6 (1.5%)

The demographic characteristics of the final participant sample are summarised in Table 1. The median age of the participant sample was 7.1 months. Just over half of the participants were male. Almost all the participants had a known HIV status, with 1 (0.3%) being unknown and most (91.3%) being negative. The most common primary diagnosis was Sepsis followed by Respiratory Tract Disease, which together comprised most of the participant sample.

PCT was measured on admission in all participants. The value for PCT on admission ranged from 0.06ng/ml to 100ng/ml with some values reported as >100ng/ml. The median admission PCT was 1.86ng/ml. 295 participants had a PCT measurement within 48 to 72 hours of admission. From admission to within 48 to 72 hours of admission, 87 patients had an upward trend in their PCT, 2 participants showed no change in their PCT and 206 patients had a downward trend in their PCT. The PCT change from admission to within 48-72 hours ranged from -94.18 to +77.61, the median PCT change being -0.39 (IQR -4.88 – 0.07). The percentage PCT change from admission PCT to the PCT within 48 to 72 hours ranged from -95.7% to +13 300%, with the median change being -42.0% (IQR -69.2% - 25.5%).

Of the 381 participants in this study 55 died. The median admission PCT value for non-survivors (13.94ng/ml, IQR 1.0 – 100.0) was significantly higher than for survivors (1.45ng/ml, IQR 0.36 – 13.08) (p <0.0001, 95% CI 1.28 – 15.12). The median PCT at 48-72 hours for the non-survivors (12.79ng/ml, IQR 2.08 – 100.00) was significantly higher than for the survivors (1.31ng/ml, IQR 0.29 – 7.15) (p <0.0001, 95% CI 2.50 – 21.72). The median PCT change in the non-survivors (-0.12ng/ml, IQR -3.68 to +4.125) was less than the median PCT change in the survivors (-0.40ng/ml, IQR -4.88 to +0.05) (p= 0.22, 95% CI -0.59 - 4.72). The median percentage PCT change in the non-survivors (-17.85%, IQR -61.00 to +105.10) was less than the median percentage PCT change in the survivors (-44.20%, IQR -69.5 to +16.8) (p=0.12, 95% CI -5.20 – 66.00). Of those who had a decreasing PCT trend 13 (6.3%) died compared to 11(12.6%) of those who had an increasing PCT trend (p=0.24). The relative risk of mortality in those with a decrease in PCT versus those with an increase in PCT was 2.00 (95% CI 0.93 - 4.30).

Fig. 1: Receiver Operating Characteristics Curve of admission Procalcitonin to discriminate for Mortality

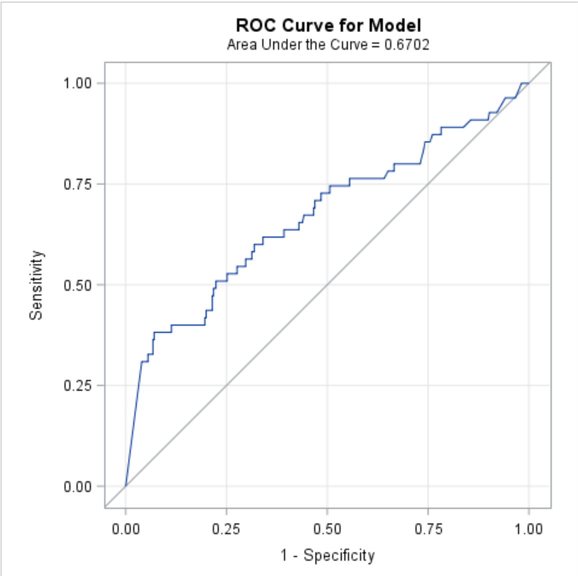

Table 2: Predicting mortality from PCT on admission			
PCT (ng/ml)	Sensitivity	Specificity	J-Statistic
1.00	76.4%	44.5%	0.205
5.00	61.8%	64.7%	0.265
10.00	54.5%	72.1%	0.266
70.76	38.2%	92.9%	0.311

Figure 1 displays the Receiver Operating Characteristics (ROC) Curve for an admission PCT to discriminate for mortality (Area Under Curve (AUC)=0.6702). Table 2 shows the sensitivity, specificity and J-statistic of the admission PCT to predict mortality calculated at various cut off points. The optimal threshold for admission PCT to discriminate for mortality was at 70.76ng/ml which had a sensitivity of 38.2% and specificity of 92.9%.

<u>Fig. 2: Receiver Operating Characteristics Curve of Procalcitonin within 48-72hours of admission to discriminate for mortality</u>

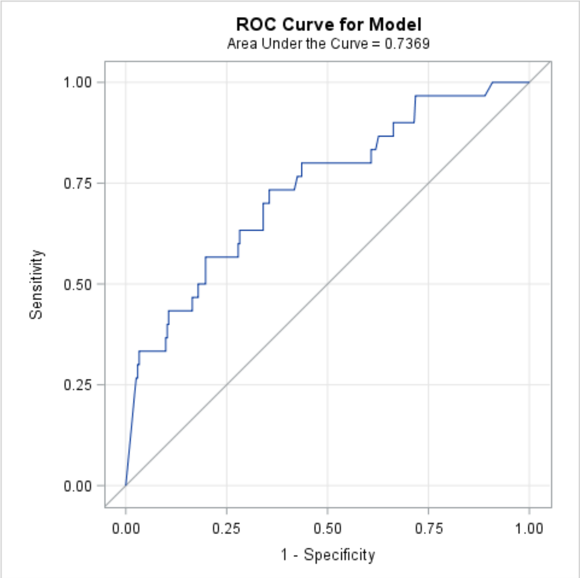

Table 3: Predicting mortality from PCT at 48-72 hours of admission			
PCT (ng/ml)	Sensitivity	Specificity	J-Statistic
1.00	80.0%	45.4%	0.254
3.16	73.3%	64.5%	0.378
5.00	63.3%	68.9%	0.322
10.00	56.7%	79.5%	0.362

Figure 2 displays the ROC Curve for PCT at 48-72 hours to predict mortality (AUC=0.7369). Table 3 shows the sensitivity, specificity and J-statistic of a PCT at 48-72 hours of admission to discriminate for mortality at various cut off points. The optimal threshold for the 48-72hour PCT to discriminate for mortality was at 3.16ng/ml which had a sensitivity of 73.3% and specificity of 64.5%.

A total of 220 participants in this study required ventilation. The number of ventilation days for the participants requiring ventilation ranged from 1 day to 66 days (median=2 days). The median admission PCT value for participants requiring ventilation (2.03ng/ml, IQR 0.45 – 19.96) was higher than for those not requiring ventilation (1.49ng/ml, IQR 0.34 – 12.81) (p=0.1792, 95% CI 0.63 – 0.060). The median PCT change in participants requiring ventilation (-0.23ng/ml, IQR -2.72 to +0.52) was significantly less than for those not requiring ventilation (-0.76ng/ml, IQR -6.34 to -0.05) (p= 0.0044, 95% CI -1.67 - -0.16). The median percentage PCT change in participants requiring ventilation (-34.3%, IQR -69.10 to +70.30) was significantly less than for those not requiring ventilation (-51.95%, IQR -70.10 to -17.45) (p= 0.0367, 95% CI -28.4 - -0.70). Table 4 displays the Spearman correlation coefficients between admission PCT, PCT change and percentage PCT change and ventilation. The relative risk of requiring ventilation for those with an increase in PCT compared to those with a decrease in PCT was 1.40 (95% CI 0.19 – 1.66).

Table 4: Spearman Correlation Co-effecients between Procalcitonin values and Ventilation days

	PCT admission	PCT change	PCT percentage change
Spearman correlation co-effecients	0.04552	0.14418	0.10436
p-value	0.4127	0.0208	0.095

The length of PICU for the total participant sample range from 1 to 66 days (median=6). There was no significant correlation between the length of PICU stay and admission PCT(p=0.7579), the PCT change (p=0.2034) or the percentage PCT change (p=0.2625).

Discussion

The aim of this study was to evaluate the association between PCT and PICU mortality, length of PICU stay and mechanical ventilation in our setting. Neonatal, surgical and trauma patients were excluded due to the substantial differences in the literature in the interpretation of PCT in these patients.[5,6,9] Findings in this study revealed a higher median admission PCT in the non-survivor group compared to the survivor group (13.94ng/ml vs 1.45ng/ml, p<0.001). Similar findings were reported in a study by Hatherill et al (273ng/ml vs 82ng/ml, p=0.03)[18] as well as Aygun et al where the researchers reported a difference in the mean admission PCT between the non-survivor and survivor groups (57.41ng/ml vs 9.38ng/ml, p=0.022).[1] The median PCT at 48-72hours of admission was also higher in non-survivors (12.78ng/ml vs 1.31ng/ml, p<0.001). Various studies have been done to assess the association between PCT levels and the risk of mortality.[1,10,11,13] Aygun et al reported in their study that admission PCT at a threshold of 6.38ng/ml had a sensitivity 81.8% and a specificity 80.8% to discriminate for mortality and an AUC of 0.838.[1] In the present study admission PCT had a sensitivity of 60.0% and specificity of 65.95% to discriminate for mortality at a threshold of 6.0ng/ml. The strongest profile, using the calculated J-statistic, was found at the 48-72hour PCT at a threshold of 3.16ng/ml which displayed a sensitivity 73.3% of and specificity of 64.5%. The ROC curve for PCT to discriminate for mortality also had a greater AUC at 48-72 hours (0.7369 vs 0.6702). The present study also assessed trends in PCT and revealed a greater percentage of the participants with an increasing PCT died than those who had a decreasing trend (12.6% vs 6.3%, p=0.24) with the relative risk of mortality in participants with an increasing trend being 2.00 (95%CI 0.92 - 4.30). Non-survivors also had less of an absolute decrease in PCT (median = -0.12ng/ml, IQR -3.68 to +4.125; p=0.22) and percentage PCT decrease (median= -17.85%, IQR -61.00 to +105.10; p=0.12) than survivors. Although not statistically significant, these findings are supported by the findings of Naidoo et al which reported a greater percentage of the study participants with an increasing PCT trend died than those with a decreasing PCT trend (66.7% vs 40.6%, OR=2.92, CI 1.18-7.22).[11] The meta-analysis by Liu et al also reported that non-clearance of PCT in patients with sepsis was associated with an increased risk of mortality (relative risk 3.05, 95% CI 2.35 - 3.95).[10] Furthermore, Hatherill et al demonstrated that the absence of a decreasing PCT trend after initial treatment for sepsis was associated with an increased mortality rate (44% vs 9%, p=0.02).[18] Mechanical ventilation is a frequently used modality of treatment in the PICU which has been described as a strong independent risk factor for mortality.[1,3] Aygun et al reported that the participants who required mechanical ventilation had higher admission PCTS (>10ng/ml, p=0.28).[1] The present study displayed a weak positive correlation between increasing PCT and ventilation days (Spearman correlation coefficient 0.14418, p=0.0208). The present study did not reveal any significant association between PCT, PCT change and length of PICU stay. Sepsis during a PICU admission is a known risk factor for mortality.[2] PCT rises in response to bacterial sepsis. Researchers postulate that higher levels of PCT correlate with the severity of infection and therefore poorer outcomes.[1,13] The development of sepsis might explain the significant median difference between the survivors and non-survivors in the present study. The use of serial PCT measurements provides more prognostic information than that of a single measurement.[4,6,14] The present study highlighted the strength of measuring PCT at 48-72 hours of admission. The profile for the 48hour PCT to discriminate for mortality was stronger than that at of an admission PCT. Furthermore, increasing trends during this time frame is associated with an increased risk of mortality. Such association potentially reflects a lack of response to treatment and should prompt urgent re-evaluation of the patient.

Study Limitations

This study did have limitations. It was a retrospective study with a small sample size. Collected data was reliant on accurate registries and electronic records. It also unknown how the patients who were excluded, due to missing PCT values or who had no admission PCT measured, would had affected the results. Furthermore, the study excluded surgical and trauma patients and the results cannot be generalised to this group of patients.

Conclusion

The present study demonstrated that procalcitonin on admission PICU does display some ability to discriminate for mortality. Serial measurements provide greater prognostic information. Non-survivors had a significantly greater median admission PCT, median PCT at 48-72 hours and a lower median PCT decrease than survivors. In this study, a PCT value above a threshold of 3.16ng/ml at 48-72 hours of admission was optimal for mortality prediction based on the calculated J-statistic. PCT that remains above 3.16ng/ml during this time frame could serve as a red flag for clinicians to re-evaluate the management plan of these patients. Due to the small sample size of this study, further studies with a larger sample size are recommended. Furthermore, as this study excluded trauma and surgical patients, a study evaluating prognostic capabilities of PCT in this cohort of patients is also recommended.

References

1. Aygun F. Procalcitonin Value Is an Early Prognostic Factor Related to Mortality in Admission to Pediatric Intensive Care Unit. Crit Care Res Pract. 2018;2018.

2. Siddiqui I, Jafri L, Abbas Q, Raheem A, Haque AU. Relationship of serum procalcitonin, c-reactive protein, and lactic acid to organ failure and outcome in critically ill pediatric population. Indian J Crit Care Med. 2018;22(2):91–5.

3. Pudjiadi AH, Yanti M, Tumbelaka AR. Prognostic factors of death in children admitted to pediatric intensive care unit, Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Paediatr Indones [Internet]. 2002 [cited 2019 Jun 25];42(11):254–60. Available from: https://paediatricaindonesiana.org/index.php/paediatrica-indonesiana/article/view/1035

4. Poddar B, Gurjar M, Singh S, Aggarwal A, Baronia A. Reduction in procalcitonin level and outcome in critically ill children with severe sepsis/septic shock—A pilot study. J Crit Care. 2016;36:230–3.

5. Bobillo-Perez S, Rodríguez-Fanjul J, Jordan Garcia I. Is Procalcitonin Useful in Pediatric Critical Care Patients? Vol. 13, Biomarker Insights. 2018.

6. Downes KJ, Fitzgerald JC, Weiss SL. Utility of Procalcitonin as a Biomarker for Sepsis in Children. J Clin Microbiol. 2020;58(7).

7. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Pediatr Crit Care Med. 2020;

8. Ramasawmy D, Pillay M, Hardcastle TC. Correlation of procalcitonin to positive blood culture results in a sample of South African trauma ICU patients between 2016 and 2017. Eur J Trauma Emerg Surg. 2020;

9. Samsudin I, Vasikaran SD. Clinical utility and measurement of procalcitonin. Clinical Biochemist Reviews. 2017.

10. Liu D, Su L, Han G, Yan P, Xie L. Prognostic value of procalcitonin in adult patients with sepsis: A systematic review and meta-analysis. PLoS One. 2015;

11. Naidoo K, De Vasconcellos K, Skinner DL. Procalcitonin kinetics in the first 48 hours of ICU admission is associated with higher mortality in critically ill patients with community-acquired pneumonia in a setting of high HIV prevalence. South African J Anaesth Analg. 2018;24(5):128–34.

12. Downes KJ, Weiss SL, Gerber JS, Klieger SB, Fitzgerald JC, Balamuth F, et al. A

pragmatic biomarker-driven algorithm to guide antibiotic use in the pediatric intensive care unit: The optimizing antibiotic strategies in sepsis (OASIS) study. J Pediatric Infect Dis Soc. 2017;6(2):134–41.

13. Meng FS, Su L, Tang YQ, Wen Q, Liu YS, Liu ZF. Serum procalcitonin at the time of admission to the ICU as a predictor of short-term mortality. Clin Biochem. 2009;42(10–11):1025–31.

14. Baranwal A, Singh V, Muralidharan J, Sachdeva N. Serial Procalcitonin Correlated well with Organ Dysfunction and outcome of Pediatric Septic Shock. Crit Care Med [Internet]. 2019 Jan;47:809. Available from: http://journals.lww.com/00003246-201901001-01620

15. Ryoo SM, Han KS, Ahn S, Shin TG, Hwang SY, Chung SP, et al. The usefulness of C-reactive protein and procalcitonin to predict prognosis in septic shock patients: A multicenter prospective registry-based observational study. Sci Rep. 2019;9(1).

16. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. Vol. 95, Journal of Biomedical Informatics. 2019.

17. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81.

18. Hatherill M, Tibby SM, Turner C, Ratnavel N, Murdoch IA. Procalcitonin and cytokine levels: Relationship to organ failure and mortality in pediatric septic shock. Crit Care Med. 2000;

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

Health Sciences Research Ethics Committee

04-Mar-2020

Dear **Dr Augusto Luyo Sanchez**

Ethics Clearance: **The Association between Serum Procalcitonin Levels and Outcomes of Patients Admitted to Two Tertiary Paediatric Intensive Care Units in the Bloemfontein Academic Complex: A Retrospective Analytical Study**

Principal Investigator: **Dr Augusto Luyo Sanchez**

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-HSD2019/2251/2403**

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 00011992; REC 230408-011; IORG 0010096; FWA 00027947
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa

B: Subsequent Letter of approval from Research Ethics Committee (After amendments)

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

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

21-May-2020

Dear **Dr Augusto Luyo Sanchez**

Ethics Number: UFS-HSD2019/2251/2403

Ethics Clearance: **The Association between Serum Procalcitonin Levels and Outcomes of Patients Admitted to Two Tertiary Paediatric Intensive Care Units in the Bloemfontein Academic Complex: A Retrospective Analytical Study**

Principal Investigator: **Dr Augusto Luyo Sanchez**

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

SUBSEQUENT SUBMISSION APPROVED

With reference to your recent submission for ethical clearance from the Health Sciences Research Ethics Committee. I am pleased to inform you on behalf of the HSREC that you have been granted ethical clearance for your request as stipulated below:

I would like to make the following changes to my data collection instrument:
- The sub-category "Septicaemia" under Primary Diagnosis changed to "Sepsis"
- This is found in the protocol:
- Under the heading 10.Measurements -10.1 Variables on page 14 of the research protocol
- In Annexure A Data Capture Form on Page 23 of the research protocol

This was done to correct a typo in these areas as sepsis, and not septicaemia, is clearly defined in the protocol. Subsequently this is reflected in the final electronic RedCap Data Capture form under the section "Primary Diagnosis" on page 1.

I have also changed the definition of the age criteria in my protocol as follows:
- On page 13 under Section 9.3.1 Inclusion Criteria, the definition of 1 month has been changed to = 30.44 days, as per the definition on the RedCap software. This was done so that the RedCap software can calculate the age accurately for all participants.

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 request for ethical clearance and we wish you continued 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 00011992; REC 230408-011; IORG 0010096; FWA 00027947

C: Permission from DOH

health
Department of Health
FREE STATE PROVINCE

12 February 2020

Dr A Luyo Sanchez
Dept. of Paediatrics and Child Health
UFS

Dear Dr A Luyo Sanchez

Subject: The association between serum procalcitonin levels and outcomes of patients admitted to two tertiary paediatric intensive care units in the Bloemfontein academic complex: A retrospective analytical suty.

- 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 and Pelonomi Hospital** nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** sebeelats@fshealth.gov.za / makenamr@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: 17/02/2020

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

www.fs.gov.za

D: Permission from NHLS

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: 4 December 2019

Requestor: Dr A.M. Luyo Sanchez

Project Name: "The Association between Serum Procalcitonin Levels and Outcomes of Patients Admitted to Two Tertiary Pediatric Intensive Care Units in the Bloemfontein Academic Complex: A Retrospective Analytical Study"

Dear Dr. Luyo Sanchez,

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

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

May your project be successful.

Regards,

NATIONAL HEALTH LABORATORY SERVICE
06 DEC 2019
Acting
BUSINESS MANAGER
UNIVERSITAS ACADEMIC LABORATORIES

Mr. Pakiso Letanta
Acting Business Manager

Chairperson: Prof Eric Buch Acting CEO: Dr Karmani Chetty
Physical Address: 1 Modderfontein Road, Sandringham, Johannesburg, South Africa Postal Address: Private Bag X8, Sandringham, 2131, South Africa
Tel: +27 (0) 11 386 6000/ 0860 00 NHLS(6457) www.nhls.ac.za
Practice number: 5200296

E: Permission from HOD

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

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

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

06 November 2019

Dear Dr SM Le Grange

Dr Augusto Luyo-Sanchez (Student number: 2017498169)
Study leader: Dr MA Pienaar

The association between serum procalcitonin levels and outcomes of patients admitted to two tertiary Paediatric intensive care units in Bloemfontein Academic Complex: A retrospective analytical study.

I, André Venter, hereby grant Dr Augusto Luyo-Sanchez 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.

Yours faithfully

Prof A Venter

6/11/2019.
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
Prof SC Brown: T: +27 (0)51 405 3254, E: Gnpdscb@ufs.ac.za / Dr A van der Vyver: T: +27 (0)51 405 3184, E: Gnpdavdv@ufs.ac.za

F: Copy of the research protocol approved by the HSREC

The Association between Serum Procalcitonin Levels and Outcomes of Patients Admitted to Two Tertiary Paediatric Intensive Care Units in the Bloemfontein Academic Complex: A Retrospective Analytical Study

Researcher:

Dr. A.M. Luyo Sanchez, MBChB(UKZN)

Registrar, Department of Paediatrics and Child Health
Faculty of Health Sciences
University of the Free State

Study Leader:

Dr M.A. Pienaar, MBChB, MMed (UFS), FC Paed (CMSA)

Consultant, Department of Paediatrics and Child Health
Faculty of Health Sciences
University of the Free State

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1. Abbreviations

CRP – C-reactive protein

ICU – Intensive Care Unit (usually in reference to an adult ward)

ng/ml – nanograms per millilitre

NHLS – National Health Laboratory Services

PCT – Procalcitonin

PH – Pelonomi Hospital

PICU – Paediatric Intensive Care Unit

PIM score – Paediatric Index of Mortality score

PRISM score – The Paediatric Risk of Mortality Score

UAH – Universitas Academic Hospital

ug/L – Microgram per litre

2. Definitions

Aetiology – the cause of a disease

Biomarker – a naturally occurring molecule within the body which can be measured to indicate a certain disease or biological process

Carcinoma – medical term for a type of cancer

Critical care - the specialized management of patients who require comprehensive care and constant monitoring usually done within the hospital ward known as the intensive care unit

Endogenous peptide – a compound originating within the body

Immuno-paresis – weakening of the immune system

In-transit care – medical management of a patient done during transfer from one institution to another

Inotropes – a specific class of drugs commonly used in the management of shock by acting on the heart muscle to improve blood circulation

Length of stay – recorded commonly in hospital notes as the number of days the patient was admitted to a specific ward or hospital

Mechanical ventilation – is a means by which the breathing of a patient is done or assisted with the use of a specialised machine referred to as a mechanical ventilator

Mortality - death

PCT Kinetics – term describing the change in the amount of procalcitonin within the body

Physiological – in reference to physiology; in medicine a science describing the normal function of the body and its various organ systems

Prognosis – predicting the likely outcome or progression of a disease

Sepsis – a medical condition characterised by the presence of a harmful organism within the human body manifesting as a severe illness

Septic shock – shock is a medical condition where there is inadequate oxygen supply to vital organs resulting in impaired function caused by the presence and progression of sepsis

Serum – referring to within the blood system

Ventilation days – the number of days which a patient is on a ventilator during their admission

3. <u>Introduction</u>

The severity of disease and risk of mortality should be assessed in all patients admitted to the paediatric intensive care unit (PICU) in order to provide effective and timely treatment. (1–5) Scoring systems have been developed to assess the risk of mortality with the most widely used scoring systems being the PRISM and PIM2 scores. (1–3) These scoring systems do not accurately prognosticate patients at an individual level and cannot be used to determine the severity of disease. (2) Independent risk factors for mortality in patients admitted to the PICU include mechanical ventilation frequency, inotropic drug use, length of hospital-stay and the presence of sepsis. Sepsis remains a major cause of mortality and morbidity in the paediatric population both in and out of the ICU setting. An early diagnosis of sepsis is crucial in children as urgent appropriate intervention is required to adequately treat the infection and prevent complications and death. (1,3–6) Biomarkers such as C-reactive protein (CRP) and Procalcitonin (PCT) have been used to aid in the early the diagnosis of sepsis. PCT has been established as a superior diagnostic marker of sepsis in comparison to CRP.(1,6–15) Several studies in the South African paediatric population which have validated the diagnostic value of PCT in sepsis. (11,13,15) Some studies have investigated the prognostic value of PCT to determine its ability to predict mortality, the results of which have been conflicting. (1,3,5,7,8,10,16,17) In the South African adult population a statistically significant association was shown between the absolute value of PCT at 48 hours of admission to the ICU and the risk of mortality. (17) No study has been done in the paediatric population in South Africa to evaluate such association in the PICU setting.

4. <u>Literature Review</u>

<u>Procalcitonin</u>

Procalcitonin (PCT) is an endogenous peptide primarily secreted by the parafollicular C cells of the thyroid gland and has been described as a precursor to the hormone calcitonin. (1,3,5–7,13–15,17) Other suggested sites of origin include the lung, liver and kidneys. (14,15) PCT levels are generally undetectable or low (<0.1ng/ml) in healthy individuals (1,14,17) In 1993 *Assicot et al.* described PCT in the context of sepsis and demonstrated a rise in response to a pro-inflammatory stimulus and bacterial endotoxins. It is widely accepted as a reliable biomarker in the early diagnosis of bacterial sepsis. (1,3,6,7,14,15,17) In bacterial infections levels may go beyond >100 000 times the normal value. The physiological role of PCT in bacterial sepsis is not fully understood. In theory, PCT, due to its similarity with calcitonin, plays a role in calcium metabolism in patients with bacterial sepsis as they frequently develop hypocalcaemia. However, a correlation between an increase in PCT levels and a subsequent rise in calcitonin levels has not been demonstrated. In bacterial sepsis there appears to be no considerable correlation between PCT and calcium metabolism. In contrast, a rise in PCT levels from neuroendocrine tumours and small cell carcinomas of the lung is associated with an increase in calcitonin. (1,14)

In the context of bacterial sepsis PCT rises more rapidly than C-reactive protein(CRP) (1) The rise in PCT can be detected as early as 2 hours after exposure to a bacterial endotoxin. It rises significantly after 3-4 hours, plateaus by 8-12 hours and has a half-life of 25 – 30 hours. (6,14) In the last decade various investigators have reported on the role of PCT in the context of bacterial sepsis with regards to diagnostic capabilities, disease monitoring, therapeutic guidance and prognostic value. (1,3,5–7,11,13–15,17)

Procalcitonin in the Diagnosis of Bacterial Sepsis

	Author	Age of Participants	Results/ Findings
PCT in Pyrexia without a clinical source	Luaces-Cubell et al.	1 – 36 months	PCT at cut-off 0.9ng/ml to detect bacterial infections has a sensitivity of 86.7% and specificity of 90%(6)
	Mahajan et al.	</= 36 Months	PCT at cut-off 0.6ng/ml to detect bacterial infections has a sensiticity of 51% and specificity of 93%(6)
PCT in Urinary Tract Infections	Liao et al.	Meta-analysis </= 2 years	In children with urinary tract infections, PCT levels >0.5ng/ml strongly predicted the presence of renal parenchymal involvement(6,14)
PCT in LRTI	Zhu et al.	10 months - 16 years	PCT is a sensitive marker in distinguishing bacterial and non-bacterial aetiology of pneumonia(6,14)
	Toikka et al.	1 month - 17 years	In children with pneumonia, PCT above 2ng/ml suggests bacterial aetiology. However, PCT below this optimum cut-off does not exclude bacterial infection(6,14)
PCT in Meningitis	Dubos et al.	1 month -16 years	PCT above an optimum cut-off value of 0.3ng/ml had a 99% sensitivity and 83% specificity for bacterial meningitis(14)
	Henry et al	Meta-analysis	PCT is a reliable serum biomarker to rapidly differentiate viral and bacterial meningitis(14)
PCT in Neonatal Sepsis	Bobillo-Perez et al.	Systematic review	Multiple factors may affect procalcitonin levels in neonates: physiological rise, gestation, perinatal conditions such as respiratory distress syndrome. Appropriate reference ranges for PCT levels in neonates are not well established(6)
	White et al.	Newborn, suspected sepsis within 24 hours of life	PCT at a cut-off of 0.5ng/ml had a sensitivity of 48 % and specificity of 74%. At a higher cut-off of 10.ng/ml, to account for physiological rise, improved PCT specificity to 98% but worsened sensitivity to 22%(15)

PCT is a valuable biomarker in the diagnosis of bacterial sepsis in children. It frequently has a better sensitivity and specificity than CRP for bacterial sepsis. (1,3,6,8,10–15). It assists in the diagnosis of urinary tract infections, bacterial meningitis and bacterial sepsis in children with fever without a known clinical source. There are conflicting studies reporting on the ability of PCT to help differentiate bacterial and non-bacterial pneumonia. Although some studies report PCT levels above an optimum cut-off may help in the diagnosis of bacterial pneumonia, many investigators conclude that PCT levels below an optimum cut-off does not reliably exclude bacterial aetiology. In neonates, many factors may affect

PCT levels, including non-infectious pathologies. Many investigators suggest further studies are required to establish appropriate reference ranges in this population group.(6,14,15)

Diagnostic value of Procalcitonin in Haemato-Oncology Patients

In haemato-oncology patients, diagnosing bacterial infections remains challenging. PCT induction may be reduced in patients with neutropenia or those undergoing chemotherapy. Despite immunosuppressed states, PCT levels still increase in response to a pro-inflammatory stimulus. A debate remains with regards to an appropriate PCT cut-off to detect bacterial infections. In neutropenic patients, the cut-off may lie low between 0.1 to 1.5ng/ml. *Gunasekaran et al.* identified a possible optimal cut-off of 0.7ng/ml, which despite its poor sensitivity of 45-55% had a specificity of 70-83%. Most researchers agree further studies are required to establish an appropriate PCT cut-off. (6,10,14)

Diagnostic value of Procalcitonin in Surgical and Trauma Patients

Surgery induces an inflammatory response. (6,13) Identifying a biomarker which could differentiate between non-infective and infective related inflammation is crucial in the management of these patients. In children and adults, the response of PCT is dependent on the characteristics of the surgery. In abdominal surgery, PCT may rise to 2ng/ml and return to normal within 24-36 hours post-surgery. Patients undergoing cardio-pulmonary bypass may show PCT levels elevated as high as 10ng/ml without the presence of sepsis. Patients after a liver transplant may have PCT levels elevated for up to a week before returning to normal. Therefore, serial PCT measurements, as oppose to single specific cut-offs, is more useful in alerting the clinician to the possibility of septic complications. (6)

Similarly, inflammation after a traumatic injury may mask underlying sepsis. (6,13) Due to lack of research done, findings from studies in the adult population has been extrapolated to paediatric patients. The rise in PCT depends on the severity and type of trauma. In peripheral isolated injuries, PCT rise may be mild. Patients with abdominal trauma may show PCT increase within the range seen in patients after abdominal surgery. Burn injuries induce a severe inflammatory response as well as a degree of immuno-paresis. Due to nature of the injury, burn wound infections are difficult to identify and subsequently manage. In South Africa, *Martinez et al.* reported on the use of PCT in detecting sepsis in burn victims in their burn unit. Patients with culture confirmed sepsis had an average PCT value of 39.4ng/ml. However, studies suggest PCT levels as low as 0.5ng/ml as an early indication of sepsis. This burn unit used a cut-off of 2.0ng/ml, in combination with the American Burn Association SIRS/sepsis criteria, as an indication to start antibiotic therapy. Further studies are required to evaluate the efficacy of this protocol in reducing mortality and morbidity from sepsis. (13)

Procalcitonin in Guiding the Duration of Antibiotic Therapy

Clinicians appear to unnecessarily lengthen antibiotic therapy due to non-reassuring clinical and laboratory findings. Antibiotic overuse may have serious adverse effects. (3,6,9–15,17–19) Evidence based protocols are required to safely guide antibiotic duration without compromising clinical outcome. (6,9,12,18,19) The PRORATA trial, by *Bouadma et al.*, is a case-control multi-centre study that analysed the effect of a PCT based algorithm in reducing antibiotic exposure in adult non-surgical patients in the critical care setting. The results reported a successful reduction in duration of antibiotic therapy without any significant difference in mortality resulting from sepsis. (6,19)

The application of a PCT-based antibiotic protocol in the paediatric population has not been extensively researched in large trials.(5,9,12) In the PRORANI study by *Launes et al.*, the implementation of a PCT-guided protocol at single centre in Spain resulted in a 2-day reduction in antibiotic exposure after its introduction. (6,12) The OASIS II study, conducted by *Downes et al.*, evaluated the ability of a biomarker-based algorithm in reducing antibiotic exposure in patients with systemic inflammatory response syndrome, without confirmed bacterial infections, and concluded no overall reduction in antibiotic duration in the participants. (6,9,11,13)

Prognostic Value of Procalcitonin

It is important to assess the risk of mortality in patients admitted to an intensive care unit. (1,3,7,16) In the adult population, elevated procalcitonin (PCT) levels, above 10ng/ml, is associated with the increased need for mechanical ventilation, inotropic support and blood transfusions. Investigators identify these interventions as independent risk factors for mortality, thereby hypothesised that PCT may be a marker of mortality. (1,7) Various studies have been done to assess the association between PCT levels and the risk of mortality. *Meng et al.* reported that a PCT >10ng/ml at the time of admission to ICU was a strong predictor of short-term mortality, better than both CRP and the APACHEII score. Multiple studies have supported the cut-off of 10ng/ml as a predictor of short-term mortality. (1,3,16) In South Africa, a study conducted by *Naidoo et al.* suggested that the admission PCT level may be inferior predictor of mortality in comparison to the PCT level at 48 hours of admission. The study results showed the risk of mortality was increased in patients whose PCT levels increased or remained above 10ng/ml at 48 hours. The investigators considered that persistently elevated PCT may be indicative of treatment failure.(17) A study by *Poddar et al* evaluated the prognostic value of the change in serum PCT levels in adults admitted to the ICU with a diagnosis of sepsis or septic shock. The investigators concluded that a single value at the time of admission could not aid in predicting the prognosis of a patient. However, a decrease in serum PCT levels within 4 days of admission was associated with survival. The study reported a median decrease of 9.73ng/ml in the survivor group, whilst the non-survivor group had median increase of 5.95ng/ml. A rise or no change in PCT levels during the first four days of ICU admission therefore serves as a red flag to alert clinicians to the ineffectiveness of the treatment of these patients.(7)

In children most studies have focused on the diagnostic value of PCT rather than the prognostic value.(3,5) Outside of the critical care setting, *Gunasekaran et al.* reported that a PCT level >5ng/ml on admission was associated with a 7-fold increase of mortality in haemato-oncology patients admitted with suspected bacterial infection.(10) In the critical care setting, *Siddiqui et al.* conducted a retrospective analysis to evaluate the prognostic value of PCT, CRP and lactic acid levels in the critical care setting. They reported lactic acid levels were the more reliable biomarker among the three to predict multi-organ dysfunction and mortality. No statistically significant association between increased PCT and risk of mortality was established. The study had some recognised limitations such as a limited sample size and that it was done in a single centre. Importantly, the retrospective analysis meant only patients who had PCT levels done were included in the study. In this unit PCT is only done when there is clinical suspicion of infection, therefore selection bias could not be ruled out. (3) A study by *Achra et al.* also reported elevated PCT values as an independent predictor of mortality in children admitted to paediatric ICU. The study results further concluded a decreased risk of mortality in patients whose PCT values dropped by more than 80% during the first 72 hours of admission. (8) *Poddar et al*, who previously investigated PCT kinetics in the adult population, conducted a pilot study in the paediatric setting to investigate if PCT reduction could predict 28-day mortality. The study included 25 participants, 14 survivors and 11 non-survivors. The median reduction of PCT 17.3ng/ml in the survivor group, whilst in the non-survivor group there was a median increase of 1.1ng/ml. Expressed as a percentage change from the admission PCT, the survivor group had on overall reduction of 75.5% whilst the non-survivor group had an overall increase of 200.3% which was deemed statistically significant. This small pilot study concluded children admitted with sepsis or septic shock are less likely to die if the PCT decreased by >4ng/ml or >50% from the baseline and suggested a percent reduction as better prognostic marker than absolute values.(5) In a study by *Aygun et al.* the investigators evaluated the association between PCT and CRP levels on admission and clinical outcomes of patients in the PICU. The investigators concluded that both elevated CRP and PCT levels are associated with the need for mechanical ventilation, inotropic support, development of acute kidney injury and an increased risk of mortality. PCT elevation above 10ng/ml was associated with 2-fold increase in risk of mortality. This finding is supported by similar findings in adult patient studies. The investigators acknowledged that value of the study is limited by its sample size, but suggested it provided some information in the apparent gap in data in the paediatric population. (1)

In South Africa, the prognostic value of procalcitonin (PCT) has not thoroughly been evaluated. Most studies, conducted out of the critical setting, were focused on the diagnostic value of PCT. In many instances, obtaining PCT levels is usually limited to critically ill children requiring admission to PICU. This selection bias makes assessing the prognostic value of serum PCT levels difficult. (11,15) No study has been conducted in South Africa with the aim to evaluate the prognostic value of PCT in the paediatric critical care setting.

Conclusion

The risk of mortality should be assessed in all patients admitted to the paediatric ICU in order to deliver effective critical care services. The physiological role of PCT is not fully understood. Its value in the early diagnosis of bacterial infection has been widely accepted, although appropriate cut-off values in different clinical scenarios is still being determined. The prognostic value of PCT is also being investigated. In the adult population, high PCT values on admission to ICU and those that remain the same or that increase during admission have been identified as independent markers to predict the risk of mortality. There is a paucity of research done to evaluate the prognostic value of PCT in the paediatric population. Some small-scale studies have been published with conflicting results. In South Africa, the prognostic value of PCT has not been thoroughly evaluated in paediatrics. In this setting, PCT levels are usually reserved for patients who are assessed as having severe disease, usually requiring PICU admission. This study therefore aims to investigate the association between serum PCT levels and PICU outcomes in the paediatric population to further evaluate alternative uses of PCT in this setting.

5. Problem Statement:

Studies report an association between elevated serum PCT levels and an increased risk of PICU mortality, length of PICU stay and number of ventilator days. This assists in determining the prognosis of patients admitted to the PICU, which guides clinicians in making critical decisions in the management of these patients.

The problem identified pertains to the lack of South African based studies that investigate the association between serum PCT levels and PICU mortality, length of PICU stay and number of ventilator days. In the context of a lower-middle income setting, an understanding of its clinical utility in this setting is crucial in guiding its use.

6. Research Question:

What is the association between serum PCT levels (taken on admission and the change in PCT levels within 48 - 72 hours of admission) and the outcomes (mortality or survival at discharge from PICU, length of PICU stay and the number of ventilator days) of patients admitted to a PICU at two tertiary hospitals in the Bloemfontein Academic Complex over a two year period from January 2017 to December 2018?

7. Aim of the study:

To investigate the association between serum PCT levels (taken on admission and the change in PCT levels within 48 - 72 hours of admission) and the outcomes (mortality or survival at discharge from PICU, length of PICU stay and the number of ventilator days) of patients admitted to a PICU at two tertiary hospitals in the Bloemfontein Academic Complex over a two year period from January 2017 to December 2018?

8. Objectives:

8.1 Primary Objectives

1) To determine admission serum PCT levels and the serum PCT levels between 48 – 72 hours of admission in patients admitted to a PICU at two tertiary hospitals in the Bloemfontein Academic Complex over a two year period from January 2017 to December 2018.

2) To calculate the change from serum PCT levels obtained at admission to PCT levels obtained between 48 - 72 hours of admission in patients admitted to the PICU at two tertiary hospitals in the Bloemfontein Academic Complex over a two year period from January 2017 to December 2018.

3) To determine the primary outcomes of patients (mortality or survival at discharge from PICU) admitted to the PICU at two tertiary hospitals in the Bloemfontein Academic Complex over a twoyear period from January 2017 to December 2018.

4) To determine the secondary outcomes of patients (length of PICU stay and the number of ventilator days) admitted to the PICU at two tertiary hospitals in the Bloemfontein Academic Complex over a two year period from January 2017 to December 2018.

8.2 Secondary Objectives

1) To compare the admission serum PCT levels to the primary outcomes (mortality or survival at discharge from PICU) of patients admitted to the PICU at two tertiary hospitals in the Bloemfontein Academic Complex over a two year period from January 2017 to December 2018.

2) To compare the change from serum PCT levels obtained at admission to PCT levels obtained between 48 - 72 hours of admission to the primary outcome (mortality or survival at discharge

from PICU) of patients admitted to the PICU at two tertiary hospitals in the Bloemfontein Academic Complex over a two year period from January 2017 to December 2018.

3) To compare the admission serum PCT levels to the secondary outcomes (length of PICU stay and the number of ventilator days) of patients admitted to the PICU at two tertiary hospitals in the Bloemfontein Academic Complex over a two year period from January 2017 to December 2018.

4) To compare the change from serum PCT levels obtained at admission to PCT levels obtained between 48 - 72 hours of admission to the secondary outcomes (length of PICU stay and the number of ventilator days) of patients admitted to the PICU at two tertiary hospitals in the Bloemfontein Academic Complex over a two year period from January 2017 to December 2018.

9. Method

9.1 Study design

This study will be a retrospective analytical cross-sectional medical record review.

9.2 Setting

The study will be conducted at the PICU in the Bloemfontein academic hospital complex in the Free State, consisting of Universitas Academic Hospital and Pelonomi Hospital, that uses a combination of electronic and paper records.

Universitas Academic Hospital (UAH) is a tertiary level state hospital located in Bloemfontein, South Africa, that services the Free State Province. The hospital also accepts referrals from Northern Cape and Lesotho. The hospital has a 5 bed multi-disciplinary PICU where critical care services are provided for children up to the age of 13 years. Patients are referred from the outpatients department, ward or peripheral hospitals

Pelonomi Hospital (PH) is tertiary level regional hospital located in Bloemfontein, South Africa, which provides services to the southern Free State as well as a trauma unit providing services the Free State Province. The hospital has a multi-disciplinary ICU where 5 beds are allocated for PICU services for children up to the age of 13 years. These 5 allocated beds within the unit are managed by the department of Paediatrics. Patients are referred from the outpatients department, ward or peripheral hospitals.

These hospitals make use of National Health Laboratory Services (NHLS), where quantitative serum PCT levels are determined using the Elecsys® BRAHMS PCT assay in the Cobas® e immunoassay analyser.

9.3 <u>Participants</u>

9.3.1 <u>Inclusion criteria</u>

1) Male or female patients admitted to the PICU at UAH and PH, during the period of 01 January 2017 to 31 December 2018
2) Between the ages 1 month (28 days) to 60 months

9.3.2 <u>Exclusion criteria</u>

1) Patients who did not have a PCT done on admission
2) Elective post-surgery PICU admissions
3) Patients admitted due to trauma or burn injuries
4) Patients with incomplete medical records in which critical information, such as admission PCT level or primary outcome, cannot be obtained by the researcher

9.4 <u>Sample Size</u>

This study will include all eligible cases between 01 January 2017 – 31 December 2018.

The researcher estimates that sample size will be approximately 900 participants.

10. <u>Measurement</u>

10.1 <u>Variables</u>

The following data will be collected by the researcher

Variable Name	Type	Units	Range/Allowable values
Age on admission	Numeric	Months (1month=28 days)	1 – 60

Sex	Categorical	Option	Male, Female, Not recorded
HIV status	Categorical	Option	Positive, Negative, Not recorded
Primary Diagnosis	Categorical	Option	Respiratory tract disease, Neurological disease, Septicaemia, Cardiovascular disease, Intoxications, Haematology-Oncology, Other
PCT level done on admission?	Categorical	Option	Yes, No, Not recorded
PCT value on admission	Numeric	ug/L	0.01 to 100.00, >100
PCT level done between 48 hours – 72 hours of admission?	Categorical	Option	Yes, No, Not recorded
PCT value obtained between 48 hours – 72 hours of admission	Numeric	ug/L	0.01 to 100.00, >100
Change in PCT value from admission to 48 – 72 hours of admission expressed as an integer value	Numeric	ug/L	+/- 0.01 to 100.00, unable to calculate (PCT>100)
Change in PCT value from admission to 48 – 72 hours of admission expressed as a percentage change from admission PCT	Numeric	Percent	-99.0 to undetermined maximum value
Primary outcome on discharge from PICU	Categorical	Option	Mortality, Survival, Not recorded
Length of PICU stay	Numeric	Days	1 to undetermined number of days

Patient Ventilated?	Categorical	Option	Yes, No, Not recorded
Number of ventilator days	Numeric	Days	0 to undetermined number of days, not applicable

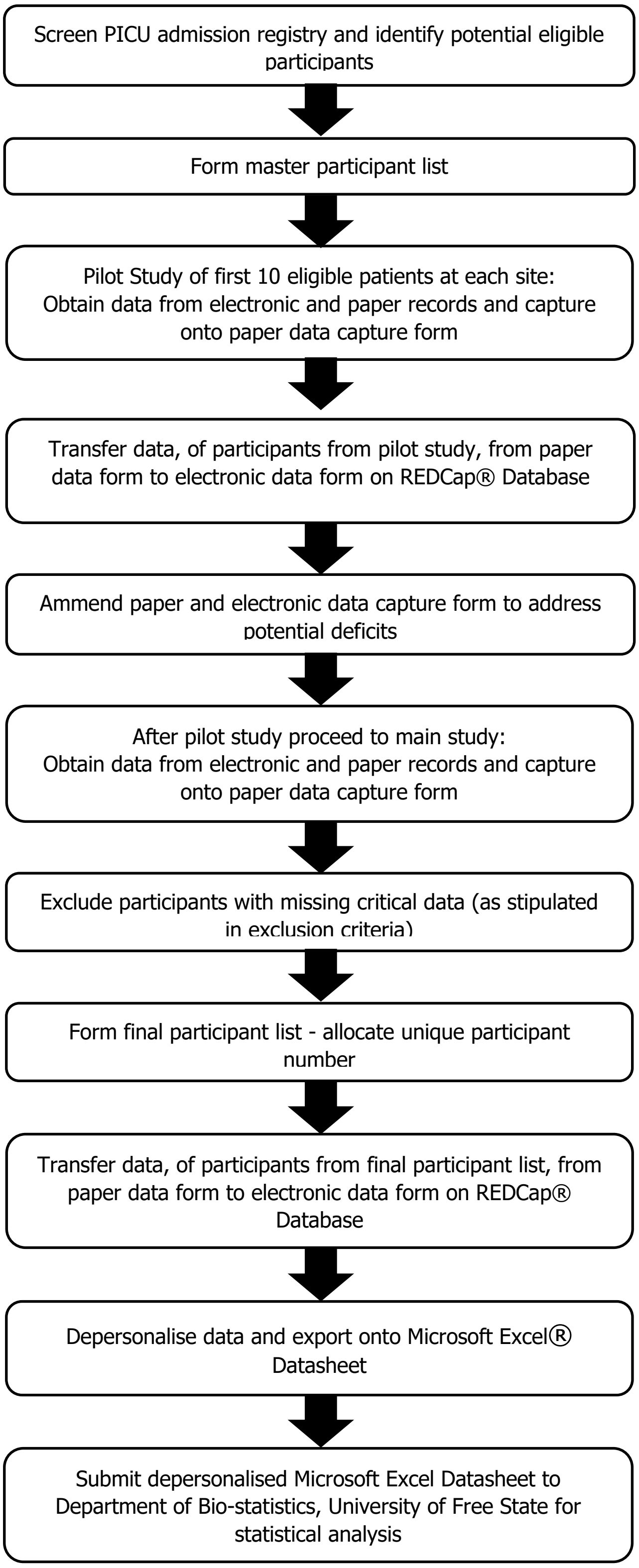
10.2 Data sources

Eligible participants will be identified from the paper and electronic admissions registry available at each PICU and a master participant list will be compiled. The researcher will obtain the data from eligible participants on the master participant list from patient electronic and paper records and capture it onto a paper data collection form designed by the researcher. (Annexure A) These paper data collection forms will be kept in a secure location, protected from unauthorised access. Participants with critical data missing, as stipulated in the exclusion criteria, will be excluded and the remaining participants will form the final participant list. Each patient will be allocated a unique participant number. The proposed paper data capture form will be transcribed onto the REDCap® (Research Electronic Data Capture) computer application as an electronic version of the data collection form. REDCap® is a secure web application for building and managing databases. The use of REDCap® is only authorised after obtaining approval for the study from the respective ethics committees. REDCap® allows only authorised access to the data. Authorised access will be granted to the researcher and the supervisor. The data of participants from the final participant list will be transferred from the paper data collection form onto the REDCap® electronic data forms. After the data has been entered and quality checked, it will be depersonalised and exported to a Microsoft Excel® data collection sheet. The depersonalised Microsoft Excel® data collection sheet will be submitted for analysis by a bio-statistician from the Department of Bio-Statistics, University of Free State. (See 10.4 Diagram 1)

10.3 The Pilot Study

A pilot study will be conducted after approval from the Ethics Committee has been obtained. The pilot study will include the first 10 eligible participants from each institution who meet the criteria to be included in the study. The required information will be captured on the data capture form (Annexure A) and thereafter the depersonalised data will be transferred to an Excel data collection sheet. Any issues identified with either of these tools will be attended to and amendments will be made to improve its efficiency prior to the commencement of the study. The participants used in this pilot study will be included in the final participant sample of the study.

10.4 Diagram 1:



11. <u>Bias</u>

11.1 <u>Selection Bias</u>

Exclusion of patients who did not have admission PCT values measured may underrepresent patients who had normal or elevated PCT values who died and therefore potentially influence the study results.

Exclusion of patients due to their primary diagnosis of trauma, burn injury or elective post-surgery admission may potentially exclude patients who still died due to sepsis related complications. This may potentially influence the study results.

11.2 <u>Information Bias</u>

As it is a retrospective study some information may be incomplete or missing. The data collected is reliant on accurate capturing of the required information in medical and electronic records. Incorrect, incomplete or missing information may impact on the study results.

12. <u>Statistics</u>

After the data has been collected, the numerical variables of the PCT values (on admission and the change from admission to 48-72 hours of admission) may be categorised into groups depending on the distribution of the collected data to evaluate the association with the predefined outcomes.

The numerical variables of the PCT values obtained may be potentially categorised as follows:

PCT on admission	Change in PCT (PCT on admission – PCT between 48 to 72 hours of admission)
Participants with PCT value **below** a critical threshold on admission:	• PCT decreased (+ change) • PCT increased (- change) • PCT unchanged (0 change)
Participants with PCT value **above** a critical threshold on admission:	• PCT decreased (+ change) • PCT increased (- change) • PCT unchanged (0 change)

Analysis will be done by the department of Biostatistics, University of the Free State. Data will be summarised by means of frequencies and percentages for categorical data, and means and standard deviations or medians and percentiles for numerical data. Appropriate statistical tests (Chi-square, Fisher, T-tests, Kruskal-Wallis etc.) will be performed at 5% significance level.

13. <u>Ethics</u>

Prior to data collection, approval for this study will be obtained from the Health Sciences Research Ethic Committee of the University of the Free State, the Free State Department of Health, the Department of Paediatrics University of Free State and the National Health Laboratory Services.

Consent of patients is not required as this a retrospective cross-sectional review of medical records. Information collected for this study will all be collected by the researcher who will fill in data collection forms which will be kept in a secure location accessible only by the researcher and supervisor. A unique participant number will be allocated to each participant. Patient confidentiality will be maintained by the researcher by transferring only the depersonalised data onto a Microsoft Excel® data collection sheet. The depersonalised data will exclude all potential identifiers of a participant and stored under unique participant numbers known only by the researcher. Only depersonalised data will be submitted for analysis by the bio-statistician.

14. <u>Value of the Study</u>

Once the study is completed the results will be reported on and made available to the Department of Paediatrics and Child Health UFS and the FS Department of Health.

This study will be exploring alternative uses of serum PCT in our setting. It will describe the association between PCT levels and the risk of PICU mortality. This may prompt clinicians to be more critical of the admission serum PCT level and its subsequent change, or lack thereof, during a patients PICU admission. The results of the study may provide a step towards establishing PCT guided clinical protocols in the management of paediatric patients.

The results may be useful to other PICU's in South Africa and may prompt further research on PCT in the South African paediatric population.

A report of the results of the study will be submitted for publication in a relevant medical journal.

15. <u>Limitations of the Study</u>

This study has potential confounders, as a retrospective study these confounders may be difficult to account for.

Potential confounders include:

Timing of the first dose of antibiotics. Delay, for whatever reason, in the administration of antibiotics in the unit may negatively impact the outcome of a patient

Management prior to admission in PICU. Many patients are referred from another institution, including primary health care facilities. Inefficient management prior to admission may negatively impact the outcome of the patient. This may also include in-transit issues not attended to, for example lack of adequate vascular access to administer appropriate fluids.

As a retrospective study another limitation includes reliance on an accurate admission registries and good quality medical records. Incorrectly documented information may affect the study results.

16. Time Frame

Planning and Protocol	July – October 2019
Ethics Committee Submission	November 2019
Department of Health Submission	January 2020
Pilot Study and Data Collection	February 2020 – April 2020
Data and Statistical Analysis	May – June 2020
Report Writing	July – August 2020 (Ammended)
Report Submission	August 2020 (Ammended)

17. Budget

All costs of the study will be for the account of the researcher. Costs involved in this study will be mainly for stationery and printing and is calculated based on the estimated number of participants of this study. Miscellaneous cost may involve transport costs between the two sites.

Paper	R 400.00
Printing	R 600.00
Stationary / Miscellaneous	R 300.00
TOTAL	R1300.00

18. References

1. Aygun F. Procalcitonin Value Is an Early Prognostic Factor Related to Mortality in Admission to Pediatric Intensive Care Unit. Crit Care Res Pract. 2018;

2. Solomon LJ, Morrow BM, Argent AC. Paediatric Index of Mortality scores: An evaluation of function in the paediatric intensive care unit of the Red Cross War Memorial Children's Hospital. South African J Crit Care. 2014;

3. Siddiqui I, Jafri L, Abbas Q, Raheem A, Haque AU. Relationship of Serum Procalcitonin, C-reactive Protein, and Lactic Acid to Organ Failure and Outcome in Critically Ill Pediatric Population. Indian J Crit Care Med. 2018;

4. Pudjiadi AH, Yanti M, Tumbelaka AR. Prognostic factors of death in children admitted to pediatric intensive care unit, Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Paediatr Indones [Internet]. 2002 [cited 2019 Jun 25];42(11–12):254–60. Available from: https://paediatricaindonesiana.org/index.php/paediatrica-indonesiana/article/view/1035

5. Poddar B, Gurjar M, Singh S, Aggarwal A, Baronia A. Reduction in procalcitonin level and outcome in critically ill children with severe sepsis/septic shock—A pilot study. J Crit Care. 2016;

6. Bobillo-Perez S, Rodríguez-Fanjul J, Jordan Garcia I. Is Procalcitonin Useful in Pediatric Critical Care Patients? Biomarker Insights. 2018.

7. Poddar B, Gurjar M, Singh S, Aggarwal A, Singh R, Azim A, et al. Procalcitonin kinetics as a prognostic marker in severe sepsis/septic shock. Indian J Crit Care Med. 2015;

8. Achra A, Narsaria P, Lodha R, Kabra SK, Kapil A. Procalcitonin in pediatric intensive care unit of a tertiary care hospital. Clin Epidemiol Glob Heal. 2016;

9. Downes KJ, Weiss SL, Gerber JS, Klieger SB, Fitzgerald JC, Balamuth F, et al. A pragmatic biomarker-driven algorithm to guide antibiotic use in the pediatric intensive care unit: The optimizing antibiotic strategies in sepsis (OASIS) study. J Pediatric Infect Dis Soc. 2017;

10. Gunasekaran V, Radhakrishnan N, Dinand V, Sachdeva A. Serum Procalcitonin for Predicting Significant Infections and Mortality in Pediatric Oncology. Indian Pediatr. 2016;

11. Karsas M, Becker P, Green R. Serious bacterial infections in febrile young children: Lack of value of biomarkers. South African J Child Heal. 2016;

12. Launes C, Esteban E, Balaguer M, Alsina M, Cambra FJ, Jordan I. Procalcitonin-guidance reduces antibiotic exposure in children with nosocomial infection (PRORANI). Journal of Infection. 2016.

13. Martinez R, Rode H. Role of procalcitonin in paediatric burn wound sepsis. South African Med J. 2018;

14. Memar MY, Varshochi M, Shokouhi B, Asgharzadeh M, Kafil HS. Procalcitonin: The marker of pediatric bacterial infection. Biomed Pharmacother. 2017;

15. White D. Can a negative procalcitonin level guide antibiotic therapy in early-onset neonatal sepsis? South African J Child Heal [Internet]. 2008 Jan 23 [cited 2019 Jun 25];1(4):146. Available from: http://www.sajch.org.za/index.php/SAJCH/article/view/33

16. Meng FS, Su L, Tang YQ, Wen Q, Liu YS, Liu ZF. Serum procalcitonin at the time of admission to the ICU as a predictor of short-term mortality. Clin Biochem. 2009;

17. Naidoo K, De Vasconcellos K, Skinner DL. Procalcitonin kinetics in the first 48 hours of ICU admission is associated with higher mortality in critically ill patients with community-acquired pneumonia in a setting of high HIV prevalence. South African J Anaesth Analg. 2018;

18. Chiotos K, Gerber JS, Himebauch AS. How Can We Optimize Antibiotic Use in the PICU?*. Pediatr Crit Care Med. 2017;

19. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet. 2010;

19. Annexure A:

DATA CAPTURE FORM

Patient Hospital Number

Assigned Participant Number

Date of birth (DD/MM/YYYY)

Date of admission (DD/MM/YYYY)

Age on admission (Months)

Sex

M ☐ F ☐ Not Recorded ☐

M =1

F =0

Not recorded =3

HIV status

Positive ☐ Negative ☐ Not recorded ☐

Positive =1

Negative =0

Not recorded =3

Primary Diagnosis

Septicaemia	☐	Septicaemia =1	
Respiratory tract disease	☐	Respiratory tract disease =2	
Neurological disease	☐	Neurological disease =3	
Cardiovascular disease	☐	Cardiovascular disease =4	
Intoxications	☐	Intoxications =5	
Haematology-Oncology	☐	Haematology-Oncology =6	
Other	☐	Other =0	

PCT done on admission?

Yes ☐ No ☐ Not recorded ☐

Yes =1
No =0
Not recorded =3

PCT value on admission (ug/L)

PCT done between 48 – 72 hours?

Yes ☐ No ☐ Not recorded ☐

Yes =1
No =0
Not recorded =3

PCT value between 48 - 72 hours (ug/L)

Change in PCT value from admission to 48 – 72 hours of admission expressed as an integer value (ug/L or unable to calculate)

Change in PCT value from admission to 48 – 72 hours of admission expressed as a percentage change from admission PCT (% or unable to calculate)

Primary Outcome on discharge from PICU

Survival ☐ Mortality ☐ Not recorded ☐

Survival =0

Mortality =1

Not recorded=2

Date of discharge (DD/MM/YYYY)

Length of PICU stay

(Date of Discharge – Date of admission)

Ventilated?

Yes ☐ No ☐ Not recorded ☐

Yes =1

No =0

Not recorded =3

Number of ventilator days (days)

G: REDCap® Data Capture Form

Data Capture Form

Assigned Participant Number
____

Hospital Number
____

Date of Birth (DD/MM/YYYY)
____

Date of Admission (DD/MM/YYYY)
____

Age on Admission (Months)
____

Sex

○ Male ○ Female ○ Not recorded

HIV Status

○ Positive ○ Negative ○ Not recorded

Primary Diagnosis

○ Sepsis
○ Respiratory tract disease
○ Neurological disease
○ Cardiovascular disease
○ Intoxications
○ Haematology-Oncology
○ Other

PCT done on admission?

○ Yes ○ No ○ Not recorded

PCT value on admission (ug/L)
____

PCT done between 48 - 72 hours?

○ Yes ○ No ○ Not recorded

PCT value between 48 - 72 hours (ug/L or n/a)

____

Change in PCT value from admission to 48 - 72 hours of admission expressed as an integer value (ug/L, unable to calculate or n/a)

____

Change in PCT value from admission to 48 - 72 hours of admission expressed as a percentage change from admission PCT (%, unable to calculate or n/a)

____

Primary Outcome on discharge from PICU

○ Survival ○ Mortality ○ Not recorded

Date of discharge (DD/MM/YYYY)

____

Length of PICU stay (days)
(Date of discharge - Date of admission+1)

____

Ventilated?

○ Yes ○ No ○ Not recorded

Number of Ventilator Days (Days)

____

H: Instructions to authors of the named peer review journal

Southern African Journal of Critical Care

The *SAJCC* is an academic medical journal publishing original research, reviews and editorials in the fields of Intensive Care, Emergency Medicine and Critical Care Nursing. The Journal is published bi-annually and accredited by the South African Department of Higher Education and Training (DoHET).

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If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki (2013), and should include a statement on independent ethical review. Where appropriate, a statement must be made that informed consent was taken from human participants, and/or whether the need for informed consent was waived.

Please also refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structures to ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchers have been adhered to.

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- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
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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.

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Guideline word limit: 3 000 words (excluding abstract and bibliography)

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 title of the manuscript should concisely describe the study but should not include the outcome. 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 question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. At the end of the introduction clearly state the aim or objective of the study. The primary and secondary outcomes should be specified.

In the Methods section describe in sufficient detail so that others would be able to replicate the study should they need to. Sections of the methods that have been described in previous publications need only be referenced. The statistical methods should be described. Where appropriate, sample size calculations should be included to demonstrate that the study is not underpowered.

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. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

The discussion should be confined to an interpretation of your results with respect to your stated aim and if applicable, a comparison to the results of similar studies. The strengths and weaknesses of your study should be discussed.

The conclusion should be confined to an interpretation of the results of the study and a recommendation if applicable.

- May include up to 6 illustrations or tables.
- References should only include the most recent and relevant articles. A maximum of 30 references is advised.

Structured abstract

- This should be no more than 250 words, with the following 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 research tools/instruments, 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.
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