STUDENTS' CORNER
RESEARCH ARTICLE

Predictors of clinical outcomes in patients with sepsis: A retrospective study from a tertiary care hospital in Pakistan

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Abstract

Objective: To assess associations between various clinic-demographic factors and clinical outcomes among patients treated for sepsis.

Methods: The retrospective study was conducted at the Aga Khan University Hospital, Karachi, and comprised data of all patients aged >18 years diagnosed with sepsis from January to December 2019. Multivariable logistic regression was used to evaluate independent associations between predictors and outcomes. Data was analysed using R packages.

Results: Of the 1,136 patients, 621(54.6%) were male and 515(45.3%) were female. The overall mean age was 59.05±16.91 years. Female gender (odds ratio: 1.029; 95% confidence interval: 1.03-1.64) was found to be an independent predictor of septic shock, while hypertension (odds ratio0.75; 95% confidence interval: 0.59-0.95) emerged as a protective factor. Chronic kidney disease (odds ratio: 1.539; 95% confidence interval: 1.14-2.07) was an independent predictor of prolonged length of stay, while older age appeared to be protective (odds ratio: 0.98; 95% confidence interval: 0.98-0.99). Mortality was associated with a significantly lower odds of Escherichia coli on culture (odds ratio: 0.26; 95% confidence interval: 0.12-0.54).

Conclusion: Independent associations were found between specific patient characteristics and adverse clinical outcomes.

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Sepsis is a serious medical condition that can quickly progress to shock, organ failure, and death if not treated promptly. Septic shock is characterised by hypotension despite vasopressin therapy, with in-hospital mortality rates approaching 20-50%. Almost half of the patients with severe sepsis have positive blood culture results with the presence of bacteraemia, in which gram-positive bacteria pathogens remain a common cause of sepsis.[1] In a study conducted in Pakistan, *Escherichia (E.) coli* was found to be the most prevalent isolate in both survivors and non-survivors of septic shock, with organisms, such as *Staphylococcus (S.) aureus, Acinetobacter* and *Enterococcus species*, also being detected.[2] Patients with sepsis are classically considered to be patients who have a high risk of complications and death. Sepsis is an especially serious threat to patients with severe illness in the intensive care unit (ICU).[2]

In 2017, there were 48.9 million cases of sepsis globally with a mortality rate of 22.5%, and sepsis accounted for 20% of all deaths worldwide. There are substantial regional variations in the prevalence and mortality of sepsis, with around 85% of cases and deaths from sepsis occurring in low- and middle-income countries (LMICs) globally.[2,3] In Pakistan, the mortality rate of sepsis can be as high as 42% which is almost twice the global mortality rate.[4] Women with septic shock have a greater likelihood of dying in the hospital than men, though men are more likely to develop sepsis.[3] The most common documented co-morbid condition in patients with sepsis is hypertension (HTN) (56.2%).[5] Patients with type 2 diabetes mellitus (T2DM) have an increased risk of developing sepsis and septic shock, and they constitute 20.1-22.7% of all sepsis patients.[6] However, T2DM does not adversely affect outcomes of sepsis.[7] Non-dialysis chronic kidney disease (CKD) has additionally been found to be an independent risk factor for death in patients with septic shock.[8] Culture-positive sepsis patients are more critical than patients with negative blood cultures. Serum lactate, serial procalcitonin and white blood cell (WBC) counts are reliable prognostic factors for septic shock.[9-11]

Sepsis places a significant strain on Pakistan's healthcare system due to inadequate resources and delays in presentation.[12] Length of stay (LOS) is a crucial measure of healthcare resource usage and patient expenditures[13] which is a dire problem in an LMIC like Pakistan. There is a paucity of research from Pakistan examining the predictive value of patient variables on adverse outcomes in sepsis. Examining these many factors and their effects on morbidity and mortality will enable better management of

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high-risk patients and better resource allocation. Moreover, while the spectrum of microorganisms involved in neonatal sepsis has been studied to some extent in Pakistan[2,14] there is a lack of research on the organisms that induce sepsis in adults. This affects the choice of empirical therapy and is, therefore, an important area that should be further studied.

The current study was planned to assess the association between several clinic-demographic factors and adverse clinical outcomes in patients with sepsis treated in a a tertiary care setting.

Materials and Methods

The retrospective study was conducted at the Aga Khan University Hospital (AKUH), Karachi, and comprised data from January to December 2019 that was retrieved using non-probability consecutive sampling technique. The study used International Classification of Disease (ICD-10) codes to identify all patients aged >18 years diagnosed with sepsis based on Sepsis-3 criteria that defines sepsis as an increase of at least 2 points in the Sepsis-related Organ Failure Assessment (SOFA) score during hospital stay, with suspected or confirmed infection.[15] There was no exclusion criterion, and data of patients with incomplete laboratory investigation was also included.

The sample size was calculated using OpenEpi[16] with approximate annual inpatient volume of patients with sepsis being 1,500, expected mortality rate of around 25%[4] with 95% confidence interval (CI).

A structured proforma was used to gather data from medical records from the online patient data system. Demographic information about the patients, comorbidity conditions, clinical characteristics, and outcomes were noted.

Demographic details included age and gender. Comorbid conditions included T2DM, ischaemic heart disease (IHD), CKD, HTN, and a history of smoking. Blood cultures reported the details of growth of microorganisms and specific types of microorganisms causing sepsis. In addition, the laboratory parameters included white blood cell (WBC) count and inflammatory markers, such as C-reactive protein (CRP), procalcitonin and lactate. Outcomes included mortality, septic shock and prolonged LOS (PLOS). As per institutional guidelines, septic shock is defined using Sepsis-3 criteria as vasopressor requirement to maintain a mean arterial pressure of 65mmHg or greater, and serum lactate level >2mmol/L (>18 mg/dL) in the absence of hypovolaemia.[15]

In earlier research, PLOS threshold was defined as a hospitalisation >75th percentile of the total sample.[17] which in the current study was 9 days. Hence, hospitalisation >9 days was considered PLOS.

Data was analysed using R, R Core Team (2020). The R packages data frames-pliers (dplyr), odds ratio (OR), Epi-tools, and Glmnet were used for cleaning and analysing the data along with the base R packages.

The primary outcome was mortality, while the secondary outcomes were hospital mortality and ICU LOS. Mean±standard deviation for continuous variables, and frequencies with percentages for categorical variables were used to express descriptive data. The link between exposures (demographic features, co-morbids, blood culture, antibiotic use and inflammatory markers) and outcomes (septic shock, PLOS and mortality) was established using univariate and multivariable logistic regression. Based on clinical plausibility and significance (p<0.25 on univariate analysis), the variables were added to the multivariable model. ORs were calculated with 95% CI. P<0.05 was regarded as significant.

Results

Of the 1,136 patients, 621(54.6%) were male and

Table-1: Clinico-demographic data (n=1,136).

Variable	n (%) or mean±SD
Age (years)	59.05±16.91
Gender Male	621 (54.6)
Female	515 (45.3)
Hypertension	652 (57.3)
Ischaemic heart disease	87 (7.6)
Diabetes mellitus	533 (46.9)
CKD	332 (29.2)
Smoking	90 (7.9)

CKD: Chronic kidney disease.

Table-2: Blood culture results (n=1021).

Variable	n (%) or mean±SD
Positive culture	242 (23.7)
Organisms	n=242
Bacteria	224 (92.5)
Gram positive	97 (43.3)
1. *Staphylococcus species*	60 (26.7)
2. *Streptococcus species*	15 (6.6)
3. *Corynebacterium species*	11 (4.9)
4. *Enterococcus species*	7 (3.1)
Gram Negative	127 (56.7)
1. *E. Coli*	79 (53.2)
1. *Klebsiella species*	17 (7.5)
2. *Pseudomonas species*	12 (5.3)
3. *Enterobacter species*	6 (2.6)
Fungus	16 (6.6)
1. *Candida species*	15 (93.7)
2. Other	1 (6.2)
Treatment modalities	
Antibiotics Data Available	1012 (89.0)
1. Pip/Taz	511 (50.5)
2. Ceftriaxone	260 (25.7)
3. Meropenem	123 (12.1)
4. Vancomycin	52 (5.1)

SD: Standard deviation.

515(45.3%) were female. The overall mean age was 59.05±16.91 years. HTN was the most common co-morbid 652(57.3%), followed by T2DM 533(46.9%), CKD 332(29.2%), and IHD 87(7.6%) patients (Table 1).

Of the 1,021(89.9%) patients who had a blood culture done in AKUH, 242(23.7%) showed organism growth. The remaining 115(10.1%) patients had blood cultures done at other hospitals. Out of the positive cultures at AKUH, 224(92.5%) had bacterial growth and 16(6.6%) had fungal growth. Gram-negative bacteria 127(56.7%) was the most common aetiology of sepsis, followed by gram-positive bacteria 97(43.3%). Out of the gram-negative bacteria, E. coli 79(53.2%) was the most common, followed by Klebsiella species 17(7.5%), Pseudomonas species 12(5.3%) and Enterobacter species 6(2.6%). Similarly, out of the gram-positive, 60(26.7%) were Staphylococcus and 15(6.6%) were Streptococcus species. All these 1,012(89.9%) patients received antibiotics. The most prescribed antibiotic was piperacillin/tazobactam 511(50.5%), followed by ceftriaxone 260(25.7%) (Table 2).

After univariate logistic regression (Table 3), data was subjected to multivariable logistic regression, which showed that the female gender was an independent predictor of septic shock, HTN was a protective factor, CKD was an independent predictor for PLOS, older age was a protective factor, and mortality was associated with a significantly lower odds of E. coli on culture (Table 4).

Discussion

The current study was planned to evaluate the link between patients' clinic-demographic features and clinical outcomes in patients with sepsis. The study focussed on 3 outcomes of sepsis; development of septic shock, PLOS, and mortality. The study discovered a significant link between the female gender and comorbid HTN with the development of septic shock, and there was a link between CKD and younger age with PLOS.

The study showed that females were more likely to develop septic shock than males, which is inconsistent with earlier findings of a lower likelihood of females developing severe sepsis and septic shock.[3,17,18] The relationship between gender and sepsis-related outcomes, particularly mortality, has been well-studied, with inconclusive outcomes.[19] The current study showed a protective effect of HTN against the development of septic shock. In contrast, previous studies have shown HTN to be the most frequent co-morbidity in these patients, with a study showing higher mortality due to septic shock in patients with HTN.[20] PLOS is associated with an increased risk of hospital-acquired infections (HAIs), particularly in older patients, as well as shortages of beds and an increased financial burden on patient.[21,22] In contrast, the current study showed that younger age and CKD were positively associated with PLOS in patients presenting with sepsis. Literature supports renal failure

Table-3: Univariate analysis to identify factors associated independently with septic shock, prolonged length stay of hospital and mortality.

Variable	Septic shock		Prolonged length of stay		Mortality	
	Crude OR (95% CI)	*p*-value	Crude OR (95% CI)	*p*-value	Crude OR (95% CI)	*p*-value
Age (???)	0.99 (0.99-1.00)	0.93	0.98(0.98-0.99)	0.001*	0.99(.98-1.00)	0.249*
Gender						
Female	1.029 (1.03-1.64	0.028*	1.15 (.88-1.51)	0.300	1.02(.79-1.32)	0.839
Male	-	-	-	-	-	-
Comorbid						
Hypertension	.75 (.59-.95)	0.02*	0.88(0.67-1.16)	0.392	0.80(.62-1.04	0.091*
Ischemic heart disease	1.04 (.67-1.61)	0.84	1.42 (0.88-2.29)	0.144*	0.64(0.38-1.08)	0.093*
Diabetes mellitus	0.91 (0.47-1.16)	0.47	0.89 (0.68-1.17)	0.41	0.79(0.61-0.68)	0.069*
CKD	1.22 (.95-1.58)	0.115*	1.47(1.10- 1.96)	0.0081*	1.17(0.89-1.44)	0.251
Smoking	0.93 (0.60-1.43)	0.73	0.99 (0.60-1.63)	0.97	0.85 (0.52-1.36)	0.492
Clinical parameters and outcomes						
Positive Culture	1.47 (1.10-1.97)	<0.001*	0.89(0.64-1.25)	<0.001*	0.93(0.684-1.28)	0.784
Organisms						
Bacteria	0.43(0.13-1.36)	0.142*	2.33 (0.51-10.58)	0.26	0.41(0.15-1.14)	0.077*
1. Gram positive	0.77(0.45-1.31)	0.33	1.43(0.78-2.63)	0.242*	1.40(0.78-2.50)	0.252
A. *Staphylococcus Species*	0.56(0.31-1.00)	0.049*	1.34(0.7-2.6)	0.38	0.97(0.51-1.84)	0.93
B. Others	-	-	-	-	-	-
2. Gram Negative	-	-	-	-	-	-
A. *E. Coli*	0.85(0.49-1.48)	0.57	1.28(0.68-2.40)	0.44	0.26(0.12-0.54)	<0.001*
B. Others	-	-	-	-	-	-
Treatment modalities						
Antibiotics	1.54(1.05-2.26)	0.027*	1.13(0.72-1.76)	0.58	1.27(0.83-1.93)	0.26
Piperacillin/Tazobactam	1.07(0.84-1.34)	0.595	0.92(0.69-1.20)	0.53	0.93(0.72-1.19)	0.57
Ceftriaxone	1.17(0.89-1.55)	0.252	0.9(0.64-1.24)	0.53	1.06 (0.78-1.42)	0.71
Meropenem	0.89(0.61-1.3)	0.55	1.19(0.79-1.82)	0.40	1.22(0.82-1.81)	0.31
Vancomycin	0.88(0.50-1.53)	0.65	1.02(0.53-1.95)	0.94	1.08(0.60-1.96)	0.78
Clinical investigations						
CRP	1.002(0.998-1.01)	0.318	0.99 (0.98-0.99)	0.0073*	0.999 (0.995-1.00)	0.766
WBCs	0.997(0.988-1.01)	0.576	0.99 (0.98-1.00)	0.519	1.007 (0.997-1.02)	0.156*
Procalcitonin	0.999 (0.995-1.00)	0.75	0.997 (0.992-1.00)	0.477	1.006 (1.001- 1.01)	0.0209*
Lactate	0.991 (0.940-1.04)	0.726	0.97(0.91-1.03)	0.446	1.013(0.957-1.06)	0.649

* < 0.25 and < 0.05 bold italics; OR: Odds ratio, CI: Confidence interval, E: Escherichia, CKD: Chronic kidney disease, CRP: C-reactive protein, WBC: White blood cell.

Table-4: Multivariable logistic regression to identify factors associated independently with septic shock, prolonged hospital length of stay and mortality.

Variable	Adjusted OR (95% CI) Septic Shock	*p*-value
Gender		
Female	1.29 (1.01-1.65)	0.040*
Male	Reference	-
Hypertension		
Yes	0.706 (0.547-0.910)	0.007*
No	Reference	-
CKD		
Yes	1.257 (0.956-1.65)	0.102
No	Reference	-
Culture Growth		
Positive	0.881 (0.035-22.4)	0.929
Negative	Reference	-
Culture Growth		
Bacterial	0.456 (0.123-1.31)	0.192
Non-Bacterial organisms	Reference	-
Culture Growth		
Staph species	0.605 (0.327-1.11)	0.107
Non-staph species	Reference	-
Antibiotics Given		
Yes	1.411 (0.946-2.12)	0.094
No	Reference	-
Prolonged hospital stay		
Age (???)	0.983 (0.975-0.991)	<0.001*
IHD		
Yes	1.472 (0.891-2.38)	0.122
No	Reference	-
CKD		
Yes	1.539 (1.14-2.07)	0.0047*
No	Reference	-
Culture Growth		
Positive	0.793 (0.221-2.26)	0.687
Negative	Reference	-
Culture Growth		
Gram Positive	1.39 (0.752-2.58)	0.291
Gram negative	Reference	-
Mortality		
Age (????)	0.999 (0.991-1.01)	0.876
Hypertension		
Yes	0.915 (0.664-1.26)	0.589
No	Reference	-
IHD		
Yes	0.709 (0.41-1.18)	0.199
No	Reference	-
DM		
Yes	0.831 (0.618-1.12)	0.223
No	Reference	-
Culture Growth		
Bacterial	0.568 (0.198-1.631)	0.286
Non-Bacterial	Reference	-
Culture Growth		
E. coli	0.278 (0.125-0.567)	<0.001*
Other bacteria	Reference	-

* < 0.25 and < 0.05 bold italics; OR: Odds ratio, CI: Confidence interval, IHD: Ischaemic heart disease, CKD: Chronic kidney disease, DM: Diabetes mellitus.

as a risk factor associated with PLOS in ICU.[23] Further research is necessary to identify patient factors associated with PLOS specifically in patients with sepsis to allow early identification and better management in patients at risk.

According to the current study, E. Coli on culture was linked to a comparatively decreased risk of death. This is in contrast to earlier findings showing that gram-negative bacteraemia, including E. coli, is associated with increased mortality rate.[24]

The current study has some limitations. Certain laboratory investigations and blood culture reports were not available universally in the cohort. Given the relatively greater cost of laboratory investigations at the study site, being a private tertiary care institution, some patients opted to obtain laboratory investigations, including cultures, at subsidised rates from nearby hospitals prior to admission at AKUH. Some data related to antibiotic treatment received prior to admission at AKUH was also not available in the institutional online patient data system. There was also a lack of information on the time of development of septic shock i.e., if it was present at initial presentation, or developed during hospital stay. Lastly, given that some patients obtained blood cultures and received antibiotic treatment prior to admission at AKUH, it is not known if all blood cultures were collected before the initiation of antibiotics or not.

Conclusion

There was a strong association between specific patient characteristics and various sepsis outcomes. The findings can be used for risk stratification when a patient presents with sepsis to allow better management and to anticipate any complications that may arise.

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Author Contribution:

AA and RSM: Conceptualized the study
MA, SJ, MA and IA: Study design and drafting the protocol.
MA: Statistical analysis.
MA, MA SJ. IA: Drafting the initial version.
All the authors were responsible for reviewing, editing and final approval.