UNIVERSITY of RWANDA

COLLEGE OF MEDICINE & HEALTH SCIENCES
SCHOOL OF MEDICINE & PHARMACY

DEVELOPING A TOOL TO PREDICT OUTCOMES IN SURGICAL PATIENTS WITH SEPSIS AT UNIVERSITY TEACHING HOSPITALS OF KIGALI (CHUK) AND BUTARE (CHUB)

Dissertation submitted in partial fulfillment of the requirements for the award of the degree of Masters of Medicine in General Surgery of the University of Rwanda

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Kigali May, 2019

DECLARATION

The researcher:

I, Dr. Irénée NIYONGOMBWA hereby declare to the best of my knowledge that this dissertation "**Developing a tool to predict outcomes in surgical patients with sepsis at University Teaching Hospitals of Kigali (CHUK) and Butare (CHUB)**" is my original work and it has not been submitted by anyone to any other university for the award of a degree.

Signature: ……

Dr. Irénée NIYONGOMBWA
Date: May 20, 2019

The supervisor:

I hereby declare that this dissertation "**Developing a tool to predict outcomes in surgical patients with sepsis at University Teaching Hospitals of Kigali (CHUK) and Butare (CHUB)**" was submitted by Dr. Irénée NIYONGOMBWA with my approval.

Signature: ……..

Dr. Jennifer RICKARD
Date: May 20, 2019

AKNOWLEDGEMENTS

My gratitude goes first to Dr. Jennifer RICKARD who bravery supervised this work. Her patience, availability, encouragements and guidance contributed a lot to this great achievement.

Many thanks to Professor Ahmed KISWEZI for his acceptance to co-supervise this project. His critical thinking and scientific support associated with moral support in great humility made this work feasible

I am very grateful to Dr. Faustin NTIRENGANYA, the academic Head of Department who supported this work from the very beginning of its conception. His advices and guidance express a high level of teaching skills, coaching and mentorship.

I am thankful to the staff of the departments of surgery of both CHUK and CHUB for their unconditioned love and support in many different ways.

A big thank you from the bottom of my heart to you all who contributed in one way or another, on the long way towards this great achievement.

May God bless you all.

DEDICATION

To God the Almighty,
To my father late Augustin and my mother Marthe
To my brothers Germain, Emile and Benjamin
To my sisters Alice, Rosine, Adeline and Albertine
And, especially to my beloved MAHORO Marie Claude

I humbly dedicate this work

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LIST OF ABREVIATIATIONS

1. SCCM: Society of Critical Care Medicine
2. ESICM: European Society of Intensive Care Medicine
3. ICU: Intensive Care Unit
4. GSICU: General Surgery Intensive Care Unit
5. CPOD: Chronic Obstructive Pulmonary Disease
6. APACHE II: Acute Physiology, Age, Chronic Health Evaluation II
7. GS: General Surgery
8. VTE: Venous Thrombo-Embolism
9. KPS: Karnofsky Performance Scale
10. CMS: Center for Medicare and Medicaid Services
11. SIRS: Systemic Inflammatory Response Syndrome
12. MAP: Mean Arterial Pressure
13. PaO2: Partial pressure of arterial oxygen
14. FiO2: Fraction of Inspired Oxygen
15. SOFA: Sequential (Sepsis-related) Organ Failure Assessment score
16. qSOFA: quick Sequential (Sepsis-related) Organ Failure Assessment score
17. ED: Emergency Department
18. AUROC: Area Under Receiver Operator Characteristic curve
19. LMIC: Low and Middle Income Countries
20. MEWS: Modified Early Warning Score
21. NEWS: National Early Warning Score (NEWS)
22. KiSS: Kigali Surgical Sepsis Score
23. GCS: Glasgow Coma Scale
24. LOHS: Length of Hospital Stay
25. CHUK: Centre Hospitalier Universitaire de Kigali (University Teaching Hospital of Kigali)
26. CHUB: Centre Hospitalier Universitaire de Butare (University Teaching Hospital of Butare)
27. A & ED: Accidents and Emergency Department
26. IOF: Impaired Organ Function
27. MmHg: Millimeters of mercury
28. GIT: Gastro-Intestinal Tract
29. BP: Blood Pressure
30. HR: Heart Rate
31. RR: Respiratory Rate
32. SPSS: Statistical Package for Social Sciences
33. MODS: Multiple Organ Dysfunction Syndrome
34. CI: Confidence Interval
35. µL: micro-liter
36. SPO_2: Peripheral capillary oxygen saturation
37. Mmol: Millimoles
38. dL: Deciliter
39. HIV/AIDS: Human Immunodeficiency Virus/Acquired Immuno-Deficiency Syndrome

40. ART: Anti-Retroviral Therapy
41. IRB: Institutional Review Board

ABSTRACT

Background: Sepsis is common in surgical patients, and its presence influences the outcomes in those to undergo surgery. Factors such as advanced age, presence of comorbidities and many other conditions increase mortality in surgical patients with sepsis. There is no single test to diagnose sepsis, but a set of criteria that have kept evolving from 1991 onwards. The current definition of sepsis generated in 2016 introduced the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score simplified into quick Sequential (Sepsis-related) Organ Failure Assessment score qSOFA score that not only helps to define sepsis but also to identify patients who are likely to die from it. The qSOFA score has been validated in high income countries but some authors advocated for its recalibration.

Objectives: The aim of this study was to develop a prognostic tool accurate in predicting outcomes in surgical patients with sepsis who presented at University Teaching Hospital of Kigali (CHUK), University Teaching Hospital of Butare (CHUB) and in other centers with limited resources

Methods: This was a prospective cohort study conducted over a period of one year from February 2018 to January 2019. The patients recruited in the first 6 months at CHUK served as the derivation cohort and those recruited in the next 6 months from both CHUK and CHUB served as the validation cohort. We used a pre-established questionnaire for data collection, the data were entered in excel, and analyzed in STATA version 14. Appropriate statistical tests were used for the derivation of the Kigali Surgical Sepsis (KiSS) score and its prognostic accuracy was tested by comparing it with qSOFA score in terms of sensitivity, specificity and their area under receiver operator characteristic (AUROC) curves.

Results: A total of 288 patients were recruited with 144 in each cohort. The mean age was 36.5 and median age was 32.6. Males were 117/288 (40.6%) and females were 171/288 (59.4%). The mean LOHS was 22.9 days. The overall intensive care unit (ICU) admission rate was 51.4% and in-hospital mortality rate was 21.7%.

Factors associated with hospital mortality were age above 55 years ($p = 0.034$), presence of comorbidities ($p = 0.069$), hypotension ($p = 0.014$), tachycardia ($p = 0.061$), tachypnea ($p = 0.028$), decreased level of consciousness ($p = 0.021$), presence of GIT perforation ($p = 0.026$) and number of impaired organ function ($p = 0.035$). A predictive score (KiSS score) consisting of six parameters was derived from these factors and compared to qSOFA score.

The sensitivity of KiSS score in predicting mortality was 73% (vs 52% for qSOFA), and the specificity was 97% (vs 87% for qSOFA). The predictive validity for hospital mortality was assessed by Area under Receiver Operator Characteristic (AUROC) curve and it was 0.939 (95% CI, $p<0.001$) for KiSS and 0.684 (95% CI, $p<0.001$) for qSOFA.

Conclusion: The Kigali Surgical Sepsis (KiSS) score developed from this study was found to be superior to the qSOFA score in predicting hospital mortality. The KiSS score showed an added advantage of stratifying surgical patients to be operated on into those with good prognosis, those with variable prognosis and those with poor prognosis.

Key words: Outcomes, sepsis in surgery, qSOFA score, limited resources, KiSS score, sensitivity, specificity, mortality, morbidity.

CHAPTER I: INTRODUCTION

Sepsis is one of the major determinants of outcomes in surgical patients and the identification of patients with possible sepsis is vitally important because timely recognition and appropriate, effective treatment substantially improves survival. As there is no single test that is diagnostic for sepsis, clinicians still rely on clinical judgment, augmented by validated clinical criteria to identify sepsis among patients with infection.

The definitions of sepsis and septic shock go back to 1991 by what is referred to as sepsis-1 (1), but kept evolving as they were revised in 2001 (sepsis-2)(2) then lastly in 2016 by task forces generated by national societies including the Society of Critical Care Medicine (SCCM) and The European Society of Intensive Care Medicine (ESICM) in what is referred to as sepsis-3 (3).

In 2016, sepsis was redefined as a life-threatening organ dysfunction caused by a dysregulated host response to infection(3). Organ dysfunction is defined by the 2016 SCCM/ESICM task force as an increase of two or more points in the Sequential Organ Failure Assessment (SOFA) score. Septic shock is a type of distributive shock that has circulatory, cellular, and metabolic abnormalities and is associated with a greater risk of mortality than sepsis alone(3). Septic shock includes patients who fulfill the criteria for sepsis who, despite adequate fluid resuscitation, require vasopressors to maintain a mean arterial pressure (MAP) ≥65 mmHg and have a lactate >2 mmol/L (>18 mg/dL).

Regarding predictions from the SOFA score, patients who fulfill criteria for sepsis and septic shock have a predicted mortality of ≥10 percent and ≥40 percent respectively (3).

A number of scores were developed to predict outcomes in emergency and critical patients, with only SOFA score (simplified into qSOFA) being sepsis related. Since outcomes in surgical patients can be determined by underlying sepsis, to identify and predict outcomes in such patients, which is the main goal of this study would help to positively influence their outcomes.

CHAPTER II: BACKGROUND

1. Incidence of sepsis

Severe sepsis and septic shock have a significant and increasing impact on public health, and are one of the leading causes of mortality. The incidence of these syndromes at both Emergency departments and ICUs has increased over the last thirty years with an increasing number of deaths occurring despite a decline in overall in-hospital mortality(4).

Population incidence and hospital prevalence of severe sepsis reported from studies across Europe, United States of America and Australia and found the estimated incidence of severe sepsis per 100000 population ranging from 48 in Norway to 104 in Spain)[6]. In US, more than 500,000 adult patients with severe sepsis are received per year in Emergency Departments(5). Sepsis is common in surgical patients, and those account for nearly one-third of sepsis cases in the United States(6,7).

2. Risk factors for developing sepsis

In developed countries, the main variables influencing the incidence of severe sepsis and septic shock are increasing aging of the population (relative risk for sepsis being thirteen times higher

for patients aged 65 and above than in younger patients)(8) and the increasing prevalence of underlying comorbidities.
In addition to advanced age and increasing prevalence of comorbidities, black people have a higher incidence of severe sepsis and septic shock and they tend to develop these syndromes at a younger age compared to white people. It is not yet clear whether the worse outcomes of black people with severe sepsis and septic shock are due to genetic factors, poverty or a higher prevalence of subjacent comorbidities in black population(9).
Regarding gender, men have a higher prevalence of severe sepsis and septic shock than women, and gender differences do not seem to be solely mediated through sex hormones since this lower rate of sepsis syndromes observed in women is present over all range of ages(8,10).
The most prevalent comorbidities associated with sepsis are diabetes followed by chronic heart failure and chronic obstructive pulmonary disease (COPD) (6). Respiratory and abdominal infections are associated with a worse prognosis than other foci of infection and are linked with inadequate empirical antimicrobial treatment(4).

3. Risk factors for mortality in patients with sepsis

Independent risk factors of mortality of severe sepsis and septic shock most constantly identified in epidemiological studies include: the number of organ failures (commonly assessed by SOFA), the underlying comorbidities and the severity of acute illness assessed by Acute Physiology, Age, Chronic Health Evaluation II (APACHE II) score (11).
Other independent associations with death identified in low resourced settings were hypoxia and systolic hypotension in Malawi(12), Glasgow Coma Scale (GCS), Karnofsky Performance Scale (KPS) at admission, tachypnea, leukocytosis and thrombocytopenia in Uganda(13).

4. Sepsis and general surgery

In the general surgery (GS) patients, the impact of sepsis has been under-estimated as a cause of morbidity and mortality in the perioperative period. Surgeons pay specific attention to venous thromboembolism (VTE), perioperative myocardial infarction, and surgical site infections in the prevention of perioperative complications. However, an analysis of the 2005-2007 National Surgical Quality Improvement Program Perspective database (from the American College of Surgeons National Surgical Quality Improvement Program) revealed that the incidences of sepsis and septic shock exceed those of pulmonary embolism and myocardial infarction by 10-fold(14).
Of 363 897 general surgery patients, sepsis occurred in 8350 (2.3%), septic shock in 5977 (1.6%), pulmonary embolism in 1078 (0.3%), and myocardial infarction in 615 (0.2%). Thirty-day mortality rates for each of the groups were as follows: 5.4% for sepsis, 33.7% for septic shock, 9.1% for pulmonary embolism, and 32.0% for myocardial infarction. The septic-shock group had a greater percentage of patients older than 60 years (no sepsis, 40.2%; sepsis, 51.7%; and septic shock, 70.3%). The need for emergency surgery resulted in more cases of sepsis (4.5%) and septic shock (4.9%) than did elective surgery (sepsis, 2.0%; septic shock, 1.2%). The presence of any comorbidity increased the risk of sepsis and septic shock 6-fold and increased the 30- day mortality rate 22 fold(15).
In general surgery ICU patients, sepsis is predominantly caused by intra-abdominal infection. In a study published in 2010 by Moore *et al*, the abdomen was the source of infection in 69% of

general surgery ICU patients. Septic shock had a mortality rate of 36%, and those who survived septic shock had prolonged ICU stays(14).
The above two studies emphasize the need for early recognition of patients at risk via aggressive screening and the rapid implementation of evidence based guidelines

5. Sepsis in Low and Middle Income Countries

The burden of sepsis is even greater in Low and Middle Income Countries where in addition to delayed consultations, significant challenges exist in triage and diagnosis as primary care physicians are scarce and busy, and there are limited variables to estimate the severity of sepsis. In addition to this, patients with severe sepsis (as per sepsis-2 definition) and septic shock are rarely admitted to the ICU mainly because of its high bed occupancy and perceived futility for such patients.
Few studies available in sub-Saharan Africa highlight the prevalence of HIV infection in the region as an additional factor worsening the outcomes in patients with sepsis.
A prospective cohort study done in Malawi in 2014 to assess mortality risk among adults presenting to an African teaching hospital with sepsis and severe sepsis in a setting of high HIV prevalence and widespread antiretroviral therapy (ART) uptake analyzed 213 patients (181 with sepsis and 32 with severe sepsis). Among them, 161 (75.6%) patients were HIV-positive.
The overall mortality was 22%, rising to 50% amongst patients with severe sepsis. The mortality of all sepsis patients commenced on antiretroviral therapy (ART) within 90 days was 11/28 (39.3%) compared with 7/42 (16.7%) among all sepsis patients on ART for greater than 90 days.
In Uganda, a prospective observational study reporting the management and outcomes of 382 severely septic patients in two hospitals found that 84.9% of patients were HIV-infected with a median CD4+ T cell (CD4) count of 52 cells/mm^3 (IQR, 16–131 cells/mm^3). Overall mortality was 43.0%, with 23.7% in-hospital mortality and 22.3% post-discharge mortality. Discharge Karnofsky performance scale (KPS) and early fluid resuscitation were significant predictors of post-discharge mortality. Among HIV-infected patients, CD4 count was a significant predictor of post-discharge mortality (13).
To date, there are no data on incidence, source or outcomes of sepsis in surgical patients in Rwanda, but as other countries of sub-Saharan Africa, sepsis presentation and outcomes are different from those expected in high income countries.
The prevalence of HIV among surgical patients in Rwanda was studied by Makanga et al in 2007, in a 3-month prospective study conducted at University Teaching Hospital of Butare, and among 165 patients studied (M: F ratio of 2.11:1), 6.7% were HIV seropositive. Females were 54.5% and the most affected population ranged between 30 and 39 years of age (16).
In addition to HIV infection, Rwanda shares other factors including delayed presentation, limited staff, equipment, diagnostic tests, medications, and ICU beds with other sub-Saharan African countries.

CHAPTER III: LITERATURE REVIEW

The definitions of sepsis and septic shock have rapidly evolved since the early 1990s, and even the current ones that reflect expert opinion from task forces generated by national societies including the Society of Critical Care Medicine (SCCM) and The European Society of Intensive Care Medicine (ESICM) are not unanimously accepted. For example, the Center for Medicare

and Medicaid Services (CMS) still continues to support the previous definition of SIRS, sepsis, and severe sepsis.
Currently, sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection(3).

Organ dysfunction is defined as an increase of two or more points in the SOFA score.

This organ dysfunction score is not diagnostic of sepsis nor does it identify those whose organ dysfunction is truly due to infection but rather helps to identify patients who potentially have a high risk of dying from infection. The validity of this score was derived from critically-ill patients with suspected sepsis by interrogating over a million intensive care unit (ICU) electronic health record encounters from ICUs both inside and outside the United States [2]. Septic shock is a type of vasodilatory or distributive shock defined as sepsis that has circulatory, cellular, and metabolic abnormalities that are associated with a greater risk of mortality than sepsis alone(3).
Septic shock includes patients who fulfill the criteria for sepsis who, despite adequate fluid resuscitation, require vasopressors to maintain a mean arterial pressure (MAP) ≥65 mmHg and have a lactate >2 mmol/L (>18 mg/dL).
At the severe end of the severity of illness spectrum of both infectious (sepsis, septic shock) and noninfectious conditions comes multiple organ dysfunction syndrome (MODS), which is a progressive organ dysfunction in an acutely ill patient, such that homeostasis cannot be maintained without intervention. There are no universally accepted criteria for individual organ dysfunction in MODS but progressive abnormalities of the organ-specific parameters of the brain (GCS), respiratory (Partial pressure of arterial oxygen (PaO2)/fraction of inspired oxygen (FiO2) ratio), hematology (platelet count), liver (serum bilirubin), renal (Serum creatinine or urine output) and cardiovascular (Hypotension and vasopressor requirement) are commonly used to diagnose MODS and are also used in scoring systems to predict ICU mortality.
Along with this new conceptual definition for sepsis, members of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) task force proposed qSOFA (quick Sequential [Sepsis-related] Organ Failure Assessment) score.
This is a modified version of the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score using simple clinical criteria to potentially assist bedside clinicians in identifying, among patients with infection, those with sepsis or those likely to develop it or potentially at risk of dying from it.
The qSOFA score is easy to calculate since it only has three components (Respiratory rate ≥22 cycles /minute, Altered mentation and Systolic blood pressure ≤100 mmHg), each of which are readily identifiable at the bedside and are allocated one point. The qSOFA score was originally validated in 2016 as most useful in patients suspected as having sepsis outside of the intensive care unit (ICU) [2]. It has since been prospectively validated in the emergency department (ED) with similar or better predictive validity for the selected outcomes expected to be more common following sepsis than the more complex measures tested (SOFA and the Logistic Organ Dysfunction System) that require a greater number of clinical and laboratory variables(17,18).
When evaluating the validity of clinical criteria to identify patients with suspected infection who are at risk of sepsis, among non-ICU encounters, qSOFA had a greater predictive validity

(AUROC = 0.81; 95%CI, 0.80-0.82) than SOFA (AUROC = 0.79; 95%CI, 0.78-0.80; *P* < .001) and SIRS (AUROC = 0.76; 95% CI, 0.75-0.77; *P* < .001). Relative to qSOFA scores lower than 2, encounters with qSOFA scores of 2 or higher had a 3- to 14-fold increase in hospital mortality across baseline risk deciles (19).

In a prospective study of patients presenting to emergency departments (ED) in France, Switzerland, Spain, and Belgium, Freund *et al* (2016) evaluated the predictive validity of qSOFA. Among 879 patients presenting to the ED with suspected infection, the predictive validity of qSOFA for in hospital mortality was similar to that of the full SOFA score (3% mortality for qSOFA and SOFA scores less than 2 versus 24 and 18 % mortality for qSOFA and SOFA scores greater than or equal to 2, respectively). The investigators confirmed that the predictive validity of qSOFA in the ED setting was similar to that of the full SOFA score and that the addition of lactate did not improve predictive validity. In addition, qSOFA performed better than systemic inflammatory response syndrome (SIRS) criteria and severe sepsis to predict in-hospital mortality (AUROC of 0.80 versus 0.65)(20).

Similar findings were reported in patients with suspected infection who eventually required admission to the ICU: qSOFA calculated before their ICU admission had greater accuracy than SIRS for predicting mortality and ICU free days (21).

However, in contrast to ED patients and those outside ICU, among patients with infection in the ICU, qSOFA had statistically worse predictive validity. A retrospective analysis of 184,875 ICU patients with an infection-related diagnosis reported that both qSOFA and SIRS were inferior to SOFA in predicting in hospital mortality in ICU settings (AUROC, 0.75 versus 0.60)(22).

Among the limitations of the above two analyses(20,21), a high percentage of missing values(20) and poor generalizability to all EDs or ICUs as well as to lower- and middle-income settings (21) were highlighted, obviating the need of similar studies in different countries all over the world, especially in low and middle income settings. Moreover, since there are reports that other early identification scores including the modified early warning score (MEWS) and the national early warning score (NEWS) outperformed qSOFA for predicting death and ICU transfer in non-ICU patients [5], further studies that demonstrate improved clinically meaningful outcomes due to the use of qSOFA compared to clinical judgement are warranted before it can be routinely used to predict in hospital mortality.

After comparing diagnostic accuracy of SIRS and qSOFA for organ dysfunction, Williams et al, (2016), found that SIRS and qSOFA showed similar discrimination for organ dysfunction (AUROC 0.72 vs 0.73). The qSOFA was specific but poorly sensitive for both organ dysfunction (96.1% and 29.7% of specificity and sensitivity respectively) and mortality prediction (91.3% specific and 49.1% sensitive). Although qSOFA≥2 showed high specificity, poor sensitivity may limit its utility as a bedside screening tool. Thus, in their conclusion, the authors advocated for its recalibration (23).

CHAPTER IV: PROBLEM STATEMENT

In their daily practice, surgeons practicing in Low and Middle Income Countries (LMIC) face many critical patients who, have sepsis or septic shock at the time of presentation. At University Teaching hospital of Kigali (CHUK) and in other centers with similar settings, in addition to the delay in patients' presentation for different reasons, the limited availability of surgeons (0.46 surgeons per 100000 populations in Rwanda) and ICU beds is of concern. When

a surgeon is called to review patients at Emergency Department (ED) or in other departments, he could find that some are too critical to withstand major surgery despite adequate optimization measures. To address these issues, a rapid and practical thinking is required to establish an efficient management plan in terms of preoperative optimization, ICU bed booking, selection of patients to be operated, type of surgery to be performed (definitive or staged) and family education and counseling about the decision to operate or not and possible outcomes.

There is no single scoring system specific to septic surgical patients in terms of outcome prediction. The available scoring systems to predict outcomes for critical patients in general have been criticized for their complexity and applicability in a setting with limited resources.

CHAPTER V: JUSTIFICATION OF THE STUDY

Available scores require further adjustments and testing, particularly in lower- and middle-income settings where context (for example, timing of presentation to the hospital among patients with a suspected infection) might vary considerably and such contextual factors might affect predictive validity.
A simplified and inexpensive tool taking into account the local setting with limited resources is needed to help surgeons in effective surgical planning and management of critical patients presenting at ED of CHUK, CHUB and other centers operating in settings with limited resources.

In addition to outcomes and other baseline characteristics of sepsis never described before in surgical patients in Rwanda, this study aimed at identifying gaps specific to CHUK and CHUB context in outcomes prediction and proposed a predictive score that could serve as a simplified but accurate tool to predict outcomes in critical surgical patients with sepsis syndromes taking into account the setting with limited resources.
Research question: Can we develop a tool to accurately predict outcomes in surgical patients with sepsis syndromes at CHUK and CHUB?
Hypothesis: A clinical score considering local factors can accurately predict outcomes in surgical patients with sepsis syndromes at CHUK and CHUB

CHAPTER VI: AIM AND OBJECTIVES OF THE STUDY

1. Aim:

To design a prognostic tool accurate in predicting outcomes (In hospital mortality and ICU admission) in surgical patients with sepsis who present at CHUK, CHUB and in other centers with limited resources.

2. Objectives:

a. General objective:

To develop a tool that will be used to accurately predict outcome in patients presenting with sepsis or septic shock at CHUK.

b. Specific Objectives:

1. To identify surgical patients with sepsis syndromes who present at CHUK.

2. To calculate the ICU admission rate and hospital mortality rate in surgical patients with sepsis at CHUK.

3. To describe factors associated with in hospital mortality in surgical patients with sepsis at CHUK.

4. To design the Kigali Surgical Sepsis Score (KiSS score) a scoring system to predict outcomes in surgical patients with sepsis

5. To validate the KiSS score at CHUK and CHUB

CHAPTER VII: METHODS

1. Study settings

This study was conducted in both University Teaching Hospitals of Kigali (CHUK) and Butare (CHUB). CHUK is a 400-bed teaching and referral hospital in Nyarugenge District, Kigali, Rwanda. The surgery department of CHUK has 120 inpatient beds including 48 of general surgery. There are an estimated 140 general surgery operations each month with 80 emergency and 60 elective operations [19]. Within the Intensive Care Unit of CHUK, there are 7 intensive care unit beds and 4 high-dependency unit (HDU) beds.
CHUB is a 500-bed teaching and referral hospital in Huye District, Southern province, Rwanda, with 103 surgery beds and 5 ICU beds. CHUK and CHUB are the main public tertiary level hospitals in Rwanda.

2. Study design:

This was a prospective observational cohort study of surgical patients who presented at CHUK with sepsis in 2018/2019, with an enrollment period of 12 months. The derivation of the score was done at CHUK in the first 6 months (from February 2018 to July 2018) and the validation was done on two cohorts of patients from both CHUK and CHUB in the next 6 months (from August 2018 to February 2019).

3. Study population:

All surgical patients aged 16 years and above who presented at CHUK with sepsis from February 2018 to January 2019 and all surgical patients aged 16 years and above who presented at CHUB with sepsis from August 2018 to January 2019. Sepsis was defined as suspected infection and two or three points on qSOFA score. It comprises patients in sepsis and those in septic shock.

4. Selection criteria

a. Inclusion criteria:

All adult surgical patients and children aged 16 years and above presenting with or developing sepsis in hospital prior to surgery, at CHUK from February 2018 and at CHUB from August 2018 who consented for the study.

b. Exclusion criteria:

Excluded from this study were patients who declined enrollment, children below 16 years, and those who were expected to be referred to another health facility.

5. Sample size calculation:

Based on hospital registries, we estimated that there are 24 surgical patients with sepsis at each month at CHUK. Based on previous studies, we estimated the mortality to be 21% (ranging between 17 and 26) (24,25).
Over a one-year period, we anticipated enrolling 288 septic patients and expected 60 deaths. We used the first half as a derivation cohort and the second half as a validation cohort. For the derivation cohort, we expected 144 patients with 30 deaths.

6. Variables:

The clinical and demographic variables we studied are:

- Age and sex
- Vital signs: Blood Pressure, Pulse Rate, Respiratory Rate, Peripheral oxygen saturation (SPO2), Temperature (in degrees Celsius), AVPU and Glasgow Coma Score (GCS), Urine Output
- Preoperative use of oxygen (L/min)
- qSOFA score
- Impaired Organ Function (defined in this study for Cardiovascular (SBP < 90 mmHg), CNS (GCS < 15), coagulation (Platelet count < 150 000/mL), renal (creatinine < 1.2 mg/dL or 110 mmol/L), liver (bilirubin < 1.2 mg/dL or 20mmol/L) and respiration (SPO2 < 90%).
- Sepsis syndrome stage: sepsis, septic shock (as per sepsis-3 definitions)
- Source of infection (based on clinical assessment of the treating physician)

Laboratory data included:

- White cell count (total and differential), hemoglobin, platelets,
- Serum urea and creatinine
- Electrolytes: sodium, potassium, chloride

Operative data included:

- Surgery intention: staged or definitive

Outcomes included:

- Primary outcome: Hospital death
- Secondary outcomes: ICU admission, length of hospital stay and post-operative complications (Reoperation, Surgical Site Infection, malnutrition, progression of sepsis to septic shock, and transfusion)

7. Enrollment, data collection and management:

In the first 6months, surgical patients presenting with sepsis on admission at Accident and Emergency Department, or who developed sepsis while in the surgical wards waiting for surgery at CHUK from February 2018 to July 2018 were assessed for the eligibility criteria. In addition to documented or suspected infection, a qSOFA score of 2 and above was used for screening of patients to be enrolled in the study. An informed consent was obtained from eligible patients after being offered the opportunity to accept or decline the enrollment.

Enrolled patients were followed up and observed for the advent of expected outcomes.
Patients recruited in these 6 months formed a cohort for derivation of the KiSS score.
In the following 6 months (from August 2018 to January 2019), two cohorts of surgical patients with sepsis (one from CHUK and another from CHUB) were enrolled and analyzed for validation of the new KiSS score.
In this study, a surgical patient was defined as any patient with a surgical condition. A surgical condition was considered as any disease necessitating a surgical intervention as part of management or any disease that has surgery among treatment options.
Upon admission, patients were assessed for eligibility, interviewed and examined after consenting for the study. Obtained data were recorded on data capture sheet. Demographic data such as age and sex were obtained. Patients' initial clinical assessment including a brief history about the current disease, duration of symptoms and preexisting medical and/or surgical conditions.
Initial assessment included vital signs, Glasgow Coma Scale, and AVPU score.
Impaired Organ Function (IOF) was defined as any of the following: Cardiovascular (systolic blood pressure <90 mmHg), neurologic (Glasgow Coma Scale <15), Coagulation (Platelet count <150,000/mL), renal (creatinine < 1.2 mg/dL or 110 mmol/L), Liver (bilirubin < 1.2 mg/dL or 20 mmol/L) and respiration (SPO_2 <90% on room air)
Diagnosis, sepsis syndrome stage, were also checked for. The source of infection was recorded.
Operative data (Resuscitation measures& outcomes, intraoperative findings & events, performed surgery & duration and post-operative disposition) were recorded. Patients were regularly followed for occurrence of in hospital complications.
Outcomes were documented and compared to the qSOFA score severity. A new score was designed and validated by correlation of its severity to patient outcomes.
Expected outcomes were:

- **Primary outcome**: Hospital death
- **Secondary outcomes**: ICU admission and length of hospital stay (LoHS),

8. Statistical analysis

Data were entered in the computerized excel form and cleaned for errors and possible omissions. The data were imported into STATA version 14 and checked again for possible errors and omissions. Descriptive statistics were used to describe demographic and other baseline characteristics of patients. Chi-square tests were used to determine factors associated with mortality among surgical patients with sepsis.

Factors with a p value <0.1 on univariate analysis were entered into a multivariate regression model where factors with a p value <0.05 were considered statistically significant. Factors with a variance inflation rate above 10 were excluded and the remaining factors were used for derivation of the KiSS score. The prognostic accuracy of Kiss score was assessed by comparison of its area under receiver operator characteristic curve with the preexisting qSOFA score.

9. Ethical considerations

a. Confidentiality

Data were stored on a password-protected computer and patient information were de-identified prior to data analysis.

b. Direct benefits to study participants and community

The direct benefit to study participants and their families was through education on sepsis. In addition, we anticipate long-term benefits to patients and the community through improved patient care in septic patients at CHUK and CHUB.

c. Potential harm to study participants and community

This study was designed in a way not to have any negative impact on the well-being of involved patient.

There was no monetary cost to the patient

Medical files were handled gently and with respect to avoid any damage

d. Informed consent

Informed consents were obtained from all patients after clear and concise explanations of the purpose, potential risks and benefits of the study. Patients were explained about the right to refuse study enrollment or withdraw their consent later.

Patients were informed that their decision would not have any impact on treatment decisions or medical management. For patients who were having altered mentation or impaired judgement for any other reason, a consent was obtained from a legal representative or closest relative, the same due to consent for surgery, meaning that for the patients who were too sick or mentally unstable, the close care-taker was requested to sign the informed consent.

Patients below legal age of consent (aged below 18 years) were required to give an assent in addition to the consent from a parent or a legal guardian/representative.

A statement verifying informed consent was visible on the first page of the questionnaire

e. Ethical approval

Ethical approval was obtained from Institutional Review Board of the University of Rwanda prior to study enrollment. In addition to UR/IRB approval, this study was presented to and approved by both CHUK and CHUB ethical committees.

10. LIMITATIONS OF THE STUDY

This study has a number of limitations that we had to address. Sepsis has now new definitions since 2016 and some available data were considering old definitions. For this study not to be affected by that, for enrollment, we used qSOFA score which was proposed after sepsis was redefined, and tested on patients with sepsis syndromes as per new 2016 sepsis-3 definition. Another limitation was the measurement of PaO2/FiO2 ratio in the Emergency Department settings for assessing pulmonary dysfunction. To address this, SPO2 was used as an alternative to PaO2/FiO2 ratio.

CHAPTER VIII. RESULTS

1. Baseline characteristics of the derivation cohort

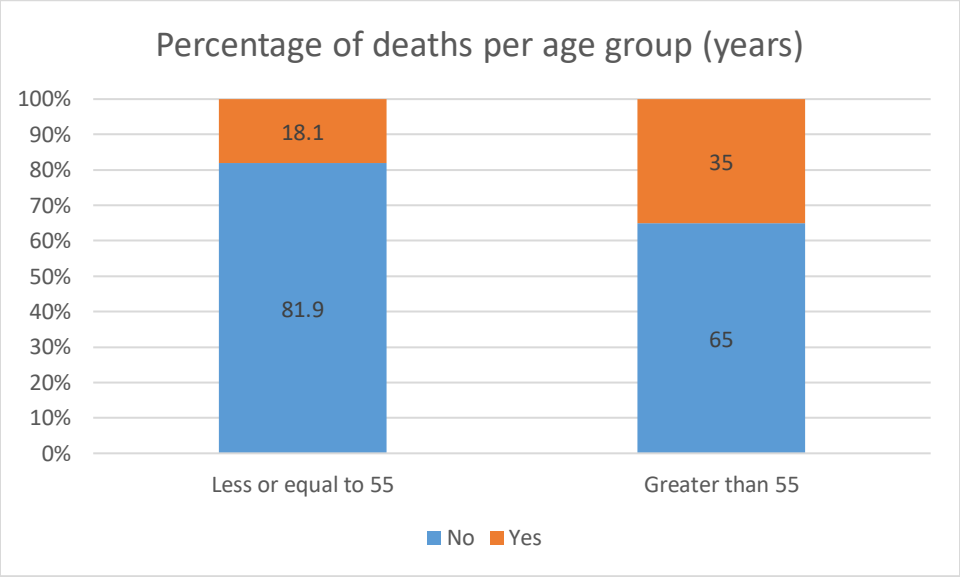
The first phase of the study was conducted on a cohort of 144 patients including 56 (38.9%) males and 88 (61.1%) females.

The patients' age was ranging from 16 to 87. The mean age was 36.8 and the median age was 31.5.

Of the 144 enrolled patients, 122 (84.7%) were aged from 16 to 55 years. Only 22 (15.3%) were older than 55 years.

Among 136 patients whose primary outcome was known and documented, 116 were younger than or aged 55 years with 21 (18.1%) deaths recorded. The remaining 20 were older than 55 years and among them, 7 (35%) died

Figure 1: ***Mortality in two age groups***



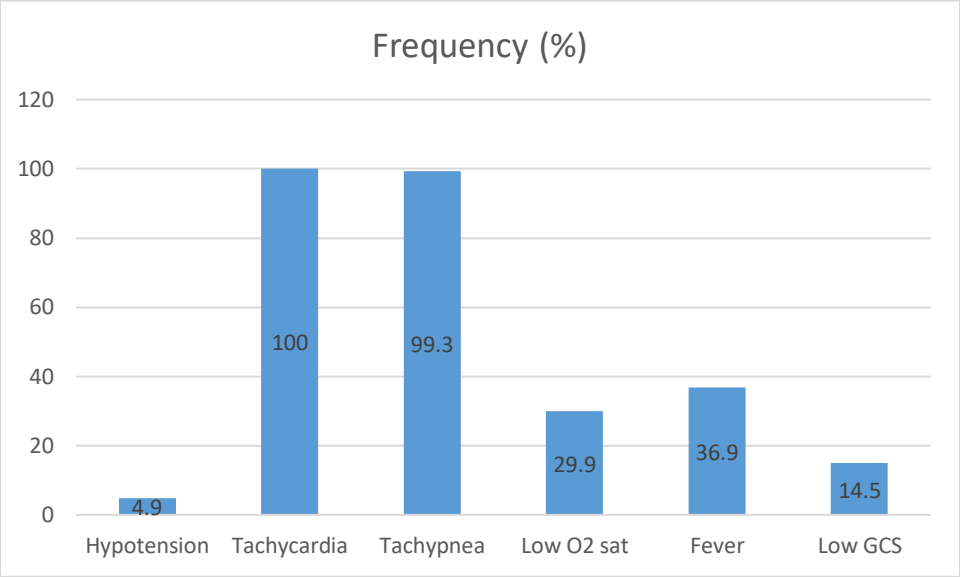
The mean symptoms duration by the time they presented to the hospital and assessed by a surgeon was 9 days.

In our study, 26 (18%) patients had at least one comorbidity, and the most frequently encountered were hypertension (n=9), HIV (n=6), gastritis (n=6), and diabetes (n=3)

All of 144 studied patients presented with tachycardia (HR>100 beats per minute), but only 7 (4.9%) had hypotension defined as SBP less than 90mmHg. Among those 144 patients, 143 (99.3%) were tachypneic with a respiratory rate of 22 or above. Of 141 patients whose temperature was recorded, fever (temperature above 37.5) was only present in 52 (36.9%) patients.

There was 21 (14.5%) of 144 patients who had decreased level of consciousness.

Figure 2: ***Frequency of vital parameters***



Of 136 patients, 104 required preoperative oxygen supplementation, 22 (22.1%) of them died and 61 (58.6%) ended up in ICU. Among 32 who did not require oxygen, only 5 (15.6%) died and 10(31.3%) required post-operative ICU admission.

Post-operative complications were frequent in patients who required preoperative oxygen supplementation compared to those who presented with normal oxygen saturation (42.9% vs 12.5).

Regarding organ dysfunction, of 142 patients analyzed for this variable, 87 (61.3%) patients had one organ dysfunction; 35 (24.6%) patients had 2 organ dysfunction; 10(7%) patients had 3 organ dysfunction; 3(4.1%) patients had 4 organ dysfunction. Seven (4.9%) did not show evidence of any organ dysfunction.

Table 1: ***Frequency of number of failing organs***

Number of IOF	Number	Percentage
None	7	4.9
One	87	61.3
Two	35	24.6
Three	10	7
Four	3	2.1

Of 142 patients, lungs were the most frequently failing organs with 124 (87.3%) followed by kidneys with 49 (34.5%). Other less frequently failing organs were cardiovascular with 28 (19.7%), coagulation: 18 (12.6%) and CNS: 13 (9.1%). Only 3 of 144 patients had their bilirubin checked and were found to have evidence of liver dysfunction.

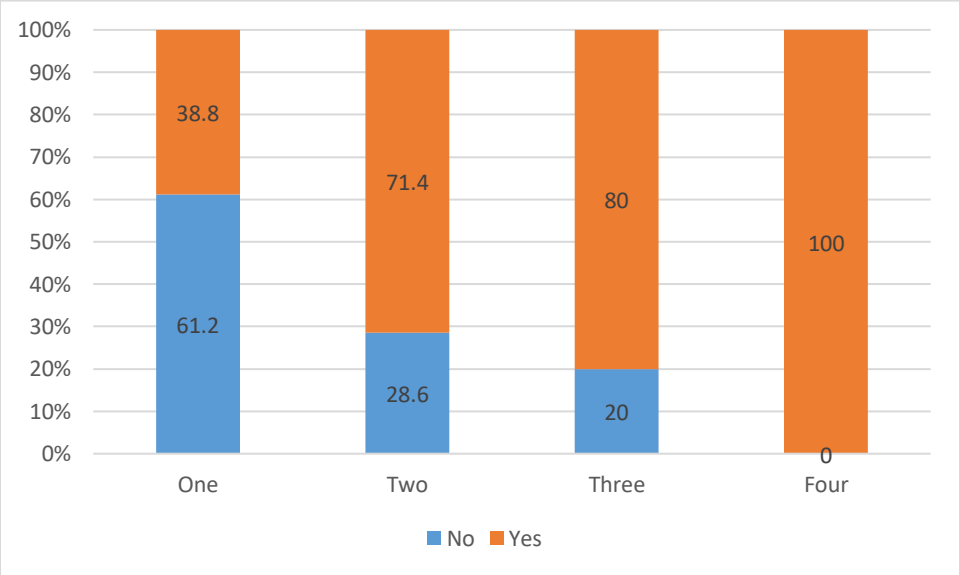
The mortality rate of 16.5% found in patients with 1 impaired organ function was increased to 30-35% for those with 2 to 4 impaired organ function.

Table 2: ***Mortality per number of impaired organ function (IOF)***

Number of impaired organ function	Death				Total	
	No		Yes			
	No.	%	No.	%	No.	%
0	7	100	0	0	7	100
1	71	83.5	14	16.5	85	100
2	19	65.5	10	34.5	29	100
3	7	70	3	30	10	100
4	2	66.7	1	33.3	3	100
Total	106	79.1	28	20.9	134	100

The ICU admission rate was increasingly proportional to the number of impaired organ function being 38.8%, 71.4%, 80% and 100% for 1, 2, 3, and 4 organ dysfunction respectively.

Figure 3: ***Frequency (%) of ICU admissions per number of impaired organ function (IOF)***



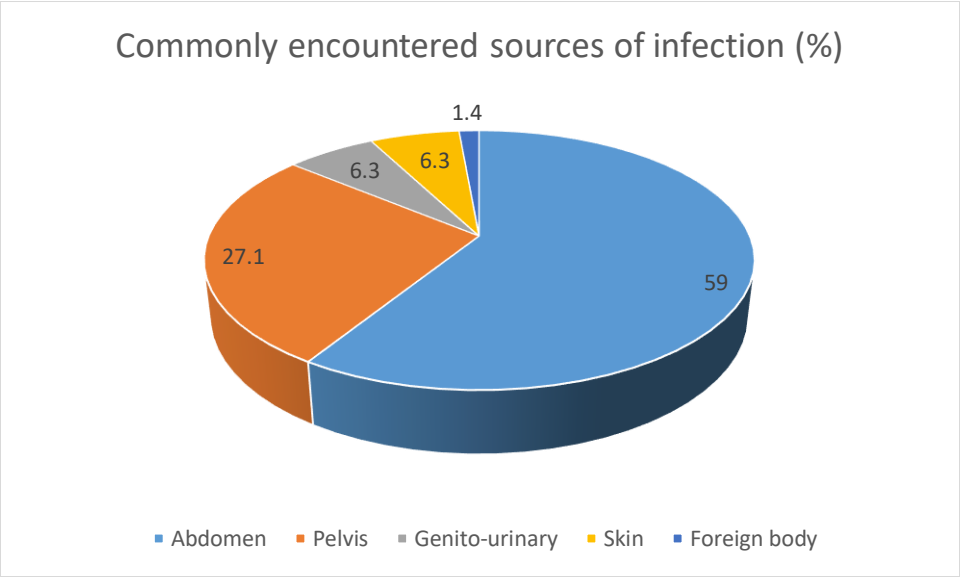
The complications rate was 28.6% in patients without evidence of impaired organ function, while it ranged between 33.3% and 66.7% for those with one or more organ dysfunction.

Peritonitis was commonly encountered in surgical patients with sepsis found in 128 (88.9%) patients of 144. Among these 128 patients with peritonitis, 58 (45.3%) had GIT perforation including 27 (21%) with peptic ulcer (PU) perforation, 23 (17.9%) with small bowel perforation, 5 (3.9%) with appendicular perforation and 3(2.3%) with large bowel perforation. Other causes

of peritonitis were peritonitis post cesarean delivery: 34 (26.5%), bowel gangrene: 14 (10.9%), liver abscess: 5(3.9%) and tubo-ovarian abscess: 5(3.9%)

The common sources of infection were abdomen with 85 (59%) patients, followed by pelvis: 39 (27.1%); genito-urinary system: 9 (6.3%); skin: 9 (6.3%) and foreign body: 2 (1.4%).

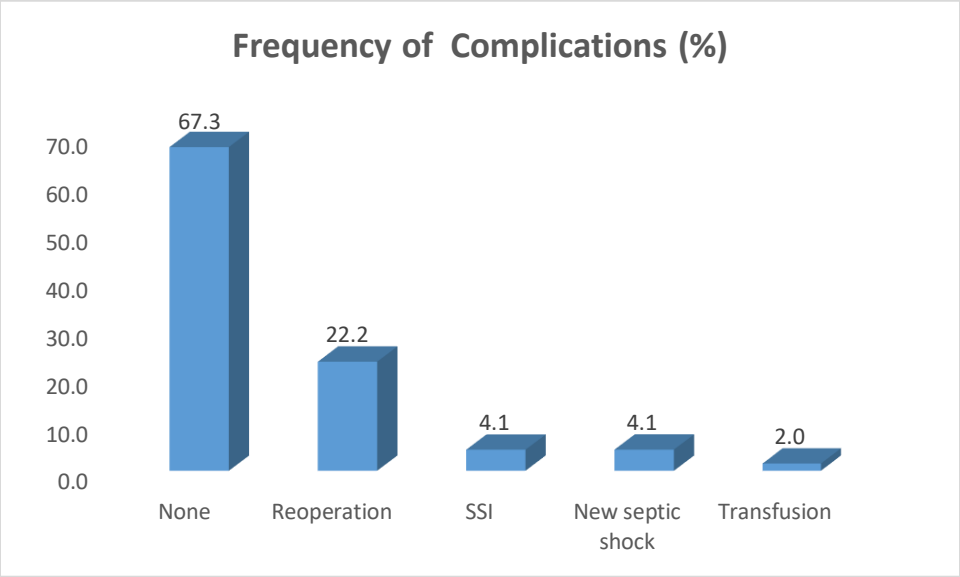
Figure 4: ***Commonly encountered sources of infection***



The overall complications rate was 32.6% (47 of 144) while the overall ICU admission rate was 50% (71 of 142)

Frequently encountered complications included reoperation: 32 (22.2%); progression of sepsis to septic shock: 6 (4.1%); Surgical Site Infection: 6 (4.1%) and anemia amenable to transfusion: 3 (2.0%).

Figure 5: ***Frequency of complications***



The overall in-hospital mortality rate was 20.6% (28 of 136).

2. Derivation of the KiSS score

The factors associated with hospital death in the derivation cohort are shown in the table below:

Table 3: ***Chi-square test of association between the dependent (Death) and independent variables***

Variables	N(total)	N(deaths)	%(deaths)	P value
Preoperative oxygen supplementation	104	22	22.1	0.427
*Age > 55 years	20	7	35	0.034
*Presence of comorbidities	26	14	53.8	0.069
*Systolic blood pressure < 90 mmHg	7	5	71.4	0.014
Heart rate >100	136	28	20.6	0.372
*Heart rate >130	37	14	37.8	0.061
Respiratory rate >22	134	28	20.9	0.609
*Respiratory rate >24	119	28	23.5	0.028
Peripheral capillary oxygen saturation (SPO2) < 90%	41	9	21.9	0.355
Temperature > 37.5˚C	83	16	19.2	0.817
*Glasgow coma scale < 15	21	8	38	0.021
*Number of impaired organ function >2	48	14	29.1	0.035
*Gastro-intestinal tract perforation (GIT) perforation	52	17	32.7	0.026
Leukocytosis (WBC > 10. 000)	87	14	16	0.346
Abnormal potassium (K^+) , sodium (Na^+), chloride (CL^-)	58	11	18.9	0.157

Renal dysfunction (creatinine > 1.2 mg/dL or 110 ɱmol/L)	47	10	21.2	0.351
Platelet count < 150 000/ɱL	21	4	19	0.621
Preoperative transfusion	41	5	12.2	0.411

*Statistically significant variables

Factors associated with hospital mortality were age >55 (P value: 0.034), presence of one or more comorbidities (P value: 0.069), hypotension with SBP <90 mmHg (P value: 0.014), Heart Rate >130 (P value: 0.061) tachypnea with respiratory rate greater than or equal to 24 cycles per minute (P value: 0.028), decreased level of consciousness with GCS below 15 (P value: 0.021), GIT perforation (P value: 0.026) and two or more organs dysfunction (P value: 0.035).

The above 8 statistically significant parameters were entered into a logistic regression model, and multicollinearity was checked using the Variance Inflation Factor (VIF). Variables used to derive a scoring system included age, presence of comorbidities, systolic BP <90 mmHg, respiratory rate >24 breaths per minute, decreased level of consciousness (assessed by GCS) and GIT perforation.

Table 4: ***The Kigali Surgical Sepsis (KiSS) score***

Parameter	Score
Age > 55 years	1
Presence of comorbidities*	1
Systolic blood pressure < 90 mmHg	1
Respiratory rate >24	1
Glasgow coma scale < 15	1
Gastro intestinal tract perforation	1

* Comorbidities: Presence of one or more additional conditions other than the primary condition.

3. Validation of the KiSS score

Baseline characteristics of patients in the validation cohort are shown in the summary table below:

Table 5: ***Summary table of patients' characteristics for both derivation and validation cohorts***

Variable	**Derivation cohort**		**Validation cohort**		**Total encounters**	
	N	%	N	%	N	%
Total enrolled patients	144	100	144	100	288	100
CHUK enrolled patients	144	100	75	52	219	76
CHUB enrolled patients	-	-	69	48	69	24
Age, mean	36.8	-	36.2	-	36.5	-
Age, median	31.5	-	33.7	-	32.6	-

Male	56	38.9	61	42.4	117	40.6
Female	88	61.1	83	57.6	171	59.4
Presence of comorbidities	26	18	16	11.1	42	14.6
Vital parameters						
Hypotension (SBP < 90 mmHg)	7	4.9	10	6.9	17	5.9
Tachycardia (HR > 100 cycles per min)	144	100	144	100	288	100
Tachypnea (RR >24 breaths per min)	143	99.3	144	100	287	99.6
Low oxygen saturation (SPO2<90%)	43	29.9	54	37.5	97	33.7
Fever (Temperature >37.5^{0}C)	83/141	58.8	87	60.4	170	59
Low Glasgow coma scale (<15)	21	14.5	24	16.6	45	15.6
Diagnosis						
Peritonitis post cesarean delivery	34	23.6	21	14.5	55	19
Gastro-intestinal tract perforation	58	40.2	62	43	120	41.6
Bowel gangrene	14	9.7	19	13.1	33	11.4
Uterine perforation/dehiscence	13	9.0	8	5.5	21	7.3
Genito-urinary infection	7	4.8	10	6.9	17	5.9
Abortion	6	4.1	5	3.4	11	3.8
Soft Tissue Infection	6	4.1	13	9.0	22	7.6
Tubo-ovarian abscess	5	3.4	1	0.7	6	2.0
Liver abscess	5	3.4	2	1.4	7	2.4
Miscellaneous	12	8.3	3	2.0	15	5.2
Complications						
Reoperation	32	22.2	41	28.4	73	25.3
New onset of septic shock	6	4.1	10	6.9	16	5.5
Surgical Site Infection	6	4.1	9	6.2	15	5.2
Transfusion	3	2.0	16	11.1	19	6.6
Total complications rate	47	32.6	76	52.7	123	42.7
Outcomes						
Mean length of hospital stay	21.2	-	24.6	-	22.9	-
ICU admission rate	71/142	50.0	76/144	52.7	147	51.4
Mortality rate	28/136	20.6	33/144	22.9	61	21.7

Abbreviations: CHUK: Centre Hospitalier Universitaire de Kigali; CHUB: Centre Hospitalier Universitaire de Butare; SBP: Systolic Blood Pressure; HR: Heart Rate, RR: Respiratory Rate; ICU: Intensive Care Unit

The application of KiSS score on the validation cohort has shown three classes of patients that can be represented by colors and represent the likelihood of mortality and ICU admission:

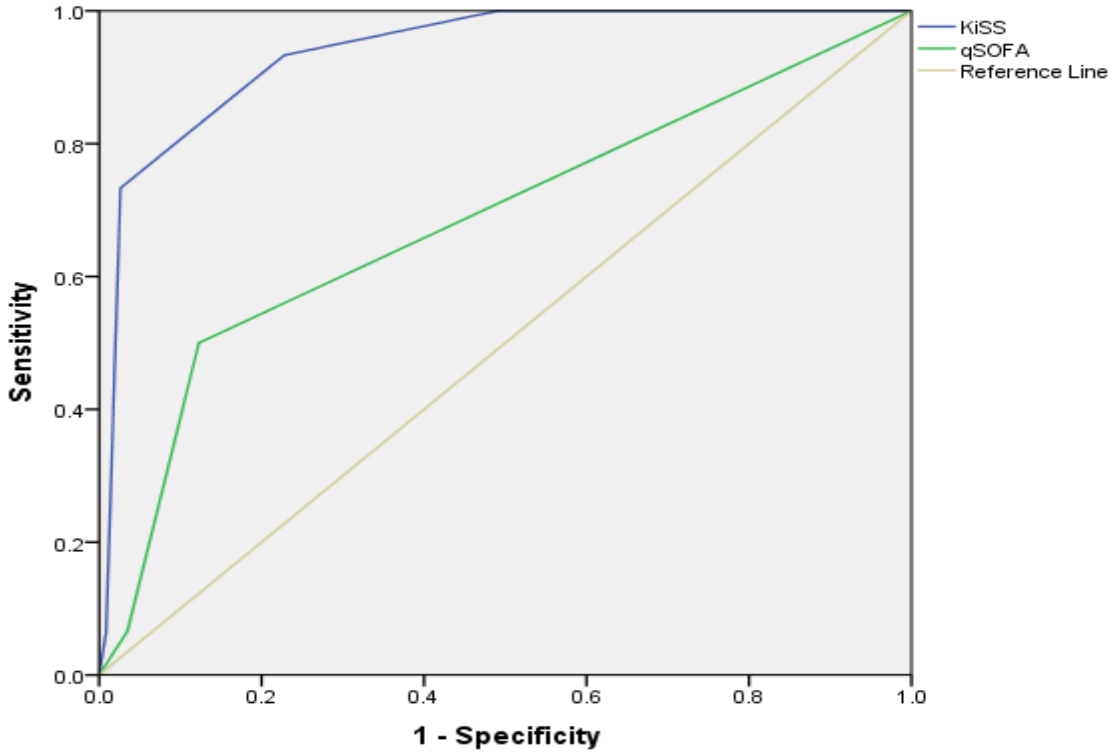
1. **The first class of patients (Green)**: Comprises patients with a KiSS score of 1 or 2. In the validation cohort, 85 (59%) were the green class of patients. These patients are expected to have good outcomes, since they have a 2.2% risk for mortality and 40% risk for ICU admission.
2. **The second class of patients (Yellow)**: Comprises patients with a KiSS score of 3 or 4. In the validation cohort, 48 (33.3%) were the yellow class of patients. These are patients whose outcomes can progress to either side (from poor to good prognosis) and they have a 51.6% risk for mortality and 64.7% risk for ICU admission.
3. **The third class of patients (red)**: Comprises patients with a KiSS score of 5 or 6. In the validation cohort, 11 (7.6%) were the red class of patients. A poor prognosis is likely in these patients as they have a 76.7% risk for mortality and 100% risk for ICU admission respectively

*Table 6**: Prediction of mortality for qSOFA and KiSS scores***

Parameter / Score	qSOFA score	KiSS score
Sensitivity	52%	73%
Specificity	87%	97%
Positive Predictive Value	50%	88%
Negative Predictive Value	88%	93%

The KiSS score was compared to qSOFA score for death prediction and KiSS score was more sensitive (73% vs 52%) and specific (97% vs 87%) for predicting mortality in surgical patients with sepsis syndromes

*Figure 6**: qSOFA and KiSS ROC curves for death prediction***



KiSS vs QSOFA for death prediction

In terms of death prediction, KiSS performed better than qSOFA with the area under ROC curve of 0.939 (95% CI, p<0.001) for KiSS and 0.684 (95% CI; p: 0.02) for qSOFA as summarized in the table below:

*Table 7**: comparison of area below ROC curves for death prediction***

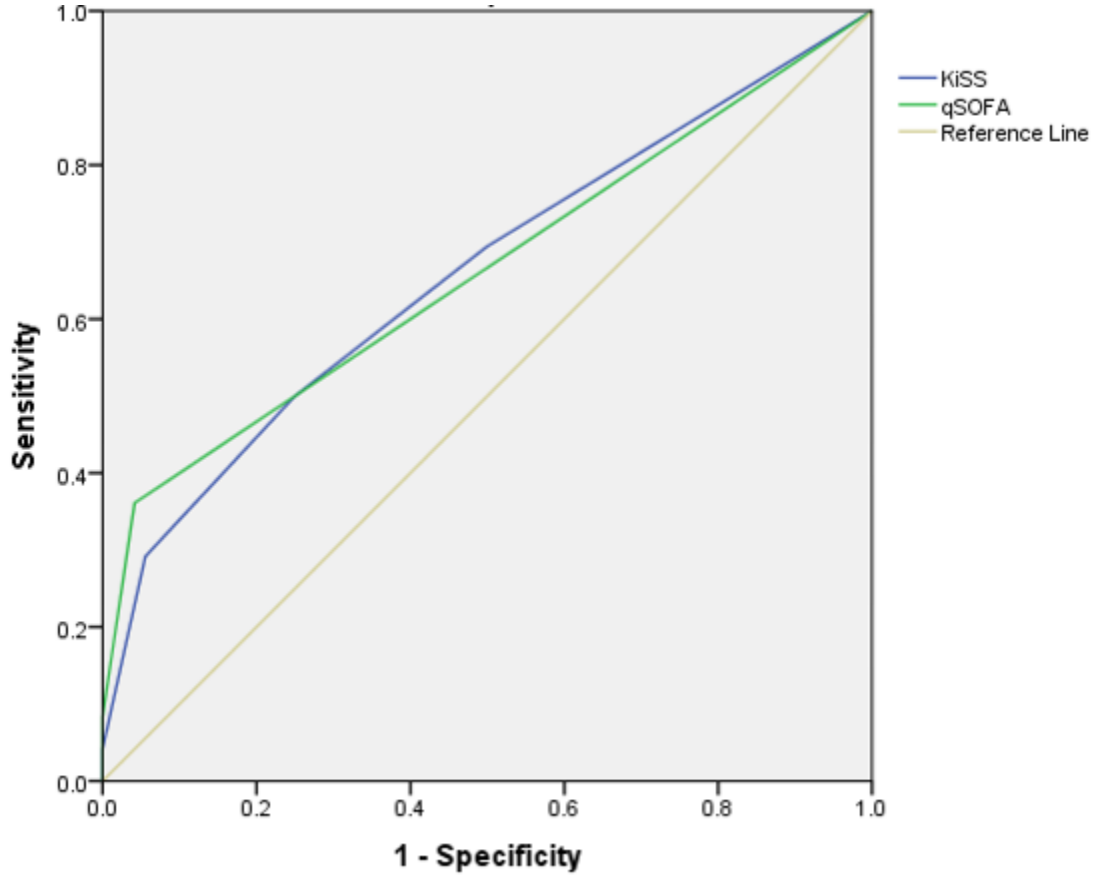
Variable	Area below ROC	95%CI	p value
KiSS	0.939	0.896-0.982	<0.001
qSOFA	0.684	0.567-0.801	0.002

The KiSS score was also compared to qSOFA score in terms of predicting ICU admission and KiSS was more specific (94% vs 60%) but less sensitive (29% vs 90%) for predicting ICU admission compared to qSOFA score

Table 8**: Prediction of ICU admission for qSOFA and KiSS scores**

Parameter / Score	qSOFA score	KiSS score
Sensitivity	90%	29%
Specificity	60%	94%
Positive Predictive Value	36%	84%
Negative Predictive Value	96%	43%

*Figure 7**: qSOFA and KiSS ROC curves for ICU admission***



There was no statistically significant difference seen between KiSS score and qSOFA score for ICU admission prediction since the AUROC curve was 0.659 (95% CI; p: 0.001) for KiSS and 0.661 (95%CI; p: 0.001) for qSOFA

*Table 9**: Comparison of area below ROC curves for prediction of ICU admission***

Variable	Area under the curve	95% CI	P value
KiSS	0.659	0.570-0.748	0.001
QSOFA	0.661	0.572-0.751	0.001

CHAPTER IX: DISCUSSION OF THE RESULTS

The newly established KiSS score is a better alternative to qSOFA score with not only a better predictive validity (AUROC = 0.939; 95%CI; P< 0.001) but also the fact that it provides much information that can help healthcare providers to stratify patients in low risk (green color), moderate risk (yellow color) and high risk (red color) patients.

The stratification of the patients was expected to help the clinician to prepare the patient and the family for the probable outcomes and to know precisely for which patient to book ICU bed (for yellow and red patients). The consent to operate on red patients must be taken by the patient and/or family after thorough discussion with the surgeon, and, if and only if the ICU bed was available (If the ICU bed was not available, such patients should be referred to another hospital with an ICU facility).

The hospital mortality with regard to qSOFA which was 13% for patients with qSOFA score less than two and 57.7% for those with a qSOFA of 2 and above was superior to the one studied by Freund *et al* (2017) on 879 patients suspected to have infection who presented at EDs in France, Switzerland, Spain, and Belgium (3% mortality for qSOFA score less than 2 versus 24 % mortality for qSOFA score greater than or equal to 2) (20).

The fact that qSOFA was specific but poorly sensitive for predicting mortality (with 87% of specificity and 52% of sensitivity) in our study, was also reported by other authors such as Williams *et al* (2016) with 91.3% and 49.1% of specificity and sensitivity respectively (23)

The predictive validity of qSOFA (AUROC = 0.684; 95%CI; P: 0.001) found in our study was inferior to the one found by Seymour et al (2016) (AUROC = 0.81; 95%CI)(19), and this is probably because of socio-economic constraints and insufficient hospital resources specific to our context that could have contributed to some patients dying while they were not expected to.

Sepsis is associated with poor outcomes including post-operative mortality, ICU admission and prolonged length of hospital stay. These outcomes worsen as sepsis advances. The mortality doubled when patients were older than 55 years compared to those aged 55 years or below (35% vs 18.1%). Other factors associated with poor outcomes (increased mortality, ICU admission, longer hospital stay and in-hospital complications) were presence of comorbidities, tachypnea of respiratory rate of 24 or above, tachycardia above 130 beats per minute,

decreased level of consciousness (GCS <15), hypotension (SBP < 90 mmHg), having a GIT perforation and two or more impaired organ function. Most of these factors were also incriminated by different authors such as Jagodiča *et al* (2006) for number of organ dysfunction (11), Waitt *et al* (2015) for hypoxia (12), and Jacob *et al* (2009) for low GCS(13).

The abdomen was commonly identified as major source of infection in our study with 85 (59%) cases, which was consistent with the findings by Moore *et al* (2011), where the abdomen represented 69% of all sources of infection (26).

The overall hospital mortality rate of 21.7% found in our study was relatively similar to the one found in other sub-Saharan countries such as Malawi (22%) by Waitt et al (2015) (12) and in Uganda (23.7%) by Jacob *et al* (2009)(13). The higher mortality found in our settings can be explained by the fact that our patients were purely surgical and presented at advanced stage of infection and also treated in low resource setting compared to those of high income countries.

CHAPTER X: CONCLUSION AND RECOMMENDATIONS

1. Conclusion

The Kigali Surgical Sepsis (KiSS) score developed from this study was found to be superior to the qSOFA in terms of sensitivity (73% vs 52%) and specificity (97% vs 87%); and showed better predictive validity for hospital mortality (AUROC = 0.939; 95% CI, p<0.001 vs AUROC = 0.684; 95% CI, p<0.001).

The KiSS score showed an added advantage of stratifying surgical patients to be operated on into those with good prognosis (green patients), those with variable prognosis (yellow patients) and those with poor prognosis (red patients).

2. Recommendations

Based on the findings of this study whose main purpose was to offer guidance to the surgeons especially those who are practicing in settings with limited resources in terms of dealing with critically ill surgical patients and their families using available resources, the following recommendations were formulated and addressed to:

a. CHUK and CHUB:

- Each surgical patient with or suspected to have a source of infection assessed by a surgeon or a surgical resident should be subjected to KiSS score for early identification of those who are likely to die from their infection
- All patients should then be classified to green, yellow or red patients using the KiSS score. The KiSS score can be used to help counsel patients and families on predicted outcomes.
- We recommend ICU booking for yellow and red patients
- A decision to operate or not on a red patient should be taken after thorough discussion between the family on one hand and surgery and anesthesia teams on the other hand.

The final decision belongs to the family and should be well documented in patient's records file

- We recommend not to operate on red patients when there is no ICU bed available. They should be sent to another center with available ICU facility.

b. The Ministry of Health

- To fund and facilitate a larger, multivariate study that may include different levels of health care facilities to validate this score probably for national or international use.
- To disseminate the KiSS score to the District Hospital and Health Center level to create awareness among all health care providers and a quick reaction at each level of care especially at those without ICU facility
- To allow a direct referral from any health facility (Health posts, Health Center or District hospital) to a center where surgical care is provided (without passing to another health facility without surgical capacity) for patients with obvious source of infection who score more than 2 points on the KiSS score.

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APPENDIX I: DATA CAPTURE SHEET

DATA COLLECTION SHEET Date: ……. /……. /…….

Project title: DEVELOPPING A TOOL TO PREDICT OUTCOMES IN SURGICAL PATIENTS WITH SEPSIS SYNDROMES AT UNIVERSITY TEACHING HOSPITAL OF KIGALI (CHUK) AND BUTARE (CHUB)

Clinical data (at Emergency Department)

- Age and sex: …….. Code: ……../……/……
- Referring health facility……..
- Symptoms duration……..
- Past medical and surgical history:
  ……..
- Regular medications:
  ……
- Karnofsky performance score at admission:
  ……
- Vital signs: Blood Pressure (mmHg): ……..... Pulse Rate (bpm) ……., Respiratory Rate (cycles/min): ……. SPO2: …….. Temperature (in0C): ……., AVPU: …… Glasgow Coma Score (GCS): ……Urine Output (ml/kg/hr): ……
- Mean Arterial Pressure (MAP): ……. Use of vasopressors (type and dose)……..
- Use of Oxygen (L/min): ……
- Scores: qSOFA: ……, SOFA: ……. SIRS: ……, MEWS: ……, NEWS: ……..
- Organ dysfunction (number and names):
  ……..…
- Diagnosis: (pre-op):
  ……
- Sepsis syndrome stage (circle): sepsis, septic shock
- Source of infection:
  ……

Laboratory data:

- White Cell Count (and differentials): ……, Hemoglobin: ……. Platelets: ……..,
- Kidney function: Serum urea: …… Serum creatinine: ……..
- Electrolytes: sodium: ……..Potassium: ……..Chloride: ……..
- Bilirubin (if available): ……..

In Theatre (Operative data):

- Resuscitation measures: Intravenous fluids (mL): ……..
- Blood products (type and amount): ……

- Analgesics: …… antibiotics received: ……..
- Immediate preoperative parameters: BP: …… PR: …….. RR: …….. SPO2: ……. GCS: …… U/O: …… Hb: …… qSOFA: …… Urea: ……. Na+: ….. K+: …….. Cl-: ……..
- Intraoperative findings: ……..
- Post op diagnosis: ……..
- Intra-operative events(tick): use of vasopressors/ heart arrhythmias/arrest/ transfusion
- Performed surgery and duration: …….. Intention (circle): staged or definitive Estimated blood loss: ……..
- Immediate post-operative vitals (At PACU admission): BP: …… PR: …….. RR: …….. SPO2: ……. GCS: …… U/O: ……
- Post-operative disposition (Ward, ICU): ……

In patient follow up (Outcomes):

- Primary outcome: In hospital death Circle): Yes No
- Secondary outcomes: ICU admission: Yes No Length of hospital stay: ……..
- In hospital complications: Reoperation SSI Malnutrition New septic shock Transfusion
- Karnofsky performance score at the time of discharge: …….
- Additional comments:

APPENDIX II: INFORMATION SHEET & CONSENT/ *IBISOBANURO NO KWEMERA KUJYA MUBUSHAKASHATSI*

Please read carefully before deciding on research participation/ *Soma neza mbere yo kwemeza niba ujya mubushakashatsi*

Purpose of the research study/ *Icyo ubushakashatsi bugamije*: To design a prognostic tool accurate in predicting outcomes (ICU admission, length of hospital stay and in hospital mortality) in surgical patients with sepsis syndromes who present at A/E Department of CHUK and in other centers with limited resources. /*Guhanga igikoresho cyakwifashishwa muguteganya ingaruka za microbes (soma mikorobe) zizahaza umubiri ku abarwayi bagana ibitaro bikuru bya kaminuza CHUK bafite uburwayi bukenera kubagwa*.

What you will do in the study/ *Icyo usabwa muri ubu bushakashatsi*: You will be asked about your past and current illnesses. You will also be examined. You may skip any questions that make you uncomfortable. You may also elect to discontinue your participation in this study at any time without any negative impact on your expected treatment */ Uzabazwa ku ndwara waba wararwaye mugihe cyashize ndetse n'ubu. Uzanasuzumwa na muganga. Wemerewe kudasubiza ikibazo cyose wumva kikubangamiye; kandi wemerewe kwivana mubushakashatsi igihe cyose wabishakira ntazindi nkurikizi cg ingaruka mu kuvurwa kwawe*

Time required/Igihe usabwa: The study will initially require about approximately 30 minutes of your time. Subsequent visits may require you 10 minutes each and their number will depend on your length of stay*/ Ubushakashatsi buzagusaba iminota nka 30 kw' ikubitiro, ariko muganga azajya agusura na nyuma amara nk' iminota icumi inshuro azaza zikazaterwa n' igihe uzamara mubitaro.*

Risks/ *ingaruka mbi* : Minimal risk is involved in this study for breach of data confidentiality but it will be minimized by storing data on a password-protected computer and de-identifying data as soon as possible /Hari amahirwe make yo kuba undi yasoma amakuru watanze kandi tuzabyirinda dukura amazina yawe kumpapuro zanditseho ayo makuru tukanazifungirana.

Benefits/ Ingaruka nziza: You will not be compensated for your participation. The study may help us understand outcomes in surgical patients with sepsis syndromes. Results provided by this study will allow us to propose adequate care plan taking into consideration local factors associated with poor outcomes. Ntabihembo bigenewe uzitabira ubu bushakashatsi, ahubwo buzadufasha kumva ingaruka a microbes zizahaza umubiri bidufashe no gushyiraho gahunda inoze yo kubavura.

Confidentiality/Kugirirwa ibanga: The information that you give in the study will be handled confidentially. Your information will be assigned a code number. The list connecting your name to this code will be kept in a locked file. When the study is completed and the data have been analyzed, this list will be destroyed. Your name will not be used in any report/Amakuru uzaduha azakoreshwa muburyo bw' ibanga. Uzahabwa code kandi impapuro zihuza amazina na

code zizabikwa mukabati gafungwa, zizanatwikwe ubushakashatsi burangiye. Ntahantu nahamwe havugwa ubu bushakashatsi hazagaragara amazina yawe.

Right to withdraw from the study/*Uburenganzira bwo kwikura mubushakashatsi*: You have the right to withdraw from the study at any time without penalty/ *wemerewe kwivana mubushakashatsi igihe cyose wabishakira ntazindi nkurikizi cg ingaruka mu kuvurwa kwawe*.

If you have questions about the study, contact/*Ukeneye ibindi bisobanuro wabaza*:
Dr Irénée NIYONGOMBWA
University of Rwanda, Postgraduate Trainee in Surgery

Telephone: +250 783317681/+250728317681 Email: ireniyong@gmail.com

If you have questions about your rights in the study, contact/ *Mugihe uburenganzira bwawe butakubahirizwa wabaza:*
Professor Kato J. Njunwa
Chairperson, Institutional Review Board

Telephone: +250788490522

Dr. Brenda Asiimwe-Kateera

Secretary, Institutional Review Board

College of Medicine and Health Sciences, University of Rwanda

Kaminuza y'u Rwanda, Ishuri ryigisha ubuzima n'ibijyanye n'ubuzima

P.O. Box 3286 Kigali, Rwanda

Email: researchcenter@ur.ac.rw

Website: http://cmhs.ur/ac/rw/

Agreement:
I agree to participate in the research study described above/*Nemeye kujya mubushakashatsi nasobanuriwe haruguru.*

Signature: _____ Date: _____

Names and signature of the person obtaining the consent Date

…… ……/……/……

APPENDIX III: ASSSENT FORM

Project title: "**DEVELOPPING A TOOL TO PREDICT OUTCOMES IN SURGICAL PATIENTS WITH SEPSIS SYNDROMES AT UNIVERSITY TEACHING HOSPITAL OF KIGALI (CHUK)**".

Investigators: Dr NIYONGOMBWA Irénée,

Tel: 0783317681/ 0728317681
Email: ireniyong@gmail.com

We are doing a research on outcomes of septic patients with sepsis syndromes. If you decide that you want to be part of this study, you will be asked by a clinician to answer questions related to the study.

You can ask questions any time, now or later. You can talk to the doctors, your family or someone else. You do not have to be in this study, no one will be mad at you if you don't want to do this. We will also ask your parents if they would like you to be in the study. Even if you say yes now, you can change your mind later.

When we are finished with this study, we will write a report about what was learnt. This report will not include your name or that you were in the study.

ASSENT

I want to take part in this study. I know I can change my mind at any time.

Name of the child: ……

Verbal assent given: yes No **Date**: …/…/……

I confirm that I have explained the study to the participant to the extent compatible with the participant understands, and that the participant has agreed to be in the study.

Name of person obtaining the assent and signature: …… Date: …/…/……

ICYEMEZO CYUBURENGANZIRA BWO KWINJIRA MUBUSHAKASHATSI (munsi y' imyaka 18)

UMUTWE WI BYIGWA: **"Guteganya ingaruka za mikorobe zizahaza umubiri mubarwayi bakenera kubagwa**".

Abashakashatsi: Dr NIYONGOMBWA Irénée, MD,

Telefoni: 0783317681/0728317681

Turakora ubushakashatsi kubijyanye n' ingaruka za mikorobe zizahaza umubiri mubarwayi baba bakeneye kubagwa". Niwemera kwitabira ubu bushakashatsi, umuganga azagira ibibazo akubaza bijanye n' indwara ufite anagusuzume. Ushobora kubaza abaganga cyangwa umuryango wawe, cyangwa undi muntu uwo ariwe wese, igihe icyo aricyo cyose.

Ntabwo ari itegeko kwitabira ubu bushakashatsi. Ntawe uzakurakarira nuba utabyitabiriye. Tuzabaza n'ababyeyi bawe niba bemera ko witabira ubu bushakashatsi. Nubwo wakwemera ubu, wemerewe kuva muri ubu bushakashatsi igihe cyose ushakiye.

Niturangiza ubu bushakashatsi, tuzandika amakuru y' ibyo twabonye ariko izina ryawe ntaho rizagaragara.

Icyemezo: Nemeye kwitabira ubu bushakashatsi

Izinary'umwana……..

Itariki …… / ……. /……

Ndemeza ko nsobanuriye uwitabiriye ubu bushakashatsi ku rwego abisobanukirwa bituma yemera kwitabira.

Amazina n'umukono by' uwasobanuriye umwana: ……

Itariki: ……/…...../……

APPENDIX IV: SOFA SCORE

System	0	1	2	3	4
Respiration PaO2/FiO2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation Platelets, x10³/uL	≥150	<150	<100	<50	<20
Liver Bilirubin, mg/dL (umol/L)	<1.2 (20)	1.2 - 1.9 (20 - 32)	2.0 - 5.9 (33 - 101)	6.0 - 11.9 (102 - 204)	>12.0 (204)
Cardiovascular	MAP ≥70mmHg	MAP <70mmHg	Dopamine <5 or Dobutamine (any dose)	Dopamine 5.1 - 15 or Epinephrine ≤0.1 or Norepinephrine ≤0.1	Dopamine >15 or Epinephrine >0.1 or Norepinephrine >0.1
CNS GCS Score	15	13 - 14	10 -12	6 - 9	<6
Renal Creatinine, mg/dL (umol/L) Urine Output, mL/d	<1.2 (110)	1.2 - 1.9 (110 - 170)	2.0 - 3.4 (171 - 299)	3.5 - 4.9 (300 - 440) <500	>5.0 (440) <200
*Catecholamine Doses = ug/kg/min for at least 1hr					

APPENDIX V: ETHICAL APPROVAL

UNIVERSITY OF RWANDA — COLLEGE OF MEDICINE AND HEALTH SCIENCES

CMHS INSTITUTIONAL REVIEW BOARD (IRB)

Kigali, 20th /11/2017

Dr NIYONGOMBWA Irénée
School of Medicine and Pharmacy, CMHS, UR

Approval Notice: No 403 /CMHS IRB/2017

Your Project Title ***"Developing A Tool To Predict Outcomes In Surgical Patients With Sepsis At University Teaching Hospital Of Kigali (CHUK)"*** has been evaluated by CMHS Institutional Review Board.

Name of Members	Institute	Involved in the decision		
		Yes	No (Reason)	
			Absent	Withdrawn from the proceeding
Prof Kato J. Njunwa	UR-CMHS		X	
Prof Jean Bosco Gahutu	UR-CMHS	X		
Dr Brenda Asiimwe-Kateera	UR-CMHS	X		
Prof Ntaganira Joseph	UR-CMHS	X		
Dr Tumusiime K. David	UR-CMHS	X		
Dr Kayonga N. Egide	UR-CMHS	X		
Mr Kanyoni Maurice	UR-CMHS	X		
Prof Munyanshongore Cyprien	UR-CMHS		X	
Mrs Ruzindana Landrine	Kicukiro district		X	
Dr Gishoma Darius	UR-CMHS	X		
Dr Donatilla Mukamana	UR-CMHS	X		
Prof Kyamanywa Patrick	UR-CMHS		X	
Prof Condo Umutesi Jeannine	UR-CMHS		X	
Dr Nyirazinyoye Laetitia	UR-CMHS	X		
Dr Nkeramihigo Emmanuel	UR-CMHS		X	
Sr Maliboli Marie Josee	CHUK	X		
Dr Mudenge Charles	Centre Psycho-Social	X		

After reviewing your protocol during the IRB meeting of where quorum was met and revisions made on the advice of the CMHS IRB submitted on 13th November 2017, **Approval has been granted to your study.**

Please note that approval of the protocol and consent form is valid for **12 months**.
You are responsible for fulfilling the following requirements:

EMAIL: research center@ur.ac.rw P.O. Box: 3286, Kigali, Rwanda WEBSITE: http://cmhs.ur.ac.rw/

1. Changes, amendments, and addenda to the protocol or consent form must be submitted to the committee for review and approval, prior to activation of the changes.
2. Only approved consent forms are to be used in the enrolment of participants.
3. All consent forms signed by subjects should be retained on file. The IRB may conduct audits of all study records, and consent documentation may be part of such audits.
4. A continuing review application must be submitted to the IRB in a timely fashion and before expiry of this approval
5. Failure to submit a continuing review application will result in termination of the study
6. Notify the IRB committee once the study is finished

Sincerely,

Date of Approval: The 20th November 2017

Expiration date: The 20th November 2018

Professor Kato J. NJUNWA
Chairperson Institutional Review Board,
College of Medicine and Health Sciences, UR

Prof JB Vice Chair

Cc:
- Principal College of Medicine and Health Sciences, UR
- University Director of Research and Postgraduate Studies, UR

CENTRE HOSPITALIER UNIVERSITAIRE
UNIVERSITY TEACHING HOSPITAL

Ethics Committee / Comité d'éthique

December 22nd, 2017 **Ref: EC/CHUK/502/2017**

Review Approval Notice

Dear Irene Niyongombwa,

Your research project: ***"Developing a tool to predict outcomes in surgical patients with sepsis at CHUK."***

During the meeting of the Ethics Committee of University Teaching Hospital of Kigali (CHUK) that was held on 22/12/2017 to evaluate your protocol of the above mentioned research project, we are pleased to inform you that the Ethics Committee/CHUK has approved your protocol.

You are required to present the results of your study to CHUK Ethics Committee before publication.

PS: Please note that the present approval is valid for 12 months.

Yours sincerely,

ETHICS COMMITTEE CHUK

Dr. Rusingiza Emmanuel
The Present, Ethics Committee,
University Teaching Hospital of Kigali

<<University teaching hospital of Kigali Ethics committee operates according to standard operating procedures (Sops) which are updated on an annual basis and in compliance with GCP and Ethics guidelines and regulations>

B.P. :655 Kigali- RWANDA www.chk.rw Tel. Fax : 00 (250) 576638 E-mail :chuk.hospital@chukigali.rw

CENTRE HOSPITALIER UNIVERSITAIRE
UNIVERSITY TEACHING HOSPITAL

CENTRE HOSPITALIER UNIVERSITAIRE
DE BUTARE (CHUB)
OFFICE OF DIRECTOR GENERAL

Huye, 05/09/2018

N° Ref: CHUB/DG/SA/09/1541/2018

Irene Niyongombwa
School of Medicine and Health Sciences

Dear Niyongombwa,

Re: Your request for data collection

Reference made to your letter requesting for permission to collect the data within University Teaching Hospital of Butare for your research proposal entitled **"Developing a tool to predict outcomes in surgical adult patients with sepsis at university teaching hospitals of Kigali (CHUK) and Butare (CHUB) "**, and based to the different approvals: **No. 403/CMHS IRB/2018** from Institution Review Board of University of Rwanda and **No: RC/UTHB/041/2018** from our research and Ethics committee, we are pleased to inform you that your request was accepted.. Please note that your final document will be submitted in our Research Office.

Sincerely,

Augustin SENDEGEYA
ctor General of CHUB

Director of Education and Research
Chairperson of Research Committee
esearch officer

HUB