INTRODUCTION

Sepsis is one of the most common, least-recognized illnesses in both the developed and developing world. It is the primary cause of death from infection despite advances in modern medicine, and carries long-term complications. Sepsis causes more deaths than prostate cancer, breast cancer and HIV/AIDS combined. It is estimated that more than 18 million people suffer from sepsis each year and more than 5 million of them die. Severe sepsis and septic shock are important causes of morbidity and mortality in patients admitted to intensive care units. These conditions are generally associated with multiple organ failure as final outcome.

Sepsis occurs in approximately 2% of all hospitalizations in developed countries. Sepsis may occur in between 6 and 30% of all intensive care
unit (ICU) patients. However, there is substantial variation in the incidence of sepsis and severe sepsis due to the heterogeneity between ICUs. In general, more than 50% of severe sepsis patients will require intensive care services.\(^5\) It is evident that the mortality rate may have decreased in recent years but the incidence of severe sepsis and septic shock appears to be increasing, by 13.7% per year ultimately increasing overall deaths.\(^7\)

The incidence of sepsis varies among different racial and ethnic groups.\(^8\) In the United States, the incidence of severe sepsis is estimated to be 300 cases per 100,000 population from the years 1999-2005. In the UK alone it claims between 36,000 to 64,000 lives per year.\(^9\) The mortality rate from severe sepsis in the developed countries has been estimated as being between 28 and 50%, ranging from 15% in patients with sepsis to 40-50% in patients with septic shock with multi-organ dysfunction syndrome (MODS).\(^9\) It has been documented that sepsis is responsible for 60-80% deaths in developing countries including Pakistan.\(^10\)

Population and the extremes of age, infants and children and the elderly are the most vulnerable and so are people with chronic illnesses like diabetes mellitus, kidney and liver disease. The number of cases has been on the rise due to aging population, increasing lifespan of people with chronic illnesses and spread of antibiotic-resistant organisms.\(^11,12\)

There are a number of studies describing the epidemiology, risk factor and its outcome of severe sepsis and septic shock in various countries worldwide,\(^7\) in developing countries, unfortunately, data on bacterial sepsis are lacking, especially in adults.\(^13\) Data on sepsis in Pakistan remains regrettably scanty. To give an example, a nationwide registry of sepsis does not exist.\(^14\)

In view of the paucity of information concerning sepsis in developing countries, and especially in Pakistan, we have developed a study aim to explore the factors associated with outcome among patients with severe sepsis and septic shock admitted to the intensive care unit, Northwest General Hospital and Research Centre Peshawar Pakistan.

**METHOD**

This prospective observational study was performed at Medical intensive care unit (MICU) at Northwest General Hospital & Research Centre from February 2014 to October 2015. (21 Months) **Patient selection:** All participants admitted to MICU were screened for eligibility. Patients less than 18 years of age or with MICU length of stay (LOS) less than 24 hours were excluded while those with severe sepsis/septic shock at MICU admission or during hospitalization were included in the study, and only the first episode of severe sepsis or septic shock was counted. Patients readmitted into MICU during the same hospitalization were not screened again. Severe sepsis and septic shock were defined according to the American College of Chest Physicians/Society of Critical Care Medicine consensus conference definitions.\(^1\) The primary outcome measure was incidence and crude hospital mortality of severe sepsis and septic shock, as well as the risk factors for death. We included patients coming from emergency room and hospital wards covering both community and hospital-acquired infections.

The data was recorded using a predesigned structured format for all new adult admission to ICU. Demographic data, source of infection, comorbid diseases, and clinical laboratory data, hospital stay and outcomes were collected prospectively. Patients were followed up until death or hospital discharge, whichever occurred earlier. Ethical approval for the study was obtained from hospital ethical committee. Data collection was standardized and performed by the main investigator along with trained sub-investigators during the study period. **Statistical analysis:** Data was analyzed using the SPSS 20 software program. Numerical variables were presented as mean ± SD. Categorical variables were described as frequency percentage. Binary logistic regression and multi-variate analysis was carried out to identify the factors associated with the survival and mortality of the patients. The level of statistical significance was set at \(p < 0.05\).

**RESULTS**

A total of 450 patients admitted to the Medical ICU during the study period were assessed for inclusion in the study sample. Of whom \(n = 268\) patients were diagnosed with sepsis. Majority 147 (54.9%) were male patients with a mean age of 54.8. The presence of septic shock was prevalent in 59.3% with average ICU stay was 5.34 days details are shown in Table-I.

Assessing the situation based on micro-organism isolates from cultures, Escherichia coli ESBL was the most commonly observed bacteria followed by Candida, Acinetobacter baumannii and Methicillin-resistant Staphylococcus aureus. Overall, the presence of microbes were more frequent among blood samples. (Table-II)

The most common source of sepsis was lung infections (42.2%) followed by urinary tract infections.
(18.7%), soft tissue infections (6.3%) abdominal infections (6%) and in 6.3% patients the source remained unknown. Details are shown in Table-III.

Factors associated with the outcome of sepsis management: Using outcome as the dependent variable, binary logistic regression was applied. All the variables commonly reported in literature were added in the model and odd ratios were estimated for potential association with the outcome of the sepsis patients. Results have shown that, gender age, length of hospital stay, was not significantly associated with the outcome of therapy (i.e. death or discharged). However, increase in number of days of hospitalization was observed to be slightly associated with the outcome of the treatment (1.086 [1.002 – 1.178], 0.046). Along with the length of hospital stay, having a positive blood culture was observed to be an important factor associated with the outcome i.e. death / discharge of the patients. Finally the risk of mortality was higher among the patients with septic shock 22.161[10.055 – 48.840], and having respiratory, kidney and central nervous system complications. Details are shown in Table-IV.

Furthermore variables found significantly associated with sepsis outcome were added in a linear regression model to predict the effect of change. Overall it is seen that septic shock alone was found responsible for death among 32.0% of the patients

| Age (years) median 58 years | 54.85±19.85 |
|-----------------------------|-------------|
| Gender                      |             |
| Male                        | 147(54.9%)  |
| Female                      | 121(45.1%)  |
| Length of hospital stay (days) | 5.34±4.23  |
| Diagnosis                   |             |
| Severe sepsis               | 109(40.7%)  |
| Septic shock                | 159(59.3%)  |
| Outcome**                   |             |
| Dead                        | 109(40.7%)  |
| Discharged                  | 159(59.3%)  |
| Blood culture               |             |
| Positive                    | 91(34%)     |
| Negative                    | 177(66%)    |
| Urine culture               |             |
| Positive                    | 68(25.4%)   |
| Negative                    | 199(74.6%)  |
| Sputum culture              |             |
| Positive                    | 49(18.3%)   |
| Negative                    | 193(72%)    |
| Mortality*                  |             |
| Severe sepsis               | 8(7.3%)     |
| Septic shock                | 101(63.5%)  |

• Calculated with reference to outcome** therefore the sum will not be 100%.

- Table-I: Baseline/Demographic characteristics of patients.
- Table-II: Micro-organism isolates from cultures.
- Table-III: Site of infection and organ involvements.

Mucor, Acid-fast bacilli (AFB), Moraxella, streph, pseudo MDR, Diphtheroid, Crimean-Congo haemorrhagic fever (CCHF), Enterococcus, Serratia, Bacteroids, E coli, Pseudomonas.
The current study is perhaps one of the very few prospective studies aiming to investigate the outcome of sepsis in private health care setting in Pakistan. Of the entire study population about 159 (59.3%) were diagnosed with sepsis shock and 109 (40.7%) were found to be suffering through sepsis. It was surprising to see that the mortality rate reported among the severe sepsis patients was 8 (7.3%), and remaining 101 (92.7%) were treated successfully and discharged. The survival rate among the severe sepsis patient revealed by this study is far higher than the studies done in global ICU setting reporting the mortality rate to be 20-50%.15,16 Comparing our results with Albert and colleagues (2003) where mortality with severe sepsis was shown to be 40.9%, interestingly our mortality with severe sepsis was low at 7.3%. This could be difficult to explain, however methodological variations in studies may make it very difficult to compare results across. Even applying the same diagnostic criteria but different design of study, inclusion and exclusion criteria may probably account for some of the differences.17 However, the mortality rate among the septic shock patients was reported to be very high 101 (63.5%), and only 58 (36.5%) patient survived the impact of the septic shock.

One of the recent multicenter study has revealed a cumulative rate of 28.4% among the patient population suffering from sepsis and septic shock.18 Comparing our results with this multicenter study it was revealed that the cumulative mortality rate of severe sepsis and septic shock was 40.7%. This is much higher in comparison to the studies done in the developed nations.19-22 Comparison with Pakistani ICU practice, it is seen that on an average the mortality rate is found to be higher than 30.0%.4 However, mortality with septic shock was comparable with (60.5% Albert & Colleagues vs. 63.5% in our study). Thus to compare our results with those of other studies around the globe, it is necessary to take into account all the differences in our study population. Quality Primary care here is patchy and early recognition of severity of illness is often missed. Our patients may present very late for a number of reasons including financial restraints and travelling from far away countryside. However, this situation somehow is in line with some observational studies23,24 that suggest the mortality rate may still be higher than reported

### DISCUSSION

The study was conducted on 159 sepsis patients and 109 sepsis shock patients in a private hospital in Peshawar, Pakistan. The mortality rate among sepsis patients was 7.3%, while 63.5% of septic shock patients died. The study used binary logistic regression to analyze factors associated with sepsis outcome.

#### Table-IV: Factors associated with the sepsis outcome.

| Variables                                | Exp (B)   | CI [95%]   |
|------------------------------------------|-----------|------------|
| Gender                                   | 1.079     | [0.661 – 1.761] |
| Age                                      | 0.986     | [0.975 – 1.007] |
| Length of hospital stay                  | 0.979     | [0.970 – 1.177] |
| Blood Culture Positive                   | 1.727     | [1.034 – 2.884] |
| Urine Culture Positive                   | 0.351     | [0.188 – 0.656] |
| Sputum Culture Positive                  | 0.803     | [0.420 – 1.534] |
| Hospital Acquired Infections             | 0.989     | [0.762 – 1.284] |
| Co-morbidities                           | 1.007     | [0.985 – 1.030] |
| Renal complications/ infections during sepsis | 4.653   | [2.336 – 9.266] |
| Respiratory complications/ infections during sepsis | 22.400 | [2.831 – 57.266] |
| CNS complications/ infection during sepsis | 2.589     | [1.357 – 4.939] |
| Gastro-Intestinal complications/ infection during sepsis | 2.021     | [0.720 – 5.673] |
| Liver complications during sepsis        | 1.164     | [0.483 – 2.803] |
| Septic shock                             | 22.161    | [10.055 – 48.840] |

#### Table-V: Predictors of Mortality.

| Model                              | R Square | Change Statistics |
|------------------------------------|----------|------------------|
| F Change                           | Standard df2 | df1  | p-value |
| Error                              |-----------|------|--------|
| 1                                  | 0.320     | 124.810   | 0.407  | 265 | 1  | 0.000 |
| 2                                  | 0.354     | 13.783    | 0.397  | 264 | 1  | 0.000 |
| 3                                  | 0.384     | 12.687    | 0.389  | 263 | 1  | 0.000 |
| 4                                  | 0.398     | 6.381     | 0.385  | 262 | 1  | 0.012 |
| 5                                  | 0.408     | 4.411     | 0.382  | 261 | 1  | 0.037 |
| 6                                  | 0.421     | 5.854     | 0.379  | 260 | 1  | 0.016 |

Model 1: Predictors: (Constant), septic shock;
Model 2: Predictors: (Constant), septic shock, Urine culture;
Model 3: Predictors: (Constant), septic shock, Urine culture, kidney complications;
Model 4: Predictors: (Constant), septic shock, Urine culture, kidney complications, CNS infections;
Model 5: Predictors: (Constant), septic shock, Urine culture, kidney complications, CNS infections, Length of Hospital in days;
Model 6: Predictors: (Constant), septic shock, Urine culture, kidney complications, CNS infections, Length of Hospital in days, respiratory infections.

*significant, binary logistic regression was applied. Dependent variable “outcome”. Model was capable to predict 82.4% of the categories.

(Model 1: R²=0.32, p=0.000). In the final model (model 6), urine culture, kidney complications, CNS infections, Length of Hospital stay in days and respiratory infections were also added to the final model and it was seen that (Model 6: R²=0.421, p=0.016), the risk of mortality further increase by 8.0%. Overall, the factors and the predictors added in model 6 were found to increase the risk of mortality among the patients by 40%. Details are shown in Table-V.
from interventional studies\textsuperscript{25} that often exclude the highest risk groups of patients, and also more formally structure the delivery of care.

\textbf{Causes of Mortality:} This is perhaps one of the challenging task to identify the factors associated with the mortality of patients. Variety of factors may have association with the survival and death of patients suffering from sepsis and septic shock. Addressing the results of the current study, it was seen that about 54.9\% of the patients were male. However, being a female was observed to be slightly contributing to mortality 1.070 [0.655 – 1.749]. In our study, we observed adult patients with sepsis for the entire duration of hospitalization. Our patients were younger, with a median of 58 years as compared with sepsis patients of European origin [median 64 years]\textsuperscript{5} those from North America [mean 60.8 years]\textsuperscript{6} And Brazil [median age 65.2 years]\textsuperscript{7}. Thus the importance of clinical parameters will be perhaps more significant to the mortality rather than a gender comparison. It was noticed that in about 34.0\% of the cases blood culture was positive for microbial growth, and in 25.4\% cases urine culture was positive. While sputum culture was positive in about 18.3\% of cases. Having a blood culture positive was more likely to be associated with the mortality 1.964 [1.101 – 3.503]. Moreover, the chance of mortality was at least 35\% higher among the patients with positive urine culture 0.351 [0.188 – 0.656].of whom 50(19.3\%) were with E.coli positive culture. These results confirm the results of the one of the recent study that reported higher mortality among the patients with UTIs and E.Coli positive culture.\textsuperscript{4}

Overall analysis revealed that odds of surviving for an elderly patients is less 0.986 CI [0.975 – 1.007]. However, chance of survival reduces by 0.979 percent with an increase in length in hospital stay. Estimating the impact of septic shock on survival of patients, it was noticed that the likelihood for death was 22.161[10.055 – 48.840] times higher among the patients suffering from septic shock, similarity the chance of death further increase by 22.400 [2.831 – 57.266] if patient have respiratory complications or lungs involvement CNS and Urinary tract infections alone or in conjunction with one another. Thus chance of mortality was highest when patient have septic shock and respiratory and urinary tract infection.\textsuperscript{4}

Finally, multivariate modeling revealed that septic shock alone may result in an increase in mortality by 32.0\% (R\textsuperscript{2} 0.320, Model 1), in addition the chance of survival further decrease by 10.0\% when patient have positive urine culture, kidney complications, CNS and respiratory infections and longer stay in hospital (Model 6). According to the literature, the most common infection sites in septic patients are the respiratory and genitourinary systems as well intra-abdominal surgical infections and indwelling catheters.\textsuperscript{13} Our results show similar findings; the most common focus of infection was Respiratory (pneumonia in 42.2\%) followed by urinary tract (18.7\%), soft tissue infections (6.3\%) abdomen (6\%) and in 6.3\% patients the source remained unknown. The mortality was significantly higher in patients with pneumonia (40.7\%), with Gram-negative organisms being the most predominant culprits.

\textbf{CONCLUSION}

Sepsis constitutes the majority of the patients admitted to the medical intensive care unit and carries a significant mortality. We have shown a prospective record of patients with severe sepsis and septic shock who were admitted to medical intensive care unit of our hospital .Results of this study revealed that the chances of recovery were poor among the patients with septic shock with a higher risk of mortality. Pneumonia and urinary tract infections were the predominant causes.

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