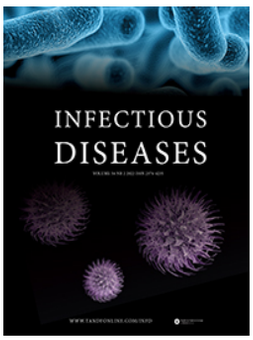

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ORIGINAL ARTICLE

Epidemiology of sepsis and risk factors for mortality in intensive care unit: a hospital based prospective study in South India

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ABSTRACT

Objective: The present study was aimed at elucidating the epidemiology of sepsis, with a special emphasis on identifying the common bacterial aetiology, proportion of infections caused by multi-drug resistant (MDR) bacteria, and risk factors associated with 28-day mortality at a university hospital in South India.

Methods: A prospective study was undertaken from January 2017 to March 2018. Adult patients with the diagnosis of sepsis requiring intensive care unit (ICU) care were recruited. Baseline clinical, epidemiological, and laboratory data were recorded, and their association with 28-day mortality was assessed using logistic regression models.

Results: 400 subjects with a qSOFA score $\geq$2 at the time of ICU admission were included in the study. The mean age was 55.7 ± 16.6 years, and 69% were males. The mean SOFA score at the time of admission was 9.9 ± 2.7. Bacterial aetiology of sepsis was established in 53.5% of cases and 24% were caused by MDR pathogens. Carbapenem resistance was observed in 37% of the Gram-negative isolates. *Escherichia coli* (34.1%) was the leading pathogen. Overall, the 28-day mortality in ICU was 40%. 38% died within 48 h of ICU admission. Hypertension and SOFA > 9, male gender, and baseline-creatinine values >2.4 mg/dl were risk factors for mortality.

Conclusions: Male gender, hypertension, SOFA > 9, and increased creatinine were identified as the predictors for mortality. Infectious aetiology remained undetected in nearly half of the cases using routine microbiology culture methods. Mortality within the first 48 h of admission to ICU is high and prompts the need for increasing awareness about early sepsis diagnosis in community health care settings.

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Supplemental data for this article can be accessed here.

Introduction

Sepsis is a complicated heterogeneous life-threatening emergency that develops due to the body's dysregulated response following infection and is associated with tissue and organ dysfunction [1]. It is associated with both higher global health-economic costs and mortality among all disease states. Increasing awareness about the early diagnosis and availability of universal guidelines for effective management of patients has led to a slight decrease in the case fatality rates among patients with sepsis over the past few years [1,2]. However, sepsis incidence continues to increase, and recent global estimates in 2017 across 195 countries suggested 48.9 million incident cases of sepsis worldwide, with 11 million total sepsis-related deaths [3].

Initiation of pathogen-specific antimicrobial therapy among patients with sepsis is often challenging due to the diverse infectious aetiology (viral, bacterial, and parasitic) and the high burden of both community and hospital-acquired infections caused by multi-drug resistant (MDR) bacteria in developing and tropical nations such as India [4]. Nation-wide assessment of the true burden, epidemiology, and risk factors for mortality among patients with sepsis remains challenging in India considering the large population, limited healthcare facilities, disparities in the healthcare practices, and quality of the care provided across the country. Nonetheless, risk-stratification based on the patient characteristics at the time of sepsis diagnosis is crucial for formulating targeted medical interventions for better clinical outcomes. Few studies from India have previously reported the predictive values of various severity assessment scoring systems, mortality rates, and the quality of care provided among patients with sepsis [5–7]. Few Indian single-centre studies are reporting the clinical and microbiological characteristics of patients with sepsis and/or infections in the ICU [8,9]. Increasing trends in the prevalence of MDR bacteria causing infections have been consistently reported from various parts of India over the past few years [10,11]. However, the impact of MDR bacteria on clinical outcomes among patients with sepsis in India remains unknown.

Herein, we report the epidemiology and risk factors associated with the 28-days mortality among patients admitted to ICUs and diagnosed with sepsis at a university teaching hospital in south India. We also report the common bacterial aetiologies and the proportion of infections caused by MDR bacteria in our settings.

Material and methods

Study design and study site

A prospective, observational study was undertaken at a large university teaching hospital (2032 beds) in south India, from January 2017 to March 2018. The study hospital is a tertiary care referral centre for medical and surgical specialties in the coastal of Karnataka. The hospital serves the regional population of nearly 1.3 million besides referrals from the nearby regions and on average, the hospital records nearly 3000 outpatients and 200 admissions each day. There are two mixed and one medical intensive care unit (ICU) with a 46-bed capacity.

Study population

Adult patients of both genders admitted to the study ICUs were considered eligible if they fulfilled our inclusion criteria. Inclusion criteria were: (1) Suspected or documented infection as a primary diagnosis by the attending clinician, (2) blood culture draws within 24 h of admission in the ICU, and (3) a quick sequential organ failure assessment (qSOFA) score $\geq$2 at the time of ICU admission. Definitions of infection in accordance with the International Sepsis Forum Consensus are routinely used by the clinicians at the study hospital and the same definitions were used in the present study cohort [12]. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated response to infection and was objectively defined in the present study as an increase in the Sequential Organ Failure Assessment (SOFA) score of two points or more with infection [1]. Pregnant women, patients staying in the ICU $\leq$24 h for routine postoperative care, and patients with severe burns (total surface area burnt $\geq$30%) were excluded from the study. We also excluded patients with sepsis that had viral, fungal, parasite, spirochaete, and rickettsial aetiologies. Besides qSOFA, other common criteria for ICU admission in our centre are the need for assisted ventilation with SpO_2 <90% despite supportive oxygen therapy.

Data collection

A case report form (CRF) to capture relevant demographic, clinical, and laboratory data was developed and validated for the present study. Clinical and laboratory data of each study subject was recorded from the time

of admission until discharge from the ICUs. SOFA, Simplified Acute Physiology Score II (SAPS II), and Acute Physiology and Chronic Health Evaluation II (APACHE II) were calculated at the time of admission to the ICU. Data were collected from the medical charts as well as the ICU and microbiology laboratory databases of the hospital.

Ethics statement

The study protocol was approved by the Institutional ethical committee (IEC KH-642/2016). Written informed consent was obtained from either the study participant or the representative before enrolment.

Detection of bacterial aetiology of sepsis

Bacterial aetiology from blood culture: In our hospital, critically ill patients with a clinical suspicion of infectious aetiology are shifted to ICUs from the wards, and blood cultures were drawn before starting antibiotic treatment and immediately transported to the laboratory. All study subjects had at least one set of blood cultures collected within the first 24 h of admission to the ICU. Always, 8–10 ml volume per bottle was collected with aseptic precautions and inoculated in BacT/ALERT-FA plus bottles (bioMérieux, France), Subcultures from positive flagged bottles were followed by identification and antimicrobial susceptibility testing using Matrix-Assisted Laser Desorption Ionisation Time-of-Flight (MALDI-TOF) VITEK®MS and Vitek-2 compact system (bioMérieux, Inc. Durham, NC) respectively. A pathogen was considered as MDR if it was non-susceptible to at least one agent in three or more antimicrobial categories [13]. Coagulase-negative Staphylococci, Viridans group of Streptococci, *Micrococcus* spp., Diphtheroides, or *Bacillus* spp. were excluded from the analysis as they were considered skin contaminants.

Bacterial aetiology from other clinical samples: Presenting clinical syndromes were classified based on the primary diagnoses of attending physicians. Organ involvement for infection was documented when there were signs of infection such as fever or hypothermia, leukocytosis, or leucopenia, along with the accumulation of pus in any organ and/or radiological signs of infection; further, it might be the growth of any pathogen from other clinical samples such as urine, lower respiratory tract samples, CSF, etc. Microbiological culture findings from other clinical samples were documented from the laboratory information system for further analysis. Patient samples that grew organisms without suggestive clinical relevance were considered non-significant by the clinical microbiologists in consultation with the treating physician and hence not considered in the final analysis.

Other laboratory investigations: Results of baseline biochemical and hematological investigations were obtained from medical records and hospital-laboratory information databases.

Subject follow-up and outcomes

The study patients were followed up until they were either transferred outward and/or discharged from the ICU. Antibiotic treatment, 28-day mortality, length of the ICU stay, and total hospital stay was documented.

Statistical analysis

Data recorded in the CRF was digitized for analysis using SPSS version 15 **(**IBM, Bangalore, South Asia**)**. Descriptive statistical tools were used to estimate the frequencies of categorical variables. Median and interquartile ranges **(**IQR**)** were reported for continuous variables. Chi-square test and univariate analysis were used to measure the association between the study variable and categorical outcomes. A p-value of $<.05$ was considered statistically significant and was reported in terms of unadjusted odds ratio and 95% CI. A comparison of medians between groups was carried out using the Mann–Whitney U-test with 95% CI. Variables that had a p-value $<.2$ on univariate analysis were included in a multivariate cox hazard proportional model. The reason for including variables with $p < .2$ was to identify any confounder that may not show a statistical significance in univariate analysis but eventually affects the odds ratio when included in the multivariate model [14]. Independent predictors for 28-day mortality among the study subjects were determined and reported in terms of adjusted hazard ratio (AHR) with 95% CI.

Results

Among a total of 4243 patient admissions in the study ICUs, 743 (17.5%) had a qSOFA score ≥ 2 and 400 subjects were finally eligible for inclusion in our study (Figure 1).

Baseline demographic and clinical characteristics

The mean age of the study subjects ($n = 400$) was 55.7 ± 16.6 years. The majority (276/400, 69%) were

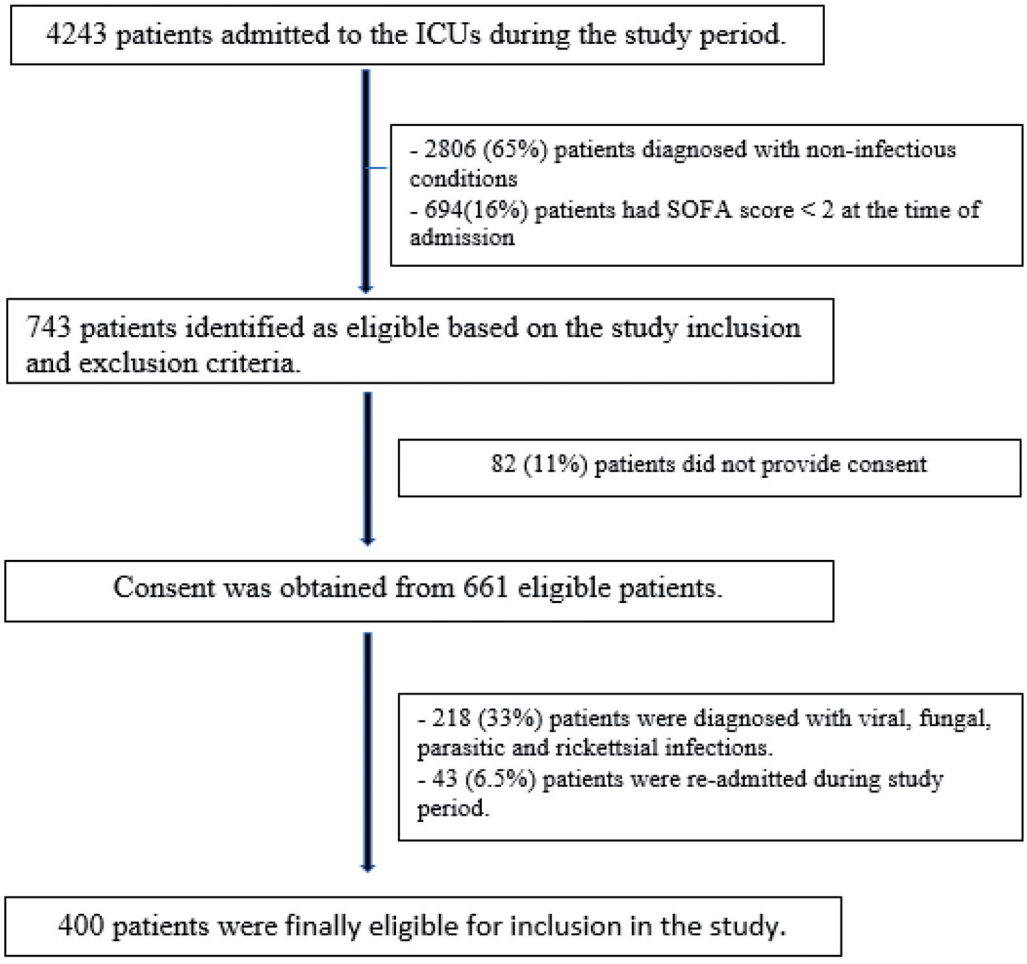

Figure 1. Flow diagram depicting initial assessment and patient's recruitment in the study.

males. Diabetes mellitus (59.2%) followed by chronic kidney disease (29.2%), and chronic obstructive pulmonary disease (COPD) (16.5%) were the common pre-morbid illnesses observed among the study subjects. Of the total 400 subjects, 335 (84%) presented initially at the emergency department. The majority (46%) of the patients had clinical symptoms/infections involving the respiratory tract followed by intra-abdominal (19%) and urinary tract (15%) at the time of admission. The mean SOFA score in patients with sepsis at the time of admission was 9.9 ± 2.7. Septic shock at the time of admission was documented among 164 (41%) of the patients and 115 (70%) of these patients were males. A description of the baseline demographic and clinical characteristics of the study population is detailed in Table 1.

Bacterial aetiology of sepsis

Among the 400 subjects, bacterial aetiology of sepsis could be diagnosed in 214 (53.5%) cases. Among these 214 cases, 99 (46.2%) patients had bacteraemia with or without other focal infections. Blood cultures did not yield any pathogens in 115 (53.7%) patients, while they had a bacterial pathogen isolated from other clinical specimens (Table 2). Gram-positive organisms were detected in 49 (23%) cases while 165 (77%) cases had Gram-negative bacterial aetiologies. We observed *Escherichia coli* ($n = 73$, 34.1%) and *Klebsiella pneumoniae* ($n = 52$, 24.2%) as the leading Gram-negative pathogens while *Beta-hemolytic Streptococci* ($n = 23$, 10.7%) and *Staphylococcus aureus* ($n = 18$, 8.4%) as Gram-positive pathogens. Among *S. aureus* isolates 2.3% (5/18) were methicillin resistant. MDR was observed in 24% ($n = 51$) of all isolates. Among the Gram-negative isolates, resistance to carbapenems was found in 37% (61/165) of isolates. Carbapenem resistance among the common bacterial isolates was seen in 65.2% (15/23) of *Acinetobacter baumannii* complex, 27% (14/52) of *K. pneumoniae*, and 11% (8/73) of *E.coli* isolate. Piperacillin-tazobactam (139/400, 34.7%) followed by ceftriaxone

(65/400,16.2%), and vancomycin (55/400,13.7%) were the initial empirical antibiotics administered in combination with other medications in the present study population.

Table 1. Baseline demographic and clinical characteristics of the study population.

Baseline characteristics ($n = 400$)	n (%)
Age	
Mean age (in years)	55.7 ± 16.6
Range	18–98
Gender	
Male	276 (69)
Female	124 (31)
Previous hospitalization	151 (37.7)
Premorbid illnesses	
Diabetes mellitus	237 (59.2)
Chronic kidney disease	117 (29.2)
COPD	66 (16.5)
Congestive cardiac failure	42 (10.5)
Cirrhosis	20 (5)
Immunocompromised state	18 (4.5)
Malignancy	11 (2.7)
Admission type	
Medical	284 (71)
Surgical	84 (21)
Trauma	21 (5.3)
Oncology	11 (2.7)
Previous intra-hospital location	
Emergency department	335 (84)
Other ICU/high-definition unit	35 (9)
Hospital ward	30 (7.5)
Presenting clinical symptoms[a]	
Respiratory infection	186 (46.5)
Intra-abdominal infection (IAI)	75 (18.5)
Urinary tract infection (UTI)	60 (15)
Skin and soft tissue infection (SSI)	51 (12.8)
Osteoarticular infection	14 (3.5)
Central nervous system infection (CNS)	13 (3.25)
Gynecological infection	9 (2.2)
Catheter-related bloodstream infection	8 (2)
Unknown	27 (6.8)
Severity at the time of admission	
Septic shock	164 (41)
Mean SOFA score (range)	9.9 ± 2.7 (3–17)
Mean APACHE II score (range)	24.9 ± 7.4 (8–43)
Mean SAPS II score (range)	53.5 ± 12.7 (26–95)
Median Charlson's comorbidity index, median (IQR)	2 (2–3)

COPD: Chronic obstructive pulmonary disease; SOFA: sequential organ failure assessment; SAPS II: Simplified Acute Physiology Score; APACHE II: Acute Physiology and Chronic Health Evaluation II; ICU: Intensive care unit.
[a]The clinical presentations (in some cases, more than one) were defined based on the major presenting clinical symptom.

Subject follow-up and clinical outcomes

Among the 400 study subjects, data from 347 patients were included in the follow-up analysis, as 53 (13.2%) patients left against medical advice (LAMA). The length of the ICU stays ranged between 2 and 35 days [median 4 (IQR: 2–9) days] and length of the hospital stay between 3 and 65 days [median 10 (IQR: 5–19) days]. Clinical recovery was observed among 198 (57%) patients, and mortality within 28-days from the time of admission was observed among 43% (149/347) patients. Overall, the ICU mortality was 40% (139/347 cases), and among these, 53 (38.1%) patients succumbed to death within 48 h of admission to the ICU. The mean age and SOFA score of the patients ($n = 53$) who succumbed to death within 48 h of admission in the ICU were 54.07 ± 17.12 years and 11.22 ± 2.9 respectively. 17/53 (32%) of these patients had bacteraemia and 22 (41.5%) were referred to the present study hospital from other hospitals.

Risk factors for 28-day mortality were assessed among the survivors and non-survivors in the final analysis. Baseline SOFA score of >9, SAPS II score of >50, and APACHE II score >23 showed sensitivities of 0.68 (95%CI: 0.61–0.74), 0.64 (95%CI: 0.57–0.71), and 0.65 (0.58–0.72) respectively, for predicting mortality among the study population (Figure S1). Age and gender did not have a significant association with mortality. Higher Charlson's comorbidity index, hypertension, SOFA score > 9, SAPS II score >50, APACHE II score >23, prolonged ICU and hospital-stay, thrombocytopenia, microbiological culture positivity (either from blood and/or other clinical specimens) had a significant association with mortality among the study population (Table 3). Hypertension ($p = .04$; AHR: 1.88; 95% CI: 1.01–3.50) and SOFA score >9 ($p = .04$; AHR: 2.09; 95% CI: 1.03–4.25) were independent risk factors for mortality among the study subjects.

Table 2. Culture positivity from various clinical samples and the common bacterial isolates.

Clinical samples, n	Overall culture positivity, n (%)	Bacteraemia, n (%)	Culture positivity without bacteraemia, n (%)	Frequently isolated bacteria, n
Blood (400)	99 (24.7)	99 (24.7)		*E. coli* (29); *K. pneumoniae* (17); *S. aureus* (13); Beta-hemolytic *Streptococci* (10); *S. pneumoniae* (6)
Lower respiratory (204)	64 (31.3)	21 (10.3)	43 (21)	*K. pneumoniae* (29); *A. baumannii complex (23)*
Urine (189)	42 (22.2)	16 (8.5)	26 (14)	*E. coli* (32); *K. pneumoniae* (6)
Wound swab/tissue/pus (83)	53 (64)	30 (36.1)	38 (46)	*Beta-hemolytic Streptococci* (17); *E. coli* (16); *S. aureus* (6)
Sterile body fluids other than CSF (28)	11 (39)	3 (10.7)	8 (28.5)	*E. coli* (5); *E. faecium* (2)
CSF (4)	1 (25)		1 (25)	*S. pneumoniae* (1)

Table 3. Risk factors for 28-day mortality among patients with sepsis.

Variable ($n = 347$)	Survivors (198)	Non-Survivors (149)	p-Value	Unadjusted odds ratio (95%CI)[a]
Age, mean (SD), years	56.4 ± 15.9	56.2 ± 17.2	.98	
Male gender	130 (65.6)	112 (75.1)	.05	1.31 (0.98–1.76)
Hypertension	113 (69.4)	69 (46.3)	**.04**	1.56 (1.01–2.39)
Diabetes mellitus	119 (60.6)	95 (63.7)	.52	
Steroids	41 (20.7)	33 (22.1)	.78	
COPD	34 (17.3)	21 (14.1)	.42	
Renal disease	59 (29.9)	47 (31.5)	.75	
Median Charlson's Comorbidity Index	3 (2–4)	2 (1–3)	**<.001**	1.70 (1.39–2.78)
SOFA > 9[b]	120 (60.6)	112 (75.2)	**.004**	1.96 (1.23–3.14)
SAPS II > 50[b]	117 (59.1)	113 (75.8)	**.001**	2.17 (1.35–3.47)
APACHE II > 23[b]	134 (67.7)	118 (79.2)	**.01**	1.81 (1.10–2.98)
ICU stay(days)	5 (3–8)	3 (2–10)	**.03**	1.10 (1.00–1.24)
Hospital stays (days)	12 (7–23)	6 (2–15)	**<.001**	1.00 (1.00–1.10)
Previous history of hospitalization	41 (20.7)	33 (22.1)	.78	
Overall culture documented infections	95 (48)	94 (63)	**.005**	1.85 (1.20–2.86)
Blood culture positivity	44 (22.2)	47 (31.5)	.07	1.56 (0.96–2.53)
Isolation of MDR- organisms	25 (12.6)	26 (17.4)	.44	
Specific empirical treatment	41 (20.7)	24 (16.1)	**.001**	0.45 (0.30–0.67)
TLC, $\times 10^3$	16.5 (12.7–22.5)	18.7 (13.1–25.8)	.12	
PaO_2, mmHg	94 (82–112.2)	82 (68–108.7)	.47	
Platelet count, $\times 10^3$	229 (123–316)	139 (64–244)	**<.001**	1.54 (1.2–1.9)
AST, mg/dl	45.5 (29.7–93)	79 (39–179)	**.002**	1.002 (1.001–1.003)
Serum urea, mg/dl	50 (30–99)	63 (39–98)	.29	
Serum creatinine	1.7 (0.9–3.0)	1.8 (1.1–3.2)	.50	
Total bilirubin, mg/dl	0.8 (0.5–1.6)	1.3 (0.6–2.5)	**.001**	1.20 (1.08–1.34)

COPD: Chronic obstructive pulmonary disease; SOFA: sequential organ failure assessment; SAPS II-Simplified Acute Physiology Score; APACHE II: Acute Physiology and Chronic Health Evaluation II; ICU: Intensive care unit; MDR: Multi drug resistant; TLC: Total leucocyte count; AST: Aspartate aminotransferase.
The bold values suggest the statistically significant difference between two comparative groups. It indicates strong evidence against the null hypothesis.
[a]Determined using univariate analysis; [b]Median severity scores among the survivors were used as the cut-off for analysis.

Further, risk factors for mortality were assessed for patients with microbiological culture documented infections. Among the 347 follow-up cases, 189 patients had microbiological evidence of infection. Overall, the mortality rate was 49.7% (94/189) among this group of patients. Death within 48 h of admission was observed among 12% (23/189) of patients. Bacteraemia and isolation of MDR organisms did not have a significant association with the clinical outcomes in the present study. Associations of individual variables (clinical, demographic, and laboratory) with clinical outcomes, determined using univariate analysis are listed below (Table 4). Male gender ($p < .01$; AHR: 2.46; 95% CI: 1.58–3.43) and baseline-creatinine values >2.4 mg/dl ($p = .003$; AHR: 1.86; 95% CI: 1.23–2.81) were identified as independent risk factors for mortality among patients with culture-positive sepsis.

Discussion

We report an important facet of bacterial sepsis involving the clinical, and epidemiological characteristics from a large Indian tertiary care hospital. Ascertainment of the source of sepsis, microbiological documentation of the aetiology in 53.5% of cases, 48 h mortality of 38%, and the associations of risk factors with the 28-day outcome in a large sepsis cohort in Indian ICU are some of the key findings of this study. Despite being a hospital-based study, the findings gain significance due to the prospective nature of the study, wide catchment area representing the common and prevailing regional and tropical infections of the land, and the practice of standard laboratory tools for the diagnosis of the wide range of infectious aetiology. We noted that 17.5% of the ICU admissions at the present study hospital were attributable to sepsis and this observation is in concordance with a recent multi-national prospective audit of 730 ICUs from 84 countries, which reported 18% of the ICU admissions were due to sepsis [15].

Much of our current knowledge regarding the burden, infectious aetiology, and clinical outcomes among patients with sepsis is derived from the clinico-epidemiological studies from High-Income Countries (HICs). The epidemiology of sepsis remains unclear in most Asian countries, including India [16]. Geographic variations in the infectious aetiology of sepsis have been reported from various tropical Asian countries outside India, and recommendations for the initiation of empirical therapy were reported [17]. Although excluded from our analysis, sepsis caused by viral, parasitic, fungal, and rickettsial infections was observed in nearly 33% of the patients, presenting with qSOFA scores ≥ 2 in our setting (Figure 1). In the present study hospital, patients presenting with acute febrile illness are routinely tested for

Table 4. Risk factors for mortality among patients with culture documented sepsis.

Variables	Survivors ($n = 95$), n (%)	Non-survivors ($n = 94$), n (%)	p-Value	Unadjusted odds ratio (95%CI)[a]
Male gender	59 (62.1)	75 (79.8)	**.01**	1.55 (1.06–2.28)
Hypertension	50 (52.6)	43 (45.7)	.34	
Diabetes mellitus	60 (63.1)	56 (59.5)	.61	
Steroid	17 (17.8)	22 (23.4)	.34	
COPD	15 (15.7)	16 (17)	.81	
Renal disease	39 (41)	32 (34)	.32	
SOFA > 9[b]	55 (57.8)	69 (73.4)	**.02**	2.00 (1.08–3.70)
SAPSII > 50[b]	52 (54.7)	70 (74.4)	**.005**	2.41 (1.30–4.46)
APACHE II > 23[b]	62 (65.2)	73 (77.6)	**.05**	
ICU-stay (in days)	5 (3–11)	7 (2–11)	**.03**	1.10 (1.00–1.24)
Hospital-stay (in days)	16 (8–30)	9 (3–19)	**<.001**	0.95 (0.93–0.97)
Previous history of hospitalization	36 (37.9)	34 (36.2)	.80	
Blood culture positivity	51 (53.7)	48 (51)	.71	
Isolation of MDR Organisms	25 (26.3)	26 (27.6)	.35	
Specific empirical treatment	27 (28.4)	17 (18)	**.01**	0.59 (0.39–0.90)
TLC, $\times 10^3$	17.1 (13.8–26.4)	17.3 (12.8–24.6)	.28	
PaO2, mmHg	93 (80–119)	88 (65–102)	.22	
Platelet count, $\times 10^3$	187 (104–306)	129 (59.7–254)	**.008**	1.01 (1.01–1.02)
AST, mg/dl	47 (31–96)	65 (34–106)	.08	
Urea, mg/dl	69 (39–111)	63 (37–101)	.91	
Creatinine	1.7 (1.0–3.1)	2.4 (1.2–3.4)	**.03**	1.19 (1.01–1.39)
Total bilirubin, mg/dl	0.9 (0.6–1.7)	1.4 (0.7–3.0)	**.01**	1.19 (1.03–1.38)

COPD: Chronic obstructive pulmonary disease; SOFA: sequential organ failure assessment; SAPS II: Simplified Acute Physiology Score; APACHE II: Acute Physiology and Chronic Health Evaluation II; ICU: Intensive care unit; MDR: Multidrug-resistant; TLC: Total leucocyte count; AST: Aspartate aminotransferase.
The bold values suggest the statistically significant difference between two comparative groups. It indicates strong evidence against the null hypothesis.
[a]Determined using univariate analysis; [b]Median severity scores among the survivors were used as the cut-off for analysis.

endemic infections such as malaria, dengue, and influenza with rapid, serological, and molecular tests as applicable, in cases of high clinical suspicion. The results of these tests are usually available within a few hours from the time of admission. In contrast, the management of patients with negative test results for common endemic infections is often challenging to clinicians, particularly in cases of infections caused by MDR bacteria. Hence, in the present study, we focussed only on establishing the characteristics of patients with high clinical suspicion and/or diagnosed with bacterial sepsis.

The source of infection was primarily the respiratory tract (46%) followed by intra-abdominal in 19% cases and urinary tract in 15% cases, among the present study population. A similar pattern with reference to the source of infection was reported in studies from India and elsewhere [9,18]. One of the important findings from the present study is that the aetiological diagnosis of sepsis using standard-of-care methods could be established in only 53.5% of the cases, which is comparable with studies that have reported the proportion of culture-negative sepsis in nearly 40–50% of the patients elsewhere [19,20]. Among the patients with culture-positive sepsis, microbiological confirmation of bacteraemia (blood culture positivity) was observed only among 46% of the cases. The culture-positivity rate (54%) from clinically indicated specimens (other than blood) collected within the first 24 h of ICU admission was higher than blood culture positivity among the present cohort. It is reasonable to assume that in some cases; blood cultures were negative due to either localized infections and/or prior administration of broad-spectrum antibiotics from their previous hospital stay. Further, the collection of only one set of blood cultures within the first 24 h of ICU admission could also be the reason for low blood culture positivity. These findings underscore the need for taking multiple blood culture sets, among patients with clinical suspicion of sepsis. In addition, broadening the sampling sites and types among patients with clinical and/or radiological evidence of localized infections might be beneficial among patient subgroups that have received prior antibiotics. However, clinical correlation of the microbiological culture findings, from clinical specimens, other than blood in settings with high levels of antimicrobial resistance and healthcare-associated infections would be extremely crucial to avoid irrational antimicrobial administration.

The mortality rate in the ICU was 40% in the present study, which is higher than 32%, reported from the SOAP study [21] and 26% from the multinational ICU audit [15] and this finding needs to be interpreted with caution. The patient demographics and baseline clinical characteristics of the present study population are comparable with the patient characteristics (mainly the mean age, gender, mean APACHE II scores at admission, and comorbidities) reported from cohorts at other tertiary care hospitals in India [9,22]. However, most of the studies reported previously from Indian tertiary care

Table 5. Details and key findings from other ICU-based studies from Indian tertiary care hospitals.

S. No	Number of study subjects	Single centre/ multi-centre	Study design	Study period, duration	Inclusion criteria	Culture positivity	Overall mortality rate	Reference
1	264	Single centre (West Bengal)	Prospective observational study	June 2006 to May 2011, 5 years	Severe sepsis, SIRS criteria.	61%	62.8%	Chatterjee S, Bhattacharya M et al. [9]
2	100	Single centre (New-Delhi)	Prospective observational study	June 2010 to June 2012, 2 years	Severe sepsis/ septic shock/ sepsis, SIRS criteria.	46%	53%	Mohan A, Shrestha P et al. [22]
3	487	Single centre (Rajasthan)	Prospective observational study	June 2011 to May 2012, 1 year	Infection in the ICU, SIRS criteria	28%	14%	Ghanshani R, Gupta R et al [8]
4	80	Single centre (Kerala)	Prospective observational study	January 2013 to December 2014, 2 years	Severe sepsis, SIRS criteria	63.7%	67.5%	Mohamed AK, Mehta AA et al. [28]
5	356	Single centre (Kerala)	Prospective observational study	June 2013 to December 2014, 18 months	Severe sepsis and septic shock, SIRS criteria.	Not mentioned	51.6%.	Paary TT, Kalaiselvan MS et al. [29]
6	400	Single centre (Karnataka)	Prospective observational study	January 2017 to March 2018, 15 months	Sepsis, Sepsis-3 criteria	53.5%	40%	Present study

hospitals included patients with sepsis/septic shock and mortality rates reported, enlisted below (Table 5) varied among these studies. In the present study, we included only patients with qSOFA $\geq$2 unlike the other studies (enlisted in Table 5) which used the SIRS criteria for inclusion. Hence, the mortality rate reported from the present study cannot be directly compared with the rates reported from the previous studies reported from India. The mortality rate within 48 h of admission in the ICU was 38%. Mean SOFA score (11.22 ± 2.9), at the time of admission for those patients that succumbed to death within the first 48 h of admission was higher than the mean SOFA score (9.9 ± 2.7), of the overall study subjects, indicating higher disease severity due to infection and delayed admission. Nearly 40% of the patients that died within 48 h of ICU admission at the present study hospital, were referred from elsewhere. These observations underscore the need for (a) increasing the awareness about early diagnosis of sepsis in community health care settings and immediate transfer of such patients to higher health care facilities equipped with ICUs; (b) early identification of high-risk sub-population that is most likely to have adverse clinical outcomes among patients with sepsis and formulating more targeted diagnostic and therapeutic interventions, based on the local clinico-epidemiological data.

Another finding from the present study that needs to be interpreted cautiously is the lack of association between infection caused by MDR-bacteria and mortality. Possible explanations for this observation include (i) MDR bacteria were primarily isolated from clinical samples other-than blood, and in such cases, it is difficult to differentiate colonizers from pathogens using routine semi-quantitative culture techniques; (ii) Piperacillin-tazobactam followed by ceftriaxone, meropenem, and cefoperazone-sulbactam were the first choice of empirical antibiotics administered in combination with other agents in the present study population. Early initiation (in compliance with the Surviving Sepsis Campaign 6 h bundle) of these broad-spectrum antimicrobial agents could have also led to the lack of association between MDR-bacterial infection and mortality, considering the bacterial aetiology (*E. coli* and *K. pneumoniae*) of sepsis among these patients.

Male gender, hypertension, baseline SOFA score >9, and increased serum creatinine values were identified as the independent risk factors for mortality among the present study cohort. Nearly 70% of the patients with sepsis and septic shock were males and the male gender was identified as an independent risk factor for mortality from the present study cohort. Male predominance in cohorts describing other severe clinical infections has been a constant observation from the present study hospital [23]. Though the exact reasons for this male predominance are unknown, it is possible that the gender disparities in health-care-seeking behaviours among the Indian adult population could be one of the important reasons [24,25]. In the present cohort, baseline SOFA

score >9 had a significant association with mortality and a similar association of SOFA score (8.9 ± 3.4) on the first day at ICU was reported from a hospital-based study in north India previously [26]. Complications of acute and chronic kidney injury with increased serum creatinine are associated significantly with poor outcomes of sepsis. Our study results in concordance with many western epidemiological studies have demonstrated these associations, the precise mechanisms by which kidney injury has a significant impact on other organs in sepsis remain unclear [27].

Our study has a few limitations: (i) Nearly 38% of the patients included in the present study were referred or transferred to our hospital from other smaller health care settings in the catchment area. The majority of these patients did not present to the study hospital with a discharge summary from their previous health care facility and therefore, we could not obtain the data regarding prior exposure to antibiotics. However, it is reasonable to assume that the prior exposure of broad-spectrum antimicrobials could have a considerable impact on the blood culture positivity; (ii) the present study could not determine the proportion of sepsis cases caused by anaerobic bacteria as anaerobic blood cultures are not a part of the routine standard-of-care methods for sepsis diagnosis in the present study hospital; (iii) quality of the care with regards to the compliance with the SSC bundles might have varied amongst different clinicians at the study hospital, but this was not assessed in the present study; (iv) the exact clinical outcomes among the patients that left against medical advice (LAMA) remains unknown in the present study and hence, we choose to exclude them in the final analysis. It is possible that the mortality rate reported in the present study could have been slightly inflated if the clinical outcomes from these patients were determined; (v) Low sensitivity of qSOFA for sepsis screening has been reported in many studies elsewhere. However, qSOFA is used widely by the clinicians in the present study hospital for the initial risk-stratification (at the time of ICU admission) and hence was used as one of the inclusion criteria in the present study.

Conclusion

The present study elucidates the risk factors associated with 28-days mortality among patients admitted with sepsis in ICU. Further, male gender, hypertension, SOFA score >9, and high creatinine levels at the time of ICU admission were identified as independent risk factors for mortality among Indian adult patients with sepsis. The present study reiterates the failure to establish the aetiological diagnosis of sepsis in nearly half of the patients clinically diagnosed with sepsis. The mortality rate within 48 h of ICU admission was noteworthy indicating the need for increasing the awareness about early diagnosis of sepsis in community health care settings.

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Ethical approval and consent to participate

The study has been approved by the local ethics committee (IEC KH-642/2016) before recruiting subjects and informed consent was obtained from every patient for participation in the study.

Consent for publication

Informed consent has been obtained for every recruited patient.

Disclosure statement

The authors declare that they have no competing interests.

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Data availability statement

All relevant data is available in the article itself.

References

[1] Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315(8):801–810.

[2] Tavaré A, O'Flynn N. Recognition, diagnosis, and early management of sepsis: NICE guideline. Br J Gen Pract. 2017; 67(657):185–186.

[3] Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the global burden of disease study. Lancet. 2020;395(10219):200–211.

[4] Schultz MJ, Dunser MW, Dondorp AM, et al. Current challenges in the management of sepsis in ICUs in resource-poor settings and suggestions for the future. Intensive Care Med. 2017;43(5):612–624.

[5] Badrinath K, Shekhar M, Sreelakshmi M, et al. Comparison of various severity assessment scoring systems in patients

with sepsis in a tertiary care teaching hospital. Indian J Crit Care Med. 2018;22(12):842–845.

[6] Divatia JV, Amin PR, Ramakrishnan N, et al. Intensive care in India: the indian intensive care case mix and practice patterns study. Indian J Crit Care Med. 2016;20(4):216–225.

[7] Todi S, Chatterjee S, Sahu S, et al. Epidemiology of severe sepsis in India: an update. Crit Care. 2010;14(1):P382.

[8] Ghanshani R, Gupta R, Gupta BS, et al. Epidemiological study of prevalence, determinants, and outcomes of infections in medical ICU at a tertiary care hospital in India. Lung India. 2015;32(5):441.

[9] Chatterjee S, Bhattacharya M, Todi SK. Epidemiology of adult-population sepsis in India: a single center 5 year experience. Indian J Crit Care Med. 2017;21(9):573–577.

[10] Ahmed SM, Jakribettu RP, Rajeevan S, et al. Five-year trend of bacterial isolates and their antibiotic resistance from automated BACTEC blood culture system from a rural medical college hospital in North Kerala, India: 2012–2016. J Acad Clin Microbiol. 2019;21(1):10.

[11] Gandra S, Mojica N, Klein EY, et al. Trends in antibiotic resistance among major bacterial pathogens isolated from blood cultures tested at a large private laboratory network in India, 2008–2014. Int J Infect Dis. 2016;50:75–82.

[12] Calandra T, Cohen J. The international sepsis forum consensus conference on definitions of infection in the intensive care unit. Crit Care Med. 2005;33(7):1538–1548.

[13] Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18(3):268–281.

[14] Adrie C, Francais A, Alvarez-Gonzalez A, et al. Model for predicting short-term mortality of severe sepsis. Crit Care. 2009;13(3):R72.

[15] Sakr Y, Jaschinski U, Wittebole X, et al. Sepsis in intensive care unit patients: worldwide data from the intensive care over nations audit. Open Forum Infect Dis. 2018;5(12):ofy313.

[16] Phua J, Koh Y, Du B, et al. Management of severe sepsis in patients admitted to asian intensive care units: prospective cohort study. BMJ. 2011;342:d3245.

[17] Limmathurotsakul D. Causes and outcomes of sepsis in southeast Asia: a multinational multicentre cross-sectional study. Lancet. 2017;5(2):e157.

[18] Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29(7):1303–1310.

[19] Gupta S, Sakhuja A, Kumar G, et al. Culture-negative severe sepsis: nationwide trends and outcomes. Chest. 2016;150(6):1251–1259.

[20] Panday RS, Lammers EM, Alam N, et al. An overview of positive cultures and clinical outcomes in septic patients: a sub-analysis of the prehospital antibiotics against sepsis (PHANTASi) trial. Crit Care. 2019;23(1):182.

[21] Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med. 2006;34(2):344–353.

[22] Mohan A, Shrestha P, Guleria R, et al. Development of a mortality prediction formula due to sepsis/severe sepsis in a medical intensive care unit. Lung India. 2015;32(4):313.

[23] Patra S, Shaw T, Eshwara VK, et al. Pulmonary melioidosis: an experience over years from a tertiary care hospital from southwest India. Indian J Med Sci. 2017;69:21–26.

[24] Sakr Y, Elia C, Mascia L, et al. The influence of gender on the epidemiology of and outcome from severe sepsis. Crit Care. 2013;17(2):R50–R59.

[25] Saikia N. Gender disparities in health care expenditures and financing strategies (HCFS) for inpatient care in India. SSM-Population Health. 2019;9:100372.

[26] Jain A, Palta S, Saroa R, et al. Sequential organ failure assessment scoring and prediction of patient's outcome in intensive care unit of a tertiary care hospital. J Anaesthesiol Clin Pharmacol. 2016;32(3):364–368.

[27] Doi K. Role of kidney injury in sepsis. J Intensive Care. 2016;4(1):1–6.

[28] Mohamed AK, Mehta AA, James P. Predictors of mortality of severe sepsis among adult patients in the medical intensive care unit. Lung India. 2017;34(4):330–335.

[29] Paary TT, Kalaiselvan MS, Renuka MK, et al. Clinical profile and outcome of patients with severe sepsis treated in an intensive care unit in India. Ceylon Med J. 2016;61(4):181.