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Frequency and Cause of Readmissions in Sepsis Patients Presenting to a Tertiary Care Hospital in a Low Middle Income Country

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Objectives: Hospital readmissions are known to be common after sepsis but unfortunately, in a developing country like Pakistan, very little is known of the frequency or cause of these readmissions in sepsis patients and even less about how they can be prevented. To our knowledge, this is the first-ever long-term follow-up study in a developing country in which frequency and cause of readmissions are being evaluated in sepsis patients.

Design: This retrospective study evaluated sepsis patients admitted at the Aga Khan University Hospital in 2017. Outcome measures included in-hospital mortality and readmission within 180 days.

Setting: Aga Khan University Hospital, Karachi, Pakistan.

Subjects: Four-hundred thirty-nine sepsis patients.

Interventions: None.

Measurements and Main Results: Respiratory infections were the most common cause of sepsis (172 [39%]) followed by urinary tract infections (86 [20%]). Mortality in sepsis was 42% (183/439) and associated risk factors included ICU admission (odds ratio, 1.57; 95% CI, 1.05–2.35; $p = 0.027$), malignancy(odds ratio, 3.50; 95% CI, 1.70–7.19; $p = 0.001$), acute kidney injury (odds ratio, 1.86; 95% CI, 1.25–2.77; $p = 0.002$), septic shock (odds ratio, 4.75; 95% CI, 3.04–7.35; $p = 0.001$), and serum lactate greater than or equal to 4 mmol (odds ratio, 5.11; 95% CI, 3.00–8.73; $p = 0.001$). Of the 256 patients that survived, 31% (79/256) were readmitted within 180 days. Infections accounted for 67% (53/79) of these readmissions. Half of these infections were new infections while an additional 26% were unclear since cultures were negative in at least one of the hospitalizations.

Conclusions: We concluded that mortality rates in sepsis are alarmingly high and even those who manage to survive are still at a great risk of getting readmitted due to a new infection in the near future. Given the limited resources available in developing countries, prevention of these infections should be given utmost importance. Unfortunately, reliable interventions to identify high-risk patients for readmissions are still inadequately characterized. Hence, we hope this study becomes a platform for larger multicenter studies in developing countries for early prediction of potential readmissions and developing precise interventions to prevent them.

Key Words: critical illness; infection; outcomes; patient readmission; sepsis; septic shock

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to an infection and is the leading cause of death from infection in the world with a global burden of around 30 million people every year and is responsible for approximately 6 million deaths (1, 2). It has remained the major cause of admissions into the ICUs and mortality around the world for a very long time and its reported incidence is continuously on the rise (3).

In addition to this, even the patients who manage to survive carry on using hospital resources in the form of readmissions which are known to further increase the risk of mortality, their quality of life and have extensive long-term implications for patients and the public (4). Each hospitalization results in severe consequences and takes a toll on the patient physically and mentally as patients experience lack of sleep, poor nutrition, medications that alter physical function and cognition, pain, and other

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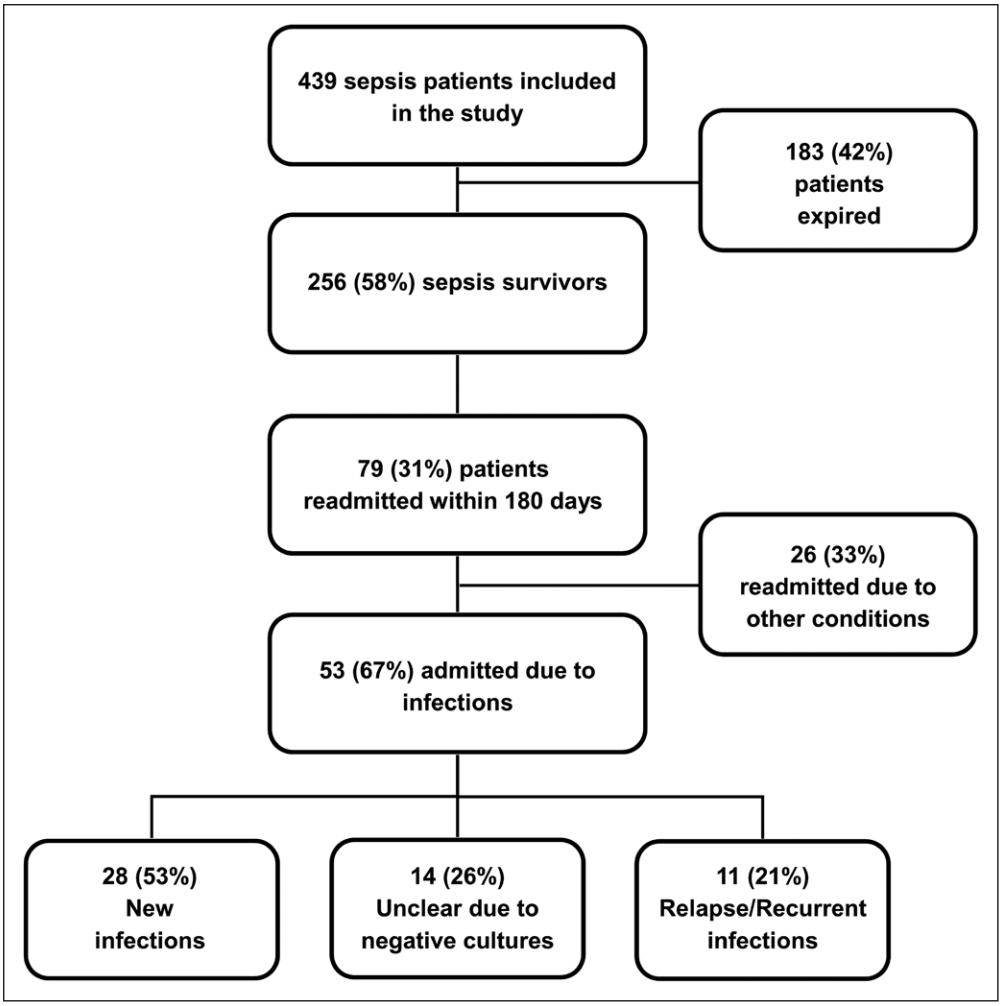

Figure 1. Flowchart of patient outcomes ($n = 439$).

discomforts. These trepidations eventually affect health, functional status, and cognition, which result in poor quality of life in the years to follow (5).

The association between sepsis survival and readmission is a relatively new field of research with previous studies mainly focusing on short-term outcomes of sepsis. Furthermore, even the few studies that have looked at the frequency of readmissions are all based in high-income countries. In a developing country like Pakistan, very little is known of the frequency or cause of these readmissions in sepsis survivor patients and even less about how they can be prevented (6). To our knowledge, this is the first-ever long-term follow-up study in a developing country in which frequency of readmissions are being evaluated in sepsis patients.

MATERIALS AND METHODS

Study Design/Data Source

This retrospective study evaluated adult patients admitted at the Aga Khan University Hospital between January 2017 and December 2017 with the diagnosis of sepsis. Aga Khan University Hospital is a 740 bedded private hospital situated in the heart of Karachi, the sixth most populous city in the world, and caters to a diverse group of patients hailing from all parts of the country and belonging to different ethnicities and socio-economic backgrounds. The study was approved by the Institutional Review Board at Aga Khan University, Karachi.

We identified all patients who were admitted in the year 2017 with the diagnosis of sepsis and/or septic shock. We defined these cases by the presence of an *International Classification of Diseases*, 9th Edition, Clinical Modification code for sepsis (995.91), severe sepsis (995.92) or septic shock (785.52). According to current literature, this approach provides a highly specific sepsis cohort and, thus, a conservative estimate of sepsis patients (7).

Operational Definitions

Index hospitalization was defined as the first time, in a series of hospitalizations, that a patient is admitted to a hospital for a specific condition or diagnosis. If the patient returned to the hospital and got admitted again, then that second stay was labeled as readmission.

Recurrent infection was defined as a new infection by the same organism at the same site after successful treatment on the index hospitalization. Relapse was defined as worsening of an existing infection after a period of improvement of symptoms.

Chronic kidney disease (CKD) was defined according to the The Kidney Disease: Improving Global Outcomes criteria. Stages G3a, G3b, G4 were classified as CKD.

Outcomes

Outcome measures included in-hospital mortality and readmission within 180 days.

Data Collection

Two-thousand six-hundred seventy-two patients were coded for sepsis and/or septic shock in the year 2017. We selected 439 patients via random sampling and reviewed their medical records to abstract clinical data to address the study's primary objectives. Sample size was calculated using the Open Epi software using a power of 80%, 95% CI, and a 6-month readmission rate of 48% (8). The minimum sample size required to achieve a representative sample was 335 patients.

There is no national database for Sepsis in Pakistan, and there are also no electronic health records in hospitals across Pakistan. Our institution stores medical information of patients in physical

TABLE 1. Characteristics of Sepsis Patients (*n* = 439)

Characteristics	Overall (*n* = 439)	Expired (*n* = 183)	Survived (*n* = 256)	*p*	Readmitted (*n* = 79)	Not Readmitted (*n* = 177)	*p*
Mean age, yr, mean ± SD	59.4 ± 17	59.4 ± 19	59.5 ± 17	0.953	60.19 ± 17	59.2 ± 17	0.647
Gender, *n* (%)				0.826			0.331
Male	245 (56)	101 (55)	144 (56)		48 (55)	96 (56)	
Female	194 (44)	82 (45)	112 (44)		31 (45)	81 (44)	
Comorbid conditions							
Charlson score, mean ± SD	3.95 ± 2.5	4.05 ± 2.6	3.88 ± 2.6	0.488	4.34 ± 2.4	3.7 ± 2.7	0.066
Diabetes, *n* (%)	181 (41.2)	61 (33)	120 (47)	0.004	41 (33)	79 (47)	0.282
Hypertension, *n* (%)	232 (52.8)	88 (48)	144 (56)	0.091	48 (48)	96 (56)	0.331
Ischemic heart disease, *n* (%)	85 (19.4)	34 (19)	51 (20)	0.726	22 (19)	29 (20)	0.034
Chronic kidney disease, *n* (%)	58 (13.2)	18 (10)	40 (16)	0.077	15 (10)	25 (16)	0.322
Malignancy, *n* (%)	39 (8.9)	27 (15)	12 (5)	< 0.001	4 (15)	8 (5)	0.849
Hospitalization factors							
Acute kidney injury, *n* (%)	186 (42)	62 (34)	124 (48)	0.002	40 (42)	84 (34)	0.639
Septic shock, *n* (%)	269 (61.3)	148 (81)	121 (47)	< 0.001	35 (61.3)	86 (81)	0.526
ICU admission, *n* (%)	152 (35)	74 (40)	78 (30)	0.031	55 (35)	123 (40)	0.984
Culture-positive, *n* (%)	132 (30)	61 (33)	71 (28)	0.055	20 (30)	51 (33)	0.564
Length of stay, d, mean ± SD	8.6 ± 7.7	7.1 ± 6.9	8.7 ± 7.7	0.371	8.5 ± 7.3	8.8 ± 7.9	0.791
Duration of antibiotics, d, mean ± SD	9.7 ± 6.2	5.3 ± 4.1	9.8 ± 6.2	0.058	10.4 ± 7.3	9.5 ± 5.7	0.278
Hospitalization in prior year, *n* (%)	248 (56.4)	111 (61)	137 (54)	0.137	46 (56.4)	97 (61)	0.246
Mean serum lactate at admission, mmol/L, mean ± SD	4.23 ± 4.1	5.9 ± 4.8	2.8 ± 2.6	0.001	4.23 ± 4.1	5.9 ± 4.8	0.143
Mean hemoglobin, g/dL, mean ± SD	10.6 ± 2.3	10.5 ± 2.5	10.6 ± 2.2	0.794	10.5 ± 2.4	10.6 ± 2.2	0.719

folders. Each patient has a unique medical record number which can be used to the access the folder. The folder contains handwritten notes from physicians, nurses, and other members of the healthcare team during all their inpatient and outpatient encounters. Researchers can only access these medical record folders after approval from the Ethical Review Committee at Aga Khan University. Once ethical approval was obtained, our research team manually went through each patient's folder to obtain the data that is presented in this research.

The independent variables in the model included patient factors (age, gender, comorbid conditions, and prior hospitalizations) and hospitalization-related factors (ICU admission, blood cultures, septic shock, central line insertion, hemoglobin level, and serum lactate at admission). Any readmissions within the next 180 days were also recorded along with reason for readmission and outcome.

Statistical Analysis

IBM SPSS Statistics Version 22.0 (IBM Corp., Armonk, NY) was used for data analysis. We compared characteristics between patients who expired during index hospitalization and those who survived by using Student *t* test or Wilcoxon rank-sum test for continuous variables, and chi-square test or Fisher exact test for categorical variables, based on cell counts. Multivariable logistic regression was used to determine associations between patient and hospitalization characteristics and mortality after being adjusted for potential confounders such as age, sex, and comorbidities, using Charlson Comorbidity Index score. A *p* value less than or equal to 0.05 was considered as significant.

RESULTS

Characteristics of Sepsis Patients

Of the 8,140 patients who were admitted in the department of medicine at the Aga Khan University Hospital, 2,672 admissions (33%) were coded for sepsis and/or septic shock in the year 2017. Four-hundred thirty-nine of these sepsis patients were selected via random sampling for detailed review of risk factors, outcome, and readmissions within 180 days (**Fig. 1**).

Among the sepsis admissions, the overall mortality rate of the 2,672 patients was 44% and mean length of stay was 8.4 ± 8.9 days. Among the 439 patients included in the study, 183 patients died (42%) during their index hospitalization. The age, sex, and Charlson score of patients who died were not significantly

TABLE 2. Source of Infection and Etiology of Sepsis Patients (*n* = 439)

Characteristics	*n* (%)
Source of infection	
Respiratory	172 (39)
Urinary	86 (20)
Unspecified	62 (14)
Skin/soft tissue	53 (12)
Gastrointestinal	35 (8)
Central line-associated	14 (3)
Neurologic	11 (2.5)
Cardiac	6 (1.5)
Organisms	
Culture-positive	132 (30)
Gram-negative organisms	82 (62)
Gram-positive organisms	38 (29)
Fungi	10 (7.5)
Acid-fast	2 (1.5)

TABLE 3. Adjusted Odds of Mortality in Sepsis (*n* = 439)

Characteristics	OR (95% CI)	*p*
ICU admission	1.57 (1.05–2.35)	0.027
Lactate ≥ 4 mmol/L	5.11 (3.00–8.73)	< 0.001
Septic shock	4.75 (3.04–7.35)	0.001
Malignancy diagnosis	3.50 (1.70–7.19)	0.001
Acute kidney injury	1.86 (1.25–2.77)	0.002

OR = odds ratio.

different from those who survived. Thirty-seven percent of patients required ICU care during index hospitalization. **Table 1** demonstrates the baseline characteristics and hospitalization factors of patients who died compared with those who survived. Respiratory infections were the most common cause of sepsis (172 [39%]) followed by urinary tract infections (86 [20%]). Culture was positive in 132 patients (30%) with gram-negative bacteria (82 [62%]) being the most common pathogens. **Table 2** summarizes the source of infections and etiology of all sepsis patients.

Factors Associated With Mortality

Mortality in sepsis was 42% (183/439). Significant risk factors associated with mortality were malignancy (odds ratio [OR], 3.50; 95% CI, 1.70–7.19), serum lactate levels at admission, ICU admission (OR, 1.57; 95% CI, 1.05–2.35), septic shock (OR, 4.75; 95% CI, 3.04–7.35), and acute kidney injury (OR, 1.86; 95% CI, 1.25–2.77). Adjusted ORs of these risk factors are presented in **Table 3**.

TABLE 4. Frequency and Cause of Hospital Readmissions in Sepsis Survivor Patients (*n* = 79)

Characteristics	*n* (%)
Cause of readmissions	
Infectious	53 (67)
Same site	31 (58)
Different site	22 (42)
Same organism	12 (23)
Different organism	19 (35)
At least one culture-negative	11 (21)
Both cultures negative	11 (21)
Noninfectious	26 (33)
Oncological	5 (20)
Planned procedure	5 (20)
Cardiac	5 (18)
Acute kidney injury	4 (16)
Stroke	3 (12)
Other	4 (16)

Frequency and Cause of Readmissions

Of the 256 patients that survived, 79 (31%) were readmitted within 180 days. Twenty percent of patients (16/79) had multiple readmissions during the 180-day period. Previous history of ischemic heart disease (p = 0.034) was the only significant risk factor for readmission. Mortality rate in readmissions was 16%. Infections accounted for 67% (53/79) of these readmissions out of which 53% (28/53) were new infections while an additional 26% (14/53) were unclear since cultures were negative in at least one of the hospitalizations. Detailed analysis of the frequency and cause of these readmissions are summarized in **Table 4** and **Figure 2**.

DISCUSSION

Sepsis is significant cause of death worldwide with mortality rates alarmingly high despite all the recent advancement in the medical world. Our study reported a mortality rate of 42% which seems to be slightly higher than similar studies around the globe (9). More worryingly, even the patients who survived were not spared from the clutches of sepsis, with almost one third of those survivors getting readmitted within 180 days. Readmissions after hospitalization with sepsis are known to be common and costly and come with grave physical as well as financial consequences.

The association between sepsis survival and readmission is a relatively new field of study with previous studies only focusing on short-term outcomes. Hence, we only found a few studies for comparison. Not even one of them was from a developing country. The landmark nationwide study by Norman et al (10) in the United States reported a 30-day readmission rate of 28%. Liu et al (11), in their study conducted in 21 community-based

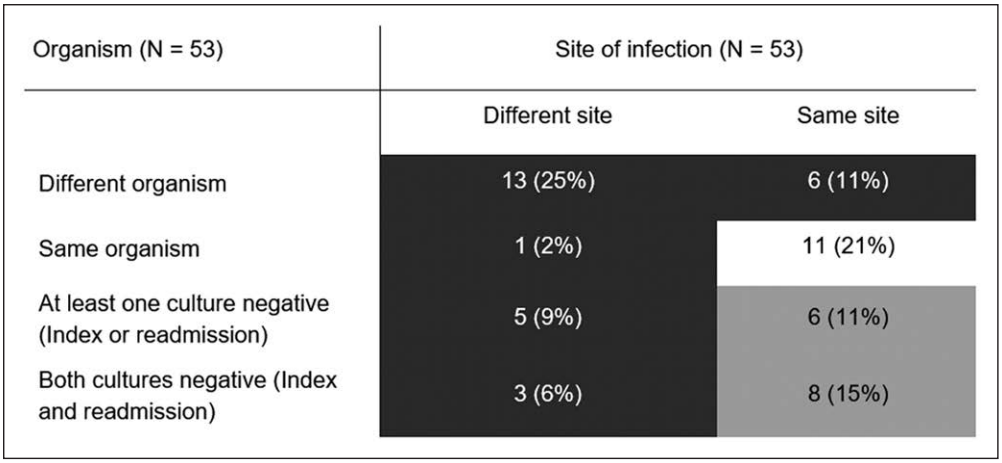

Figure 2. Index admission-readmission dyads for organism and site causing sepsis. *Dark gray cells* represent dyads with new infection ($n = 28$, 53%); *light gray cells* represent dyads for whom infection may have been new or may have been a relapse or recurrent infection ($n = 14$, 26%); the *white cell* represents dyads with a relapsed or recurrent infection ($n = 11$, 21%).

hospitals recorded a readmission rate of 17.9%. 90-day readmission rates were between 30% and 42% (12, 13). Goodwin et al (8) documented an astonishing 180-day readmission rate of 48% in a sample of 43,452 sepsis survivors admitted in all nonfederal hospitals in three U.S. states, namely California, Florida, and New York.

Several studies have noted that sepsis survivors are at a greater risk of mental illness, cognitive failure, organ dysfunction, and death (14, 15). The odds of acquiring moderate to severe cognitive impairment are three times more in sepsis survivors than in the nonsepsis population, and an additional mean increase of 1.5 times in patients with no previous history of functional disability (16). It has also been noted that prevalence of depression is considerably higher in sepsis survivors than general population estimates, and these depressive symptoms could exacerbate their cognitive and functional decline and eventually limit their ability to actively participate in rehabilitation (8). Furthermore, sepsis hospitalization is frequently associated with encephalopathy, sleep deprivation, and delirium (10).

In addition to the significant morbidity, each sepsis readmission also comes with an immense financial burden. The economic burden of sepsis has reached new spine-chilling heights with recent reports quoting an annual cost of more than $20 billion in the United States alone, making it the most expensive condition to treat in the entire U.S. healthcare system (17, 18). On average, a single readmission can cost anywhere between $25,000 and $30,000. The reason for these bloodcurdling numbers is that sepsis is typically treated in the ICU, and ICU treatment is very expensive as it includes cost of hospital stay, medicines, laboratory tests, medical equipment, procedures, staff, and taxes.

This financial burden of sepsis is even more pronounced in developing countries, like Pakistan, where all healthcare-related expenses are paid out-of-pocket by the patient with no facility of medical insurance or loans. A small glance at the per capita figures of third world countries really puts these statistics into perspective. With a per capita income of less than $1,500 compared to a mammoth $53,000 in the United States, one can imagine how overwhelming even one such readmission could be for patients and their family (19). There is usually just one bread-earner in the entire household and a prolonged hospitalization to that member could prove to be catastrophic for the entire household. Most employees live hand to mouth with very little savings or investment. Sick leave is not an option and every day spent in the hospital would mean no income for that day. Also, in most patriarchal families, a suitable replacement for the earning member would be difficult to find due to cultural issues. Families are then forced to sell all their assets or gather money by borrowing from friends and family for which it would take several years to repay. Nursing care is routinely provided by other family members in the house and this results in decreased attention to childcare and reduced earning capacity.

Our study has potential limitations. Since this was a single-center study, sepsis readmissions could possibly be underreported due to patients getting hospitalized to other healthcare centers. One major obstacle for such a study in low-income countries is the lack of proper health record systems. Aga Khan University Hospital is one of the very few institutions in the country that maintains a robust record of all patients and their hospital encounters. Hence, forming alliances with other centers for sepsis readmissions has proven to be challenging.

CONCLUSIONS

We concluded that mortality rates in sepsis are alarmingly high and even those patients who manage to survive are still at a great risk of getting readmitted due to a new infection in the near future. Given the limited resources available in developing countries, prevention of these infections should be given utmost importance. Unfortunately, reliable interventions to identify high-risk patients for readmissions are still inadequately characterized. Hence, we hope this study becomes a platform for larger multicenter studies in developing countries for early prediction of potential readmissions and development of precise interventions to prevent them.

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