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Original article

Prevalence and outcome of sepsis and septic shock in intensive care units in Addis Ababa, Ethiopia: A prospective observational study

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ABSTRACT

Background: Sepsis and septic shock are the major causes of morbidity and mortality in Intensive care Units (ICUs) in low and middle-income countries. However, little is known about their prevalence and outcome in these settings. The study aimed to assess the prevalence and outcome of sepsis and septic shock in ICUs in Addis Ababa, Ethiopia.

Methods: A prospective observational study was conducted from March 2017 to February 2018 in four selected ICUs in Addis Ababa from a total of twelve hospitals having ICU services. There were 1145 total ICU admissions during the study period. All admissions into those ICUs with sepsis, severe sepsis, and septic shock using the Systemic Inflammatory Response Syndrome (SIRS) criteria (SEPSIS-2) during the study period were screened for sepsis or septic shock based on the new sepsis definition (SEPSIS-3). All patients with sepsis and septic shock during ICU admission were included and followed for 28 days of ICU admission. Data analysis was done using the Statistical Package for Social Sciences (SPSS) software version 20.0.

Results: A total of 275 patients were diagnosed with sepsis and septic shock. The overall prevalence of sepsis and septic shock was 26.5 per 100 ICU admissions. The most frequent source of sepsis was respiratory infection (53.1%). The median length of stay in the ICUs was 5 (IQR, 2–8) days. The most common bacterium isolate was *Pseudomonas aeroginosa* (34.5%). The ICU and 28-day mortality rate was 41.8% and 50.9% respectively. Male sex, modified Sequential Organ Failure Assessment score ≥10 on day 1 of ICU admission, and comorbidity of HIV or malignancy were the independent predictors of 28-day mortality.

Conclusion: Sepsis and septic shock are common among our ICU admissions, and are associated with a high mortality rate.

African relevance

- Sepsis is a common cause of intensive care unit admissions in Sub Saharan Africa.
- The ICU and 28-day mortality of sepsis and septic shock is high.
- HIV is still a common comorbidity subjecting younger population to a high risk of sepsis and septic shock.
- Infections are more likely to be caused by multi-drug resistant organisms.

Introduction

Sepsis and septic shock are associated with high mortality and morbidity in developing countries [1]. Despite the declining trend of sepsis in high-income countries, it is still a leading cause of non-cardiac death in critically ill patients [2–4]. Global epidemiologic data from systematic reviews revealed a variable prevalence of 13–300 and 11 per 100,000 people annually for severe sepsis and septic shock respectively [5]. But, it is assumed to be higher in Sub-Saharan Africa (SSA) where data are scarce [6]. Moreover, the implementation of the current clinical

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practice guidelines is challenging in many African countries due to resource constraints [7]. Data regarding the prevalence and outcome of sepsis and septic shock are limited and the majority of treatment efforts are believed to be associated with poor outcomes [8]. Many factors are thought to contribute to poor clinical outcomes in these settings. These include; lack of microbiologic and radiologic diagnostic facilities and a shortage of appropriate antibiotics [9–11]. Furthermore, studies on bloodstream infection in Ethiopia showed a higher incidence of multi-drug resistant bacteria and a shortage of effective antibiotics in the country [11–13]. Thus, lack of adequate data on the prevalence and outcome of sepsis in Intensive Care Units (ICUs) in low and middle-income countries (LMICs) demands such studies to evaluate the magnitude and outcome of sepsis and challenges associated with their management [14].

Methods

Study area and setting

The study was a prospective, observational study, which was conducted for one year from March 1st, 2017 to February 28, 2018, at four selected hospitals in Addis Ababa, Ethiopia. One of the hospitals (i.e. St. Paul's Hospital) is a teaching institution where the majority of investigators including the principal investigator are affiliated with and included in the study without randomization for logistic reasons. The other three hospitals were selected with a simple random sampling method from 11 hospitals in Addis Ababa after deducting St. Paul's Hospital from the list. Three of the hospitals (St. Paul's Hospital, AaBET hospital, and Zewditu Memorial Hospital) are governmental and one (Landmark Hospital) is a private hospital. The total number of ICU beds is 32, which serve for managing medical, surgical, and gynecological critical cases. All patients who were admitted to the respective ICUs for sepsis and septic shock during the study period were included. The hospitals are staffed with nurses, general practitioners, and internists. St. Paul's hospital has one pulmonary and critical care specialist and none of them have infectious disease specialists. The nurse-to-patient ratio is 1:2 to 1:3. All ICUs are equipped with mechanical ventilators. Routine laboratory tests like; complete blood count, liver function test, renal function test, and electrolytes are mostly available. None of the ICUs have arterial blood gas analysis and microbiologic laboratory able to perform culture and sensitivity testing. But, samples from blood and other body fluids are sent to a central laboratory or private laboratories in the city whenever available and affordable. The annual admission to the selected ICUs is estimated between 800 and 1200 with about 25–30% ICU mortality [11].

Study population

All patients ≥18 years of age who had first ICU admission for sepsis and septic shock according to The Third International Consensus Definitions for Sepsis and septic shock (SEPSIS-3) criteria from March 1st, 2017 to February 28, 2018, were included in the study. Patients who were readmitted for sepsis or septic shock during the study period and who were unable to provide consent or not accompanied by a caretaker were excluded from the study.

Sampling procedure, data collection, and operational definitions

In SEPSIS-2 criteria, Systemic Inflammatory Response Syndrome (SIRS) was defined in a patient who met two or more of the following, namely tachycardia (heart rate >90 beats/min), tachypnea (respiratory rate >20 breaths/min), fever or hypothermia (temperature >38 or <36 °C), and leukocytosis, leukopenia, or bandemia (white blood cells >1200/mm^3, <4000/mm^3 or bandemia ≥10%). Sepsis was defined as infection or suspected infection leading to the onset of SIRS. Sepsis complicated by organ dysfunction was termed severe sepsis, which could progress to septic shock, defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation[8].

Based on the SEPSIS-3 definition, sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be represented by an increase in the Sequential (sepsis-related) Organ Failure Assessment (SOFA) score of 2 points or more. Septic shock was defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level >18 mg/dl in the absence of hypovolemia. Due to the lack of arterial blood gas analysis and serum lactate measurements in these ICUs, we were obliged to use the modified Sequential Organ Failure Assessment (mSOFA) score [16,17] to identify patients with sepsis during ICU admission. The mSOFA was calculated using the original SOFA scoring system with two modifications: the PaO_2/FIO_2 ratio was replaced with the SpO_2/FIO_2 ratio, where PaO_2 is the arterial partial pressure of oxygen, FIO_2 is fraction of inspired oxygen and SpO_2 is arterial oxygen saturation measured by a pulse oximeter. For patients on nasal flow oxygen, FIO_2 was estimated by multiplying the flow in L/min by 0.03 and add 0.21. In addition, the mSOFA score eliminates the platelet count and replace serum bilirubin with clinical assessment of scleral icterus or jaundice [16]. Patients with mSOFA score ≥2 and clinical, laboratory, or radiological evidence of infection are considered to have sepsis. Patients with persistent hypotension related to suspected infection requiring vasopressors despite adequate volume resuscitation for at least 2 h were labeled as having septic shock [15]. The adequacy of resuscitation was assessed with mean arterial pressure, urine output, and surface oxygen saturation. Acute Respiratory Distress Syndrome (ARDS) was defined according to The Berlin Definition [18]. Acute kidney injury was assessed based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [19]. Chronic organ dysfunction and reasons for ICU admission were assessed based on the Acute Physiologic and Chronic Health Evaluation (APACHE II) criteria [20]. Nosocomial infection was defined as an infection that occurs at least 48 h following hospitalization. Patients were classified as having sepsis or septic shock according to the most severe form at ICU admission. Antibiotic therapy was started within 3 h of admissions, initially with empiric drugs against all likely bacterial pathogens according to the surviving sepsis campaign guideline. All participating patients were followed until 28 days of ICU stay. Patients who were discharged before 28 days were monitored for the subsequent outcome at 28 days using their follow up records and phone calls.

During the study period, all eligible admissions with suspected sepsis or septic shock in the participating ICUs were enrolled consecutively. Patients who fulfill the Systemic Inflammatory Response (SIRS) criteria (SEPSIS 2) definition were further screened and those who met the criteria for sepsis or septic shock based on the new SEPSIS-3 definition [15] at ICU admission were included. Only the first episode of sepsis or septic shock was considered during the study period.

For patients with sepsis and septic shock who were included in the study; demographic characteristics, sources of ICU admission, reasons for ICU admission, comorbidities, preexisting organ insufficiency, modified SOFA score, length of ICU stay, length of hospital stay, vital signs, laboratory investigations, and imaging studies were collected using a structured checklist. The microbiologic studies were conducted based on the decision of treating physicians and the investigators were not involved in sample collection and processing. The quality control was made according to the laboratories' own protocol. There were four laboratory centers close to the selected hospitals capable of doing culture. All the laboratories were using Bactech blood culture incubators.

Prevalence of sepsis and septic shock and crude ICU and 28-day mortality rates were the outcome measures. We have also assessed the predictors of ICU and 28-day mortality for these patients.

Statistical analysis

Data analysis was done using the Statistical Package for Social Sciences (SPSS) software version 20.0. Variables with nominal distribution were reported with mean and standard deviation (SD) and/or median and interquartile range (IQR). Categorical variables were computed using Fisher's exact test. For continuous variables, we used Student's *t*-test or Mann-Whitney *U* test. Predictors of 28-day mortality, odds ratio (OR) and 95% confidence interval (CI) were estimated using univariate and multivariate logistic regression model, and a p-value <0.05 was considered statistically significant. All tests and variables with a p-value of ≤ 0.2 on univariate analysis were entered into the multiple regression model after controlling for age and sex. Hosmer-Lemeshow was used for the evaluation of the calibration of the regression model.

Ethical approval

This study was approved by the Institutional Review Board of St. Paul's Hospital Millennium Medical College (Reference number PM 23/209). Through a formal letter written by the Research Directorate of the Medical College, permission was obtained from the managing directors of the respective hospitals as the college has a mandate to approve studies that can be conducted nationally. Thus, there was no need for additional ethical approval in other hospitals. Written informed consent was obtained from either patients or next of kin prior to enrollment in the study after giving adequate information about the study using the local language (Amharic).

Results

Patients

There were 1145 total ICU admissions during the study period. Three-hundred three (26.5%) patients had sepsis or septic shock during ICU admission. Of these, 275 (90.8%) patients were included in the study. Of the rest 28 (9.2%) patients; 8 did not give consent and 20 died in <24 h with incomplete data. The most commonly affected age group with sepsis and septic shock was 18–39 years (Fig. 1). The median age of patients was 40 (IQR, 27–56) years and most were men (52.7%). Looking at their educational status; 73.8% were at least able to read and write. The rest 26.2% of patients were illiterate. The majority (86.2%) of patients admitted with sepsis and septic shock had reported a form of employment and the rest (13.6%) were unemployed. Community acquired infection was the documented source of infection in 182 (66.2%) patients. There were no re-admissions for sepsis or septic shock during the 28-day follow up period. Preexisting organ dysfunctions were seen in 110 (40%) patients. The most frequent pre-existing organ dysfunctions were neurologic (17.1%), kidney (9.8%), and cardiovascular (8.7%). On the other hand, the most common new-onset organ dysfunctions were ARDS (31.8%), AKI (28.3%), and acute neurologic dysfunction (22.4%). Further general characteristics of patients are indicated in Table 1.

Source of infection and comorbidities

The frequent sources of sepsis and septic shock were respiratory (53.1%), urinary tract (19.3%), and intra-abdominal (18.9%) infections. Twenty-six (9.4%) patients had more than one source of infection (Table 2). The most common comorbidity was the Human immunodeficiency virus (HIV) (19.3%), followed by diabetes mellitus (15.6%) and malignancy (12.4%). Breast cancer, cervical cancer, and leukemias were the frequently reported malignancies. Forty (14.5%) patients had more than one comorbidity (Table 3).

Microbiological culture sample was taken from blood, sputum or body fluids for 89 (32.4%) patients. For the rest 186 (67.6%) patients culture was not done based on the decision of the treating physician. The reasons reported were; 134 (48.7%) patients had received prior antibiotics and 52 (18.9%) patients could not afford culture tests at private diagnostic laboratories, when, there was temporary discontinuation of culture service at the central laboratory where tests could have been performed for free.. There was no growth of micro-organism in 60 (21.8%) patients and only 29 (10.5%) patients had microbiologic diagnosis associated with sepsis and septic shock. Among the available 29 culture-positive results, gram-negative bacilli were observed in 19, and gram-positive bacteria were seen in 9 patients. The rest one isolate was fungal species. The most common isolates were *Pseudomonas aeroginosa* in 10, *Klebsiella pneumoniae* in 7, *Staphylococcus aureus* in 5 and *Escherichia coli* in 4 patients. The antimicrobial resistance pattern showed that 20% of *Staphylococcus aureus* isolates were resistant to methicillin and all were resistant to erythromycin and gentamycin, whereas Coagulase-negative staphylococcus species were cotrimoxazole resistant. The majority (80%) of gram-positive isolates were sensitive to vancomycin. Among gram-negative isolates, *Pseudomonas aeruginosa*, and *Escherichia coli* were resistant to cotrimoxazole. The majority of gram-negative bacteria were sensitive to ceftriaxone and ciprofloxacin. Five of six culture-positive deaths had gram-negative isolates (Table 4).

Prevalence of sepsis and septic shock

The prevalence of sepsis and septic shock was 26.5 per 100 ICU admissions in our study. A total of 275 cases of new sepsis and septic

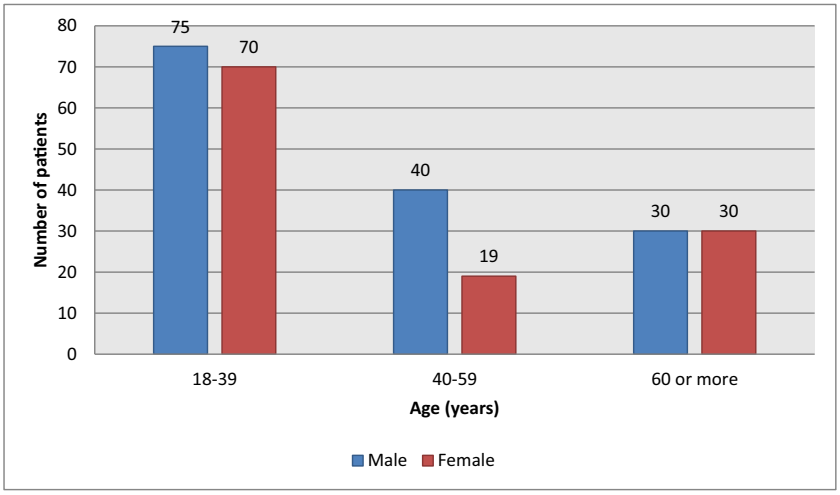

Fig. 1. Age distribution of patients with sepsis or septic shock in selected hospitals' ICU, Addis Ababa, Ethiopia, 2018.

Table 1
General characteristics of septic patients in selected hospitals' ICU, Addis Ababa, Ethiopia, 2018.

Variable	All patients N = 275	SPH N = 154	AH N = 32	ZMH N = 54	LH N = 35
Age, years Median (IQR)	40 (27–56)	46 (35–59)	43 (32–54)	40 (30–48)	47 (34–58)
Male sex, n (%)	145 (52.7)	92 (59.7)	9 (28.1)	24 (44.4)	20 (57.1)
Educational status, n (%)					
Unable to read and write	72 (26.2)	19 (12.3)	10 (31.2)	21 (38.9)	22 (62.8)
Able to read and write and above	203 (73.8)	135 (87.7)	22 (68.8)	33 (61.1)	13 (37.2)
Employment status, n (%)					
Unemployed	38 (13.8)	10 (6.5)	9 (28.1)	8 (14.8)	11 (31.4)
Employed	237 (86.2)	144 (93.5)	23 (71.9)	46 (85.2)	24 (68.6)
Source of infection, n (%)					
Community-acquired	182 (66.2)	124 (80.5)	23 (71.8)	15 (27.8)	20 (57.1)
Nosocomial	93 (33.8)	30 (19.5)	9 (28.2)	39 (72.2)	15 (42.9)
Pre-existing organ insufficiency, n (%)					
Lung	12 (4.4)	2 (1.3)	1 (3.1)	5 (9.3)	4 (11.4)
Kidney	27 (9.8)	6 (3.9)	13 (40.6)	5 (9.3)	3 (8.6)
Cardiovascular	24 (8.7)	12 (7.8)	3 (9.4)	6 (11.0)	3 (8.6)
Neurologic	47 (17.1)	28 (18.2)	5 (15.6)	5 (9.3)	9 (25.7)
None	165 (60)	106 (68.8)	10 (31.3)	33 (61.1)	16 (45.7)
New-onset organ failure, n (%)[a]	N = 491	N = 252	N = 86	N = 91	N = 62
Acute respiratory distress syndrome	156 (31.8)	80 (31.7)	31 (36.0)	23 (25.3)	22 (35.5)
Acute kidney injury	139 (28.3)	82 (32.6)	14 (16.3)	37 (40.6)	6 (9.7)
Acute neurologic dysfunction	110 (22.4)	56 (22.2)	18 (21.0)	17 (18.7)	19 (30.6)
Acute liver failure	44 (9.0)	10 (4.0)	17 (19.7)	6 (6.6)	11 (17.7)
Congestive heart failure	42 (8.5)	24 (9.5)	6 (7.0)	8 (8.8)	4 (6.5)
mSOFA on ICU admission, median (IQR)	8 (6–9)	9 (6–11)	7 (6–10)	12 (7–15)	8 (5–12)
LOS in ICU, days Median (IQR)	5 (2–8)	8 (5–11)	4 (2–7)	6 (3–9)	6 (2–8)
LOS in hospital, days Median (IQR)	9 (4–18)	11 (8–16)	10 (7–13)	14 (10–17)	8 (5–10)
Outcome at 28-days, n (%)					
Survival	135 (49.1)	62 (40.2)	27 (84.4)	25 (46.3)	21 (60)
Death	140 (50.9)	92 (59.8)	5 (15.6)	29 (53.7)	14 (40)

AH, AaBET Hospital; SPH, St. Paul's Hospital; ZMH, Zewditu Memorial Hospital; LH, Landmark Hospital; N (n), number; SD, standard deviation; IQR, interquartile range; ICU, intensive care unit; mSOFA, modified Sequential Organ Failure Assessment; LOS, length of stay; HIV, human immuno-deficiency virus.
[a] The number of new-onset organ failure is more than the total number of patients for 108 patients had multi-organ failure.

Table 2
Sources of sepsis among patients with sepsis and septic shock in selected hospitals' ICU, Addis Ababa, Ethiopia, 2018.

Source of sepsis[a]	Number (%) N = 275
Bloodstream	12 (4.4)
Device related[b]	11 (4.0)
Respiratory	146 (53.1)
Urinary	53 (19.3)
Intra-abdominal	52 (18.9)
Central nervous system	22 (8)
Soft tissue	17 (6.2)
Surgical site	13 (4.7)
Genital	14 (5.1)
Multiple sites (≥2)	26 (9.4)
Undetermined	7 (2.5)

[a] Total percentage is > 100% for 26 patients had greater than one source of sepsis.
[b] Device related: central line for hemodialysis in 8, permanent pacemaker in 1, and urinary catheter in 3 patients.

Table 3
Type of comorbid disease among patients with sepsis and septic shock in selected hospitals' ICUs, Addis Ababa, Ethiopia, 2018.

Type of comorbidity[a]	Number (%) N = 275
Hypertension	24 (8.7)
Diabetes mellitus	43 (15.6)
Congestive heart failure	9 (3.3)
Chronic liver disease	4 (1.4)
Chronic kidney disease	14 (5.1)
HIV	53 (19.3)
Ischemic stroke	6 (2.2)
Hemorrhagic stroke	3 (1.1)
Prostate cancer	5 (1.8)
Non-Hodgkin's lymphoma	6 (2.2)
Breast cancer	9 (3.3)
SLE	10 (3.6)
Cervical cancer	7 (2.5)
Lung cancer	2 (0.7)
Leukemia	5 (1.8)
Multiple (≥2)	40 (14.5)
No comorbidity	90 (32.7)

HIV: human immuno-deficiency virus; SLE: systemic lupus erythematosus.
[a] Total percentage is >100% for 40 patients had greater than one comorbidity.

shock was documented in 1710 patient-days making an incidence rate of 160.8 (95% CI 156.3–164.5) per 1000 days.

Antibiotic choice

The antibiotic choice in the majority (89.5%) of patients was done empirically and it was combination therapy in 78.8% of patients. The frequently prescribed therapies were combinations of ceftazidime plus vancomycin plus metronidazole and ceftazidime plus vancomycin each in 53 patients (Fig. 2).

Outcome of sepsis and septic shock

From a total of 275 patients with documented sepsis and septic shock, 140 (50.9%) died within 28-days of diagnosis, of whom 115 died in ICU, 10 in-hospital after transfer to the wards and the rest 15 patients died within 28 days after discharge from the hospitals. Thus the crude ICU and 28-day mortality related to sepsis and septic shock were 41.8% and 50.9% respectively. There was no significant difference in 28-day mortality among the hospitals (p = 0.18). The median length of stay (LOS) in the ICUs was 5 (IQR, 2–8) days and in-hospital LOS was 9 (IQR,

Table 4
Antibiotic resistance patterns and outcomes for bacterial isolates from patients with sepsis and septic shock in selected hospitals' ICUs, Addis Ababa, Ethiopia, 2018.

Antibiotics resistance (S/R for single isolates; percentage of resistance for number ≥2 isolates)													
Organism	n	Cfo	Cft	AmC	Met	Cip	Ery	Gen	Van	Pen	CMX	Outcome at 28-days	
												Alive (n)	Died (n)
Staphylococcus aureus, n (%)	5	2 (40)	1 (20)	–	1 (20)	4 (80)	5 (100)	5 (100)	1 (20)	3 (60)	4 (80)	4	1
Coagulase negative staphylococcus	4	1 (25)	–	–	2 (50)	1 (25)	3 (75)	–	–	1 (25)	4 (100)	4	–
Pseudomonas aeruginosa	10	8 (80)	5 (50)	5 (50)	8 (80)	3 (30)	8 (80)	4 (80)	7 (70)	9 (90)	10 (100)	8	2
Escherichia coli	4	1 (25)	1 (25)	2 (50)	4 (100)	2 (50)	4 (100)	2 (50)	1 (25)	1 (25)	4 (100)	4	–
Klebsiella pneumoniae	7	6 (86)	5 (71)	3 (43)	5 (71)	6 (86)	3 (43)	3 (43)	5 (71)	7 (100)	6 (86)	5	2
Acinetobacter baumannii	1	R	S	S	R	S	R	R	R	R	R	–	1

Cfo, cefoxitin; Cft, ceftriaxone; AmC, amoxicillin + clavulanic acid; Met, methicillin; Cip, ciprofloxacin; Ery, erythromycin; Gen, gentamycin; Van, vancomycin; Pen, penicillin; CMX, cotrimoxazole; n, number; S, susceptible; R, intermediate susceptibility or resistance.

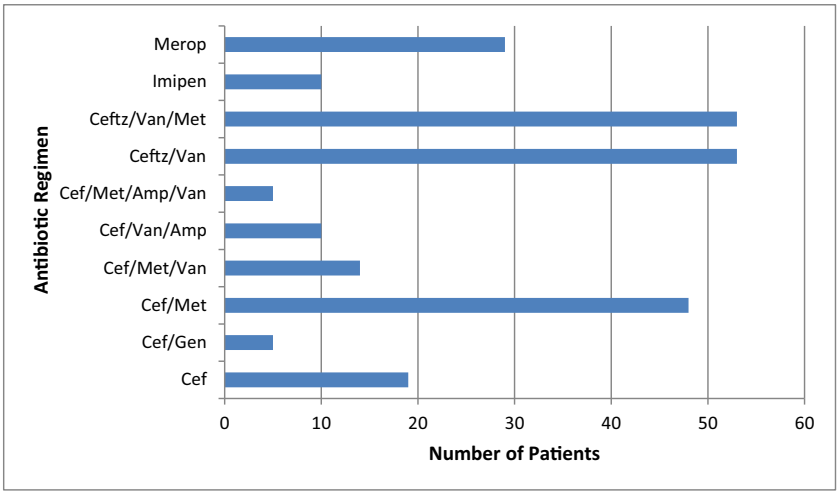

Fig. 2. Frequency of separate empiric antibiotic regimens used among patients with sepsis and septic shock in selected hospitals' ICU, Addis Ababa, Ethiopia, 2018.
Cef, ceftriaxone; Cef/Gen, ceftriaxone/gentamycin; Cef/Met, ceftriaxone/metronidazole; Cef/Met/Van, ceftriaxone/metronidazole/vancomycin; Cef/Van/Amp, ceftriaxone/vancomycin/ampicillin; Cef/Met/Van/Amp, ceftriaxone/metronidazole/vancomycin/ampicillin; Ceftz/Van, ceftazidime/vancomycin; Ceftz/Van/Met, ceftazidime/vancomycin/metronidazole Imipen, imipenum cilastatin; Merop, meropenum.

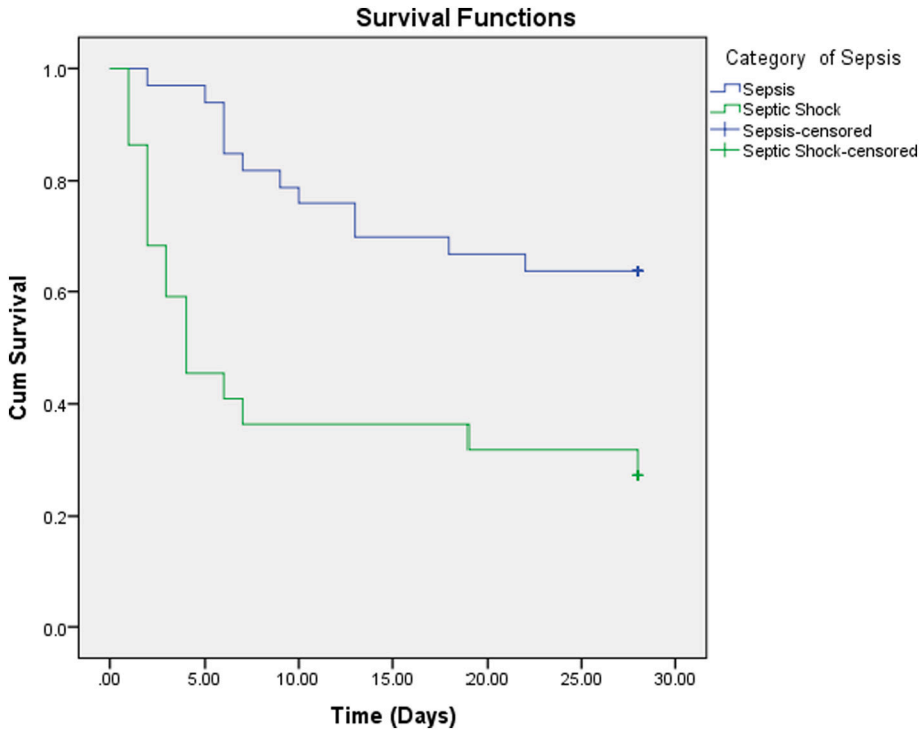

Fig. 3. Kaplan-Meier survival curve of patients with sepsis. Comparison between patients with sepsis and septic shock.

4–18) days. There was no significant difference in the ICU and in-hospital LOS among the hospitals (p-values of 0.81 and 0.76 respectively) (Table 1). The Kaplan-Meier survival analysis demonstrated higher mortality among septic shock cases than sepsis during the twenty-eight days following admission, especially in the first one-week of admission (Fig. 3).

Predictors of mortality

Male sex, mSOFA score ≥10 on day 1 of ICU admission, and co-morbidity of HIV or malignancy were the independent predictors of 28-day mortality (Table 5).

Discussion

This is a prospective observational study that looked into the prevalence and outcome of patients with sepsis and septic shock in SSA after the revised definition of sepsis (SEPSIS-3). SEPSIS-3 definition has several advantages over the previous criteria; it can adequately describe the pathophysiologic process of sepsis. It was also prepared based on three large randomized controlled trials unlike the SIRS criteria, which was by expert consensus and is neither sensitive nor specific [25–27,38].

The prevalence of sepsis and septic shock in the present study was 26.5 per 100 ICU admissions. Based on SEPSIS-3, 15.1% (n = 173) of patients had sepsis and 8.9% (n = 102) of patients had septic shock during ICU admission. The overall ICU and 28-day mortality rates of sepsis and septic shock were 41.8% (n = 115) and 50.9% (n = 140) respectively. Patients with septic shock had more than twice higher mortality rate (75.5%) than those without shock (36.4%). The clinical predictors of ICU mortality and 28-day mortality were male sex, mSOFA score ≥10 on ICU admission, and presence of comorbid HIV infection or malignancy.

The current study showed similar prevalence and ICU mortality with previous studies [21,22] in SSA. However, the 28-day mortality is lower than in previous studies [21–24]. The higher 28-day mortality in the studies by Jacob et al. [22] and Waitt et al. [21] might be attributed to higher HIV positive subjects (75–85%) in their study. On the other hand, Awuafor et al. [23] used a smaller sample size and studied only nosocomial infections which are known to carry a higher mortality risk.

Interestingly, the prevalence and outcome of sepsis in our study are different from observational studies from high-income countries (HICs) [24,26]. Another observational study by Zhou et al. [25] reported a higher incidence (37.3/100 ICU admissions) of sepsis and septic shock. But, ICU mortality was significantly lower. In another European study (SOAP study), the ICU mortality for severe sepsis was 32.2%, which is still lower than the current study [27]. Zhou et al. used the Systemic Inflammatory Response Syndrome (SIRS) criteria, often thought of as a more lenient definition of sepsis, rather than the SEPSIS-3 definition and this could have led to the inclusion of patients with less severe infection and underestimation of mortality. In the INSEP study, using the new SEPSIS-3 definition, the ICU mortality rate was comparable to our findings.

Similar to other studies [21,25,28–31]; male sex, mSOFA score ≥10, comorbidity of HIV or malignancy were predictors of poor outcome of sepsis and septic shock. Although the SOFA score has long been used to describe the sequence of organ complications, many studies on critically ill patients have demonstrated that high SOFA scores of any individual organ are associated with higher mortality [32–34]. Since arterial blood gas measurements are not always available in resource-limited settings, the use of SOFA scores for routine practice is not possible. This necessitates alternative methods of assessing sequential organ dysfunction; like mSOFA, which was recently validated in a similar setting [17]. Modified SOFA score was also found to be a predictor of mortality in other studies [35,36]. Consistent with other studies [24–26,30], the most frequent sources of infection were respiratory, followed by urinary tract and central nervous system.

The microbiologic profile isolated from septic patients has many similarities to previous observations although there are some important differences. In agreement with other studies [11,21,22,25], gram-negative pathogens were the most common isolates although gram-positive isolates have been shown to be common in studies [23,26] with a high predominance of nosocomial infections. Interestingly, in the INSEP study, gram-positive organisms were predominantly isolated from blood cultures and gram-negative organisms were the major isolates from other sites. The differences in our observed microbiologic profile are likely related to a higher percentage of sepsis caused by community-acquired infections. Our findings were also consistent with a nationwide epidemiologic study [37] in which the most common gram-negative organisms were *pseudomonas aeroginosa*, *Klebsiella pneumonia*, and *Escherichia coli*.

We computed the survival curve of patients with sepsis and septic shock and demonstrated a significant difference in prognosis between these two groups of patients. Septic shock clearly reduced early survival when evaluated at 28 days of follow-up.

Although there are no significant differences in the causative pathogens of sepsis and septic shock from most high-income countries, infections are more likely to be caused by multi-drug resistant organisms as seen in the culture and sensitivity study [39]. Empirical combination therapy is thus reasonable to cover all expected pathogens and possible resistance patterns. Based on our limited microbiologic data, a combination of ceftriaxone plus ciprofloxacin plus vancomycin can be an available and affordable empirical therapy, especially in situations where one cannot get more potent antibiotics.

The strengths of the study are; it is a prospective study that used the SEPSIS-3 definition that was applied early in such resource-limited settings, involved more than one hospital unlike other studies in SSA, and looked into the short-term outcome of sepsis and septic shock.

Our study has several limitations. First, we have used a relatively

Table 5
Predictors of 28-day mortality among patients with sepsis and septic shock in selected hospitals' ICU, Addis Ababa, Ethiopia, 2018.

Variable	28-day outcome		Univariate		Multivariate	
	Alive, n	Died, n	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Male gender	54	91	2.8 (1.8–4.5)	<0.01	1.8 (1.4–2.1)	**0.04**
Employment status (unemployed)	27	11	0.8 (0.4–1.3)	0.2	0.6 (0.2–1.6)	0.6
Length of ICU stay (≥5 days)	95	50	1.1 (0.7–1.6)	0.02	0.9 (0.5–1.2)	0.8
Length of hospital stay (≥10 days)	100	35	0.8 (0.3–1.4)	0.1	0.6 (0.2–1.5)	0.4
mSOFA score ≥10 at ICU admission	40	95	3.5 (1.8–6.8)	<0.01	3.1 (1.0–8.6)	**<0.01**
Focus of infection (blood stream)	5	7	1.5 (0.6–1.8)	0.02	1.1 (0.6–2.1)	0.08
Multiple sites of infection (≥2)	12	14	1.2 (0.5–1.6)	0.06	0.9 (0.6–1.8)	0.3
HIV-positive	17	36	2.4 (1.3–4.5)	0.01	1.7 (1.1–6.4)	**0.02**
Cancer co-morbidity	8	26	3.9 (2.7–7.1)	<0.01	2.8 (1.2–9.0)	**<0.01**
Multiple comorbidity (≥2)	17	23	1.4 (0.8–1.8)	0.07	1.1 (0.6–2.5)	0.06

n, number; mSOFA, modified Sequential Organ Failure Assessment; HIV, human immuno-deficiency virus; OR, odds ratio; CI, confidence interval.
A p-value ≤ 0.05 is statistically significant.

small sample size and included only a few centers compared with studies from high-income countries (HICs), where multiple centers and larger sample sizes were used. Second, we had a very low rate of microbiologic support in the diagnosis of sepsis and septic shock. Third, we used the new definition of SEPSIS-3, which has less known sensitivity and specificity on prospective studies. Forth, the use of a short follow-up period, which may not give a better picture of the long-term outcome of sepsis and septic shock. Finally, we studied only patients who had sepsis and septic shock during ICU admission but did not include other ICU patients who developed sepsis or septic shock during their ICU stay, which might wrongly underestimate the prevalence of sepsis and septic shock.

In conclusion, the present study shows that sepsis and septic shock are still common problems in ICUs in LMICs and is frequently associated with higher mortality. Respiratory and urinary tract infections were predominant sources of sepsis, and Gram-negative bacteria, particularly *P. aeroginosa* and *K. pneumoniae*, were the major isolates. The majority of bacterial isolates were multi-drug resistant. Male sex, mSOFA score $\geq$10 at admission, and comorbidity with HIV and malignancy were associated with worse outcomes.

Sepsis and septic shock still remain important public health problems in resource-limited settings. Therefore, the care of sepsis in these ICUs' should be improved. Further studies with larger sample sizes are also warranted to look into the challenges associated with care in these settings.

CRediT authorship contribution statement

Authors contributed as follows to the conception or design of the work; the acquisition, analysis or interpretation of the data of the work; and drafting the work or revising it critically for important intellectual content: HAM contributed 55%; TB, YW, JJL, EW, DB, BT, MN, HG, and AK contributed 5% each. All authors approved the version to be published and agreed to be accountable for all aspects of the work.

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Dissemination of results

The findings of the study were presented on the 5th annual research conference of St. Paul's Hospital Millennium College via an oral presentation on September 5, 2019. The abstract was printed in the book of abstracts of the conference.

Conflict of interest

The authors declared no conflicts of interest.

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