MODIFIED SHOCK INDEX AND RED CELL DISTRIBUTION WIDTH AS A PREDICTOR OF MORTALITY IN SEPTIC PATIENTS IN THE MEDICAL CRITICAL CARE UNIT A FIVE-YEAR RETROSPECTIVE STUDY

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March, 2024, Addis Ababa, Ethiopia

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Vital Strategies

MODIFIED SHOCK INDEX AND RED CELL DISTRIBUTION WIDTH AS A PREDICTOR OF MORTALITY IN SEPTIC PATIENTS IN THE MEDICAL CRITICAL CARE UNIT

A Five-year retrospective study

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ACKNOWLEDGMENT

I wish to express sincere gratitude and appreciation to all those who have supported and contributed to developing the proposal and final thesis work.

Foremost, I extend heartfelt thanks to my advisors: Dr. Hanan Yesuf, Dr. Amsalu Bekele, Dr. Dawit Kebede, and Dr. Deborah A. Haisch. Their invaluable guidance, expertise, and unreserved support have played a crucial role, spanning from the formulation of the research proposal to the completion of the final thesis report.

Furthermore, I extend my appreciation to the entire Medical Intensive Care Unit (MICU) team and the staff in the patient chart room, whose assistance was indispensable in collecting all the necessary data.

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ABBREVIATION /ACRONYMS

AAU----------Addis Ababa University

APACHE ---------- Acute Physiology and Chronic Health Evaluation

AUC ---------- Area Under the Curve

BP ---------- Blood Pressure

CI ----------Confidence Interval

COVID-19 ---------- Coronavirus Disease 2019

DM ---------- Diabetes Mellitus

EPI-DATA ---------- Epidemiological Data

FiO2 ----------Fraction of Inspired Oxygen

GC ----------Gregorian Calendar

HR ---------- Heart Rate

HTN ---------- Hypertension

ICU----------Intensive Care Unit

IRB ---------- Institutional Review Board

MICU ---------- Medical Intensive Care Unit

MSI ---------- Modified Shock Index

PI ----------Principal Investigator

RDW ---------- Red Cell Distribution Width

ROC ---------- Receiver Operating Characteristic

RR ---------- Respiratory Rate

RVI ---------- Retroviral Infection

SD ---------- Standard Deviation

SI ---------- Shock Index

mSOFA ---------- Modified Sequential Organ Failure Assessment

OR ----------Odds Ratio

SPO2 ---------- Oxygen Saturation

SPSS ---------- Statistical Package for the Social Sciences

TASH ---------- Tikur Anbessa Specialized Hospital

WHO ---------- World Health Organization

ABSTRACT

Background: Sepsis remains a critical public health concern, marked by elevated mortality rates and a multifaceted clinical course. Identifying reliable predictors of patient outcomes is imperative for optimizing the care and treatment of septic individuals. Existing clinical parameters and scoring systems have demonstrated varying degrees of predictive accuracy in septic patients.

Objective: To investigate the individual and combined predictive utility of modified shock index (MSI) and red cell distribution width (RDW) in septic patients admitted to the medical intensive care unit of Tikur Anbessa Specialized Hospital in Addis Ababa, Ethiopia.

Methods: A retrospective observational study spanning four months (October 1, 2023GC, to January 2024GC) involved a systematic review of historical medical records for adult septic patients admitted to the medical intensive care unit from January 2019 to December 2023.

Results: Sepsis-related mortality was 40.9% (95% CI: 35.95-45.85). The results showed a notable link between MSI and mortality. Patients with an MSI greater than 1 had a mortality odd approximately 11.814 times higher compared to those with an MSI less than 0.7 (p=0.001). The study revealed a significant association between MSI and mortality; an MSI >1 was associated with 11.814 times increased mortality odds compared to an MSI <0.7 (p=0.001). RDW >14.5% was associated with .167 times higher odds of mortality than RDW <14.5% (p=0.001, OR= .167). The Modified SOFA is also associated with mortality, with higher scores >11 indicating an elevated risk of mortality (Exp(B) = 3.977, 95% CI [1.643, 9.626]. Combining MSI and RDW improved mortality prediction in septic patients (Exp(B) = .405, 95% CI [.215, .761]).

Conclusion: Our analysis identifies gender, modified SOFA score, MSI, and RDW as critical determinants of sepsis-related mortality. The combined consideration of MSI and RDW enhances mortality prediction in sepsis cases, contributing to a nuanced understanding of sepsis management.

Keywords: Sepsis, Modified Shock Index, Red Cell Distribution Width

1.0. INTRODUCTION

1.1. Statement of the Problem

Sepsis is a serious and potentially life-threatening medical condition where the body's response to an infection becomes unbalanced, resulting in organ dysfunction and a considerable risk of death. Despite progress in critical care, sepsis continues to pose a major global health challenge, causing significant levels of illness and death. (1)

Early identification and risk stratification of septic patients are essential for providing timely and appropriate interventions that can significantly impact patient outcomes. (2)

In Ethiopia, septic patients constitute a substantial portion of admissions to medical critical care units, and identifying reliable predictors of mortality in this specific patient population is crucial for timely and effective intervention. (3)

In resource-limited settings, such as Tikur Anbessa Specialized Hospital in Addis Ababa, Ethiopia, the management of septic patients poses a substantial burden on healthcare systems due to limited resources and problems in the early identification of those critical patients.

Existing clinical parameters and scoring systems have demonstrated varying degrees of predictive accuracy in septic patients. The Modified Shock Index (MSI) and Red Cell Distribution Width (RDW) have shown promise as potential predictors of mortality in various medical conditions, including sepsis, but their utility in the specific context of Tikur Anbessa Specialized Hospital's patient population remains underexplored. MSI, which incorporates heart rate and systolic blood pressure, offers a snapshot of cardiovascular function, while RDW serves as an indicator of systemic inflammation and oxidative stress. (4, 5)

However, its utility and effectiveness as a predictor of mortality in the specific context of the Medical Critical Care Unit at Tikur Anbessa Specialized Hospital have not been adequately explored.

The patient population, healthcare practices, and local factors in Addis Ababa, Ethiopia, may introduce unique variables that influence the predictive accuracy of these parameters.

This research aims to address this critical gap in knowledge by assessing the utility of MSI and RDW as predictors of mortality in septic patients within Tikur Anbessa Specialized Hospital's MICU. Through a comprehensive investigation, including clinical data analysis and outcome correlation, this study seeks to provide evidence-based insights that can inform clinical decision-making and improve patient outcomes in sepsis management.

By shedding light on the predictive value of MSI and RDW in this specific healthcare setting, this research strives to enhance the risk stratification of septic patients, ultimately leading to more effective interventions, improved resource allocation, and a potential reduction in mortality rates.

1.2. Literature Review

1.2.1. Sepsis and Its Global Impact

Sepsis is a major healthcare problem that affects millions of people worldwide each year, with high mortality rates. (6, 7)

According to the World Health Organization (WHO), sepsis contributes to nearly 20% of all global deaths, with an estimated 11 million sepsis-related deaths annually. (8)

Despite advances in critical care medicine, sepsis remains a significant global health concern, especially in low- and middle-income countries like Ethiopia. (9) It's crucial to accurately predict mortality in patients with sepsis to ensure timely interventions and enhance their overall outcomes. (2)

1.2.2. Mortality Prediction in Sepsis

Early identification of sepsis and accurate prediction of mortality are paramount for timely intervention and improved patient outcomes. Various scoring systems, including the Sequential Organ Failure Assessment (SOFA) and the Acute Physiology and Chronic Health Evaluation (APACHE) II, have been used to assess disease severity and predict outcomes. (10, 11) However, these models often require extensive data and may not be readily applicable in resource-limited settings. These limitations underscore the need for novel and context-specific predictors, particularly in resource-constrained healthcare settings.

1.2.3. The Modified Shock Index (MSI)

The Modified Shock Index (MSI), defined as heart rate divided by systolic blood pressure, is a simple and rapid parameter that reflects both cardiac and hemodynamic status. It reflects the relation between cardiac output and systemic vascular resistance. Understanding this relationship gives us valuable information about the patient's overall hemodynamic status. (12) Initially designed as a screening tool for trauma cases, it has been suggested as a means to predict mortality in patients with sepsis. (13, 14)

Several studies have investigated the utility of MSI in septic patients.

Research conducted in the United States in 2019 examined the shock index, modified shock index, and age shock index among adults admitted to a tertiary hospital. The study found that the mortality rate was 5.1%. However, for individuals with a shock index greater than 1.0, the mortality rate significantly increased to 11.3% ($p < 0.001$). Additionally, those with a modified shock index greater than 1.3 experienced a mortality rate of 10.3%, while those with a modified shock index greater than 1 had a mortality rate of 10.0% ($p < 0.001$). (15)

A study by Liu et al. (2012) found that an elevated MSI on admission was associated with increased mortality in septic patients. When MSI or SI was used instead of heart rate and blood pressure, MSI>1.3 or <0.7 served as e stronger predictor of death. MSI>1.3 showed as a predictor of mortality with OR 4.9 (3.6 -6.6, 95% CI). (16)

In a study conducted by Devendra Prasad, K. J. et al. (2021) among individuals with co-morbidities, the initial Modified Shock Index (MSI) value upon arrival at the emergency department showed reasonable predictive accuracy for the requirement of mechanical ventilation after 24 hours. This was evidenced by an area under the curve of 0.749 (95% CI: 0.600-0.897; p-value = 0.002) and a sensitivity of 68.75% in predicting mechanical ventilation after 24 hours when the MSI was 1.59 or higher. Among those without co-morbidities, the initial MSI value upon arrival at the emergency department also demonstrated fair predictive accuracy for the need for mechanical ventilation after 24 hours, with an area under the curve of 0.879 (95% CI: 0.770-0.988; p-value <0.001) and a sensitivity of 83.33% in predicting the requirement for mechanical ventilation after 24 hours when the MSI was greater than 1.67. (17)

Another study by Borah et al. Demonstrated the prognostic importance of MSI for the prediction of in-hospital mortality and it was found that MSI of 1.75 had a significant association for predicting in-hospital mortality. It has a sensitivity of 100% and specificity of 87.23% with PPV and NPV of 33.33% and 100% for prediction of in-hospital mortality. (18)

In a study conducted by Jayaprakash et al., out of 578 individuals meeting the inclusion criteria, 169 (29%) developed myocardial dysfunction, and 23 (4%) experienced myocardial depression. After adjusting for factors such as age, gender, Charlson score, and baseline APACHE 3 score, it was found that an MSI greater than 1.3 was associated with higher odds of myocardial dysfunction (odds ratio [OR] 1.10, 95% confidence interval [CI] 1.00-1.21; p=0.058) and depression (OR 1.28, 95% CI 1.07-1.53; p=0.007). Furthermore, these associations extended to ICU mortality (OR 1.17, 95% CI 1.04-1.32; p=0.011), hospital mortality (OR 1.13, 95% CI 1.02-1.25; p=0.025), and the SOFA score. (19)

Çakir et al. studied 172 patients with sepsis, finding significantly higher levels of Shock Index (SI), Modified Shock Index (MSI), and Age Shock Index (ASI) among those who died ($p < 0.05$). For SI, the area under the receiver operating characteristic (ROC) curve was 0.649 (95% CI = 0.573-0.720, $p = 0.0003$), with a cutoff value of 1.06 (sensitivity: 62%, 95% CI: 51-72.3; specificity: 67.44%, 95% CI: 56.5-77.2). For MSI, the area under the ROC curve was 0.585 (95% CI = 0.508-0.659, $p = 0.049$), with a cutoff value of 1.69 (sensitivity: 37.9%, 95% CI: 27.7-49; specificity: 82.5%, 95% CI: 72.9-89.9). For ASI, the area under the ROC curve was 0.613 (95% CI = 0.536-0.686, $p = 0.0078$), with a cutoff value of 87.42 (sensitivity: 40.2%, 95% CI: 29.9-51.3; specificity: 82.56%, 95% CI: 72.9-89.9). (20)

Another study, featured in the European Journal of Medical Research, explored the connections between non-invasive hemodynamic parameters and the mortality rates within three days and during hospitalization for patients diagnosed with septic shock. The study found that the mortality rates within three days and during hospitalization were 8.7% and 23.5%, respectively. Through multivariable logistic regression analysis, significant links were observed between pre-vasopressor Shock Index (SI), Modified Shock Index (MSI), and Delta Shock Index (DSI) and three-day mortality in septic shock patients necessitating vasopressors, even after adjusting for various factors (p-values for trend < 0.01). The Area Under the Curves (AUCs) for pre-vasopressor SI, MSI, and DSI were 0.746, 0.710, and 0.732, respectively, for predicting three-day mortality. Additionally, notable differences were noted in the trajectory of SI, MSI, and DSI over time between survivors and non-survivors at three days and during hospitalization for patients with septic shock requiring vasopressors (determined by repeated-measures ANOVA; inter-subjects difference $p < 0.001$). (21)

These findings suggest that MSI may have value in identifying septic patients at higher risk of adverse outcomes.

1.2.4. Red Cell Distribution Width (RDW)

RDW, which measures the variation in the size of red blood cells, is being recognized as a possible indicator of mortality risk in cases of sepsis. Higher RDW levels have been associated with inflammation, oxidative stress, and unfavorable outcomes among critically ill patients. (22) RDW's utility lies in its ability to provide insights into the patient's overall health and inflammatory status. Elevated RDW has been associated with poor outcomes in various medical conditions, including sepsis. (23)

A study conducted by Sadaka et al. (2012) revealed that higher RDW levels upon admission strongly predicted hospital mortality, with a notable increase in risk across different RDW quintiles after adjusting for various factors. For instance, compared to patients with RDW levels below 13.5%, those with RDW levels ranging from 13.5% to 15.5% had an odds ratio (OR) of 4.6 (95% confidence interval [CI], 1.0-23.4; p=0.06). Similarly, patients with RDW levels of 15.6% to 17.5%, 17.6% to 19.4%, and above 19.4% had progressively higher odds ratios of 8.0, 25.3, and 12.3, respectively, all relative to those with RDW levels below 13.5%. These associations were also significant for intensive care unit mortality. The receiver-operating characteristic area under the curve (AUC) analysis demonstrated that RDW had strong discriminative power for hospital mortality (AUC = 0.74), surpassing that of Acute Physiologic and Chronic Health Evaluation II (APACHE II) and sequential organ failure assessment (SOFA) scores alone. Moreover, when RDW was added to APACHE II, the AUC increased from 0.69 to 0.77. (24)

In a study conducted by Uffen et al., they found a significant association between RDW levels and both 30-day mortality and early clinical deterioration. The odds ratio (OR) for 30-day mortality was 1.15 (95% CI: 1.04-1.28), while for early clinical deterioration, it was 1.09 (95% CI: 1.00-

1.18). The area under the receiver-operating characteristic curve (AUROC) for RDW in predicting 30-day mortality was 0.66 (95% CI: 0.59-0.72), with an optimal cut-off value of 12.95%. Similarly, for early clinical deterioration, the AUROC was 0.59 (95% CI: 0.54-0.63), and the optimal cut-off value for RDW was 14.48%. (25)

In a study conducted in Nepal, it was found that RDW can moderately predict sepsis mortality. The analysis of RDW groups revealed varying mortality rates: no mortality was observed in the RDW < 13.1 group, 3.6% mortality in the 13.1 to 14 RDW group, 22.0% mortality in the 14 to > 15.6 RDW group, and 45.9% mortality in the > 15.6 RDW group. There was a significant difference in mortality between the 14 to > 15.6 and > 15.6 RDW subgroups, with p-values of 0.003 and 0.008, respectively. (26)

A study conducted in India found that the RDW value was notably elevated in patients with severe sepsis and non-survivors compared to survivors ($p < 0.0001$). The area under the receiver operating characteristic curve was determined to be 0.852 with a 95% confidence interval of 0.796-0.909, using an RDW threshold of 17.15. This yielded a sensitivity of 88.6% and a specificity of 63.5%. (27)

RDW's role as a predictor of mortality in septic patients has gained attention, but its specificity and sensitivity in this context require comprehensive evaluation.

1.2.5. Ethiopian Context

In Ethiopia, sepsis remains a significant cause of mortality and hospital admissions. (28)

Despite advances in sepsis management, Ethiopia continues to face high mortality rates attributed to sepsis. A study conducted in the intensive care units of Addis Ababa reported 28-day mortality rates of 41.8% for sepsis and 50.9% for septic shock, respectively. Male sex, a modified Sequential Organ Failure Assessment score ≥10 on day 1 of ICU admission, and comorbidity of HIV or malignancy were identified as independent predictors of 28-day mortality. (28)

Tikur Anbessa Specialized Hospital, being a prominent tertiary care center, holds a vital role in addressing matters related to sepsis. However, local data on predictors of mortality specific to septic patients in this setting are scarce.

A study by Middleton et al., evaluated the effect of a tailored sepsis treatment protocol on patient outcomes in the Tikur Anbessa Specialized Hospital, Ethiopia, and found that despite improvement, sepsis mortality rates remain high. (6)

Given the significance of sepsis in Tikur Anbessa Specialized Hospital and the need for more accessible and accurate predictors, this research aims to investigate the utility of the Modified Shock Index and Red Cell Distribution Width as predictors of mortality in septic patients.

While MSI and RDW have shown promise as a predictor of mortality in septic patients and other critical conditions, their utility in the specific context of Tikur Anbessa Specialized Hospital in Ethiopia remains unexplored. There is a critical knowledge gap regarding the performance of MSI and RDW as a predictor of mortality in septic patients within this setting.

Therefore, the use of MSI and RDW as a predictor of mortality in septic patients is a promising area of research that could potentially improve patient outcomes.

1.2.6. Conceptual Framework

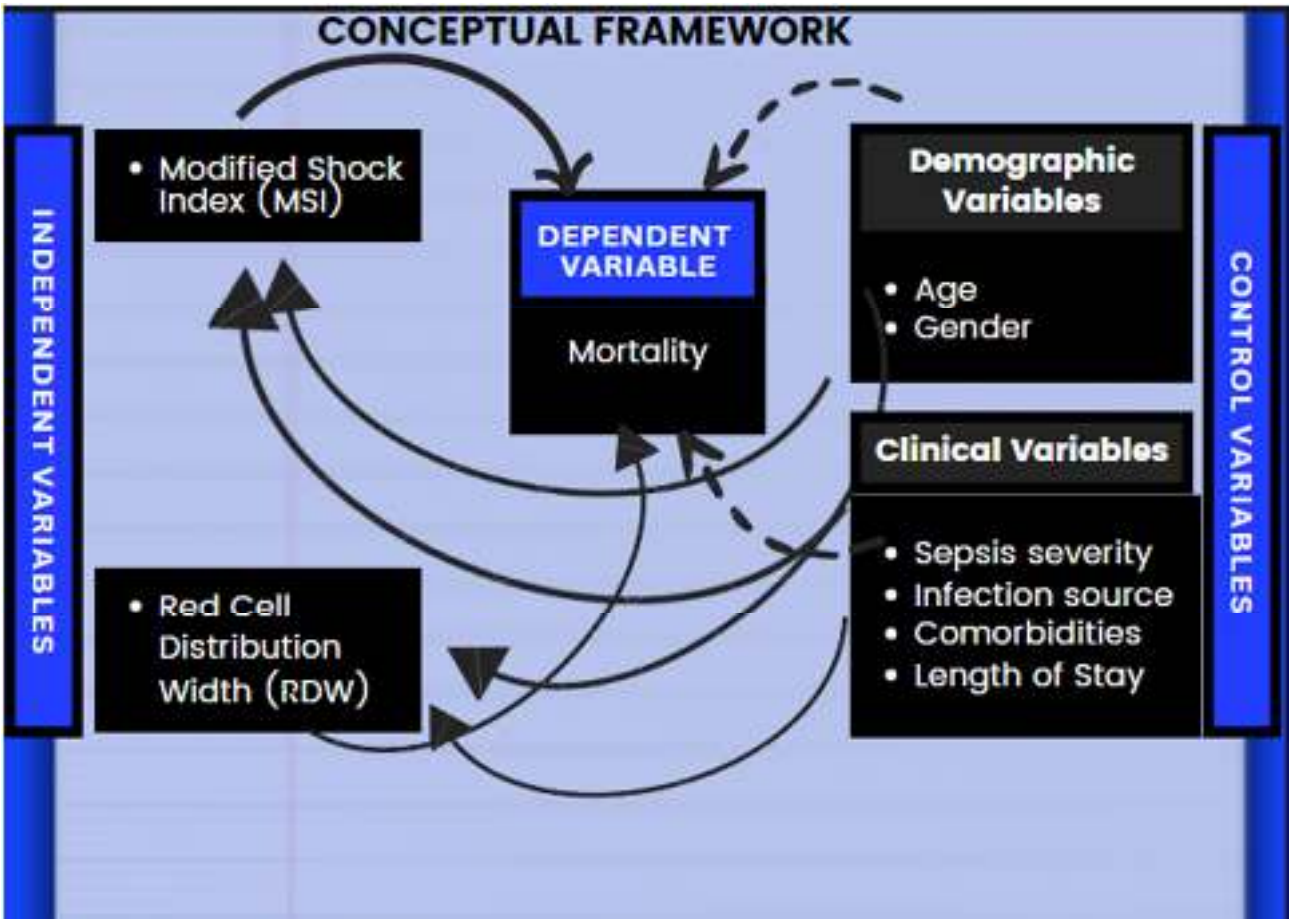

Figure 1. Conceptual Framework of the Modified Shock Index and Red Cell Distribution Width as A Predictor of Mortality in Septic Patients in The Medical Intensive Care Unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2023.

1.3. Significance of the Study

This study investigating the utility of the MSI and RDW as predictors of mortality in septic patients at Tikur Anbessa Specialized Hospital's Medical Critical Care Unit in Addis Ababa, Ethiopia, holds significant importance on several fronts.

1.3.1. Improved Patient Outcomes

Sepsis remains a significant contributor to illness and death globally, including in Ethiopia. Predicting mortality promptly and accurately is vital for tailoring the right interventions and enhancing patient outcomes. If the Modified Shock Index and RDW prove to be effective predictors, they can aid clinicians in identifying high-risk patients promptly, facilitating timely interventions, and potentially reducing mortality rates. (1)

1.3.2. Resource Allocation

The efficient allocation of limited healthcare resources is a challenge faced by many hospitals, particularly in low-resource settings. Accurate predictors of sepsis mortality can assist healthcare providers in prioritizing patients in need of more intensive care and resource allocation, optimizing the utilization of critical care resources. (28)

1.3.3. Reduction in Healthcare Costs

Sepsis places a substantial economic burden on healthcare systems due to prolonged hospital stays and intensive care requirements. Effective predictors can potentially lead to shorter hospitalizations and more targeted therapies, reducing the overall cost of sepsis management. (29)

1.3.4. Contribution to Global Sepsis Research

Sepsis is a global healthcare concern, and research conducted in diverse settings, such as Tikur Anbessa Specialized Hospital, contributes to the broader understanding of sepsis epidemiology and management. The findings of this study can add to the growing body of literature on sepsis predictors, potentially influencing international guidelines and best practices.

2.0. OBJECTIVE

2.1. General Objective

To investigate the utility of the Modified Shock Index and Red Cell Distribution Width as predictors of mortality in septic patients admitted to the Medical Critical Care Unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

2.2. Specific Objective

To assess the relationship between the Modified Shock Index and mortality outcomes among septic patients in the Medical Critical Care Unit of Tikur Anbessa Specialized Hospital.

To investigate the relationship between Red Cell Distribution Width (RDW) levels and mortality among septic patients admitted to the Medical Critical Care Unit at Tikur Anbessa Specialized Hospital.

To investigate whether combining the MSI and RDW improves the predictive capability for mortality in septic patients compared to using either parameter alone.

3.0. METHODOLOGY

3.1. Study Area

The study was conducted in the Medical Critical Care Unit of Tikur Anbessa Specialized Hospital, which is located in Addis Ababa, the capital city of Ethiopia. Tikur Anbessa Specialized Hospital, often referred to as "Black Lion Hospital," is the largest and most prominent tertiary referral hospital in Ethiopia. It serves as a major hub for medical education, patient care, and research in the country. It serves as a major healthcare center for the city of Addis Ababa and provides tertiary care services to patients from across the country. (30)

Tikur Anbessa Specialized Hospital is situated in the Kirkos sub-city of Addis Ababa and is affiliated with Addis Ababa University's School of Medicine. The hospital plays a critical role in delivering specialized medical care, particularly in the fields of internal medicine, surgery, pediatrics, Obstetrics & and gynecology, and critical care. The Medical Critical Care Unit of Tikur Anbessa Specialized Hospital is a specialized facility dedicated to the care of critically ill patients. It is equipped with advanced medical technology and staffed by a multidisciplinary team of healthcare professionals, including critical care physicians, nurses, and support staff. The MICU has more than 8 beds and provides intensive care for patients with a range of medical conditions, including sepsis, respiratory failure, and other life-threatening illnesses. (30)

The patient population at Tikur Anbessa Specialized Hospital's MICU is diverse, reflecting the cosmopolitan nature of Addis Ababa. The hospital serves both urban and rural populations from various regions of Ethiopia, encompassing a wide range of socioeconomic and cultural backgrounds.

Tikur Anbessa Specialized Hospital is selected as the study area due to its significance in the Ethiopian healthcare system and its substantial patient population, including a significant number of septic patients. The hospital's diverse patient demographics and healthcare infrastructure make it an ideal setting to investigate the applicability of the Modified Shock Index and Red Cell Distribution Width as predictors of mortality in septic patients within the context of Ethiopia.

3.2. Study Period

The study was carried out over four months from October 2023 to January, 2024GC.

3.3. Study Design

A retrospective observational study design was employed to assess the utility of the Modified Shock Index and Red Cell Distribution Width as predictors of mortality in septic patients previously admitted to the Medical Critical Care Unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

3.4. Source Population

All adults with sepsis who were admitted to the Medical Critical Care Unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, from January 2019 to December 2023.

3.5. Study Population

Adult septic patients (aged 18 and above) who meet the inclusion and exclusion criteria during the specified period, from January 2019 to December 2023. These patients were selected from the source population based on their medical records.

3.5.1. Inclusion Criteria

- Patients with age 18 and above.
- Patients admitted to the Medical Critical Care Unit of Tikur Anbessa Specialized Hospital in the period of the study.
- Patients with a confirmed sepsis in their historical medical records during their admission to the Medical Critical Care Unit of Tikur Anbessa Specialized Hospital.
- Patients with complete medical records are available for analysis.

3.5.2. Exclusion Criteria

- Patients with pre-existing conditions or comorbidities that significantly affect the MSI (Fluid loss, Hemorrhage, Pregnancy) or Red Cell Distribution Width (any level of Anemia, Sickle cell disease, Rheumatoid Arthritis) independently of sepsis.

3.6. Sample size and sampling procedure

3.6.1. Sample Size Determination

We used a confidence level of 95%, a margin of error of 5%, and an estimated mortality rate of 41.8% among septic patients(28), using the formula for estimating sample size for a proportion (binomial proportion confidence interval):

$$n = \frac{Z^2 \cdot p \cdot (1-p)}{E^2}$$

Where: Z= The desired confidence level is typically set at 95%.

P= estimate Mortality Rate: 41.8%

E= Margin of Error: 5%

$$= \frac{(1 \cdot 96)^2 \cdot 0.418 \cdot (1-0.418)}{(0.05)^2} = 374$$

3.6.2. Sampling Method

A non-probability convenience sampling method was employed, in which all eligible patient records from January 2019 to December 2023 that meet the inclusion criteria were included.

3.7. Study Variables

3.7.1. Dependent Variables

- ☞ Mortality

3.7.2. Independent Variables

- ☞ Modified Shock Index (MSI)
- ☞ Red Cell Distribution Width (RDW)

3.7.3. Control Variables

Demographic Variables:

- Age
- Gender

Clinical Variables:

- Sepsis severity
- Infection source
- Organism identified
- Resistance pattern
- Comorbidities
- Length of Stay

3.8. Operational definitions

ICU Mortality: refers to the outcome of interest, specifically whether a patient survived or died in the Medical Critical Care Unit.

Mortality assessed based on the patient's final disposition recorded in their medical records.

Modified SOFA Score: This is used to diagnose and evaluate the severity of organ dysfunction in patients with sepsis. It is calculated by evaluating the functional status of five organ systems: Respiratory system (SpO_2/FiO_2), Cardiovascular system (blood pressure), Central Nervous System (Glasgow Coma Score), Liver (Scleral icterus or jaundice), Renal (renal function test). (31)

Modified Shock Index: is calculated as the ratio of heart rate to mean arterial blood pressure. (32)

Modified Shock Index = Heart Rate (beats per minute) / Mean Arterial Pressure

The accepted value of MSI varies across different studies. However, the normal range for the MSI is generally considered to be 0.9 or 1.0. MSI greater than 1.0 is associated with increased mortality and morbidity. (32, 33)

Red Cell Distribution Width: is a measure of the variation in the size of red blood cells in a blood sample.

The cutoff value of RDW for sepsis mortality evaluation varies among studies and ranges from 12.95% to 17.0%. The optimal cutoff value for risk stratification is 14.5%. (34)

3.9. Data Collection Procedures

3.9.1. Data Collection

All necessary ethical approvals were obtained from the hospital's Institutional Review Board (IRB) to access and use patient medical records for research purposes. The source of patient data was identified, which includes the historical medical records of septic patients admitted to the Medical Critical Care Unit of Tikur Anbessa Specialized Hospital during the specified study period.

Applying the predefined inclusion and exclusion criteria, eligible patient records were identified.

A database of eligible patient records that meet the inclusion criteria was created. Document unique identifiers were created for each patient to avoid duplication and ensure traceability.

For each eligible patient record, the required data was systematically extracted using the data extraction form.

3.9.2. Data Quality Management

The study used standardized data collection forms to ensure that all relevant data points were captured.

The collected data was entered into a secure database with appropriate access controls. Data management procedures, such as validation checks, have been implemented to ensure data accuracy, completeness, and consistency.

Data quality control checks have been conducted at different stages of the study, including during data collection, data entry, and data analysis.

To reduce the risk of data entry errors, a double data entry process was implemented.

3.9.3. Data processing and analysis

The data collected was double-entered into EPI-DATA (version 4.1) software to minimize data entry errors. Then it was exported to Statistical Package for Social Sciences (SPSS) software version 27 for analysis. Descriptive statistics were generated to provide an overview of the dataset. Summary statistics, including means, medians, standard deviations, and percentiles, for continuous variables were generated. Frequency tables were created for categorical variables.

Bivariate analyses were performed to explore relationships between independent variables and the dependent variable. Multivariate statistical techniques were used to examine the combined effects of multiple independent variables on mortality. The variables from bi-variable analysis with a P-value < 0.25 were regressed in multivariate analysis. The results were presented in the form of tables, graphs, and charts. The study findings were interpreted in the context of the current literature and the study objectives.

4.0. ETHICAL CONSIDERATION

This study was conducted by the principles of the Declaration of Helsinki. Approval was obtained from the Institutional Review Board of the Internal Medicine Department of Addis Ababa University College of Medicine and Hearth Sciences.

A comprehensive research protocol was presented to the IRB detailing the study objectives, methods, data collection, and data management procedures.

The study participants' privacy was respected throughout the study.

The data collected was kept confidential, and only authorized personnel had access to the data.

Any data shared with collaborators or other researchers was de-identified to protect the privacy of the study participants.

5. RESULT

A thorough review of patient records was carried out for the period, from January 2019 to December 2023 in the ICU. It was found that there were a total of 1038 admissions during this period. Out of these admissions, 572 patients (55.1%) had sepsis when they arrived or were diagnosed with sepsis while being treated in the critical care unit.

To ensure that the study group was consistent, strict criteria for inclusion were applied. These criteria aimed to exclude patients with missing data or incomplete medical records. As a result, a total of 374 patients were chosen to be included in the study (See Figure 2).

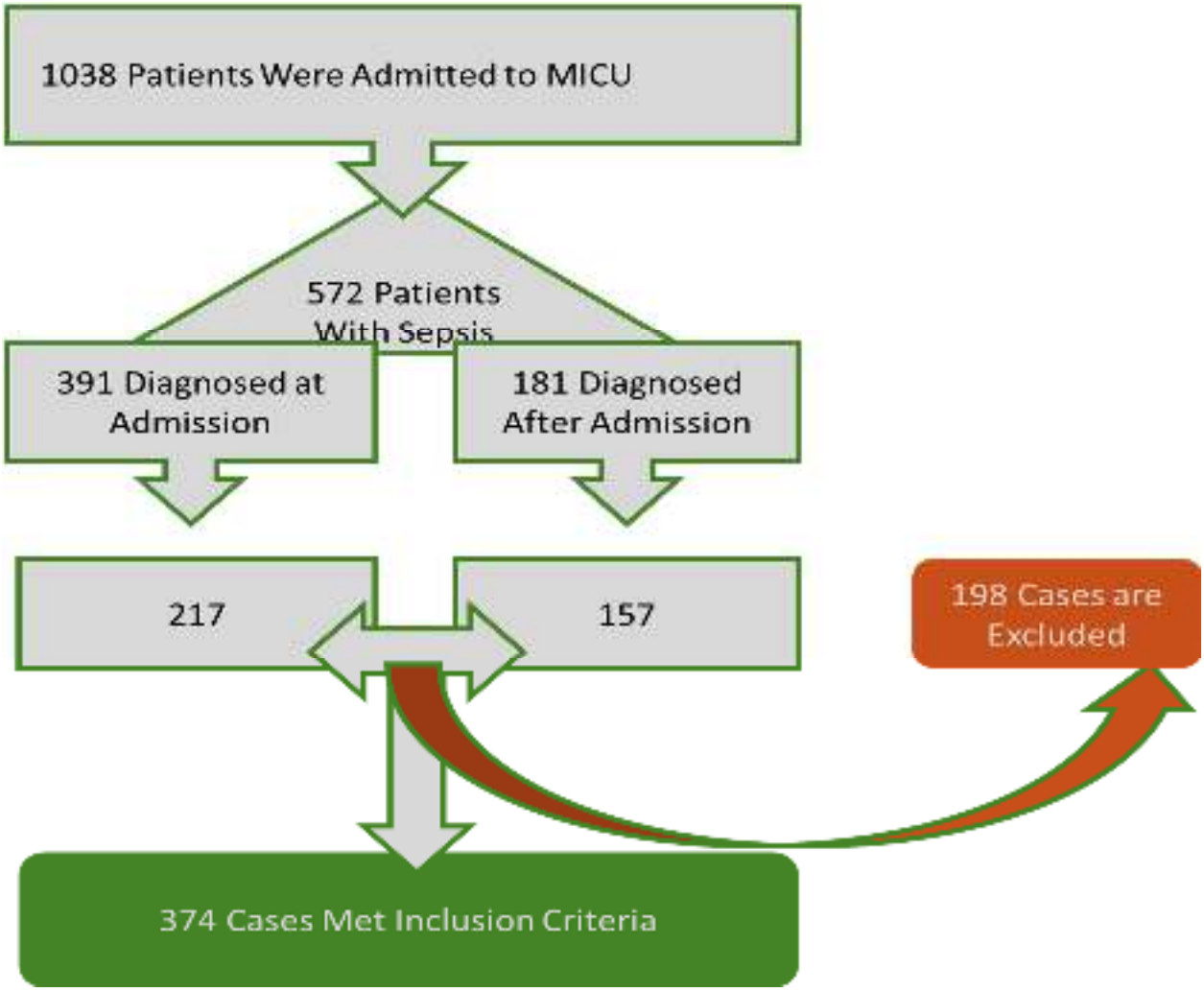

Figure 2. Study profile of predictive utility of Modified Shock Index and Red Cell Distribution Width for Mortality in Septic Patients in the Medical Critical Care Unit of Tikur Anbessa Specialized Hospital, 2024.

5.1. Demographic Characteristics of the Study Population

The analysis conducted on septic patients admitted to the Medical Critical Care Unit provides a comprehensive understanding of the cohort. The age distribution reveals a diverse group, with the majority of patients falling between the ages of 35 and 49, accounting for 32.9% of the cohort. In terms of gender, males make up the majority of the cohort at 53.2%. (See Table 1).

Table 1. Demographic Characteristics of Septic Patients Admitted to the Medical Intensive Care Unit (n=374)

Variables	Frequency	Percent
Age in Years		
18-34	112	29.9
35-49	123	32.9
50-64	66	17.6
65-74	48	12.8
75-84	23	6.1
>/=85	2	.5
Gender		
Male	199	53.2
Female	175	46.8

5.2. Clinical Characteristics of the Study Population

Patients' stay at the ICU varies, with an average of 13.98 days (median 12.00 days) and a moderate standard deviation of 9.645. A significant proportion (42.0%) have a stay of seven days or less. Comorbidities are common (52.9%), the most frequent being retroviral infection (10.2%). The main cause of sepsis is chest infection which accounts for up to 45.2% of cases and is predominantly acquired from the community by about 58%. Modified SOFA scores show different levels of organ dysfunction with more than half having a Shock Index greater than 0.7. Also, increased RDW (>14.5%) was seen in 58.3% of patients. Microbiologic cultures showed various pathogens, Acinetobacter being the most prevalent among them all. In contrast, no microbiologic culture was found in a notable percentage (38.8%). (See Figure 3 and Table 2).

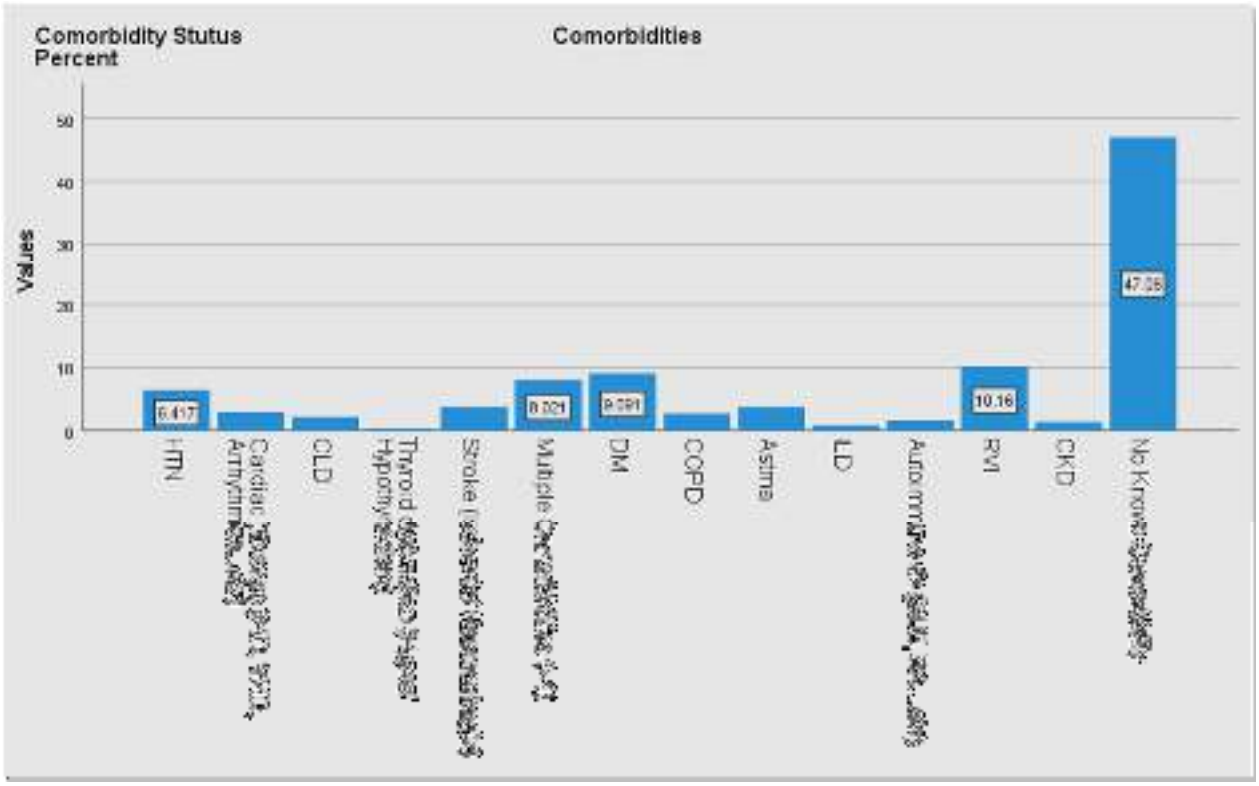

Figure 3. Comorbidity Status of Septic Patients Admitted to the Medical Intensive Care Unit (n=374)

Table 2. Clinical Information of Septic Patients Admitted to the Medical Intensive Care Unit (n=374)

Variables	Frequency	Percent
Length of Hospital Stay		
Up to 7 days	157	42.00
>7 days	217	58.00
Focus of Sepsis		
Chest	169	45.19
GI	89	23.80
GUT	22	5.88
Skin and Soft Tissue	9	2.41
Unknown	27	7.22
CNS	5	1.34
Surgical Site	21	5.61
Multiple Site	32	8.56
Source of Infection		
Community-Acquired	217	58.00
Nosocomial	157	42.00
Modified SOFA score		
0-7	174	46.5
8-11	119	31.8
>11	81	21.7
Modified Shock Index		
<0.7	76	20.3
0.7-1	127	34
>1	171	45.7
RDW		

	>14.5%	218	58.3
	</= 14.5%	156	41.7
	Microbiologic Culture		
	Acinetobacter Spp	34	9.10
	Pseudomonal Spp	10	2.70
	Klebsiella Pn.	31	8.30
	E. Coli	4	1.10
	Enterobacter Spp	4	1.10
	Citrobacter	2	.50
	No Growth	144	38.50
	No Culture	145	38.80

5.3. Clinical Outcome of the Study Population

The analysis of patient outcomes shows a comprehensive insight into the distribution of results, underscoring that the majority of individuals recover from their critical illness. In our study, the mortality rate associated with sepsis was determined to be 40.9%, with a 95% confidence interval spanning from 35.95% to 45.85% (See Figure 4).

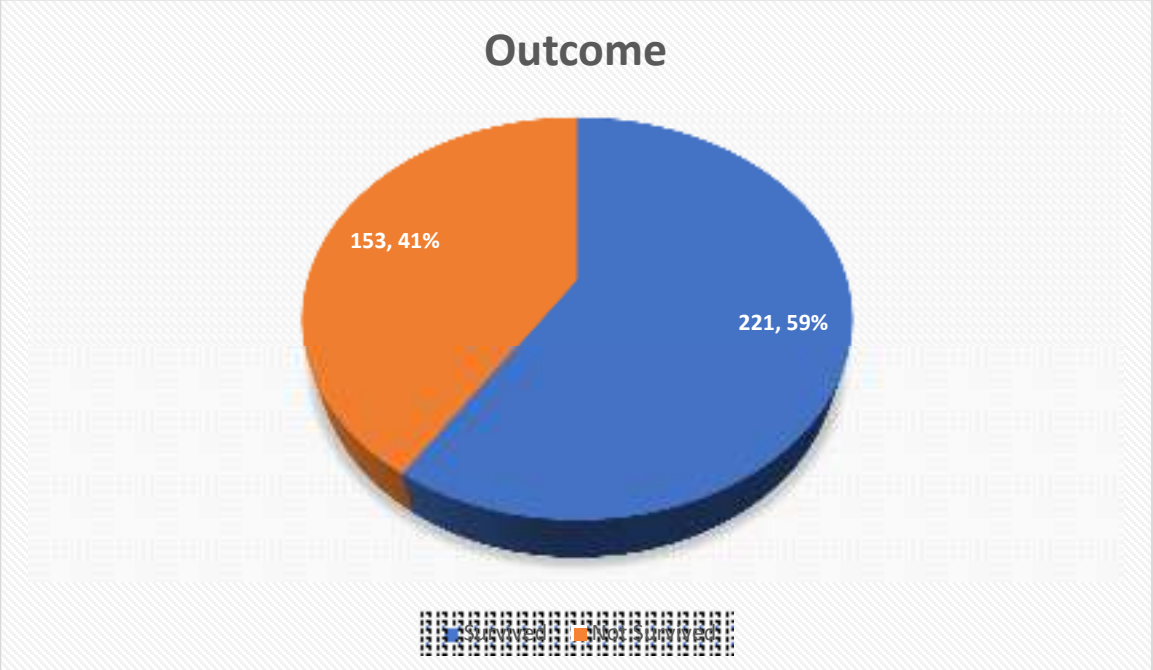

Figure 4. Outcome among septic patients admitted to the Medical Intensive Care Unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia 2024. (N=374)

5.4. Factors Associated with Sepsis Associated Mortality

Binary logistic regression analysis was conducted to assess the association between each explanatory variable and the outcome of sepsis. Bi-variable analysis revealed that gender, the focus of sepsis, modified SOFA score, modified shock index, red cell distribution width, and interventions administered are associated with the outcomes of septic patients.

In the multi-variable analysis, when variables from bi-variable analysis with a P-value < 0.025 were regressed, gender emerged as a significant determinant. Males exhibited an increased likelihood of mortality compared to females (Exp(B) = 12.72, 95% CI [5.95, 27.19]). The Modified SOFA score was found to be a significant predictor, with higher scores above 11 indicating an elevated risk of mortality (Exp(B) = 3.98, 95% CI [1.64, 9.626]). Additionally, the Modified Shock Index above 1 demonstrated a significant association with mortality (Exp(B) = 11.814, 95% CI [2.785, 50.111]). RDW found as a valuable prognostic biomarker, with higher values above 14.5% linked to an increased likelihood of mortality (Exp(B) = .167, 95% CI [.060, .464]) (See Table 5.3).

Furthermore, the combination of MSI and RDW yields an improved mortality prediction, indicated by a P value of 0.005 and an odds ratio (Exp(B) = .405, 95% CI [.215, .761]) (See Table 5.4).

Table 3. Bivariable and multivariable logistic regression analysis of septic patients admitted to the Medical Intensive Care Unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia 2024.

Variables	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
Gender	2.543	.388	43.018	1	.000	12.717	5.948	27.190
Focus of Sepsis								
Chest			7.295	7	.399			
Gastrointestinal	-.468	.544	.739	1	390	.626	.216	1.819
Genitourinary	-.955	.662	2.082	1	.149	.385	.105	1.408
Skin & Soft Tissue	-.092	.866	.011	1	.916	.913	.167	4.982
Unknown Origin	-19.828	11287.961	.000	1	.999	.000	.000	.
CNS	.409	.816	.252	1	.616	1.506	.305	7.447
Surgical Site	-2.111	1.479	2.038	1	.153	.121	.007	2.198
Multiple sites	-.025	.879	.001	1	.978	.976	.174	5.469
Modified SOFA								
0-7			14.244	2	.001			
8-11	-.280	.388	.520	1	.471	.756	.353	1.617
>11	1.380	.451	9.366	1	.002	3.977	1.643	9.626
Modified Shock Index								
<0.7			14.545	2	.001			
0.7-1	.781	.576	1.837	1	.175	2.183	.706	6.751
>1	2.469	.737	11.219	1	.001	11.814	2.785	50.111
RDW >14.5%	-1.791	.522	11.753	1	.001	.167	.060	.464
Interventions								

Resuscitation + Antibiotics			28.419	3	.000			
Plus, Vasopressor/s	-1.166	1.859	.393	1	.531	.312	.008	11.919
Plus, Corticosteroid	-1.347	1.773	.577	1	.447	.260	.008	8.395
Plus, Invasive Ventilation	1.004	1.790	.315	1	.575	2.729	.082	91.085
MSOFAvMSI	-.116	.221	.276	1	.600	.890	.577	1.373
MSIvRDW	-.904	.322	7.897	1	.005	.405	.215	.761
RDWvMSOFA	-.886	.429	4.258	1	.039	.412	.178	.956
RDWvMSOFAvMSI	.437	.285	2.341	1	.126	1.547	.885	2.707

5.5. Area Under the Curve Analysis of the Factors Associated with Sepsis Mortality

The discriminatory performance of the Modified Shock Index stands out prominently with an Area Under the Curve (AUC) value of 0.694, indicating a notable ability to distinguish between outcomes when compared to the other variables under consideration. Likewise, the Modified SOFA score exhibits moderate discriminatory ability with an AUC value of 0.591. Red Cell Distribution Width also shows moderate discriminatory capability, although slightly less, with an AUC value of 0.565. Therefore, the AUC analysis highlights the dominance of the Modified Shock Index in predictive discrimination, with the Modified SOFA score and Red Cell Distribution Width following in decreasing order of discriminatory ability. (See Table 4)

Table 4. Area Under the Curve Analysis of the Factors Associated with Mortality in septic patients admitted to the Medical Intensive Care Unit

Area Under the Curve					
				Asymptotic 95% Confidence Interval	
Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Lower Bound	Upper Bound
Modified SOFA score (mSOFA)	.591	.031	.003	.531	.652
Modified Shock Index	.694	.027	.000	.640	.748
Red Cell Distribution Width (RDW, %)	.565	.030	.032	.507	.624
MSIvRDW	.479	.030	.481	.420	.538

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

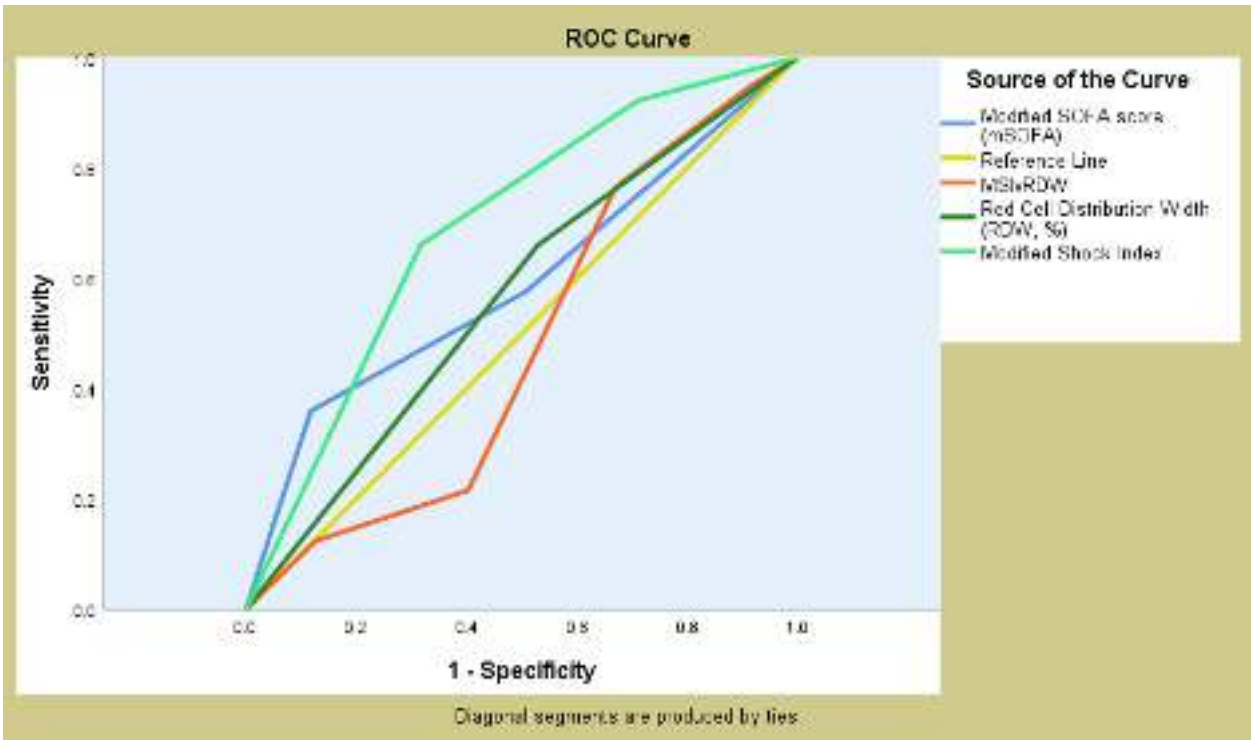

Figure 5. Receiver Operating Characteristic (ROC) curve of the Factors Associated with Mortality in septic patients admitted to the Medical Intensive Care Unit

6. DISCUSSION

The objective of this study was to identify the impact of the modified shock index and red cell distribution width, both individually and in combination, on the outcomes of septic patients. Our findings indicate a mortality rate of 40.9% with a 95% confidence interval of 35.95-45.85. Importantly, we observed statistically significant associations between gender, modified SOFA score, Modified Shock Index, and RDW with the mortality outcome.

The mortality rate observed in our study diverges from findings in various Ethiopian studies, such as Mulatu et al.'s investigation on sepsis 28-day mortality rates in Addis Ababa intensive care units, which documented a rate of 41.8%. (3, 35) Moreover, our research reveals a higher mortality rate compared to a recent study by Worku et al. on Epidemiology and Outcomes of Critical Illness and Novel Predictors of Mortality in an Ethiopian Medical Intensive Care Unit. (36). Nevertheless, it is important to highlight that our recorded mortality rate for sepsis exceeds the global estimate given by the World Health Organization (WHO), where sepsis contributes to around 20% of all worldwide deaths. (8) Possible rationales for this disparity may include advancements in critical care medicine and variations in sample sizes utilized across studies.

In our study, we observed a higher likelihood of mortality among males compared to females ((Exp(B) = 0.344, 95% CI [.181, 0.656]). This finding aligns with the study conducted by Mulatu et al in Addis Ababa ICUs. (3) Some studies have reported no significant differences in mortality between genders. Conversely, studies that do identify gender-based differences often underscore the importance of considering the interplay of biological, genetic, and environmental factors in shaping these outcomes. (37)

The Modified Sequential Organ Failure Assessment (mSOFA) score has become a crucial instrument for assessing organ dysfunction severity in septic patients, offering vital prognostic information. Our study further underscores the importance of mSOFA as a reliable predictor of mortality in sepsis, aligning with existing literature that emphasizes its efficacy in risk assessment. Notably, patients with mSOFA scores exceeding 11 demonstrated significantly heightened mortality risks (Exp(B) = 3.98, 95% CI [1.64, 9.626]), consistent with previous research illustrating a positive association between elevated mSOFA scores and adverse outcomes in sepsis. (11, 31)

Our study delves into the significance of MSI, which combines heart rate and mean arterial pressure, in detecting individuals with an increased risk of adverse outcomes during sepsis. We found a notable association between patients with an MSI greater than 1 and elevated mortality rates (Exp(B) = 11.814, 95% CI [2.785, 50.111]). These findings align with conclusions drawn in previous literature across different medical conditions. (16) Borah et al.'s study further underscores the prognostic importance of MSI, highlighting a significant association with in-hospital mortality at an MSI threshold of 1.75. (18) The MSI's ability to indicate hemodynamic compromise highlights its usefulness as an important tool for categorizing risk. A key advantage of MSI is its simplicity in calculation, as it only requires basic vital sign measurements, making it easy to use. This makes it a valuable tool for quick assessment in diverse healthcare environments, especially in resource-constrained settings.

RDW, a routine part of a complete blood count (CBC), is recognized as a potential predictor of outcomes in different medical conditions, including sepsis. Our research identified an RDW >14.5 as an additional predictor of mortality, consistent with numerous studies. This discovery aligns with a study by Haisch et al. on illness severity scores in an Ethiopian medical intensive care unit within the same setup. (38) Similarly, research by Sadaka et al. (2012) emphasized the predictive value of elevated RDW upon admission for hospital mortality. (24) Additionally, Uffen et al.'s study revealed a significant link between RDW levels and 30-day mortality, (25) while a study in Nepal demonstrated the reasonable efficacy of RDW in predicting sepsis mortality. (26) Moreover, an Indian study observed significantly higher RDW values in patients with severe sepsis and non-survivors compared to survivors. (27)

Importantly, our research uncovers a synergistic impact when simultaneously evaluating MSI and RDW in mortality prediction. The joint assessment demonstrates that the coexistence of elevated MSI and RDW correlates with a higher mortality risk. This implies that incorporating both hemodynamic and hematological factors improves the predictive ability for septic outcomes. Notably, as far as we are aware, there is no prior study comparing these two variables.

In our detailed examination, we found that various factors including age, length of stay, focus of sepsis, comorbidity, source of infection, microbiological culture, and resistance pattern did not show a statistically significant correlation with mortality. Unlike some prior studies, (39) our research didn't find age to be a significant predictor of mortality among septic patients. While age is often considered an important prognostic factor, the lack of statistical significance in our analysis highlights the importance of a comprehensive understanding of sepsis.

6.1. Strength of the Study

The study's primary strength lies in its thorough and detailed examination of sepsis outcomes within a medical ICU environment. By utilizing a substantial dataset covering five years (January 2019 to December 2023), the study gains strength and offers a comprehensive insight into patient demographics, clinical features, and results. The stringent adherence to inclusion criteria guarantees the uniformity of the study group, enhancing the credibility of the results.

By integrating a range of variables encompassing demographic details, clinical indicators, and interventions, a detailed examination of sepsis cases is made possible. Employing statistical techniques like logistic regression aids in pinpointing key mortality predictors, thereby enriching the current body of knowledge concerning sepsis outcomes.

Furthermore, the study employs a multidimensional approach by considering individual variables and exploring the combined effects of the variables. This comprehensive analysis adds depth to understanding mortality predictors in septic patients.

The detailed presentation of results through tables and figures enhances the clarity and accessibility of the findings. Moreover, the inclusion of a visual representation of the patient selection process and outcomes profile adds transparency to the research methodology.

6.2. Limitation of the study

Although our research offers valuable insights into mortality predictors in sepsis, it is crucial to recognize limitations that may impact the applicability and interpretation of the results.

The retrospective design of this study poses inherent limitations. Relying on historical data collected from patient records may introduce selection biases, missing data issues, and limited control over data quality.

Conducted within a single medical institution, the study's external validity is constrained. Patient demographics, disease presentations, and treatment practices may differ across healthcare settings, limiting the generalizability of our findings to a broader population.

The sample size, while substantial, may not fully capture the heterogeneity of septic patients.

Our study focused on a specific set of variables related to hemodynamics, hematological markers, comorbidities, and interventions. While these factors are clinically relevant, the omission of other potential contributors, such as genetic factors or specific treatment protocols, limits the comprehensiveness of our predictive models.

The study period spans from January 2019 to December 2023, during which sepsis management practices may have evolved.

The research duration covers from January 2019 to December 2023, a period coinciding with the COVID-19 pandemic, likely influencing the rates of medical ICU admissions and mortality.

7. CONCLUSION

In summary, this study looks at what influences mortality in septic patients at the Medical Critical Care Unit of Tikur Anbessa Specialized Hospital in Addis Ababa, Ethiopia, from January 2019 to December 2023. We found several patterns as well as key factors that influence sepsis management.

Our findings suggest that sex, modified SOFA score, modified shock index, and red cell distribution width (RDW) are key factors in sepsis-related deaths. These factors affect patient outcomes differently, showing that predicting sepsis outcomes is complex. Interestingly, we discovered a combined effect of modified shock index and RDW that adds new insights to predicting sepsis outcomes.

8. RECOMMENDATIONS

8.1. Recommendations for the Clinicians

The study underscores the significance of using prognostic indices, such as the modified SOFA and shock index, and RDW, in terms of predicting sepsis-related mortality. Thus, clinicians can include validated tools in their regular assessments and, therefore, stratify risks and offer appropriate interventions more expediently.

Healthcare professionals are advised to employ a comprehensive and synergistic approach in evaluating patients with sepsis. By considering the combined impact of variables such as MSI and RDW, alongside other pertinent factors, the precision of mortality predictions can be improved, thereby facilitating more nuanced clinical decision-making.

8.2. Recommendation For the Researchers

Researchers are encouraged to include new biomarkers in their research on sepsis. It is essential due to the dynamic nature of sepsis, and the constant development of new sepsis biomarkers allows researchers to adjust their predictive models. The identification of new markers improves the prediction outcomes and assists in developing customized sepsis interventions.

Future research should also strive for the involvement of multiple centers to increase the generalizability of results.

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ANNEX

Annex 1. Structured Data Extraction Form

Study Title: Predictive Utility of Modified Shock Index and Red Cell Distribution Width for Mortality in Septic Patients at Tikur Anbessa Specialized Hospital's Medical Critical Care Unit, Addis Ababa, Ethiopia

Section I: Patient Information

1. Patient Identification Number: _____
2. Age (years): _____
3. Gender: Male ☐ Female ☐
4. Date of Admission to ICU: [DD/MM/YYYY] _____
5. Date of Discharge/Outcome: [DD/MM/YYYY] _____
6. Length of stay in the ICU in days: _____
7. Length of stay in the hospital in days: _____

Section II: Clinical Information

8. Vital Signs (at diagnosis of sepsis):

HR: _____ BP: _____ RR: _____ Temperature: _____ SPO2: _____

9. Source of infection: Community-acquired ☐ Nosocomial ☐
10. mSOFA Score at initial diagnosis: _____
11. Modified Shock Index at diagnosis of sepsis: _____
12. Red Cell Distribution Width (RDW, %) at diagnosis of sepsis: _____
13. White Blood Cell Count (cells/μL) at diagnosis: _____
14. Focus of Sepsis: ☐ ☐GI ☐ Chest ☐ GUT ☐Surgical Site ☐Skin and ☐ Soft Tissue ☐CNS ☐Unknown focus ☐ Multiple site

15. Any micro-organisms identified from culture and Site? _____

16. Resistance Pattern of the identified organism: ☐ 1-2 drugs resistant ☐ 3 or more drug-resistant

17. Comorbidities: ☐ HTN ☐ DM ☐ RVI ☐ Others _____

18. Interventions/ Treatment: ☐ Antibiotics ☐ Fluid Resuscitation ☐ Vasopressors ☐ Steroid ☐ Mechanical Ventilation

Section III: Outcome

19. Outcome the patient: ☐ Survived ☐ Not survived

20. Cause of death (if not survived): Sepsis-related ☐ Not sepsis-related

Section IV: Data Collector Information:

Name: _____ Date: _____ Signature: _____

Annex 2. Instruments Used In This Study

Annex 2.1. Modified Sequential Organ Failure Assessment (mSOFA) Score

RESPIRATORY		
SPO2/FIO2	>400 0	**0**
	>315 to ≤400	**1**
	>235 to ≤315	**2**
	>150 to ≤235	**3**
	≤150	**4**
LIVER		
SCLERAL ICTERUS OR JAUNDICE PRESENT	Yes= 3	**NO= 0**
CARDIOVASCULAR		
BLOOD PRESSURE	No Hypotension	**0**
	MAP < 70mmHg	**1**
	Dopamine ≤5 or Dobutamine (any dose)	**2**
	Dopamine >5, Epinephrine ≤0.1, or NE ≤0.1	**3**
	Dopamine >15, Epinephrine >0.1, or NE >0.1	**4**
CNS		
GCS	15	**0**
	13-14	**1**
	10-12	**2**
	6-9	**3**
	<6	**4**

RENAL		
CREATININE, MG/DL	<1.2	**0**
	1.2-1.9	**1**
	2-3.4	**2**
	3.5-4.9	**3**
	>5	**4**