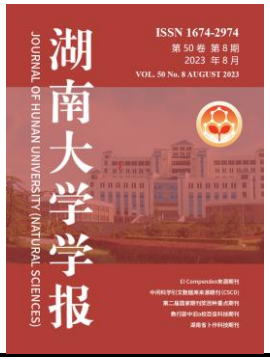

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Evaluation of Severity, Antibiotic Prescribing Patterns, and Outcomes of Sepsis in the ICU Using the APACHE-IV Scale

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Abstract: Sepsis, the body's systemic immune response to infection, can execute organs. This study assessed the prevalence, severity, prescribing pattern of antibiotics, and outcomes of sepsis. This observational-analytical prospective investigation was conducted on 70 ICU patients admitted with severe sepsis and septic shock in health care. The severity of illness was assessed by Acute Physiology and Chronic Health Evaluation IV (APACHE-IV). Antibiotic prescribing trends were also assessed to optimize therapeutic failure risk assessment for septic ICU patients. Fisher's exact test and Pearson-Chi square test were used to determine the statistical relationship between age, APACHE-IV score, therapeutic outcome, and microbial growth studies across different parameters. The clinical and laboratory profiles of the survivor and non-survivor groups were compared using one-way ANOVA. Results showed that sepsis occurred in one quarter (25.1%) of ICU-admitted patients. APACHE-IV has under-predicted death rates as the Actual Mortality Rate (AMR = 50%) is higher than the average APACHE-IV predicted mortality rate (PMR = 36.6%). The use of combination antibiotics is more prevalent in empiric therapy than in definitive therapy. Gram-negative organisms were the most prevalent cause of sepsis in the ICU. Meropenem was the most prescribed empiric antibiotic either as monotherapy or in combination, whereas colistin was the most prescribed antibiotic in definitive therapy either alone or in combination. This study concluded that sepsis is associated with high mortality. Continuous calibration of severity scales can improve patient outcomes. Judicious use of antibiotics is highly recommended as the last resort of antibiotics for treating sepsis. This study focused on optimizing antibiotic stewardship programs to improve treatment options for critically ill septic patients in ICUs. It integrates APACHE IV scoring and provides a comprehensive analysis of antibiotic choices.

Keywords: APACHE score, intensive care unit, antibiotic intervention, SAP, culture sensitivity.

使用"急性生理学和慢性健康评估 IV"量表评估重症监护病房脓毒症的严重程度，抗生素处方模式和结果

摘要：败血症，身体对感染的全身免疫反应，可以执行器官。本研究评估了抗生素的患病率，严重程度，处方模式和败血症的结果。这项观察分析前瞻性调查是对 70 名重症监护病房患者进行的，这些患者在医疗保健中患有严重败血症和脓毒性休克。通过急性生理学和慢性健康评估 IV 评估疾病的严重程度，还评估了抗生素处方趋势，以优化脓毒性重症监护病房患者的治疗失败风险评估。费舍尔的确切检验和培生-志广场检验用于确定跨不同参数的年龄，急性生理学和慢性健康评估 IV 评分，治疗结果和微生物生长研究之间的统计关系。使用单向方差分析比较幸存者和非幸存者组的临床和实验室概况。结果显示，四分之一（25.1%）的重症监护病房入院患者发生脓毒症。急性生理和慢性健康评估 IV 具有预测不足的死亡率，因为实际死亡率（50%）高于平均急性生理和慢性健康评估 IV 预测死亡率（36.6%）。联合抗生素的使用在经验性治疗中比在确定性治疗中更为普遍。革兰氏阴性菌是重症监护室脓毒症最常见的原因。美罗培南是单药或联合用药中最常使用的经验性抗生素，而粘菌素是单独或联合治疗中最常使用的根治性抗生素。这项研究的结论是败血症与高死亡率相关。持续校准严重程度量表可以改善患者的治疗结果。强烈建议明智地使用抗生素作为治疗脓毒症的最后手段。这项研究的重点是优化抗生素管理计划，以改善重症监护室重症脓毒症患者的治疗选择。它集成了阿帕奇四世评分并提供抗生素选择的全面分析。

关键词：急性生理学和慢性健康评估评分，重症监护室，抗生素干预，手术抗生素预防评分，培养敏感性.

1. Introduction

Sepsis is a systemic immunological reaction of the body to an infectious process that can result in organ failure and death [1]. In Intensive Care Units (ICUs), the major causes of mortality include severe sepsis and septic shock [2]. Despite substantial improvements in the pathophysiology of this clinical situation, resuscitation therapies, and hemodynamic monitoring tools, it remains one of the most important reasons for mortality and morbidity in critically ill septic patients [3, 4].

There is no assessment methodology for sepsis patients approved to check the severity of sickness. Without a framework in place, analyzing sepsis outcome studies can be challenging. As a result, Mortality Prediction Systems are being utilized as tool for assessing the performance of ICU [4,5]. There are numerous uses for predictive scoring systems.

Mortality prediction systems play a crucial role in predicting the outcomes of individual patients by minimizing risks and enhancing the decision-making basis. Prognostic scoring systems can aid in the evaluation of ICU's quality by allowing evaluation and judgment of its general performance to a huge, representative database [5,6].

However, quantifying the global epidemiological burden of sepsis is challenging. It is estimated that annually, sepsis affects more than 30 million individuals, with the potential for 6 million deaths [6,7]. According to the Surviving Sepsis Campaign 2012, sepsis-related death rates were approximately 41% in Europe and 28% in the United States. In addition to that an estimated 60-80% of deaths in developing countries like Pakistan occur due to sepsis. However, this difference disappeared when disease severity was considered [7]. This indicates that mortality associated with sepsis varies based on patient variables.

2. Methodology

At the intensive care unit of a health care facility, a prospective observational-analytical study was conducted. This study was approved by the Institutional Ethical Review Board of Jinnah University for Women, reference # JUW/IERB/034/2021. The study lasted six months, from August 2022 to January 2023. The study included medical data of 70 of 320 patients admitted to the ICU with septic shock, sepsis, or both according to the following eligibility criteria.

2.1. Inclusion Criteria

- Adult patients of both genders;
- Critically ill patients with sepsis admitted to ICUs and prescribed antibiotics;
- Patients admitted to ICUs for more than 24 hours;
- These patients were followed up until they were

discharged from the hospital or expired.

2.2. Exclusion Criteria

- Patients admitted to hospital wards other than ICUs;
- Patients discharged or shifted to other wards within 24 hours;
- Patients admitted to ICUs but not prescribed antibiotics;
- Patients readmitted to ICUs.

In this study, the predicting mortality of ICU patients with severe sepsis and septic shock was evaluated using the APACHE-IV, and the results were compared with actual mortality indices [8,9], to understand the prescribing pattern of antibiotics in order to optimize the antimicrobial use in septic patients, to assess the therapeutic efficacy of the available prescribed therapeutic regimen of antibiotics and evaluation of risk factors associated with therapeutic failure. Furthermore, the calculated severity of illness score has been associated with various risk factors such as age, gender, co-morbidities, etiological pathogens, class of antibiotic and its therapeutic efficacy.

3. Study Design

3.1. Statistical Analysis

The results were analyzed using Statistical Package for the Social Sciences (SPSS) 20. Demographics are expressed as the count, mean, standard deviation and percentage. The association between different parameters is determined by Fisher's exact test and Pearson – Chi square. The difference in the mean clinical and laboratory profiles of the survivor and non-survivor groups was analyzed using one-way ANOVA. Values of $P < 0.05$ were considered significant, and $P < 0.001$ was considered highly significant for all statistical comparisons.

3.2. Data Collection

To assess the antibiotic prescribing pattern, observational data will be collected by assessing the patient's present medical findings.

Data will be collected for:

- Demographic details;
- Previous medical history;
- Diagnostic workup;
- Physiological outcome measures.

The following data were collected to measure the APACHE IV score, which contains the following parameters [9,10].

3.2.1. Patient's Age

This parameter is self-describing.

3.2.2. Patient Acute Physiological Parameters

a) Temperature, b) mean arterial pressure (mmHg), c) heart rate (min), d) respiratory rate (min), e) mechanical ventilation, f) FiO_2 (%), g)pO_2 in millimeters of mercury, h) pCO_2in millimeters of mercury, i) arterial pH, j) Sodium+ (mEq/L), k) urine output in milliliter/24hour, l) creatinine (mg/dL), m) urea (mEq/L), n) blood sugar level (mg/dL), o) albumin (g/L), p) bilirubin (mg/dL), q) hematocrit (%), r) white blood cells (x1000/mm^3), and s) Glasgow Coma Scale.

3.2.3. Evaluation of the Chronic Health Condition

To evaluate the chronic health condition of the patients, whether they had severe organ system deficiency or compromised immune system, we evaluated some parameters/conditions, which included:

- Chronic renal failure;
- Cirrhosis;
- Hepatic failure;
- Metastatic carcinoma;
- Lymphoma;
- Leukemia/myeloma;
- Immunosuppression and AIDS.

3.2.4. Admission Information of the Patient

This covers patients admitted immediately from the emergency room, shifted from another ward or hospital, or transferred back to the intensive care unit.

3.2.5. Diagnosis at the Time of Admission

This parameter is self-describing.

3.2.6. Thrombolytic Treatment

Thrombolytic treatment is administered or not to patients with acute myocardial infarction.

3.2.7. Requirements for Ventilator Support

This parameter is self-describing.

3.2.8. Software

Using the following online software the data obtained from critically ill septic patients were transformed into APACHE-IV Score and Predicted Mortality Rate [11].

4. Results

This study examined critical care unit patients with sepsis from August 2022 to January 2023, and out of 320 patients, 70 met the criteria for septic shock and severe sepsis. In this study, there were 48 male and 22 female participants. Most of the patients under examination were admitted directly from the emergency ward to the ICU, while a lesser number were transferred from other healthcare facilities. The study participants' mean age was 53.64 ± 15.13 years, ranging from 24 to 90. The graph depicts the number of survivors and non-survivors by the age group. No

association was found between age and mortality, as shown in Fig. 1. Table 1 lists all co-morbidities observed in the patients, including respiratory sepsis, which was the most common, followed by sepsis with multi-organ damage, among others.

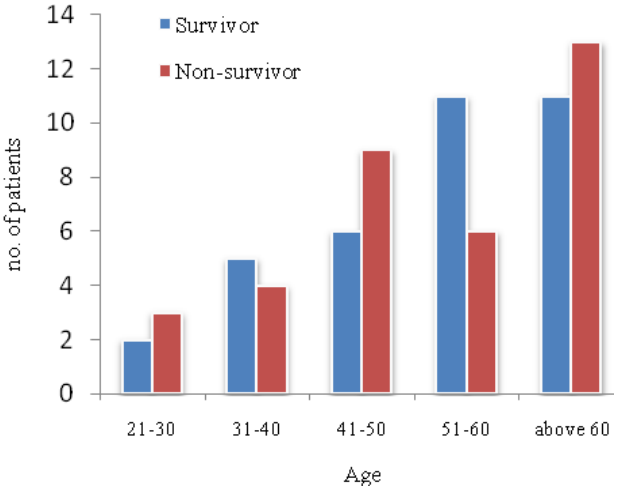

Fig. 1 Association of age with survival rate (p-value: 0.646)

Table 1 Diagnosis of patients on admission, sepsis with co-morbidities

	Diagnosis (Sepsis + comorbidities)	No. of patients n (%)
A	Sepsis	5 (7.1)
B.	Sepsis + Respiratory Disorder	25(35.7)
C.	Sepsis + Liver Disorder	6 (8.6)
D	Sepsis + Meningoencepalitis	2 (2.9)
E.	Sepsis + Renal Disorders	8 (11.4)
F.	Sepsis + Metabolic Disorders	2 (2.9)
G	Sepsis + Gastrointestinal Disorders	2 (2.9)
H	Sepsis + Multi Organ Damage	20(28.6)

In this study, out of 70 study patients, 35 had expired, resulting in an actual mortality rate (AMR) of 50%.The predicted mortality rate (PMR) mean for APACHE-IV was 36.6%, suggesting an overall mortality under-prediction. The standardized mortality rate (SMR) measured by taking the ratio of AMR by PMR was 1.36, as shown in Table 2. Furthermore, the actual mortality percentage overruled the predicted mortality percentage in each category of the APACHE IV score, as shown in Fig. 2.

Table 2 Standardized mortality rate Of ICU patients

Variable	Mean Score	Predicted mortality rate (PMR) %	Actual mortality rate (AMR) %	Standardized mortality rate (SMR) = AMR/PMR
APACHE IV	85.48 ± 30.3	36.6	50	1.36

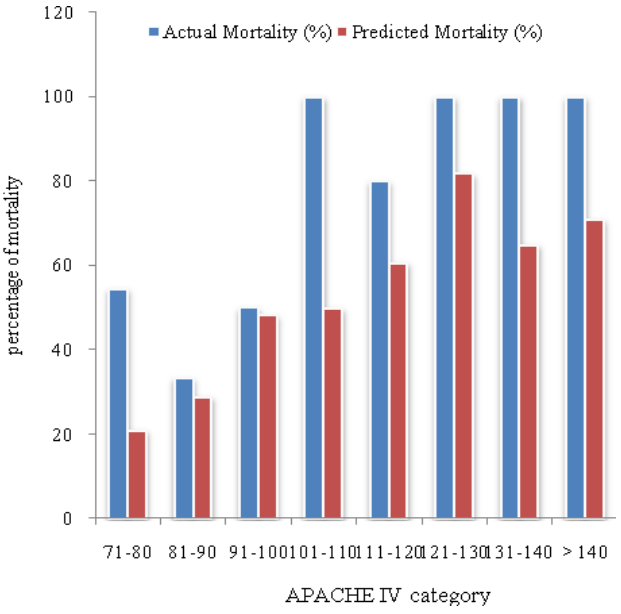

Fig. 2 Comparison of actual mortality with predicted mortality in APACHE IV score

4.1. Clinical Profile

The clinical profiles (pulmonary, renal, hepatic, electrolytes and vital signs) of survivors and non-survivors were analyzed using one-way ANOVA. The results revealed no significant differences in the mean temperature, heart rate, PO2, CO2, pH, creatinine, urea, blood sugar level, albumin, bilirubin, hematocrit, red blood cell count, platelets, total leukocyte count, HCO3, alkaline phosphatase, phosphate, hemoglobin, chloride, SGOT, SGPT, GGT, PT, APTT, and INR between the survivor and non-survivor groups. However, compared with non-survivors, survivors showed significantly higher arterial pressures (p-value 0.028), respiratory rates (p-value 0.008), Glasgow coma scale (p-value 0.000), urine production (p-value 0.000), and SPO2 (p-value 0.002). Additionally, the survivor group had a significantly lower FiO2 % (p-value 0.000) than the non-survivor group, as shown in Table 3.

The survivor and non-survivor patients were compared for their clinical profile, pulmonary function, renal function, liver function, electrolytes, and vital signs using one-way ANOVA. Values are Mean ± SD using statistical tool SPSS 20, P values are: ***p < 0.001 is highly significant, **p < 0.01 is significant.

Samples from ICU patients were sent for culture sensitivity testing to determine the most definitive therapy. The results revealed that out of 90% of the patients tested, only 44% had positive bacterial growth. Among these, 33% showed a single pathogen and 11% showed multiple growth. The pathogenic etiologies of the isolated organisms are shown in Fig. 3.

During admission, 90% went through the culture sensitivity test, and by testing culture sensitivity, 46% patients had no bacterial growth, whereas 44% patients showed either single or multiple bacterial growths.

Patients with single bacterial growth had *Pseudomonas aeroginosa or Staphylococcus spp.* or *Acinetobacter spp.* or *Aspergillus* or *E. coli Chryseobacterium indologenes* and patients with multiple growth had a combination of *Enterococcus spp. + Candida albicans + E.coli + P.aeruginosa* or *Acinetobacter + Aspergillus + Gram-positive + Pus cells* or *Corynebacterium spp + Salmonella* or *Candida albicans + Acinobacter spp.*

Table 3 Comparison of clinical and laboratory profiles of survivors and non-survivors

Clinical Profile			
Parameters	**Survivor Mean ± S.D**	**Non Survivor Mean ± S.D**	**p-value**
Mean arterial pressure (mmHg)	108.58 ± 20.76	97.85 ± 19.26	0.028*
Mean heart rate (bpm)	92.83 ± 13.01	96.09 ± 20.95	0.435
Respiratory rate (/min)	21.06 ± 5.68	16.79 ± 7.37	0.008***
Glasgow Coma Scale (GCS)	11.64 ± 3.55	5.79 ± 2.36	0.000***
Urine output (ml/24hr)	1100 ± 440.78	702.94 ± 453.93	0.000***
Spirometry			
FiO2 (%)	26.38 ±9.74	43.82 ± 7.39	0.000***
pO2 (mmHg)	104.83 ± 55.81	103.57 ± 64.36	0.93
pCO2 (m mol/ L)	34.19± 7.66	41.43 ± 21.31	0.06
SpO2 (%)	91.328 ± 12.25	76.366 ± 25.44	0.002***
Mean arterial pH	7.37 ± 0.102	7.31 ± 0.135	0.072
Kidney Function Test			
Cr (mg/dL)	2.01 ± 1.16	1.93 ± 1.39	0.798
Urea (mg/dL)	80.53 ± 52.02	77.29 ± 47.60	0.787
Na (m mol/L)	137.28 ± 8.314	143.53 ± 15.15	0.035*
K (m mol/L)	3.98 ± 0.58	4.19 ± 0.97	0.27
Cl (m mol/L)	103.94 ± 8.98	106.40 ± 7.91	0.248
HCO3 (m Eq/L)	20.36 ± 14.28	22.49 ± 15.86	0.596
Blood sugar level (m mol/L)	167.44 ± 68.06	197.88 ± 105.11	0.153
Hematological Test			
Hematocrit (%)	32.51 ± 8.66	32.13 ± 7.52	0.845
TLC (/mm3)	15011.11 ± 10440.82	13797.06 ± 14702.91	0.69
RBCs (million/mm3)	4.05 ± 1.18	4.02 ± 0.87	0.903
Hb (g/dL)	10.56 ± 2.37	10.94 ± 2.37	0.502
Platelets (/mm3)	247722.22 ±174137.32	191411.76 ±116538.48	0.119
Liver Function Test			
SGPT (units/L)	50.33 ± 35.58	114.04 ± 241.63	0.207
SGOT (units/L)	59.80 ± 26.65	52.81 ± 54.01	0.604
GGT (IU/L)	105.75 ± 91.54	140.20 ± 204.99	0.455
Alk PO4 (U/L)	203.32 ± 211.08	158.92 ± 118.25	0.73
Bilirubin (mg/dL)	1.41 ± 1.73	0.76 ± 0.71	0.06
Albumin (g/dL)	5.30 ± 9.78	6.29 ± 15.17	0.746
Blood Coagulaton Test			
PT (sec)	13.95 ± 3.40	14.47 ± 5.67	0.674
INR	1.35 ± 0.36	1.41 ± 0.63	0.652
APTT (sec)	38.26 ± 21.50	35.05 ± 14.96	0.528

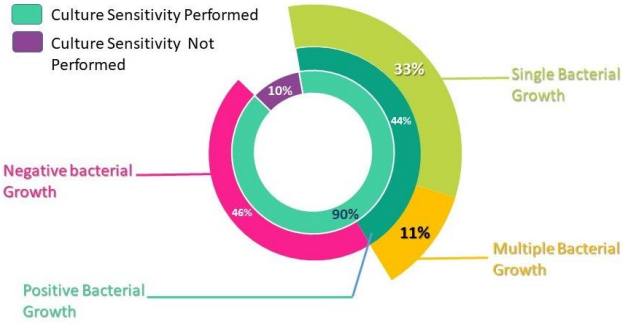

Fig. 3 Blood culture sensitivity

Table 4 shows the percentage survival of patients according to pathogenic etiology. All the patients who contracted *Pseudomonas aeroginosa, Aspergillus, carbapenem-resistant E. coli, Chryseobacterium indologenes, Candida albicans + Acinetobacter spp.* died in the tested population, whereas *Staphylococcus spand acinetobacter spp.* also showed high mortality percentages (66.6%) as compared to survival. Patients showing multiple growths have shown indecisive results with regard to survival. However, in general, multiple growths were found to be difficult to treat if they contained any resistant pathogen. Patients showing no microbial growth, their survival (61.5%) and non-survival (38.5%) rates are shown in Table 4.

Fig. 4 shows the changes in antibiotic therapy after receiving culture results. On confirmation of bacterial growth, antibiotic therapy is modified in 93% of patients, whereas the remaining 7% do not undergo any changes in their antibiotic regimen. Different patterns of change in the antibiotic regime are also mentioned.

Table 5 shows the prescribing pattern of empiric and definitive therapy. Among patients receiving

empiric monotherapy (22.9%), meropenem was the most prescribed empiric antibiotic (11.4%) followed by Ceftriaxone(5.7%), pipercillin- tozabactam (2.8%), and linezolid (2.8%). Among patients receiving definitive monotherapy (61.42%), colistin was found to be the most prescribed monotherapy (25.7%) followed by meropenem (10%), pipercillin-tozabactam (4.3%), levofloxacin (4.3%), and so on.

Table 4 Percentage survival rate with respect to pathogenic etiologies

Micro-organism		**Survivor n (%)**	**Non-survivor n (%)**	**Total**
A.	No microbial growth	24 (61.5)	15 (38.5)	39
B.	*Enterococcus spp. + Candida albicans + E.coli + P.aeruginosa*	0	2 (100)	2
C.	*Acinetobacter* + *Aspergillus* + Gram-positive + pus cell	2 (100)	0	2
D.	*Corynebacterium spp + salmonella*	2 (100)	0	2
E.	*Pseudomonas aeruginosa*	0	4 (100)	4
F.	*Staphylococcus spp.*	2 (33.3)	4 (66.6)	6
G.	*Acinetobacter spp.*	1 (33.3)	2 (66.6)	3
H.	*Aspergillus*	0	2 (100)	2
I.	*Carbapenem-resistant E. coli*	0	2 (100)	2
J.	*E. coli*	4 (100)	0	4
K.	*Candida albicans + Acinetobacter spp.*	0	2 (100)	2
L.	*Chryseobacteriumindologenes*	0	2 (100)	2
Total		35 (50)	35 (50)	70

Among patients receiving empiric combination of two antibiotics (50%), meropenem was found to be the most prescribed empiric antibiotic again in combination with vancomycin (20%) followed by pipercillin–tozabactam in combination with vancomycin (8.5%). All other combinations contributed smaller percentages. Among patients receiving a definitive combination of two antibiotics (34.28%), the combination of vancomycin and amikacin (7.1%) and colistin with meropenem (7.1%) were found to be the most prescribed combination therapies; all other combinations contributed lesser percentages, as shown in Table 5.

Among patients receiving an empiric combination of three antibiotics (27.14%), meropenem along with colistin and vancomycin was found to be the most prescribed empiric antibiotic (8%). All other combinations showed lower percentages. Among patients receiving a definitive combination of three antibiotics (4.3%), the only combination prescribed was a combination of meropenem, colistin, and vancomycin (4.3%) shown in Table 5.

Table 5 Prescribing pattern of empiric and definitive therapy

Antibiotic Regimens	**Empiric Therapy n (%)**	**Definitive Therapy n (%)**
Mono-antibiotic therapy		
Pipercillin-Tazobactam	2 (2.8)	3 (4.3)
Meropenem	8 (11.4)	7 (10)
Vancomycin	0	2 (2.8)
Ceftriaxone	4 (5.7)	2 (2.8)
Ceftazidime	0	1 (1.4)
Cefpodoxime	0	1 (1.4)
Cefixime	0	2 (2.8)
Linezolid	2 (2.8)	0
Minocycline	0	2 (2.8)
Tigecycline	0	2 (2.8)
Levofloxacin	0	3 (4.3)
Colistin	0	18 (25.7)
Total	16 (22.85)	43 (61.42)
Combination of two antibiotic therapies		
Meropenem + vancomycin	14 (20)	0
Ampicillin + metronidazole	2 (2.8)	0
Pipercillin-Tazobactam + Vancomycin	6 (8.5)	2 (2.8)
Pipercillin-Tazobactam + Trimethoprim Sulfamethoxazole	2 (2.8)	0
Meropenem + Amikacin	2 (2.8)	1 (1.4)
Pipercillin-Tazobactam + Ceftriaxone	3 (4.3)	1 (1.4)
Vancomycin + Amikacin	0	4 (5.7)
Ceftazidime + vancomycin	0	5 (7.1)
Azithromycin + Doxycyclines	2 (2.8)	0
Azithromycin + Meropenem	2 (2.8)	0
Tigecycline + metronidazole	0	1 (1.4)
Tigecycline + Colistin	0	2 (2.8)
Colistin + vancomycin	2 (2.8)	1 (1.4)
Colistin + Meropenem	0	5 (7.1)

Continuation of Table 5		
Colistin + amphotericin	0	2 (2.8)
Total	35 (50)	24 (34.28)
Combination of Three Antibiotic Therapies		
Meropenem + Colistin + Vancomycin	6 (8.6)	3 (4.3)
Pipercillin-Tazobactam + Ceftriaxone + Vancomycin	2 (2.8)	0
Vancomycin + Ceftriaxone + Metronidazole	1 (1.4)	0
Meropenem + Colistin + Fosfomycin	2 (2.8)	0
Meropenem + Ceftriaxone + Gentamicin	2 (2.8)	0
Pipercillin-Tazobactam + Vancomycin + Meropenem	2 (2.8)	0
Pipercillin-Tazobactam + Ceftriaxone + Clindamycin	2 (2.8)	0
Ceftriaxone + Metronidazole + Gentamicin	2 (2.8)	0
Total	19 (27.14)	3 (4.3)

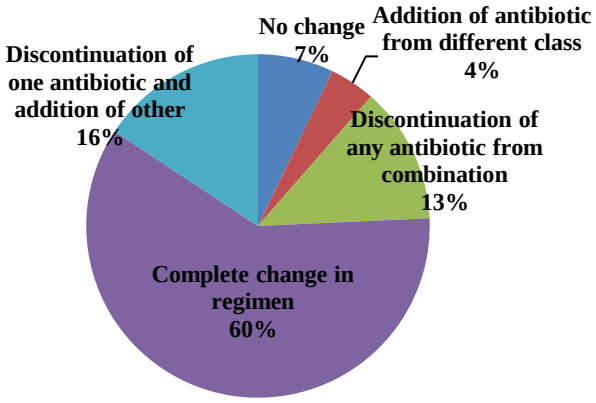

Fig. 4 Changes in antibiotic therapy after blood culture sensitivity

The trends in empiric antibiotic treatment and changes in therapy based on blood culture sensitivity tests are shown in Fig. 5. The use of monotherapy in empirical treatment is lower than that of combination therapy with two or three antibiotics. However, after obtaining the results of the blood culture sensitivity test, the prescription of monotherapy increased, whereas the number of combination therapies decreased. Among the study patients, in empiric therapy, 22.85% received monotherapy, 50% received two antibiotics, and 27.1% received three, whereas after blood

Culture sensitivity test, 61.42% received monotherapy, 34.28% received two antibiotics, received two antibiotics, and 4.3% received three antibiotics, as depicted in Fig. 5.

Fisher's exact test showed a strong association between antibiotic therapy and mortality rate, as depicted in Table 6. Although both survival (74.3%) and non-survival (45.7%) groups have shown highest percentages in patients who experienced complete change in regimen, survival has also over weighed non-survival in this group also (P = 0.008).

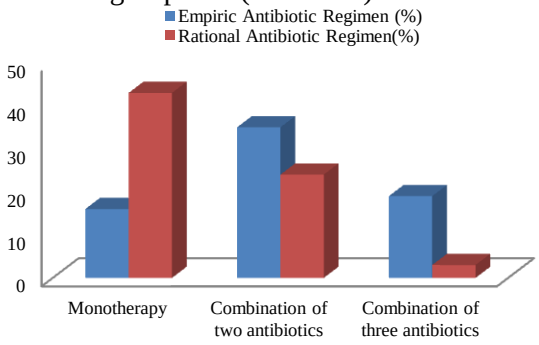

Fig. 5 Comparison of empirics and rational antibiotic regimen

Table 6 Association of mortality rate with change in antibiotic therapy (p-value 0.008)

Mortality Rate	**Comparison of Empiric Therapy and Rational Therapy**					**Total**
	No change	**Addition of antibiotics from different classes**	**Discontinuation of any antibiotic from the combination**	**Complete change in the regimen**	**Discontinuation of one antibiotic and addition of another**	
A. Survivor n (%)	1 (2.9)	2 (5.7)	5 (14.3)	26 (74.3)	1 (2.9)	35
B. Non-Survivor n (%)	4 (11.4)	1 (2.9)	4 (11.4)	16 (45.7)	10 (28.6)	35
Total	5	3	9	42	11	70

5. Discussion

This study examined sepsis patients in the intensive care unit (ICU) from August 2022 to January 2023, and out of 320 patients, 70 met the criteria for septic shock and severe sepsis; thus, the prevalence rate of sepsis among ICU patients was found to be 21.8%. According to current medical literature, the prevalence rate of sepsis among patients in the intensive care unit (ICU) is a significant concern for healthcare providers worldwide [10].

This study showed sepsis prevalence more in men (68.5% men) than in women (31.4% women). The underlying reasons for this observed gender difference require further analysis. However, numerous factors may contribute to the increased susceptibility of men to sepsis, including differences in immune responses, genetic predisposition, and lifestyle factors [12,13]. Studies have shown that male sex hormones, such as testosterone, may negatively affect the immune response to infections, leading to a high risk of severe sepsis [14]. Furthermore, lifestyle factors, such as smoking, alcohol consumption, and occupational exposure, may also play a role in the higher occurrence of sepsis in men. These factors can deteriorate the immune system and increase the risk of infections, which may cause sepsis [15].

In this study, the participants' mean age was 53.64 ± 15.13 years, ranging from 24 to 90. The results revealed no significant association between age and mortality in this patient population, as shown in Fig. 1. Although previous research has suggested that elderly age may be a risk factor for mortality in patients with sepsis and septic shock patients [16], the present study's findings are not in alliance with the previous results. It is possible that the lack of association observed in this study was due to the addition of a diverse patient population with different morbidities and disease severity.

In this study, the majority of the co-morbidity with sepsis was respiratory infection, followed by co-morbidity of multi-organ damage, among others (Table 1). This finding is in agreement with a previous study that reported that respiratory infections, such as pneumonia and acute respiratory distress syndrome (ARDS), are common causes of sepsis and are associated with a higher risk of mortality in affected patients [17].

Multi-organ damage, also known as multiple organ dysfunction syndrome (MODS), is another common comorbidity observed in sepsis patients [18]. MODS occurs because of widespread organ dysfunction caused by the systemic inflammatory response to infection. This can lead to significant morbidity and mortality in patients.

In the present study, the standardized mortality rate (SMR) measured by taking the ratio of AMR by PMR was found to be 1.36, as shown in Table 2. In the present study, the actual mortality percentage (50%) overruled the predicted mortality percentage in each category of the APACHE IV score, as shown in Fig. 2.

APACHE scoring is used in the ICU to assess disease severity, predicted mortality, estimated length of stay, and organ failure [3]. Recent studies have shown that the APACHE IV score may underestimate mortality risk in some patient populations. Several factors may cause the under-prediction of mortality risk by the APACHE IV score. These factors include changes in patient demographics, advances in medical equipment and treatment strategies, and improvements in healthcare systems. Additionally, differences in disease severity and co-morbidities between patient populations may also influence the predictive accuracy of the APACHE IV score [19]. Several prospective, observational studies found that the APACHE II score was uncalibrated [20,21].

The clinical profiles of the patients showed that higher arterial pressures (p-value 0.028), respiratory rates (p-value 0.008), Glasgow Coma Scale scores (p-value 0.000), urine production (p-value 0.000), SPO2 (p-value 0.002), and lower FiO2% (p-value 0.000) were good predictors of survival. The mean temperature, heart rate, PO2, CO2, pH, creatinine, urea, blood sugar level, albumin, bilirubin, hematocrit, red blood cell count, platelets, total leukocyte count, HCO3, alkaline phosphatase, phosphate, hemoglobin, chloride, SGOT, SGPT, GGT, PT, APTT, and INR were all found to be the same in the survivor and non-survivor groups, as shown in Table 3.

The present study showed that samples of 90% of patients of the tested population were sent for culture sensitivity testing to determine the definitive therapy. The results revealed that only 44% of the samples had positive bacterial growth. Among these, 33% showed that single pathogens (33%) were more prevalent than multiple growth (11%) in Fig. 3.

Antimicrobial resistance (AMR) has been a growing concern for public health, and the emergence of resistance in both Gram-negative and Gram-positive pathogens is exacerbating the current situation. Historically, Gram-negative pathogens have been the primary targets of antibiotic development because of their high virulence and prevalence. However, the progress of resistance against these pathogens has led to increased morbidity and mortality rates [22, 23]. Recently, there has also been a growing emergence of resistance in Gram-positive pathogens [24].

One example of the emergence of resistance in Gram-positive pathogens is the growth of methicillin-resistant Staphylococcus aureus (MRSA). MRSA is a significant public health risk worldwide and has developed resistance mechanisms against several antibiotics, including methicillin, penicillin, and cephalosporins [24].

Table 4 shows the percentage survival of patients according to pathogenic etiology. The present study showed that resistant pathogens such as *Pseudomonas aeroginosa, Aspergillus, carbapenem-resistant E. coli, Chryseobacterium indologenes, Candida albicans + Acinetobacter spp.* showed 100% mortality, followed by less resistant pathogens such as *Staphylococcus spandacinetobacter that also showed* high mortality percentages (66.6%). Patients showing multiple growths have shown indecisive results with regard to survival. However, in general, multiple growths were found to be difficult to treat if they contained any resistant pathogen. The patients showing no microbial growth had better survival (61.5%) compared with non-survival (38.5%) rates, as shown in Table 4.

Fig. 4 shows the changes in antibiotic therapy after receiving culture results. On confirmation of bacterial growth, antibiotic therapy is modified in 93% of patients, whereas the remaining 7% do not undergo any changes in their antibiotic regimen. Different patterns of change in the antibiotic regime are also mentioned.

Table 5 shows the prescribing pattern of empiric and definitive therapy. Among patients receiving empiric monotherapy (22.9%), meropenem was the most prescribed empiric antibiotic (11.4%) followed by Ceftriaxone (5.7%). Among patients receiving definitive monotherapy (61.42%), colistin was found to be the most prescribed monotherapy (25.7%) followed by meropenem (10%). Meropenem was also found to be the most prescribed empiric antibiotic in combination, and in definitive therapy, colistin was the most prescribed in combination. The results clearly depict the shift of meropenem in empiric monotherapy to colistin in definitive monotherapy.

Empiric monotherapy with meropenem has traditionally been a popular treatment for serious infections caused by Gram-negative bacteria. However, with the emergence and spread of carbapenem-resistant microorganisms, including Enterobacteriaceae, Pseudomonas aeruginosa, and Acinetobacterbaumannii, the efficacy of meropenem monotherapy is now in doubt [25]. As a result, clinicians have gradually shifted more toward colistin in definitive monotherapy for these infections.

Colistin is an older antibiotic that was discontinued because of concerns about its nephrotoxicity and neurotoxicity. However, with the increase in carbapenem-resistant gram-negative infections, colistin has become the first option for definitive therapy. Colistin works by disrupting the bacterial cell membrane, which causes cell death. Although resistance to colistin has emerged, it remains a viable option for the treatment of infections caused by multidrug-resistant gram-negative bacteria [26].

Studies have shown that colistin can be effective in treating infections caused by these resistant organisms, and it is often used in combination with other antibiotics to maximize its efficacy. However, there are concerns about the toxicity of colistin and the potential for the emergence of resistance.

The present study revealed that monotherapy increased and combination antibiotic therapy decreased after obtaining the culture sensitivity results depicted in Fig. 5

Fisher's exact test showed a strong association between antibiotic therapy and mortality rate, as depicted in Table 6. Although both survival (74.3%) and non-survival (45.7%) groups have shown the highest percentages in patients who experienced a complete change in regimen, survival has also over weighed non-survival in this group also (P = 0.008)

6. Conclusions

In conclusion, this study presents an extensive approach for intensive care units (ICUs) to optimise antibiotic stewardship and patient care for critically ill septic patients. Notably, it incorporates a comprehensive investigation of antibiotic prescribing practices using the APACHE IV scoring system, successfully addressing substantial knowledge. This study offers an alternative perspective on evidence-based clinical decision-making by highlighting the intricate connection between patient characteristics, antibiotic choice, and clinical outcomes. This cutting-edge approach paves the way for future studies and plans aimed at reducing antibiotic resistance and raising the standards of care in ICU settings.

This study utilized the APACHE-IV scale to evaluate the severity and outcomes of sepsis in the ICU, and the results showed that it is under predicting the severity. Blood culture sensitivity testing was found to be an effective tool for guiding antibiotic therapy, resulting in changes to treatment regimens and a shift toward monotherapy prescriptions. Calibrating and updating the APACHE score can assist in patient assessment and selection of diagnostic and therapeutic interventions. The accuracy of predictive models may change over time and should be regularly checked.

While the severity of disease scoring systems is simple and accessible, no sepsis system is perfect. The majority of these tools were developed for ICU patients as a whole and might not be as helpful for sepsis patients specifically. These findings emphasize the importance of continuous evaluation and updating of predictive models and treatment guidelines to ensure the best possible outcomes for sepsis patients in the ICU. Culture sensitivity should be the mainstay for prescription of antibiotics as the resistance pattern is compelling antibiotic prescriptions towards last resorts of antibiotics and leaving no choice for future management of severe infections and sepsis.

6.1. Limitations of the Study

In this study, the initial objective was to include 320 patients to assess the prevalence of sepsis. Conversely, due to factors such as patient accessibility and medical conditions, the ultimate sample consisted of 70 patients diagnosed with sepsis. This limited number of sepsis cases represents a restriction on the scope of our study.

The study's scope was constrained to a private sector hospital catering to a restricted population. Consequently, a selection prejudice may exist, and the outcomes might not precisely mirror the sepsis and outcomes across Pakistan. To obtain a more accurate representation of sepsis epidemiology and its load, multicenter studies are vital in this country.

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