PROGNOSTIC ROLE OF PROCALCITONIN IN CHILDREN WITH SEPSIS AT KENYATTA NATIONAL HOSPITAL

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DECLARATION

Student Declaration

This dissertation is my original work and has not been presented for the award of a degree in any other university.

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Supervisor's Declaration

This dissertation has been submitted for consideration with our approval as university supervisors.

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DEDICATION

This book is dedicated to my beloved husband, Mark, whose patience, support and encouragement enabled me to finally complete this thesis. And to my sister, Immaculate, for her unfaltering faith in me. And to my mother, Patricia, for her unconditional love and support in everything I do.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

ACCP/SCCM	:	American College of Chest Physicians/Society of Critical Care Medicine
CRP	:	C-Reactive Protein
FBC	:	Full blood count
KNH	:	Kenyatta National Hospital
IL	:	Interleukin
MODS	:	Multiple Organ Dysfunction Syndrome
NBU	:	Newborn unit
NICE	:	National Institute for Health and Care Excellence
NICU	:	Neonatal Intensive Care Unit
NPV	:	Negative predictive value
PICU	:	Paediatric Intensive Care Unit
PCT	:	Procalcitonin
PPV	:	Positive predictive value
SIRS	:	Systemic Inflammatory Response Syndrome
SD	:	Standard Deviation
SMART	:	Sensitive/Specific, Measurable, Available/Affordable, Responsive, Timely
TNF	:	Tumor Necrosis Factor
WHO	:	World Health Organisation

ABSTRACT

Background

Sepsis is a major cause of morbidity and mortality. The management of the early stages of sepsis plays a crucial role in the outcome of each patient. Part of this involves the use of appropriate antibiotic therapy initiated promptly for infection control. Stratification of patients based on objective markers would help determine the level of aggressiveness of management with respect to the choice of antibiotics as well as anticipated need for ICU care. The purpose of this study was to assess whether procalcitonin levels at admission and three days after admission could be used to determine patients at risk of death within 14 days of their admission.

Study Objectives

Primary Objective:

To determine the prognostic value of serum procalcitonin in children aged 7 days to 12 years with presumed sepsis at Kenyatta National Hospital.

Secondary Objective:

To determine the association between baseline CRP (C-Reactive protein) and WCC (white cell count) parameters and survival in children with sepsis at Kenyatta National Hospital.

Methodology

This was a hospital based cross-sectional study carried out at Kenyatta National Hospital between January and February 2018. Patients aged 7 days to 12 years were screened at admission for features of sepsis for eligibility into the study. Vital signs were recorded at admission and serum procalcitonin levels measured. Patients with serum procalcitonin levels above 0.25ng/ml were enrolled into the study. Serum procalcitonin levels were measured again 72 hours after admission for the patients who were still alive. Fourteen days after admission, the patient's hospital records were examined to determine the outcome of the patient (dead or alive).

Results

97 patients were enrolled into the study, 55 male and 42 female. The overall mortality rate was 30.9% (17 female and 13 male). 13% of mortalities occurred within 72 hours from admission.

Median (IQR) serum procalcitonin levels for survivors vs non-survivors was 2.41ng/ml(0.9-3.4) vs 4.16ng/ml(2.1-5.2). There was a significant association between the baseline median values and survival at 14 days (p=0.041). The median(IQR) for survivors vs non-survivors at 72 hours was 0.21ng/ml(0.1-1.0) vs 1.53ng/ml(0.5-2.24).

There was significant association between procalcitonin levels taken at 72 hours and survival (p=0.020). There was no significant association between the total white cell count and survival (p=0.282). CRP levels measured at admission showed no significant association between the baseline values and survival of patients (p value=0.085).

Conclusions

Procalcitonin was predictive of death and survival in our setting. This is similar to findings in other populations.

Serial procalcitonin measures improved the predictive value of the test with the difference between the two groups increasing with subsequent procalcitonin measurements.

Serum procalcitonin was a better biomarker of poor outcome in sepsis among children than CRP and WBC.

CHAPTER ONE: INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction and Epidemiology

Sepsis is a clinical syndrome characterised by a systemic inflammatory response following dissemination of pro-inflammatory markers and antigenic material within the body. It is mediated in part by inflammatory markers such as interleukins and tumour necrosis factor whose actions include but are not restricted to the alteration of permeability of the systemic circulation resulting in egress of intravascular fluid with reduction of the effective circulating volume resulting in multiple organ hypo-perfusion and dysfunction. It involves a broad spectrum of severity, from sepsis to septic shock to organ failure. It contributes largely to causes of morbidity and mortality in children worldwide [1].

The epidemiology of sepsis in the paediatric population tends to vary between different studies due to the difference in era, diagnostic criteria, population and location. Watson et al reported population based incidence and outcome of sepsis among children aged 18 or below in 7 states in the USA in 1995. The incidence was 0.56 cases per 1000 children per year. Infants had the highest incidence at 5.16 per 1000 the 10-14year old group had 0.20 per 1000. The overall hospital mortality rate was 10.3% with little variation based on age [2].

In a study of a population comparable to that in Watson's study [2], Hartman et al. found a rise in prevalence of sepsis cases by 81%. This was from 1995 to 2005. He also noted a reduction in case fatality rate from 10.3% to 8.9% in the same period [3].

The recognition of sepsis in its earliest course is important in ensuring the best possible outcomes in patients and is guided by careful assessment of the children who are at a particular risk of adverse outcome, and the early clinical manifestations [4].

A large proportion of childhood deaths under 5 years in developing countries can be attributed to deterioration along the sepsis pathway (infection to sepsis to multi-organ dysfunction). It has been estimated that infection related cases accounts for approximately 60% of deaths in children under the age of 5, with the most common fatal diseases being

pneumonia, diarrhoea, malaria and measles. Out of the approximately 7.5 million deaths in children aged less than 5 years, a large proportion are secondary to sepsis, the inflammatory pathway common to most deaths associated with infectious diseases [5].

In a Canadian prospective cohort study comprising 869 paediatric hospital admissions, systemic inflammatory response syndrome (SIRS)occurred in 82% of hospital admissions. Of these 23% had sepsis, 4% had severe sepsis, 2% had septic shock; overall, 6% of the study population died [6].

In recent years, although great strides have been made in the treatment of infectious diseases, the mortality rate of sepsis patients still ranges from 20% to 50% [7]. Treatment of sepsis is expensive, and the use of medical resources in resource limited areas places a heavy burden on the facilities [8]. Early stratification of patients could inform the use of third line antibiotics in empirical treatment of patients for whom biomarkers suggest a higher risk of adverse outcomes. This would potentially improve outcomes, reduce costs by avoiding unnecessary use of first line antibiotics in such patients as well as reducing the duration of in patient treatment.

The goal of the initial phase of treatment for children with sepsis is to rapidly recognise those with infections who have sepsis and are at risk for rapid progression to septic shock, as well as those with septic shock. Septic shock is associated with high morbidity and mortality [7]. In addition, delayed recognition of septic shock has repeatedly been associated with worse clinical outcomes in adults and children. This was demonstrated in a prospective cohort study of 91 children in community hospitals with septic shock, where they reported that there was a significant increased risk of death for each hour delay in the initiation of the appropriate resuscitation or the persistence of haemodynamic instability [9].

The potential prognostic role of procalcitonin has been widely studied in patients with sepsis. Studies have reported a marked improvement in procalcitonin clearance in patients who survived compared to non-survivors in sepsis, suggesting that procalcitonin reduction

might be correlated to the outcome of the patient and that serial procalcitonin readings throughout hospitalisation could assist in planning the appropriate treatment to provide better patient outcome [10].

While clinical features and vital parameters such as heart rate, temperature and respiratory rate enable us to make the diagnosis of sepsis, in our setting, they are often also used as the main tools for risk stratification which leads to delayed identification of critically ill children. Other laboratory tests that are available such as culture often take several days to produce results making them unsuitable for involvement in acute management.

This study aims to demonstrate that high serum procalcitonin levels measured within the first few hours of admission and subsequently during treatment can be used to identify critically ill patients who are most likely to have an adverse outcome of death. The choice of 14 day mortality as the primary outcome for our study was due to the hypothesis that early mortality was due to the severity of acute sepsis and to the effectiveness of treatment rather than underlying chronic or undiagnosed illnesses which were more likely to contribute to long term mortality in patients presenting with sepsis. This was similarly hypothesised in a study by Adrie et al who established a prognostic model for predicting 14-day mortality in ICU patients with severe sepsis [11].

This study is also justified by the lack of local studies on the role of procalcitonin in sepsis in our setting for the paediatric age group. The one study currently available that was carried out in Kenyatta National Hospital by Mwachinga et al was among adults and it showed that a significant reduction in procalcitonin levels by more than 30% in the first 48 hours was associated with a good outcome [12].

1.2 Criteria for Sepsis Categorisation

Sepsis is a critical condition that requires prompt identification and quick onset of treatment. The use of a structured set of clinical observations for assessment ensures that patients at risk of adverse outcomes from sepsis receive timely and appropriate management.

The spectrum of sepsis ranges from SIRS (Systemic inflammatory response syndrome), to The Spectrum of Sepsis ranges from SIRS (Systemic inflammatory response syndrome), to complete circulatory collapse with multiple organ dysfunction syndrome and in extreme cases, death. The clinical criteria for diagnosis of sepsis is summarized in the Table 1.

Table 1: Clinical Criteria for Diagnosis of Sepsis

SIRS Criteria: (meets ≥ 2 SIRS definition, 1 of which must be abnormal temperature or leukocyte count)[14]

- Temperature of more than 38°C or less than 36°C
- Heart rate of more than 2SD above the median rate for their age
- Respiratory rate of more than 2SD above the median rate for their age
- Abnormal white blood cell count (>12,000/µL or < 4,000/µL or >10% immature forms) [Annex 3].

Sepsis Criteria: (SIRS + Source of Infection)
Suspected or confirmed source of infection

Severe Sepsis Criteria: (Sepsis + 1 Organ Dysfunction Criteria)
Organ Dysfunction Criteria: Renal dysfunction(urine output <0.5ml/kg/hr), CNS dysfunction (GCS<13), Coagulation abnormalities (INR >1.5)

Septic Shock Criteria: (Sepsis + Cardiovascular Dysfunction + ≥ 1 Organ Dysfunction)
Cardiovascular dysfunction despite adequate fluid resuscitation OR ARDS(Acute Respiratory Distress Syndrome) OR ≥ 2 other organ dysfunction

Organ Dysfunction Criteria eg renal dysfunction (urine output <0.5ml/kg/hr), CNS dysfunction (GCS<13), Coagulation abnormalities (INR >1.5) [15]

Adapted from The ACCP/SCCM Consensus Conference Committee.[13]

1.3 Biomarkers in Sepsis

Although there has been considerable increase in the knowledge of the mechanisms involved in systemic inflammation, sepsis continues to have a high mortality rate in critically ill patients [16]. Therefore, there is increased demand for tools of prognostication in patients with severe sepsis. Identification of patients at high risk of mortality after admission to the hospital, through a quick laboratory parameter may help in determining therapeutic interventions, such as changes in treatment protocols or further diagnostic procedures aimed at preventing complications such as shock and multiple organ failure that could have a negative impact on patients' outcome [17].

Biomarkers have come under considerable interest for use in the care of critically ill patients. Proposed sepsis biomarkers include procalcitonin [18], C-reactive protein (CRP) [19] various interleukins (ILs) [20] and lactate [21].

Of these, procalcitonin has been the most studied and, in the United States of America and Switzerland is now being included in routine clinical practice and guideline recommendations [22].

The use of different biomarkers reflecting different pathophysiological pathways may play a role in improved assessment and management of critical illnesses [23][24][25].

The ideal biomarker for sepsis should be SMART. This means that it must be specific and sensitive. It should be measurable with a reasonable degree of accuracy. It should also be readily available when needed. It must be both responsive and reproducible. And finally it must produce results in a timely fashion to guide risk assessment and treatment [26].
Other properties of a useful sepsis biomarker should include the following:
It adds value to the clinical evaluation,
It reduces the duration to a definitive diagnosis,
differentiate between infectious and non-infectious aetiologies of inflammation and its complications such as organ dysfunction and shock,
differentiate between bacterial, viral and fungal infections.

Furthermore, the utility of a biomarker is enhanced if it accurately reflects the severity of infection and the septic process and has a short half life. This means that it rises rapidly after the inception of the infective process allowing early diagnosis and similarly drops rapidly following effective therapy inferring that the right choice of antibiotic therapy was initiated and does so more accurately than conventional clinical signs and laboratory tests [27].

1.4 Procalcitonin

1.4.1 Procalcitonin Biology

Procalcitonin is a peptide that was first identified in the 1970s by Leonard Deftos and Bernard Roos as a biosynthetic precursor of the hormone calcitonin [28]. It is a 116 amino-acid protein encoded by the CALC-I gene on chromosome 11, which produces calcitonin and several additional free peptides after several post-translational modifications. It has a molecular weight of approximately 13kDa [29].

Procalcitonin concentrations in the serum of healthy subjects are undetectable or low, generally less than 0.01ng/mL but can increase 1000-fold during active infection. It has a half-life of about 25-30 hours [30].

Procalcitonin is synthesised physiologically in low quantities by the thyroid C cells. In bacterial infection procalcitonin is synthesised ectopically in extrathyroidal neuroendocrine tissues in the lung and intestine [31]. Synthesis is triggered by bacterial endotoxin. Dandona et al investigated the effects of endotoxin on procalcitonin concentrations in healthy human subjects [32]. Serial samples were taken before and after the endotoxin injection within a 24hr period. The procalcitonin concentrations went from undetectable (less than 10pg/ml) at 0, 1 and 2 hours, to detectable at 4 hours. They peaked at 6 hours and plateaued at 8 to 24 hours strongly suggesting that the level of procalcitonin rises in response to a proinflammatory stimulus, mainly that of bacterial origin.

1.4.2 Procalcitonin as a Biomarker

Procalcitonin is considered a SMART biomarker [26][27]. Clinical signs such as leukocytosis, fever, heart rate, respiratory rate and other responses to systemic inflammation may be consistent with sepsis and infection but they are neither sensitive nor specific for sepsis and can occur in noninfectious states [33]. The specificity as well as negative predictive value of procalcitonin are reported to have been significantly improved in the latest assays by the enhanced functional assay sensitivity of the amplified cryptate emission technique [34][35]. It's biostability enables it to be measured within a realistic clinical window and it is both available and relatively affordable. It is also reflective of the disease severity as well as the effectiveness of interventions [36]. It has a short half-life of 25 hours, [30] which enables multiple timely measurements that mirror the changes of the underlying illness due to treatment. This gives it an advantage over the use of standard tests like blood cultures which require time to incubate.

1.4.3 Role of Procalcitonin in Sepsis

By 2011, 46 studies had been published evaluating the efficacy of procalcitonin as a biomarker for sepsis [37]. Procalcitonin has been evaluated for both its prognostic and diagnostic role in sepsis with mixed results with some studies suggesting that initial procalcitonin is not the most reliable biomarker for diagnostic purposes, but that serial procalcitonin concentrations may be useful in monitoring the outcome of sepsis [38].

Studies on the role of procalcitonin clearance as a potential prognostic biomarker in septic patients have reported marked improvements in procalcitonin clearance in patients who survived compared to non-survivors which suggested that procalcitonin clearance played a prognostic role in patient outcome and that repeated procalcitonin readings throughout hospitalisation may guide antibiotic leading to shorter duration of antibiotic use [39].

There have been studies that reported differences in procalcitonin levels between surgical patients and medical patients with sepsis and septic shock. The higher procalcitonin levels in surgical patients were hypothesized to be secondary to transient bacteraemia or, ischaemia [42]. Procalcitonin levels were also found to differ for patients with neonatal

sepsis. A meta-analysis reported that for diagnosis of neonatal sepsis, the sensitivity of procalcitonin ranged from 80 to 100% [43].

There is insufficient data regarding the role of procalcitonin in fungaemia. The levels of procalcitonin in candidaemia do not demonstrate a significant increase of procalcitonin as in bacteraemia. A retrospective analysis by Charles et al on bacteraemia and candidaemia in 50 non-neutropenic adult patients reported a markedly lower procalcitonin level in candidaemic patients [44].

Procalcitonin has not been shown to be affected by low neutrophil counts. A meta-analysis comprising of 30 studies that were assessing procalcitonin levels in patients with neutropenia found procalcitonin to be useful, although not diagnostic for bacteraemia [40]. Procalcitonin levels also to do not seem to be affected by use of corticosteroids especially when compared to CRP [41].

1.4.4 Procalcitonin in Antimicrobial Stewardship

Procalcitonin has been studied for its role in antimicrobial stewardship because of its capacity to distinguish between bacterial and viral infections. Müller et al proposed a procalcitonin-guided diagnostic algorithm for patients with sepsis which indicated that procalcitonin levels of <0.1 μg/L ruled out bacterial infection, so antibiotics were unnecessary. Similarly, the use of antibiotics was discouraged if the procalcitonin level was <0.25 μg/L [45]. This algorithm was simple and practical (Figure 1).

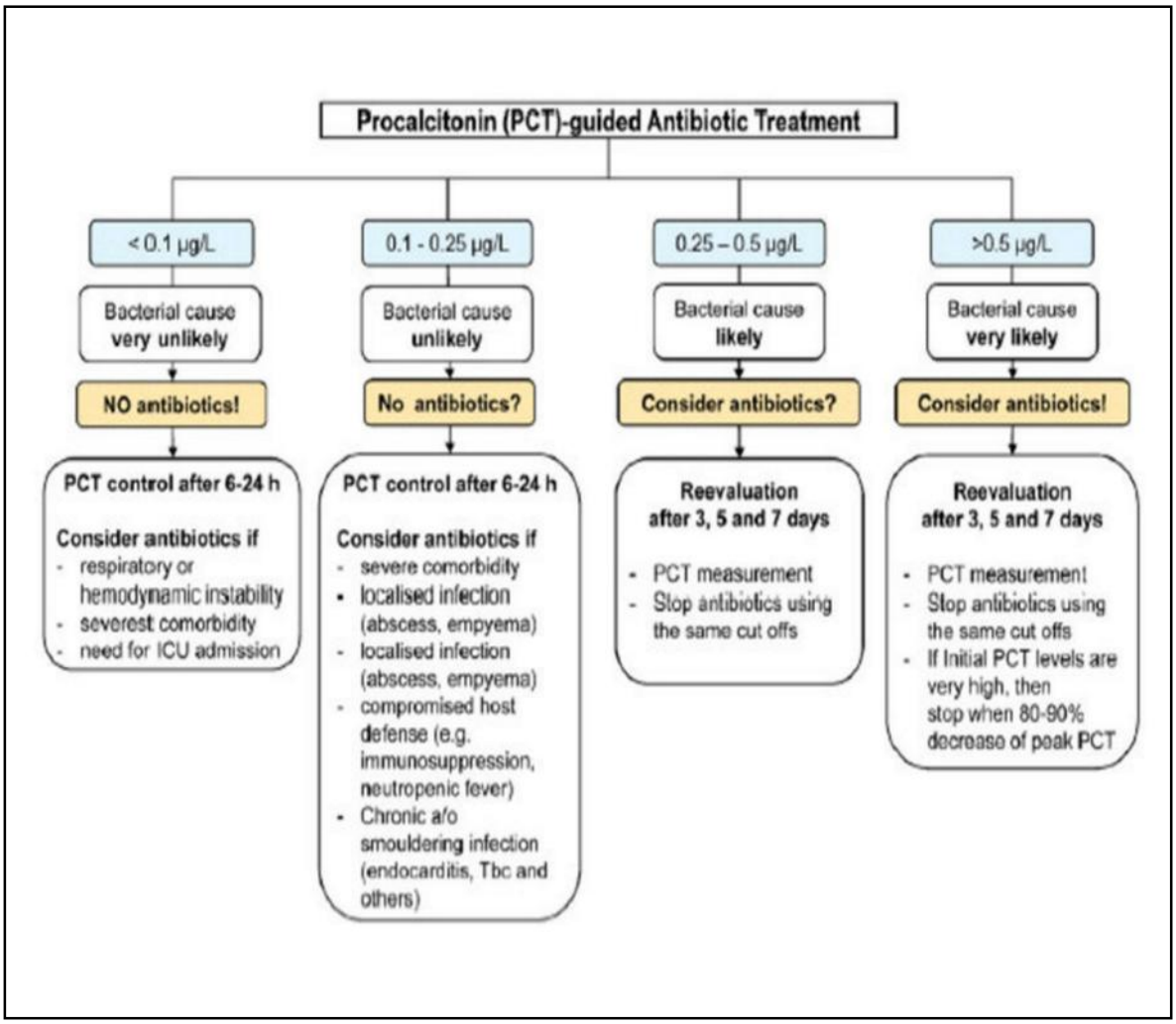

Figure 1: Proposed algorithm for procalcitonin guided antibiotic therapy Adopted from Müller, "Circulating biomarkers as surrogates for bloodstream infections." [45].

Using this algorithm we were able to set our cut off procalcitonin level at 0.25ng/dL to include all patients with a likelihood of bacterial infection. This strengthened our inclusion criteria in targeting patients with sepsis based on their clinical presentation and allowed us to measure a reduction of >50% in serum procalcitonin levels from admission.

1.4.5 Procalcitonin as a Prognostic Biomarker

Procalcitonin has been widely researched as a prognostic biomarker with studies suggesting that its decrease in patients with elevated baseline serum procalcitonin levels corresponds with improvement in patient outcome which translate to good out. The reverse is true, with rising procalcitonin corresponding with poor prognosis.

A prospective study by Karlsson analysed the predictive value of procalcitonin decrease in 242 adult patients with severe sepsis at baseline and at 72 hours for 155 patients. They found that mortality was lower in patients whose PCT concentration decreased > 50% (by 72 hours) compared to those with a < 50% decrease [46]. Poddar et al carried out a prospective observational study comprising of 25 children and found that those with severe sepsis or septic shock were less likely to die if they had a reduction of >50% in the first 4 days of intensive care [47]. A systematic review and meta analysis by Arora et al on the levels of procalcitonin in survivors and non-survivors of sepsis in adults concluded that procalcitonin levels in early stages of sepsis were significantly lower among survivors as compared with non-survivors of sepsis [48].

Another study by Yong et al examined the relationships between procalcitonin, bacterial infection, sepsis-induced multiple organ failure, and mortality rate in children. This was a cohort study involving 78 children sepsis. They found that procalcitonin was persistently increased among children with multiple organ failure and death from bacterial sepsis [49].

Some studies used more than two procalcitonin concentrations on each patient to improve on its efficacy as a prognostic marker. One such study by Ruiz-Rodríguez et al from Spain measured procalcitonin levels on patients with septic shock and multi-organ dysfunction at 0, 24, 48 and 72 hours. Procalcitonin clearance was higher in survivors than in non-survivors. Mortality was associated with sustained high procalcitonin levels [50].

Jensen et al also carried out a prospective observational study in Denmark involving 472 patients involving both adult and paediatric patients admitted at a tertiary referral hospital. Daily procalcitonin measurements were carried out during the study period and correlated

to mortality within a 30 and 90 day follow up period. They found that a single high procalcitonin level was an early independent predictor of all-cause mortality in a 90-day follow up period. Mortality risk increased for every day that procalcitonin increased [51].

1.4.6 Comparison of Procalcitonin with other Biomarkers

Other studies have focussed on the use of more than one biomarker to assess the prognostic value of procalcitonin against other biomarkers. One such study was by Hatherill M et al who studied procalcitonin along with IL-10 and TNF to predict organ failure and mortality in paediatric septic shock. They measured each biomarker level at admission and again at 24 hours. In survivors and non-survivors the admission procalcitonin was 83 vs 273ng/ml, IL-10 was 62 vs 534pg/ml and TNF was 76 vs 480 pg/ml. They concluded that the admission procalcitonin, like TNF and IL-10, was associated with the severity of organ failure and risk of mortality in children with septic shock. A decline in procalcitonin after 24 hrs of treatment suggested a favourable prognostic value [52].

Another study by Casado-Flores et al on comparison of serum procalcitonin with CRP levels and neutrophil count in children with suspected sepsis found that the rise in serum procalcitonin levels was greater in patients with septic shock or organ failure. Procalcitonin levels in the study did not vary with the patient's age unlike with CRP. Procalcitonin levels also showed a quick rise in children with sepsis and displayed a greater prognostic value than neutrophil count or CRP [53].

Oberhoffer et al also compared procalcitonin with other biomarkers in 242 patients admitted to the ICU with sepsis to predict outcome and found that procalcitonin had the highest area under the curve (AUC) when compared to the other clinical markers. This indicated that procalcitonin was be a better marker than leukocyte count or CRP in identification of patients at risk of poor clinical outcome [54].

1.4.7 Other Factors Affecting Procalcitonin Concentrations

Besides bacterial sepsis, procalcitonin may be detected at significant levels in conditions characterised by intense inflammation and induction of pro-inflammatory cytokines.

Characteristic examples include non-bacterial infections such as viral or fungal infections, non-infectious processes such as pancreatitis, major surgery, severe burns, trauma acute graft-vs-host disease, autoimmune diseases, para-neoplastic syndromes, cardiogenic shock and heat stroke [55].

The newborn period was also associated with increased levels of procalcitonin even in the absence of infection. A study by Sachse et al on 75 healthy newborn infants demonstrated that at 12–47 hours after birth a large proportion of the newborns had procalcitonin levels of >2µg/L. Procalcitonin concentrations decreased after 48hours and there was a significant difference between the time periods 12–23 h and ≥48 h after birth(P <0.001) [56]. Altunhan et al found there was no statistically significant difference in procalcitonin levels between the patients with sepsis and those without sepsis within the first 24 hours after birth. They found a mean procalcitonin of 0.51ng/ml in newborns with sepsis and a mean of 0.48ng/ml in those without sepsis [57].

Since procalcitonin levels were age dependent and not sepsis dependent in the early days of life, newborns less than 7 days were excluded from the study.

CHAPTER TWO: STUDY JUSTIFICATION AND OBJECTIVES

2.1 Study Justification and Utility

Paediatric sepsis is major cause of morbidity and mortality. Currently in our setting risk stratification of patients suspected to have sepsis is based on clinical findings such as temperature, respiratory rate, blood pressure and oxygen saturation. While these findings have a crucial role in the monitoring of the patient's progress, they may be potentially subjective and not specific to infection and therefore prone to error making them unreliable as the sole tools for this role. Use of microbiological cultures takes several days to produce results during which time the patients's condition may have changed drastically.

There is an absence of data regarding the use of procalcitonin in patients with sepsis in the paediatric population at Kenyatta National Hospital. With the considerable amount of research done worldwide this study aims to contribute to the body of evidence in support of the use of procalcitonin.

The benefit of the use of procalcitonin to the patients involved will be the use of a quick and objective test to assess severity of illness at admission leading to faster identification of patients at risk of poor outcome and, if necessary, change of initial antibiotic treatment to a more appropriate regimen. Serial procalcitonin levels will also be used to assess the response of the patient to treatment thus allowing the clinician to identify patients with poor response and adjust treatment accordingly.

In the long run the use of procalcitonin will contribute to reduced mortality from sepsis as well as prevention of antibiotic resistance from prolonged use of ineffective drugs.

The study hopes to introduce procalcitonin to our setting as a marker of severity of illness and a prognostic tool for prediction of likelihood of mortality.

The longterm goal of the study is to contribute to the creation of new policy guidelines that will require all paediatric patients with features of sepsis to have at least a baseline

procalcitonin level for risk stratification as well as serial procalcitonin levels for critically ill patients to monitor their response to treatment.

2.2 Research Question

Is there a prognostic role for serum procalcitonin in paediatric patients aged 7 days to 12 years with sepsis at Kenyatta National Hospital?

2.3 Study Objectives

2.3.1 Broad Primary Objective

To determine the prognostic value of serum procalcitonin in children aged 7 days to 12 years with sepsis at Kenyatta National Hospital.

Specific Primary Objectives:

To determine the association between baseline serum procalcitonin levels and survival in children with sepsis at Kenyatta National Hospital.

To determine the association between 72 hour serum procalcitonin levels and survival in children with sepsis at Kenyatta National Hospital.

2.3.2 Secondary Objective

To determine the association between baseline white cell count parameters and CRP and survival in children with sepsis at Kenyatta National Hospital.

CHAPTER THREE: RESEARCH METHODOLOGY

3.1 Study Design

This was a hospital based cross-sectional study.

3.2 Study Site

Patients were recruited and followed up at the paediatric wards Kenyatta National Hospital. Kenyatta National Hospital is a national teaching and referral hospital located 4 kilometers away from the Central Business District in the capital city of Kenya, Nairobi. The hospital provides outpatient and inpatient services to both children and adults from all over the country and neighbouring countries. Children aged 7 days to 12 years are admitted in the paediatric section of the hospital. There are 4 paediatric wards with a total bed capacity of 240.

Each paediatric ward has an acute room, where the very sick children receive emergency care. The average admission of children aged 7 days to 12 years is estimated at 450 children in the general paediatric wards per month. Most children are admitted through the paediatric emergency unit where postgraduate paediatric residents carry out triage, initiate the emergency care of sick children and admit to the general paediatric wards.

3.3 Study Population

Children aged 7 days to 12 years admitted to the general paediatric wards.

3.3.1 Inclusion Criteria

Children aged between 7 days to 12 years. Diagnosis of SIRS or sepsis based on clinical features (fever, tachycardia or tachypnoea) or laboratory findings (abnormal white cell count, positive cultures)

Informed consent from parent or guardian

3.3.2 Exclusion Criteria

Initial Procalcitonin level less than 0.25ng/l

Trauma or burns patients

Post surgery patients

Autoimmune diseases

3.4 Case Definitions

SIRS (Systemic inflammatory response syndrome): Refers to a generalized inflammatory response that is defined by having two or more of the following criteria: Abnormal core temperature, elevated heart rate, elevated respiratory rate and abnormal white cell count.

Sepsis: SIRS in the presence of infection whether proven or suspected.

Severe sepsis: Sepsis and at least one sign of organ hypoperfusion or organ dysfunction.

Septic shock: A subset of sepsis with underlying circulatory abnormalities that are severe enough to substantially increase the risk of death.

MODS (Multi-organ Dysfunction Syndrome): Refers to the increasing impairment of at least two organ systems in a very ill patient that makes it impossible to sustain homeostasis in the absence of medical intervention as a complication of sepsis.

3.5 Sample Size Calculation

This was calculated using Fisher's formula.

$$n = \frac{(Z^2 \times P(1-P))}{e^2}$$

z = 1.96

p = The proportion of inpatient mortality in 869 paediatric patients with sepsis at admission(6%) [6]

e = precision 0.05

$$n = \frac{\mathbf{1.96^2 \times 0.06\ (1-0.06)}}{\mathbf{0.05^2}}$$

n = 87

87 was the minimum number of patients to include in the study. We opted to add 10 to this number due to expected drop out rate from mortalities between the first and third day of measuring serum procalcitonin levels. The final number of participants in the study was 97.

3.6 Sampling Method

All children aged 7 days to 12 years who were to be admitted to the wards from the paediatric emergency unit were screened. Patients with abnormal temperature were examined for tachypnea and tachycardia based on their age group [Annex 3]. Consecutive enrolment of all children meeting the inclusion criteria was done till the desired sample size was achieved. Data was collected during a 2 month period from January 2018 to February 2018.

3.6.1 Patient Recruitment Procedure

Patients who met the inclusion criteria on admission were recruited into the study. Study participant were enrolled into the study after triage and admission by the admitting clinician at the paediatric emergency unit and after the guardian has given informed consent.

The parent/guardian was informed on the details of the study, its benefits to the child and risks regarding the study, in English or Kiswahili, before consent was obtained. The clinician explained that the child would be examined during the study to recognise deterioration in condition and if present, the primary clinician would immediately be alerted especially if a diagnosis of sepsis had been missed (for ethical reasons). The parent/guardian was assured that this is a minimal risk study and it would not delay the management of their child.

Once the patient was enrolled into the study, demographic data was recorded on the questionnaire. This included a study identity number, age and sex.

A focused clinical exam was performed and recorded in the questionnaire. This included recording of temperature, heart rate, and respiratory rate. The recordings were then compared to normal for age reference values.

The procedures done were as described below:
Temperature recording using a digital thermometer
Respiratory rate counted for one minute using digital timer and recorded.

Oxygen saturation and pulse rate using a pulse oxymeter.

Capillary refill time measured in seconds.

3.7 Study Variables

3.7.1 Independent Variables

Sociodemographic:

Age in months

Sex, either male or female

Clinical:

Temperature in degrees celsius

Respiratory rate, in breaths per minute

Pulse rate, beats per minute

Oxygen saturation

Procalcitonin levels;

3.7.2 Dependent Variable

Inpatient death versus survival within 14 days.

3.8 Study Tools

A standardised questionnaire was used for collecting data from the enrolled participants. The questionnaire included:

The patient's demographic data

Focused clinical exam done as per the questionnaire to recognise clinical signs including temperature, respiratory rate, heart rate, and capillary refill at first contact with patient.

Procalcitonin levels at admission and at 72 hours.

Outcome (survived/died) at 14 days from admission date was recorded.

3.9 Study Procedure

3.9.1 Clinical Methods

A research assistant was trained on relevant data collection. She was instructed on how to identify patients eligible for the study. She also received practical lessons on how and when to collect the blood samples and how to appropriately fill in the questionnaire. This training was carried out for a period of one week during which she was familiarised with the objectives of the study and equipped with the necessary materials required before onset of data collection. Data collection ran over a period of two months. Consecutive sampling of eligible patients was conducted. Patients were then followed up for 14 days to determine outcome of the patient.

3.9.2 Laboratory Procedures

Sample collection

Approximately 0.5 mls of blood for procalcitonin level assessment was drawn by the clinical officer from the patient's peripheral vein using standard aseptic technique. The blood was collected in a red top vacutainer. The sample was then transported at room temperature to the Paediatrics and Child Health department laboratory for processing. All baseline samples were processed on the same day within 2 hours. The samples were collected at admission and repeated at 72 hours after admission. A sample for complete blood count was not be taken. Instead, the baseline complete blood count taken at admission for all patients with features of sepsis was accessed from the patients file and the results tabulated.

Method

The procalcitonin test was run using the Finechek Quantitative Immunoassay Analyzer leased from Chem-Labs Limited. About 2 drops of the patient's serum and a drop of the appropriate reagent was put on the cassette that was then inserted into the machine. The laboratory technician would input the appropriate code for procalcitonin. The machine would then run the test. This took approximately 15 minutes to provide the results.

3.9.3 Quality Assurance

The blood samples were drawn by trained medical personnel, the clinical officer. A blood sample of 0.5ml to 1 ml was drawn using an aseptic technique and collected in a red vacutainer for transport to the lab for analysis. The results were recorded immediately and the principle investigator was notified. All results were tabulated in a data collection chart. The principal investigator and supervisor were the only people with access to the data collection chart.

In order to ensure the accuracy of measurement and the comparability of measured data, the optical part of the analyzer was calibrated on a regular basis as per the manufacturer's specifications. A known quality control sample was run along with the test at random to confirm the validity of the value of the test.

3.10 Data Management

Variables of interest were collected from the patients records and entered into SPSS version 20. Univariate analysis was carried out to determine the distribution of continuous variables and the appropriate measures of central tendency used to summarise the same. Proportions were used to summarise categorical variables and means and standard deviations used as the measure of central tendency for continuous variables with normal distribution.

Univariate analysis of procalcitonin levels showed that this variable had a positively skewed distribution making the use of median and interquartile range the appropriate measures of central tendency for this variable.

For continuous variables with a normal distribution parametric tests (students T test) were used to compare patients who died with those who did not while non parametric tests were used for comparison of procalcitonin levels between patients who died and those who survived given that the distribution of procalcitonin was skewed.
Results were summarised using tables and charts.

3.11 Ethical Considerations

Permission was sought from Kenyatta National Hospital and the University of Nairobi Ethics and Review Research Committee. (KNH/UON-ERRC)

Confidentiality was maintained at all times with identities of participants protected. All participants were given identification numbers. No personal information was shared.

Benefits to the patient- The participants received health education on management of sepsis.

Risks- No experimental treatment was undertaken in this study. All procedures were done with utmost care to ensure the least discomfort to the patient with minimal risk of acute or long term complications to the participants.

All participants whose parents or guardians gave consent to have their children participate in the study were recruited. Participation in the study was free and voluntary.

CHAPTER FOUR: RESULTS

4.1 Patient Characteristics

A total of 261 patients were screened for features of SIRS and sepsis during the data collection period from January 2018 to February 2018 at Kenyatta National Hospital. 112 patients were excluded as they did not meet the inclusion criteria. 144 patients met the SIRS criteria for presumed sepsis. A further 22 patients were excluded as their parents/guardians declined to give consent after the study was explained to them. After giving consent 30 patients had baseline procalcitonin results of less than 0.25ng/ml and were excluded from the study. A final number of 97 patients participated in the study. During the study, a total of 17 patients died within the first 72 hours from admission. 80 patients had a second sample of procalcitonin measured. A further 13 patients died within the next 14 days.

4.2 Study Profile of Children Recruited for the Study

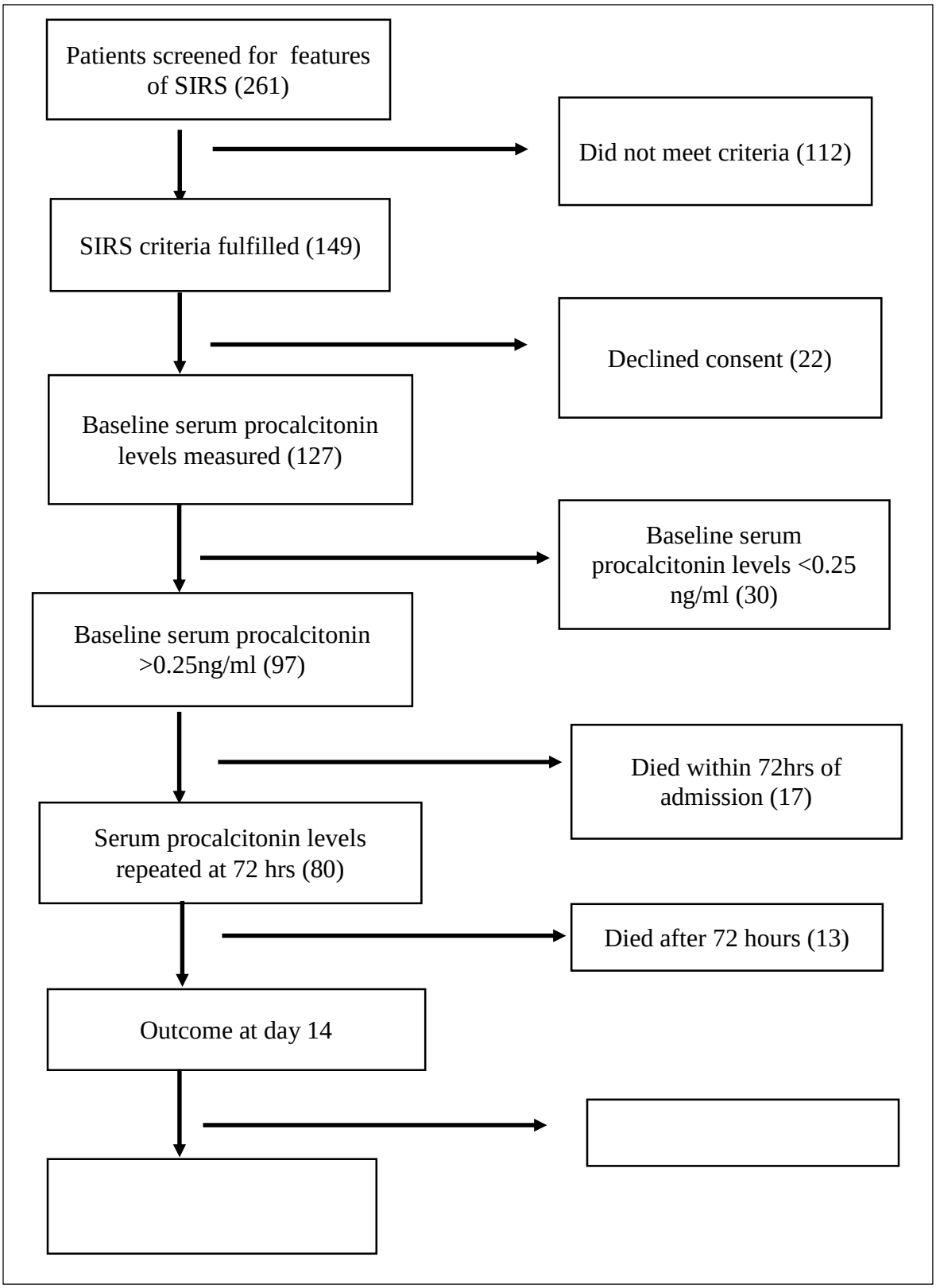

Figure 2: Flow chart of participant recruitment

4.3 Baseline and Clinical Characteristics

The following table shows the descriptive characteristics of participants in the study.

Table 1 : Descriptive Characteristics of the Study Population

Characteristic	Category	Frequency(%)
Sex	Male	55 (56.7)
	Female	42(43.3)
Age categories	7 days-28 days	8(8.2)
	1-12 months	44(45.4)
	13-60 months	37(38.2)
	>60 months	8(8.2)
Diagnosis at admission	Pneumonia	36(37.1)
	Meningitis	25(25.7)
	Septic shock	15(15.5)
	Neonatalsepsis	6(6.2)
	Others	15(15.5)

97 patients who satisfied the inclusion criteria were recruited in a consecutive manner. 55 were male and 42 were female. Of the total number of patients, the largest age category involved infants aged between 1 and 12 months (45.4%).

The most common diagnoses at admission for patients with sepsis were pneumonia (37.1%) and meningitis (25.7%). Septic shock was diagnosed in 15.5% of patients.

Table 3: Baseline Vital Characteristics

Variable	Mean/Median (SD/IQR)
Mean temperature (SD)	38.4 (0.7)
Mean oxygen saturation (SD)	89.3 (7.0)
Mean capillary refill (SD)	2.3 (0.9)
Mean pulse rate (SD)	150 (21.0)
Median respiratory rate (IQR)	66.0 (56.0-72.0)

The mean temperature was 38.4^0 C and the mean oxygen saturation was 89.3%. The mean capillary refill time was 2.3 seconds. The median pulse rate and the median respiratory rate were 150 beats per minute and 66 breaths per minute respectively. All vital parameters were outside the normal ranges since abnormal temperature, respiratory rate and pulse rate were part of the inclusion criteria. Oxygen saturation was below the normal range.

4.4 Clinical Symptoms Reported at Admission

The following were the symptoms that the participants presented with at admission in order of frequency.

Table 4: Symptoms present at admission and duration

Symptom	n (%)	Duration (days), Median (IQR)
Hotness of the body	62 (63.9)	3.0 (2.0-7.0)
Cough	33 (34.0)	4.0 (2.5-7.0)
Difficulty in breathing	24 (25.7)	3.0 (2.0-4.0)
Convulsions	29 (29.8)	1.0 (1.0-3.0)
Diarrhea	16 (16.4)	3.0 (2.0-4.5)
Vomiting	13 (13.4)	2.5 (1.3-4.5)
Refusal to breastfeeding	6 (6.3)	3.0 (2.5-5.0)
Reduced level of consciousness	6 (6.3)	1.0 (1.0-1.0)
Irritability	5 (5.2)	1.0 (1.0-3.0)
Neck stiffness	1 (1.0)	1.0
Lower limb swelling	1 (1.0)	1.0
Abdominal pain	1 (1.0)	1.0
Anterior neck swelling	1 (1.0)	1.0

The patients presented with different symptoms at the time of admission. Despite abnormal temperature being confirmed in all the patients admitted, only 63.9% presented with hotness of body as the main presenting symptom with a median duration of 3 days. Cough and difficulty in breathing were also common in our study population (34.0% and 25.7%) which contributed to the high number of participants diagnosed with pneumonia. Convulsion were reported in 29.8% of the population with a median duration of 1 day. The least common presenting complaints were neck stiffness, lower limb pain, abdominal pain and neck swelling.

4.5 Case Fatality of Sepsis by Age-Groups

The chart below shows the observed case fatalities among the participants in each age group.

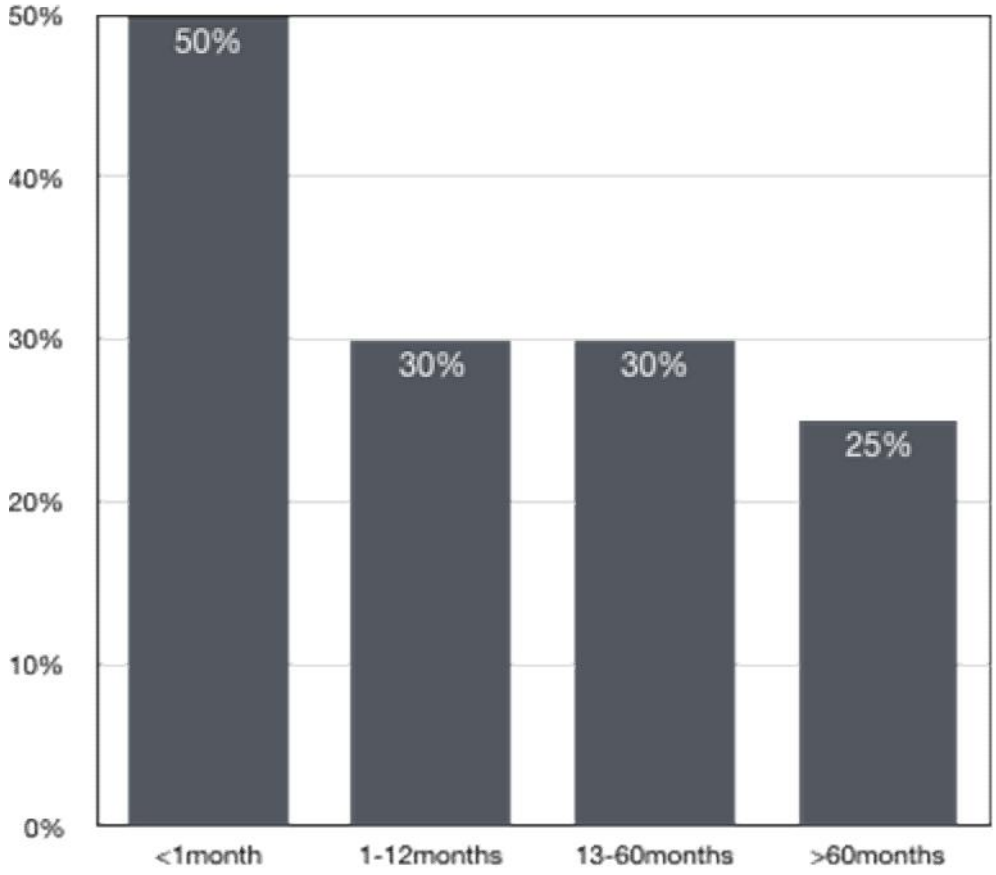

Figure 3: Case fatality of sepsis by age

The age group with the highest mortality rate was in the neonates who had a 50% mortality rate. The group with the lowest mortality rate was in the participants over 5 years at 25%. The mortality rate between within the 1-12 month and the 13-60 month groups were both 30%.

4.6 Case Fatality by Diagnosis

The chart below represents the case fatalities according to the diagnosis given at admission.

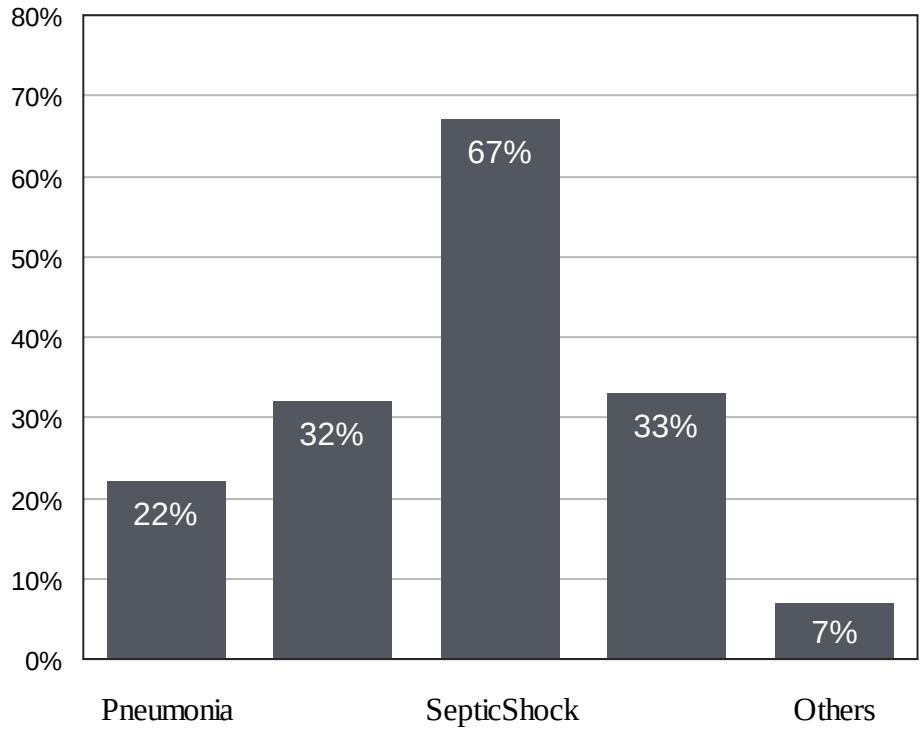

Figure 4: Case fatality according to diagnosis

The patients who were admitted with a diagnosis of septic shock had the highest mortality rate at 67%. Meningitis and Neonatal sepsis had a mortality rate of 32% and 33% respectively. Pneumonia had a mortality rate of 22%.

4.7 Association between Procalcitonin and Clinical Outcome

Table 5: Association between procalcitonin levels and outcome

Variable (n)	Group	Mean (SD)	Median (IQR)	Pearson coefficient of skewness (mean-median)/sd	p Value (X^2)
Procalcitonin(ng/ml) Day1 (97)	Alive (67)	2.74(3.18)	2.41(0.9-3.4)	0.10	**0.041**
	Dead (30)	7.47(9.63)	4.16(2.1-5.2)	0.34	
Procalcitonin(ng/ml) Day3 (80)	Alive (67)	0.71(0.93)	0.21(0.1-1.0)	0.54	**0.020**
	Alive (67)	0.71(0.93)	0.21(0.1-1.0)	0.54	**0.020**

Procalcitonin levels were taken at admission and repeated on the 3rd day for patients who were still alive. A total of 97 patients had a baseline serum procalcitonin measured at admission. 17 patients died before the 72 hour mark following admission. Only 80 patients had a 2nd serum procalcitonin level measured. The measures of central tendency and skew are summarised in the table above. The Pearson coefficient of skewness showed a positive skew of the distribution of values of procalcitonin with two of the four values are greater than 0.2. There was a significant association between baseline serum procalcitonin levels and outcomes. The mean serum procalcitonin levels of patients who survived at admission was 2.74ng/ml while the mean procalcitonin for those who did not survive was 7.47ng/ml. The median for survivors was 2.41ng/ml and for non survivors was 4.16ng/ml. The p value based on their median levels was 0.041 showing significant correlation.

The procalcitonin levels measured on the 3rd day (n=80) showed a mean of 0.71ng/ml in survivors and 1.56ng/ml in non-survivors. This showed a significant drop in procalcitonin levels for both categories as was expected once treatment was started. The p value for median procalcitonin levels against outcome was 0.020, showing even greater significance than baseline procalcitonin.

4.8 Association between Baseline Laboratory Parameters and Survival

Table 2 : Association between baseline laboratory parameters and outcome

Variable	Group	Mean(sd)	Median	Pearson skewness coefficient (mean-median)/sd	p Value (X^2)
WBC ($X10^9$)	Alive (67)	14.48(8.90)	11.99	0.28	0.282
	Dead (30)	17.85(9.47)	14.07	0.40	
Immature Granulocytes(%)	Alive	1.03(1.47)	0.6	0.29	0.709
	Dead	1.02(1.18)	0.7	0.27	
CRP (mg/dL)	Alive (36)	29.98(40.48)	5.30	0.61	0.085
	Dead (7)	51.81(39.63)	77.00	-0.64	

At admission blood samples were taken by the admitting clinician for baseline laboratory tests. These tests were at the discretion of the clinician therefore even though all patients had a complete blood count, not all patients had CRP levels measured where the clinician did not request for one. Only 43 (44%) patients had a baseline CRP level measured. The blood samples were taken before initiation of antibiotic therapy. Differences between the survivors and non-survivors were performed using non parametric tests as was the case for the procalcitonin levels. Pearson coefficients for skewness were significant (-0.2 > Pearson coefficient > 0.2).

There was no significant association between the medians of the total white cell count and survival of the patient (p=0.282). Similarly there was no significant association between the median of the immature granulocytes and outcome of the patient (p=0.709). CRP levels taken at admission showed no significant correlation between baseline amounts and clinical outcome of patients (p=0.085).

CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Discussion

This study set out to determine the prognostic role of procalcitonin in paediatric patients aged 7 days to 12 years with sepsis at Kenyatta National Hospital.To the best of our knowledge a similar study involving the prognostic role of procalcitonin in sepsis has only been carried out among the adult population in our setting[12].

The participants were followed up for up to 14 days during the duration of their admission and observed outcomes (survival or death) were compared to baseline and 3rd day procalcitonin levels as well as baseline FBC and CRP for some patients.

We recruited a total of 97 patients who presented with features of sepsis. Of the 97, 56.7% were male with a female:male ratio of 1:1.3. The participants had a median age of 11months with 53.6% of the population aged one year or under. The total number of participants under 5 years were 91.8%.

The patients were admitted with various diagnoses of which pneumonia was the most common (37.1%). Other studies have identified respiratory infections as the most common underlying conditions in paediatric patients with severe sepsis. Hartman et al showed that respiratory infections accounted for 49.8% of all cases of sepsis in 2005 [3]. Sepsis as a definitive primary diagnosis was not common in our study even when the features of sepsis were all recorded by the clinician at admission. This is not an uncommon observation as the diagnosis of sepsis is often overlooked in favour of descriptive diagnoses such as severe pneumonia and meningitis.

The outcome of interest in our study was mortality within 14 days of admission. The study had an overall mortality rate of 30.9%. This was significantly higher than similar studies on paediatric patients with sepsis. Watson et al found a 10.3% in-hospital mortality rate among paediatric patients with sepsis [2]. We speculate the high mortality rate may have been due to bias in our selection of study participants as relatively stable patients were not

included in the study. This may also be due to individual variation in immune response to illness.

Mortality rate by age showed the highest case fatality within the neonatal group with 50% mortality. Infant mortality rate was 30% and for patients aged 1-5 years was also 30%. These values showed some similarities to a study by Weiss et al on sepsis outcomes which reported a neonatal mortality rate of 26%, infant mortality rate of 31%, and a 21% mortality rate for patients aged 1-5 years [60].

The diagnosis with the highest mortality rate was septic shock (67%). This finding was similar to a local study by Hirani et al that reported an overall mortality rate of 70% among paediatric patients with septic shock in Kenyatta National Hospital [61].

The main objective of the study was to determine an association between serum procalcitonin levels and outcome. We found significant correlation between procalcitonin levels and outcome ($p=0.041$). The 3rd day serum procalcitonin level was carried out on 80 participants after 17 patients died within 72 hours of admission. Both groups of patients demonstrated an overall decline in procalcitonin levels which was attributed to a positive response to treatment. There was a significant association between procalcitonin levels at 72hours and outcome ($p=0.020$). This value showed an even stronger association than the baseline values. This confirmed our hypothesis that there was an association between baseline serum procalcitonin levels and outcome. It was noted that outcome was not specifically based on the percentage decline from day 1 to day 3 but rather on the absolute values of procalcitonin. The patients who had very high procalcitonin levels at admission were more likely to have a poor outcome even when the levels showed significant reduction by day 3.

The Pearson coefficient of skew was used to show a positive skew of the distribution of values of procalcitonin. Two of the four values are greater than 0.2 which indicated severe skewness making the median and interquartile ranges the best measures for central tendency [63]. This also precluded the use of parametric tests for comparison of patients

without transformation of the distribution to a normal distribution by performing logarithmic, square root or inverse transformation. Non-parametric tests were therefore used for comparison of the patient groups based on the outcomes of interest.

Our secondary objective was to determine the association between baseline CRP and WCC and outcome. The role of this objective was to compare procalcitonin with the readily available options that were already in use at the hospital. The choice to take either of these samples at admission was at the admitting clinicians discretion as these two tests were readily available and commonly prescribed for critical patients. It was however noted that there was poor uptake of CRP as a baseline test with only 44% of patients getting one done. This limited our ability to compare the prognostic value of procalcitonin against CRP.

The baseline white cell count for patients at admission showed no significant correlation between baseline values and outcome (p=0.28). This was similar to a study by Lam et al who reported no significant correlation between WCC and outcome in patients with sepsis (p=0.62) [62]. Immature granulocytes also measured at admission did not demonstrate any prognostic value (p=0.709). There was no correlation between CRP levels and patients' outcome (p=0.085). Again these findings were similar to others that found poor correlation between CRP and survival such as the study by Oberhoffer et al that demonstrated that procalcitonin was a superior prognostic biomarker compared to leukocytes and CRP in predicting poor outcome [54].

5.2 Study Limitation

The cost of the study limited the number of the procalcitonin measurements that could be measured for each patient to a maximum of two samples.

Only 43% of patients had a baseline CRP which limited our ability to accurately compare its prognostic value to serum procalcitonin.

5.3 Conclusions

Serum procalcitonin levels in children with sepsis at admission were associated with inpatient all cause mortality.

Serial procalcitonin values may increase the predictive value of the test with the difference between both groups increasing with subsequent procalcitonin measurements.

Serum procalcitonin was a better biomarker of poor outcome in sepsis among children than CRP and WBC.

5.4 Recommendations

Serial procalcitonin levels should be considered as a biomarker to monitor clinical progress and response to treatment in paediatric patients.

Further research on a larger population size is recommended to examine whether the outcome in this study is applicable to the general population.

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ANNEXES

ANNEX 1: LETTER TO ERC

The Chairperson,
Ethics, Research and Standards Committee,
Kenyatta National Hospital and University of Nairobi,
P.O. Box 20723,
NAIROBI

Thru'
The Chairperson,
Department of Paediatrics and Child Health

Dear Sir/Madam,

RE: SUBMISSION OF MASTERS DEGREE RESEARCH PROPOSAL FOR APPROVAL

I wish to submit my research proposal for approval by your esteemed committee. I am currently a second year student pursuing a Master's Degree in Paediatrics and Child Health at the University of Nairobi, College of Health Sciences.

Yours Sincerely,

Dr. Mary Muange,
Department of Paediatrics and Child Health,
College of Health Sciences.
University of Nairobi.

ANNEX 2: QUESTIONNAIRE

Data Collection Form

Date……Serial Study Number……..

Hospital Admission Number …….

Sex…. Male [ ] Female [ ]

Age in months ……..

1. Diagnosis at admission

……

2. Symptoms at admission and Duration

……

3. Vital Signs

Temperature (∘c) ……

Pulse rate(beats per minute) ……..……

Respiratory Rate (breaths per minute) ……..

Oxygen saturation (%)……..……..

Capillary refill time (seconds) ……..

4. Sepsis Category

……

5. Was Baseline FBC taken at admission? If yes indicate parameters from patient's file (checked at 72hours)

WCC(White cell count $x10^9$) ……..

Differentials ($x10^9$):

Neutrophils……..……Lymphocytes……..

Basophils …… Monocytes …….……

Eosinophils …….……

Immature Granulocytes(%)…….

Platelet count ……

Haemoglobin (g/dl) ……..

6. Procalcitonin Level

Admission ……..

At 72 hours ……

7. Was CRP taken at admission? If yes indicate level

Admission CRP level ……..

8. Outcome

[Discharge] [Death]

9. Date of Discharge or Death if not still admitted

…….. .....

ANNEX 3: REFERENCE RANGES

Parameter	**Reference Ranges**				
	4-7 Weeks	2-6 Months	6-12 Months	1-5 years	**6-12 years**
White cell count ($x10^9$ /l)	6.0-18.0	6.0-17.5	6.0-17.5	5.0-17.0	**4.5-14.5**
Neutrophils ($x10^9$ /l)	1.2-7.5	1.0-8.5	1.5-8.5	1.5-8.5	**1.5-8.0**
Lymphocytes ($x10^9$ /l)	3.0-13.5	4.0-10.5	4.0-10.5	1.5-9.5	**1.5-7.0**
Monocytes ($x10^9$ /l)	0.1-1.7	0.2-1.2	0.2-1.2	0.2-1.2	**0.2-1.0**
Basophils ($x10^9$ /l)	<0.11	<0.11	<0.11	<0.11	**<0.11**
Eosinophils ($x10^9$ /l)	<0.81	<0.81	<0.81	<0.81	**<0.81**
Immature Granulocytes	>10%	>10%	>10%	>10%	**>10%**
Haemoglobin (g/dl)	9.4-13.5	11.4-14.1	11.5-13.5	11.5-13.5	**11.5-15.5**
Platelets ($x10^9$ /l)	150-400	150-400	150-400	150-400	**150-400**

Children's reference ranges adapted from North Bristol Trust NHS. [58]

Vital Signs Reference Ranges

Age Range	Heart Rate Reference Range	Respiratory Rate Reference Range	Temperature Reference Range
<5 months	90-150	25-40	36.6-37.5
6-12 months	80-140	20-30	36.6-37.5
1-3 years	80-130	20-30	36.6-37.5
3-5 years	80-120	20-30	36.6-37.5
6-12 years	**75-1120**	**20-30**	**36.6-37.5**

Children's vital signs reference ranges adapted from American College of Emergency Physicians. [59]

ANNEX 4: BUDGET

ACTIVITY/ITEM	NUMBER	COST PER UNIT	AMOUNT (Ksh)
Preparation of data collection tools	120 questionnaires, 120 consent forms, 240 kits for sample collection, 1 procalcitonin analyzing machine	120 questionnaires and consent forms each page costing 5ksh, total= 3,600ksh. Procalcitonin analyzing machine = free 240 kits each at 800ksh = 192,000	ksh 195,600
Personnel hiring and training	2 personnel to assist in collection of data for 60 days	10,000ksh per person	20,000ksh
Pre-testing data collection tool	Principal researcher will be involved	free	—-
Data Collection and Communication	Airtime	3000 ksh for 60days	3000 ksh
Data Management and Analysis	Writing materials Buying software	10,000ksh writing material 30,000ksh Buying software and consultation	40,000ksh
Printing and Binding	Cost in printing Cost in Binding	5,000ksh in Binding 3,000ksh in printing	8,000ksh
10% contingence			10,000ksh
TOTAL PROJECT EXPENSES			**276,600ksh**

ANNEX 5: TIMEFRAME

Number	Activity	Estimated Time
1	Proposal Development and Presentation	4 months
2	Submission of proposal for ethical approval	1 month
4	Data Collection	3 months
5	Data Analysis	2 months
6	Thesis writing	3 months
7	Thesis submission	July 2018

ANNEX 6A: CONSENT INFORMATION DOCUMENT

Study Title: Prognostic role of procalcitonin in children with sepsis at Kenyatta National Hospital

Patient Consent Form

Introduction

I am a postgraduate student currently doing my masters in Paediatrics and Child Health at the University of Nairobi. I am conducting a research project for which I require your participation.

This study will focus on children with sepsis which is a common illness in children caused by how their bodies react to infection. It is a common cause of hospital admission and can even lead to death in severe cases. Procalcitonin is a protein that is found in the blood of children with sepsis and usually increases in amount as the infection becomes worse.

Reasons for doing the study

This study will attempt to find out if there is any association between procalcitonin levels in blood for children with sepsis and the severity of their illness, as well as determining some risk factors influencing their progress while in the ward.

Study procedure

The study will include children aged between 1 month to 5 years who are presumed to have sepsis and who require inpatient care. This will be based on your child's symptoms and signs.

You will be asked some questions by the research assistant regarding the child's illness. The research assistant will also examine the child and record the findings. A small blood sample will be taken from your child at admission and again after 3 days. This blood will be used to check the procalcitonin levels in your child's blood.

The information obtained will be entered in forms and subsequently stored safely in a computer for research and educational purposes.

Your results will not be shared with other participants in the study and your identity and that of the patient will be kept private.

Benefits of participation

Your participation in the study will enable us to collect valuable information that will be useful in treating children with sepsis in the future and will enable us to save other children's lives.

Risk of Participation

There are minimal risks involved in participating in the study. There will be some discomfort when drawing a blood sample. However the amount required will be very small and will not harm the patient.

ANNEX 6B: CONSENT FORM

Investigators note: This consent form confirms your decision to participate in this study. Your participation in this research is completely voluntary. If you decide to participate, you may withdraw at any time without consequences or explanation. The results of the study will be treated with strictest confidence.

Parents/Guardians note: My signature below indicates that I have understood the above conditions of participation in this project. I have had the opportunity to have my questions answered satisfactorily.

I VOLUNTARILY AGREE THAT MY CHILD BE PART OF THIS STUDY.

Parent/Guardian (name) ……..…….

of (Patient's Name) ……..

Signature/Thumbprint……..……

Investigator signature …….

Date ……

For further information, you may contact the following:

1. Dr. Mary Muange (Principal Investigator)
   Phone number: 0728498300
2. Dr. Reel (Supervisor)
   Phone number: 0722555712
3. Dr. Kumar (Supervisor)
   Phone number: 0733733505
4. Kenyatta National Hospital- UoN ERC Secretariat
   P.O. Box 20723 code 00202
   Tel: 726300-9 ext 44102
   Fax: 725272

Idhani ya Fomu Ya Ridhaa

Kichwa cha Utafiti: Kuchunguza kama kipimo cha procalcitonin kwa watoto walio na sepsis kinaweza kutabiri jinsi ugonjwa utakavyo pona.

Utangulizi:

Mimi ni mwanafunzi katika chuo kikuu cha Nairobi idara ya Paediatrics na afya ya watoto. Natekeleza utafiti ambaounahitaji ushirikiano wako.

Mtazamio wa utafiti huu ni watoto wanaougua sepsis. Huu ni ugonjwa unaosababishwa na kuenea kwa bakteria mwilini. Ni mojawapo wa sababu kuu za kulazwa hospitalini. Procalcitonin ni kipimo kinachopatikana katika damu ya watoto walio na sepsis na kipimo chake hutumiwa kuongonza matibabu.

Sababu ya Kufanya Utafiti Huu

Utafiti huu utajaribu kufafanua kama kuna uhusiano kati ya kipimo cha procalcitonin katika damu na jinsi ugonjwa ulivyoenea na kuthibitisha mafanikio ya matibabu.

Taratibu za Utafiti

Utaratibu huu utalenga watoto kati ya mwezi mmoja na miaka tano wanaoshukiwa kuwa na sepsis na wanao hitaji matibabu.

Utaulizwa maswali na mdadisi msaidizi kuhusu kuugua kwa mtoto. Mdadisi huyu atamkagua ma kurekodi mapato yake. Kiasi kidigo cha damu kitachukuliwa kutoka mtoto wako atakapolazwa na baada ya siku tatu. Damu hii itatumiwa kuchunguza kiasi cha procalcitonin katika damu ya mtoto wako.

Matokeo yataandikwa katika fomu na kuhifadhiwa katika kompyuta kwa minajili ya masomo na utafiti.

Matokeo ya mtoto wako hayataonyeshwa kwa mtu yeyote bila ruhusa yako.

Manufaa ya Kushiriki Katika Utafiti

Kushiriki kwako kutatuwezesha kupata ujuzi ambao utauwa na manufaa kwa matibabu ya mwanao na watoto wengine siku za usoni.

Hatari za Kushiriki

Hakuna hatari kubwa tunayotarajia kwa mtoto wako. Kiwango cha damu kniachohitajika i kidigo sana.

Fomu ya Ridhaa

Ilani ya mdadisi: Minajili ya fomu hii ya idhini ni kukupa ujuzi kukuwezesha kufanya uamuzi kuhusu kuwakilishwa. Kuhusika kwako ni kwa hiari yako. Ukiamua kutohusika unaweza kujiondoa wakati wowote bila kujieleza.

Ilani ya Mzazi: Sahihi yangu hapo chini ni ishara kuwa nimeelewa juu ya kushiriki katika utafiti huu. Maswali yangu yote yamejibiwa kwa ukamilifu.

NIMEKUBALI MTOTO WANGU AWE KATIKA UTAFITI HUU.

Mzazi (Jina) ……..

wa …….

Sahihi ……

Sahihi ya Mtafiti ……..

Tarehe …….

Mawasiliano

Ukiwa ma maswali yoyote ya ziada unaweza kuwasiliana na watafiti.

1. Dkt Mary Muange (mtafiti mkuu)
   Nambari ya simu: 0728498300
2. Dkt Reel (msimamizi)
   Nambari ya simu: 0722555712
3. Dkt Kumar
   Nambari ya simu: 0733733505
4. Hospitali kuu ya Kenyatta- UoN ERC Secretariat
   Sanduku la posta 20723 - 00202 Nairobi
   Tel: 726300-9 ext 44102
   Fax: 725272