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Incidence, Risk Factors, and Clinical Outcomes of ICU-Acquired Sepsis: A Prospective Multicenter Observational Study

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Abstract

Background: Sepsis remains a leading cause of mortality in intensive care units (ICUs). This study aimed to determine the incidence, risk factors, and clinical outcomes of ICU-acquired sepsis in Northern Iran.

Methods: This prospective multicenter observational study was conducted over a 6-month period in 9 ICUs across 3 general hospitals affiliated with Mazandaran University of Medical Sciences, Northern Iran. All eligible ICU patients who met the inclusion criteria were consecutively enrolled during the study period. Data were collected using a researcher-designed checklist and the Modified Sequential Organ Failure Assessment score. Patients were followed up for 30 days after ICU admission. Data were entered into SPSS software version 26 and analyzed using the Kolmogorov–Smirnov, chi-square, Fisher's exact, and Mann–Whitney U tests. Multivariable logistic regression analysis was also performed to identify factors associated with sepsis.

Results: A total of 1,166 patients were recruited, of whom 141 (12.1%) developed ICU-acquired sepsis. The 30-day mortality rate among septic patients was 46.1% (65/141), and the mean ICU length of stay was 24.13 ± 20.004 days. Independent risk factors for ICU-acquired sepsis included age 40 – 59 years (OR = 3.056, 95% CI: 1.207 – 7.742, P = 0.018), prior admission to infectious diseases wards (OR = 2.804, 95% CI: 1.061 – 7.409, P = 0.038), admission for renal disorders (OR = 11.148, 95% CI: 3.597 – 34.556, P < 0.001), receipt of mechanical ventilation (OR = 3.625, 95% CI: 2.205 – 5.958, P < 0.001), and combined enteral and parenteral nutritional support (OR = 3.066, 95% CI: 1.530 – 6.146, P = 0.002).

Conclusions: ICU-acquired sepsis was associated with a high mortality rate despite its relatively low incidence. Age 40 – 59 years, prior admission to infectious diseases wards, renal disorders, mechanical ventilation, and combined nutritional support were identified as independent risk factors. These findings may contribute to the identification of high-risk patients and the development of targeted preventive strategies in ICU settings. However, because the observational design precludes causal inference, future prospective studies are needed to validate these findings.

Keywords: Sepsis, Incidence, Risk Factors, Treatment Outcome, Intensive Care Units

1. Introduction

Sepsis is a major healthcare challenge (1) and one of the leading causes of preventable mortality worldwide (2). It is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (3). According to the most recent Global Burden of Disease study, approximately 48.9 million cases of sepsis are reported

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globally, with 11 million deaths (19.7% of all global deaths) attributed to sepsis and its complications (4). Sepsis is also recognized as one of the most important causes of morbidity and mortality in intensive care units (ICUs) (5). A study conducted in China demonstrated that sepsis affects one-fifth of ICU patients, with a 90-day mortality rate of 35.5% (6). Similarly, a recent study conducted in Egypt reported a sepsis prevalence of 24% among ICU patients (7).

The burden of sepsis is not evenly distributed across populations and geographic regions; its incidence is higher in low- and middle-income countries than in high-income countries (8). This disparity may be attributed to several factors, including limited access to healthcare services, delayed diagnosis and treatment, and a higher prevalence of infectious diseases (9). In addition, various risk factors have been identified in relation to the development and outcomes of sepsis in ICU patients. These include demographic characteristics such as advanced age and male sex, as well as comorbidities, severity of organ dysfunction, intensive care interventions, and surgery-related factors (10). Emergency surgery and postoperative blood transfusion have been identified as surgery-related risk factors for sepsis, whereas patient-related factors such as male sex, heart failure, diabetes, and chronic kidney disease are also associated with an increased risk of postoperative sepsis (11). Moreover, psychiatric disorders, alcohol misuse, and socioeconomic status may contribute to both the occurrence of sepsis and its adverse outcomes (12).

The clinical outcomes of sepsis depend heavily on early recognition and timely therapeutic intervention (13). Sepsis is associated with profound physiological, psychological, and economic consequences. It can lead to multiple organ dysfunction, including acute kidney injury (14), acute respiratory distress syndrome (15), cardiac arrhythmias such as atrial fibrillation (16), and disseminated intravascular coagulation (17). Beyond physiological complications, patients frequently experience anxiety, depression, and post-traumatic stress disorder (18). Sepsis survivors often face long-term consequences, including late mortality, immune system dysfunction, recurrent infections, reduced quality of life, and unplanned hospital readmissions (19). Therefore, early prediction of clinical outcomes in patients with sepsis is of critical importance, as it can guide therapeutic strategies and ultimately reduce mortality (20).

Hospital admissions for sepsis have been increasing over time, yet the true incidence is likely still underestimated. Although mortality rates appear to have declined, prolonged hospital stays and frequent readmissions impose a considerable burden on healthcare resources and costs (21). In this regard, a study conducted in the United States estimated that the annual cost of sepsis exceeds 24 billion dollars (22). Over the past decades, numerous epidemiological studies have investigated sepsis; however, most of the available data have been derived from high-income countries (23). Moreover, many of these investigations were retrospective, and discrepancies between recorded information and actual clinical circumstances may introduce limitations and affect the reliability of their findings. Consequently, such studies may not accurately reflect the risk factors associated with sepsis-related mortality in ICUs (24). Furthermore, the lack of sufficient data on the incidence and outcomes of sepsis in ICUs in low- and middle-income countries highlights the need for studies assessing its magnitude, its outcomes, and the challenges associated with its management (25).

To our knowledge, no published data are currently available on the incidence of ICU-acquired sepsis in Iran based on the SEPSIS-3 definitions. Most prior Iranian studies have focused on hospital-acquired infections or specific patient groups. For example, a study from Kermanshah reported a hospital-acquired infection prevalence of 16.9% among ICU patients (26). A national meta-analysis of 22 studies including 14,683 neonates reported a pooled prevalence of neonatal sepsis in Iran of 15.98% (95% confidence interval [CI]: 11.96 – 20.46%), with substantial heterogeneity across provinces (27). Another study from Shiraz reported a 62.3% incidence of sepsis among patients with severe ischemic stroke admitted to the ICU (28). However, these studies either focused on hospital-acquired infections, were restricted to specific subpopulations, or did not apply the SEPSIS-3 definition to adult ICU patients. To address this gap, the present prospective, multicenter study in Northern Iran was designed to simultaneously determine the incidence, risk factors, and clinical outcomes of ICU-acquired sepsis in adult ICU patients using the SEPSIS-3 definitions and the modified Sequential Organ Failure Assessment (mSOFA) score. The findings are anticipated to provide essential baseline information for physicians and nurses to facilitate the early recognition and management of patients at risk of sepsis and, ultimately, to improve related clinical outcomes.

2. Methods

2.1. Study Design

This prospective, multicenter observational study was conducted over 6 months (21 December 2024 to 21 June 2025) in 9 ICUs at 3 general teaching hospitals (Imam Khomeini, Bu-Ali Sina, and Razi) affiliated with

Mazandaran University of Medical Sciences. The study aimed to evaluate the incidence, risk factors, and clinical outcomes of sepsis. These hospitals were selected to ensure the inclusion of a broad spectrum of critically ill patients, thereby enhancing the generalizability of the findings. A consecutive sampling method was employed throughout the study period, whereby all eligible patients admitted to the participating ICUs were enrolled in order of admission. This approach minimized selection bias and accurately reflected the target ICU population.

The inclusion criteria were as follows: (i) informed consent provided by the patient or a family member, (ii) age ≥ 18 years, and (iii) absence of sepsis at the time of ICU admission. The exclusion criteria were (i) an ICU stay of less than 48 hours, (ii) development of sepsis within the first 48 hours after ICU admission, and (iii) transfer to other healthcare facilities outside the study setting. For patients with multiple ICU admissions, only the first admission was considered.

2.2. Study Tools & Definitions

In accordance with the SEPSIS-3 definition, sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection and identified by an increase of ≥ 2 points in the Sequential Organ Failure Assessment (SOFA) score (29). The original SOFA score requires a comprehensive set of laboratory parameters (including serum bilirubin, platelet count, and lactate) across its six organ systems. However, in this study, these laboratory values were not uniformly available for all ICU patients because of resource limitations. Therefore, the mSOFA score was applied (30).

The mSOFA was originally developed for use in resource-constrained settings where the full laboratory panel required by the original SOFA is not uniformly available (31), and its feasibility has been demonstrated in other low-resource ICU settings (32). Mulatu et al. also used the mSOFA for sepsis assessment in Ethiopian ICUs (25).

The mSOFA score evaluates five organ systems, including respiratory, hepatic, cardiovascular, central nervous system, and renal, each scored from 0 to 4, yielding a maximum total score of 20. First, the respiratory component was modified: the PaO_2/FiO_2 ratio was replaced with the SpO_2/FiO_2 ratio, where PaO_2 is the arterial oxygen partial pressure, FiO_2 is the fraction of inspired oxygen, and SpO_2 is the arterial oxygen saturation measured by pulse oximetry. For patients receiving oxygen via nasal cannula, FiO_2 was estimated by multiplying the flow rate (L/min) by 0.03 and adding 0.21. The respiratory score is assigned as follows: SpO_2/FiO_2 > 400 (0 points), 316 – 400 (1 point), 236 – 315 (2 points), 151 – 235 with respiratory support (3 points), and ≤ 150 with respiratory support (4 points). Second, the coagulation component (platelet count) was entirely omitted, and serum bilirubin was replaced with the clinical assessment of jaundice or scleral icterus. In this modified scoring system, the hepatic component is binary: the absence of clinical jaundice or scleral icterus is scored as 0, and its presence is scored as 3, with no intermediate levels (1, 2, or 4) assigned. The remaining three components were scored according to the original SOFA criteria. The cardiovascular component was scored based on mean arterial pressure (MAP) and vasopressor requirements: MAP ≥ 70 mmHg (0 points), MAP < 70 mmHg (1 point), dopamine ≤ 5 µg/kg/min or any dobutamine (2 points), dopamine > 5 µg/kg/min or epinephrine/norepinephrine ≤ 0.1 µg/kg/min (3 points), and dopamine > 15 µg/kg/min or epinephrine/norepinephrine > 0.1 µg/kg/min (4 points). The central nervous system component was assessed using the Glasgow Coma Scale: 15 (0 points), 13 – 14 (1 point), 10 – 12 (2 points), 6 – 9 (3 points), and < 6 (4 points). Finally, the renal component was scored by serum creatinine: < 1.2 mg/dL (0 points), 1.2 – 1.9 mg/dL (1 point), 2.0 – 3.4 mg/dL (2 points), 3.5 – 4.9 mg/dL (3 points), and ≥ 5.0 mg/dL (4 points) (30). This modification was specifically designed to reduce laboratory requirements in resource-limited settings where comprehensive laboratory measurements are not uniformly available. By omitting platelet count and substituting serum bilirubin with a clinical assessment, the mSOFA allows for feasible and consistent organ dysfunction scoring in settings where the full panel of SOFA laboratory tests cannot be routinely obtained.

In this study, the origin of sepsis was defined according to the CDC/NHSN surveillance framework, which classifies an infection as healthcare-associated when there is no evidence that it was present or incubating at the time of admission (33). Consistent with this framework, patients who had sepsis at ICU admission or within the first 48 hours were excluded (n = 152; Figure 1). Consequently, all 141 sepsis cases included in the final analysis were diagnosed after the first 48 hours of ICU admission and were classified as ICU-acquired sepsis. For all patients, the prior ward of admission was recorded at the time of ICU admission. This variable was subsequently entered into the multivariable logistic regression model as an independent exposure variable to assess its association with the subsequent development of ICU-acquired sepsis.

Microbiological investigations were performed at the discretion of the attending physicians, and the research team was not involved in sample collection or processing. Quality control procedures were conducted according to each laboratory's internal protocols. Three laboratory centers located within the participating hospitals were capable of culturing blood samples. All laboratories used BACTEC blood culture incubators.

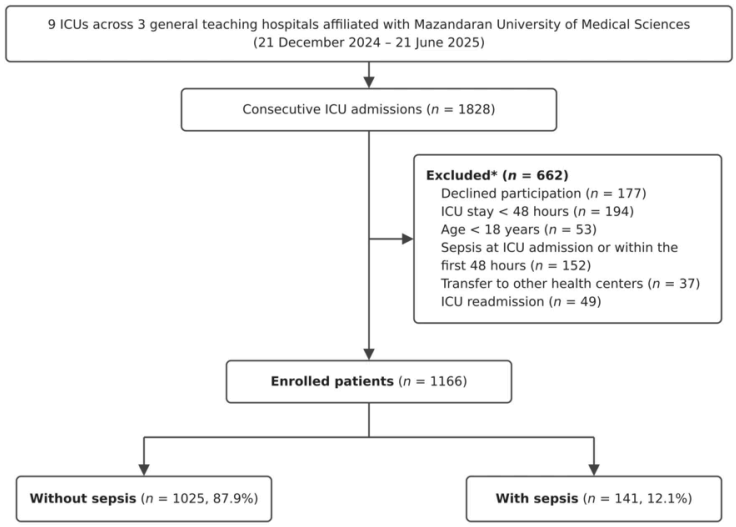

Figure 1. Flowchart of Patient Enrollment in the Study Period. * Each patient is counted only once, in the first exclusion category for which they met the criteria. The sum of exclusion events (n = 662) equals the difference between the 1828 admissions and the 1166 patients included in the final analysis.

2.3. Data Collection

During the study period, all eligible ICU patients who met the inclusion criteria were consecutively recruited. Data were extracted by the researcher from medical records and, when necessary, supplemented through direct communication with medical and nursing staff. To ensure accurate ascertainment of incident sepsis, the baseline mSOFA score was calculated for all patients using the clinical and laboratory values documented at ICU admission, which were recorded within the first 24 hours of ICU stay (reported in Table 1). After this initial calculation, the mSOFA score was reassessed daily for all patients throughout their ICU stay by a single dedicated researcher to ensure consistency and minimize inter-rater variability. These daily scores were used solely as a screening tool to detect new cases of organ dysfunction and were not included in the final statistical analysis. Sepsis cases were not identified solely through discharge coding or routine clinical diagnoses; instead, any new organ dysfunction was actively screened for using these daily mSOFA calculations. The final diagnosis of sepsis required confirmation by the attending intensivist based on clinical, laboratory, or radiological evidence of infection.

The following variables were recorded: mSOFA score within the first 24 hours of admission, hospital type, demographic characteristics, initial ward of admission, reason for ICU admission, comorbidities, need for vasopressor therapy, Renal Replacement Therapy (RRT), nutritional therapy, and mechanical ventilation. Microbiological culture results (when available) were also collected according to the suspected site of infection. Infection sites included the respiratory tract, urinary tract, bloodstream, central nervous system, wounds/soft tissues, catheter sites, and intra-abdominal infections. Pathogens were categorized as Gram-positive bacteria, Gram-negative bacteria, or fungi. Additional data included receipt of antibiotics before sepsis diagnosis, receipt of antibiotics within one hour of sepsis onset, corticosteroid or immunosuppressive therapy, ICU length of stay, and patient outcomes within 30 days of admission.

Sepsis occurrence and diagnosis were monitored until discharge. ICU length of stay was measured until the time of discharge. All patients were followed for 30 days after ICU admission. For patients discharged before 30 days, outcomes (survival or death) were assessed by telephone follow-up.

Because the mSOFA was designed to minimize laboratory requirements, the only laboratory value required for its calculation was serum creatinine, which

Table 1. Baseline and Clinical Characteristics of Participants [a]

Variables	All Patients (n = 1166)	With Sepsis (n = 141)	Without Sepsis (n = 1025)	P-Value
Demographics				
Age (y)	63.49 ± 18.72	66.45 ± 17.13	63.08 ± 18.90	0.068 [b]
Weight (kg)	72.16 ± 15.11	71.43 ± 14.02	72.26 ± 15.26	0.954 [b]
mSOFA Score	3.59 ± 2.55	6.16 ± 2.38	3.24 ± 2.36	< 0.001 [b]
Gender				0.229 [c]
Male	683 (58.6)	76 (53.9)	607 (59.2)	
Female	483 (41.4)	65 (46.1)	418 (40.8)	
Education				0.307 [c]
Illiterate	477 (40.9)	60 (42.5)	417 (40.7)	
Primary & Secondary	582 (49.9)	73 (51.8)	509 (49.6)	
University	107 (9.1)	8 (5.7)	99 (9.7)	
Employment Status				0.154 [c]
Employed	314 (26.9)	29 (20.6)	285 (27.8)	
Retired	406 (34.8)	48 (34.0)	358 (34.9)	
Housewife	432 (37.0)	61 (43.3)	371 (36.2)	
Unemployed	14 (1.2)	3 (2.1)	11 (1.1)	
Comorbidities				
Hypertension	645 (55.3)	82 (58.1)	563 (54.9)	0.470 [c]
Diabetes	451 (38.6)	55 (39.0)	396 (38.6)	0.012 [c]
Respiratory Disorders	98 (8.4)	6 (4.2)	92 (8.9)	0.155 [c]
Cardiovascular Disorders	431 (37.0)	62 (43.9)	369 (36.0)	0.066 [c]
Renal Disorders	117 (10.0)	27 (19.1)	90 (8.8)	< 0.001 [c]
Hyperlipidemia	303 (26.0)	40 (28.4)	263 (25.6)	0.491 [c]
Thyroid Disorders	110 (9.4)	17 (12.0)	93 (9.1)	0.256 [c]
Malignancies	117 (10.0)	20 (14.2)	97 (9.5)	0.080 [c]
Number of Comorbidities				< 0.001 [c]
None	246 (21.1)	19 (13.5)	227 (22.1)	
One	263 (22.6)	28 (19.8)	235 (22.9)	
Two	259 (22.2)	30 (21.3)	229 (22.3)	
Three	220 (18.9)	44 (31.2)	176 (17.2)	
Four or more	178 (15.3)	20 (14.2)	158 (15.4)	
Clinical Characteristics				
Hospital				0.716 [c]
Imam Khomeini	417 (35.8)	51 (36.2)	366 (35.7)	
Bu-Ali Sina	421 (36.1)	47 (33.3)	374 (36.5)	
Razi	328 (28.1)	43 (30.5)	285 (27.8)	
Previous Admission Ward				0.115 [c]
Emergency	684 (58.7)	86 (60.9)	598 (58.3)	
Surgery	177 (15.2)	18 (12.8)	159 (15.5)	
Internal Medicine	146 (12.5)	18 (12.8)	128 (12.5)	
Neurology	115 (9.9)	9 (6.4)	106 (10.3)	
Infectious Diseases	44 (3.8)	10 (7.1)	34 (3.3)	
Reason for ICU Admission				< 0.001 [c]
Trauma	119 (10.2)	9 (6.4)	110 (10.7)	
Respiratory Problems	312 (26.8)	36 (25.5)	276 (26.9)	
Gastrointestinal Disorders	78 (6.7)	6 (4.2)	72 (7.0)	
Renal Disorders	73 (6.3)	23 (16.3)	50 (4.9)	
Neurological Problems	366 (31.4)	54 (38.3)	312 (30.4)	
Pre- or Post-Operative Monitoring	127 (10.9)	2 (1.4)	125 (12.2)	
Other	91 (7.8)	11 (7.8)	80 (7.8)	
Treatments Received				
Mechanical Ventilation	445 (38.2)	104 (73.7)	341 (33.3)	< 0.001 [c]
Renal Replacement Therapy	77 (6.6)	29 (20.6)	48 (4.7)	< 0.001 [c]
Vasopressors	237 (20.3)	76 (53.9)	161 (15.7)	< 0.001 [c]
Nutritional Support				< 0.001 [c]
Enteral	392 (33.6)	85 (60.3)	307 (29.9)	
Parenteral	69 (5.9)	10 (7.1)	59 (5.7)	
Enteral + Parenteral	53 (4.5)	25 (17.7)	28 (2.7)	
None	652 (55.9)	21 (14.9)	631 (61.6)	

[a] Values are expressed as No. (%) or mean ± SD.
[b] Mann-Whitney test.
[c] Chi-square test or Fisher's exact test.

was available for nearly all patients. Missing laboratory values (eg, platelet count, serum bilirubin, and lactate) were not used in the mSOFA and therefore did not affect its calculation. There were no missing data for any of the variables included in the multivariable logistic regression model, as these were extracted from structured admission records and, where necessary, supplemented by telephone follow-up for patients discharged before 30 days. A complete-case approach was therefore used for all analyses.

2.4. Outcomes

Primary outcome: mortality within 30 days of ICU admission

Secondary outcome: ICU length of stay

2.5. Ethical Considerations

This study was conducted in strict accordance with the ethical principles of the Declaration of Helsinki and the institutional research guidelines of Mazandaran University of Medical Sciences. The study protocol was approved by the Ethics Committee of Mazandaran University of Medical Sciences (Ethics Code: IR.MAZUMS.REC.1403.355). Before the study began, all participants or their legal guardians received adequate information about the study objectives and procedures, and written informed consent was obtained from all of them.

2.6. Data Analysis

Data analysis was performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA). Qualitative variables were summarized as frequencies and percentages. Quantitative variables were described as mean ± standard deviation, median, interquartile range, and range. The normality of continuous variables was assessed using the Kolmogorov–Smirnov test, as well as measures of skewness and kurtosis. Categorical variables were compared between the sepsis and non-sepsis groups using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using the nonparametric Mann–Whitney U test. The incidence of ICU-acquired sepsis was calculated as the number of patients who developed sepsis after the first 48 hours of ICU admission (numerator) divided by the total number of at-risk patients included in the final analysis (denominator), multiplied by 100. The denominator included all patients who met the inclusion criteria, had an ICU stay of at least 48 hours, and were sepsis-free at ICU admission. Patients who developed sepsis within the first 48 hours or who stayed in the ICU for less than 48 hours were excluded from the denominator to ensure an accurate estimation of the true incidence of ICU-acquired sepsis. Multivariable logistic regression analysis was conducted to identify independent risk factors associated with sepsis.

To evaluate the predictive performance of the baseline mSOFA score in identifying patients who subsequently developed sepsis, a receiver operating characteristic (ROC) curve analysis was performed. The mSOFA score, calculated within the first 24 hours of ICU admission, was used as the test variable, and the development of sepsis after the first 48 hours of ICU stay was used as the outcome (reference) variable. The area under the ROC curve (AUC) and its 95% confidence interval (CI) were calculated. An AUC of 0.5 indicated no discrimination, whereas an AUC of 1.0 indicated perfect discrimination. All statistical analyses, including the ROC analysis, were performed using IBM SPSS Statistics for Windows, version 26.

3. Results

3.1. Participants' Characteristics

During the study period, 1,828 patients were consecutively admitted to the ICUs. Of these, 1,166 patients were included in the final analysis, of whom 141 (12.1%) developed ICU-acquired sepsis (sepsis occurring after the first 48 hours of ICU stay) (Figure 1). The distribution of the wards from which septic patients were admitted is presented in Table 1 (Emergency Department: 60.9%, Surgery: 12.8%, Internal Medicine: 12.8%, Neurology: 6.4%, and Infectious Diseases: 7.1%).

The mean age of septic patients was 66.45 ± 17.13 years, and the majority were male (53.9%). Regarding educational status, 51.7% were at least literate. Most patients with sepsis reported having an occupation, and only 2.1% were unemployed. Patients with sepsis also had a higher mean mSOFA score within the first 24 hours of ICU admission (6.16 vs 3.24). The most common comorbidity among septic patients was hypertension (58.1%), followed by cardiovascular disease (43.9%) and diabetes (39.0%). Notably, 66.7% of these patients had more than one comorbidity. The baseline characteristics of all patients are presented in Table 1.

Regarding pharmacological therapies administered to patients with sepsis before sepsis onset, 57 patients (40.4%) received corticosteroids, 15 patients (10.6%) received immunosuppressive agents, and 104 patients (73.8%) received antibiotics. Furthermore, 132 patients (93.6%) received antibiotics within the first hour of sepsis diagnosis.

3.2. Sites of Infection & Isolated Organisms

Positive culture results were reported in 127 septic patients. The most common sources of infection were the respiratory tract (92 patients, 65.2%), followed by the bloodstream (76 patients, 53.9%) and the urinary tract (39 patients, 27.6%). Other identified sources included wounds/soft tissues (12 patients, 8.5%), the central nervous system (7 patients, 4.9%), catheter-related infections (3 patients, 2.1%), and intra-abdominal infections (3 patients, 2.1%). Notably, 84 patients (59.6%) had more than one source of infection, and the source remained unknown in 11 patients (7.8%). The distribution of isolated pathogens is presented in Table 2.

Table 2. Distribution of Infection Sites & Isolated Organisms in Septic ICU Patients

Culture Type	No. (%)
Sputum Culture	
Gram-Positive	
Staphylococcus	9 (9.8)
Enterococcus	3 (3.3)
Gram-Negative	
Serratia	15 (16.3)
Klebsiella	18 (19.6)
Pseudomonas	17 (18.5)
Enterobacter	7 (7.6)
Acinetobacter	19 (20.7)
Stenotrophomonas	4 (4.3)
Urine Culture	
Gram-Negative	
E. coli	12 (30.8)
Klebsiella	4 (10.3)
Acinetobacter	1 (2.6)
Pseudomonas	2 (5.1)
Enterobacter	2 (5.1)
Fungi	
Candida	10 (25.6)
Yeast	2 (5.1)
Unknown	
Mixed	6 (15.4)
CSF Culture	
Gram-Positive	
Staphylococcus	2 (28.6)
Gram-Negative	
Serratia	1 (14.3)
Pseudomonas	1 (14.3)
Streptococcus	1 (14.3)
Acinetobacter	2 (28.6)
Wound/Soft Tissue Culture	
Gram-Positive	
Staphylococcus	1 (8.3)
Gram-Negative	
Serratia	3 (25.0)
Klebsiella	2 (16.7)
Pseudomonas	2 (16.7)
Enterobacter	3 (25.0)
Acinetobacter	1 (8.3)
Blood Culture	
Gram-Positive	
Staphylococcus	27 (35.5)
Enterococcus	3 (3.9)
Gram-Negative	
Serratia	1 (1.3)
Pseudomonas	22 (28.9)
Streptococcus	11 (14.5)
Acinetobacter	9 (11.8)
Stenotrophomonas	1 (1.3)
E. coli	1 (1.3)
Fungi	
Candida	1 (1.3)
Catheter Culture	
Gram-Positive	
Staphylococcus	2 (66.7)
Gram-Negative	
Pseudomonas	1 (33.3)
Intra-Abdominal Culture	
Gram-Negative	
Klebsiella	1 (33.3)
Pseudomonas	1 (33.3)
E. coli	1 (33.3)

3.3. Factors Associated with Sepsis

After adjustment for potential confounders in a multivariable logistic regression analysis, several factors were identified as significant independent predictors of ICU-acquired sepsis (Table 3). An age of 40 – 59 years (OR = 3.056, 95% CI: 1.207 – 7.742, P = 0.018) and prior admission to infectious diseases wards (OR = 2.804, 95% CI: 1.061 – 7.409, P = 0.038) were significantly associated with an increased risk of sepsis. Among treatment-related factors, receiving mechanical ventilation (OR = 3.625, 95% CI: 2.205 – 5.958, P < 0.001) and combined enteral and parenteral nutrition (OR = 3.066, 95% CI: 1.530 – 6.146, P = 0.002) were associated with a higher risk, whereas receiving no nutritional support was associated with a lower risk (OR = 0.160, 95% CI: 0.088 – 0.291, P < 0.001). Regarding the reason for ICU admission, patients admitted for renal disorders had a substantially higher risk than those admitted for trauma (OR = 11.148, 95% CI: 3.597 – 34.556, P < 0.001), whereas those admitted for pre- or postoperative monitoring had a significantly lower risk (OR = 0.114, 95% CI: 0.017 – 0.742, P = 0.023). Patients admitted for "other" reasons also had a higher risk of sepsis (OR = 3.324, 95% CI: 1.073 – 10.303, P = 0.037); however, because this category is clinically heterogeneous, this finding should be interpreted as exploratory. Other variables, including sex, weight category, number of comorbidities, employment status, education level, and hospital type, were not significantly associated with ICU-acquired sepsis.

3.4. Outcomes

Primary outcome: The overall 30-day mortality rate was significantly higher in septic patients than in non-septic patients (65 patients [46.1%] vs. 177 patients [17.3%], respectively; P < 0.001).

Secondary outcome: The mean ICU length of stay was significantly longer in the septic group (24.13 ± 20.004 days) than in the non-septic group (8.06 ± 7.443 days; P < 0.001).

3.5. Predictive Value of Baseline mSOFA for ICU-Acquired Sepsis

The AUC was calculated to assess the predictive power of the mSOFA score for identifying patients who would develop sepsis (Figure 2). The AUC was 0.817 (95% CI = 0.787 – 0.848, P < 0.001), indicating that the tool performed well in distinguishing between patients with and without sepsis.

4. Discussion

This prospective, multicenter observational study investigated the incidence, risk factors, and clinical outcomes of ICU-acquired sepsis in Northern Iran, where epidemiological data remain limited. Previous Iranian studies on healthcare-associated infections have either focused on specific populations or used definitions other than SEPSIS-3. For instance, a study from Isfahan reported nosocomial bloodstream infections in a pediatric cardiac ICU (34), and a retrospective study from Mazandaran described the spectrum of infectious diseases among hospitalized patients without specifically evaluating adult ICU sepsis or applying the SEPSIS-3 criteria (35). Similarly, a study from Kermanshah reported a 16.9% prevalence of

Table 3. Factors Associated with Sepsis Based on Multiple Logistic Regression Analysis [a]

Variables		Odds Ratio	95% CI	P-Value
Sex				
	Male	1.000	Reference	-
	Female	1.145	0.442 – 2.965	0.780
Age Group				
	< 40 years	1.000	Reference	-
	40 – 59 years	3.056	1.207 – 7.742	0.018
	60 – 69 years	1.895	0.657 – 5.466	0.237
	70 – 79 years	2.075	0.671 – 6.416	0.205
	≥ 80 years	1.892	0.579 – 6.182	0.291
Weight Group				
	< 55 kg	1.000	Reference	-
	55 – 64 kg	1.009	0.461 – 2.207	0.983
	65 – 69 kg	0.381	0.140 – 1.033	0.058
	70 – 79 kg	1.328	0.630 – 2.799	0.456
	80 – 89 kg	0.672	0.289 – 1.564	0.357
	≥ 90 kg	0.747	0.303 – 1.842	0.526
Education				
	Illiterate	1.000	Reference	-
	Primary & Secondary	1.335	0.771 – 2.313	0.302
	University	0.974	0.338 – 2.809	0.962
Employment Status				
	Housewife	1.000	Reference	-
	Employed	0.566	0.183 – 1.752	0.323
	Retired	1.018	0.369 – 2.811	0.973
	Unemployed	2.724	0.342 – 21.690	0.344
Hospital				
	Imam Khomeini	1.000	Reference	-
	Bu-Ali Sina	0.795	0.409 – 1.545	0.498
	Razi	0.640	0.349 – 1.174	0.149
Previous Admission Ward				
	Emergency	1.000	Reference	-
	Surgery	1.912	0.893 – 4.096	0.095
	Internal Medicine	1.131	0.553 – 2.315	0.735
	Neurology	0.567	0.236 – 1.363	0.205
	Infectious Diseases	2.804	1.061 – 7.409	0.038
Reason for ICU Admission				
	Trauma	1.000	Reference	-
	Respiratory Problems	1.185	0.458 – 3.063	0.726
	Gastrointestinal Disorders	1.661	0.392 – 7.034	0.491
	Renal Disorders	11.148	3.597 – 34.556	< 0.001
	Neurological Problems	2.023	0.795 – 5.143	0.139
	Pre- or Post-Operative Monitoring	0.114	0.017 – 0.742	0.023
	Other	3.324	1.073 – 10.303	0.037
Number of Comorbidities				
	0	1.000	Reference	-
	1	1.326	0.612 – 2.875	0.474
	2	1.013	0.455 – 2.257	0.975
	3	1.861	0.822 – 4.214	0.136
	≥ 4	0.710	0.284 – 1.774	0.464
Nutritional Support				
	Enteral	1.000	Reference	-
	Parenteral	0.418	0.153 – 1.144	0.090
	Enteral + Parenteral	3.066	1.530 – 6.146	0.002
	None	0.160	0.088 – 0.291	< 0.001
Receiving Mechanical Ventilation		3.625	2.205 – 5.958	< 0.001

[a] Abbreviations: CI, confidence interval.

hospital-acquired infections in ICU patients but did not specifically address sepsis (26); a national meta-analysis of 22 studies reported a pooled prevalence of 15.98% for neonatal sepsis (27); and a study from Shiraz reported a 62.3% incidence of sepsis among patients with severe ischemic stroke admitted to the ICU (28). However, these studies were restricted to specific subpopulations, focused on hospital-acquired infections rather than ICU-acquired sepsis, or did not apply the SEPSIS-3 definition to adult ICU patients. The present study addresses this gap by providing region-specific baseline data on adult ICU-acquired sepsis, although causal inferences cannot be drawn from its observational design.

The incidence of ICU-acquired sepsis in our study (12.1%) is relatively consistent with that of the Intensive Care Over Nations Audit, which reported a global incidence of 29.5% (regional range: 13.6% – 39.3%) (36), but differs from the incidences reported in Egypt (24%) (7), China (42.5%) (5), and Ethiopia (26.5%) (25). These discrepancies likely stem from our strict exclusion of early-onset cases (sepsis within 48 hours), which removed patients with incubating infections at ICU transfer, as well as from variations in sepsis definitions and ICU case mix.

Age 40 – 59 years emerged as a significant independent risk factor, whereas older age groups did not. This finding is consistent with evidence that chronological age alone

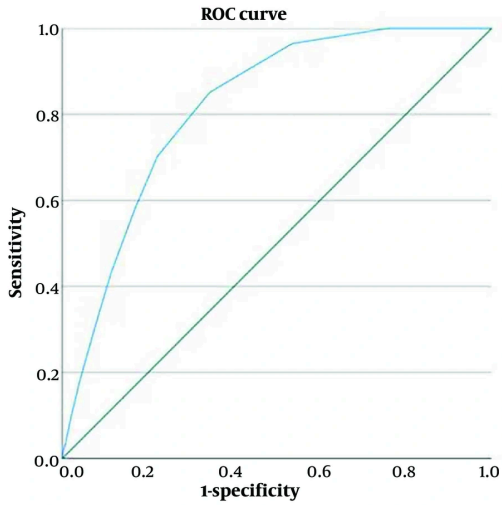

Figure 2. Receiver operating characteristic (ROC) curve to evaluate the performance of the mSOFA score model in diagnosing sepsis in patients admitted to the intensive care unit.

may not determine the risk of ICU-acquired infection. A Croatian study of mechanically ventilated patients with infectious diseases found that older age was not independently associated with ICU-acquired bloodstream infections (OR = 0.99, 95% CI: 0.71 – 1.38); instead, the duration of central venous catheterization was the only positive factor (37). This suggests that age-related risk may be mediated by invasive interventions and comorbidity burden rather than by age itself. A systematic review similarly identified age, sex, and comorbidities as nonmodifiable risk factors, whereas critical care interventions are modifiable and play a key role (10). Regarding sex, our model found no significant association (OR = 1.145, 95% CI: 0.442 – 2.965, P = 0.780). This finding contrasts with studies reporting a higher risk of sepsis in men, which may be attributed to estradiol-related inflammation, testosterone-induced immunosuppression, and X-linked genetic factors (38-40). However, a meta-analysis of 18 studies (671,861 participants) in Western Europe concluded that sex alone is not a robust independent predictor of short-term sepsis mortality; although men had higher baseline severity scores, the differences in mortality disappeared or reversed after adjustment (41). Another propensity score-matched study of 86,748 young adults with septic shock found that women had lower 28-day mortality than men, but this advantage was lost after the age of 55 years (42). Notably, our study focused on sepsis risk rather than sex-specific mortality; therefore, direct comparison with mortality studies requires caution. These discrepancies may reflect differences in study populations, sources of infection, and adjustment for confounders. Because our study was not designed to investigate sex-specific immune responses, larger prospective studies with sex-stratified analyses of both incidence and mortality are needed to clarify whether the absence of a sex difference reflects biology or limited statistical power.

Prior admission to infectious diseases wards was independently associated with ICU-acquired sepsis. Patients transferred from these wards often carry a higher baseline burden of colonization or active infection and may already have been exposed to broad-spectrum antibiotics, which select for resistant organisms (43). A French national surveillance study identified transfer from a medical unit as a risk factor for subsequent ICU-acquired *Pseudomonas aeruginosa* pneumonia (44). Similarly, many patients transferred to the ICU had already received antibiotics before admission, which was associated with a predominance of multiresistant bacteria in subsequent infections (43). These observations suggest that the infectious diseases ward acts as a reservoir for resistant pathogens, warranting heightened surveillance and empirical antibiotic strategies tailored to local resistance patterns.

Prior antibiotic administration is an inherent feature of ICU care and a potential confounder in studies of ICU-acquired sepsis. In our cohort, 73.8% of septic patients had received antibiotics before sepsis onset, which may have

contributed to the predominance of Gram-negative pathogens. Similar patterns were reported in the Brazilian SPREAD study, in which a high prevalence of hospital-acquired infections and antimicrobial resistance, particularly among Gram-negative pathogens such as *Pseudomonas* species, complicated treatment (45). In the Egyptian respiratory ICU study by Madkour et al., Gram-negative organisms, including *Klebsiella* and *Pseudomonas* species, predominated among septic patients, reflecting the regional burden of resistant pathogens (7). Nonetheless, we could not perform a formal sensitivity analysis for prior antibiotic exposure because comparable data were not collected for non-septic patients. Therefore, this limitation should be considered when interpreting our findings, and residual confounding cannot be excluded. Future prospective studies incorporating systematic antimicrobial stewardship data are needed to clarify the interplay among antibiotic exposure, antimicrobial resistance, and sepsis risk.

Admission for renal disorders was associated with a substantially higher risk of ICU-acquired sepsis. This is supported by evidence linking acute kidney injury (AKI) to a subsequent immunocompromised state. A large pediatric cohort found 2.05-fold increased odds of subsequent sepsis in children with stage 2 or 3 AKI compared with stage 1 or no AKI (46). In adult critically ill patients, sepsis developed in approximately 40% of patients after AKI, with a median onset of 5 days, establishing a temporal window for heightened surveillance (47). Furthermore, patients with renal disorders frequently require invasive interventions such as central venous catheters and RRT, which serve as additional portals of entry. A cohort of critically ill patients with acute renal failure treated with RRT found that 80.2% developed at least one infection, with pneumonia being the most frequent (48), and this vulnerability persists in more recent cohorts despite advances in critical care (49). Collectively, renal dysfunction itself, together with the invasive devices required for its management, creates a synergistic vulnerability to ICU-acquired sepsis.

Mechanical ventilation was strongly associated with ICU-acquired sepsis, consistent with its well-established role as a risk factor for ventilator-associated pneumonia, one of the most common ICU-acquired infections (50). A prospective study of patients with microbiologically confirmed ventilator-associated pneumonia found that 37% developed septic shock, with advanced age and lymphocytopenia as independent predictors of progression (51). More broadly, a retrospective cohort study identified the duration of mechanical ventilation as a significant risk factor for bloodstream infection, with the first positive blood culture appearing approximately 11 days after ICU admission (52). These data suggest that mechanical ventilation not only disrupts natural airway defenses but also serves as a marker of prolonged ICU exposure and illness severity, both of which contribute to subsequent sepsis.

Patients receiving combined enteral and parenteral nutritional support had a significantly higher risk of ICU-acquired sepsis than those receiving enteral nutrition alone (OR = 3.066, 95% CI: 1.530 – 6.146, P = 0.002). This association is unlikely to reflect a direct causal effect of the nutritional strategy itself. Instead, several lines of evidence from the present cohort support the interpretation that combined support is a marker of greater illness severity. First, parenteral nutrition alone was not significantly associated with sepsis (OR = 0.418, 95% CI: 0.153 – 1.144, P = 0.090), whereas only the combined modality was associated with an increased risk. If parenteral nutrition were intrinsically harmful, a similar or stronger association would be expected for parenteral nutrition alone. Second, combined enteral and parenteral support is typically initiated when enteral feeding alone is insufficient to meet caloric requirements, a situation that commonly arises in patients with severe illness, ileus, hemodynamic instability, or multiorgan dysfunction. The combined modality therefore serves as a proxy for the inability to tolerate adequate enteral nutrition, which is itself a marker of critical illness severity. However, the literature remains conflicting. A retrospective study of 144 critically ill patients found no significant difference in infectious complications between the enteral and parenteral nutrition groups (53). In contrast, a network meta-analysis of 26 studies (7,698 ICU patients) suggested that combined enteral and parenteral nutrition had the highest probability of reducing infection rates (54). This discrepancy may reflect differences in patient populations, the timing and duration of nutritional support, and the fact that our combined-support group likely represented a more critically ill subset. Future prospective studies with detailed data on caloric adequacy, timing of initiation, and infection surveillance are needed to clarify whether this association reflects confounding by indication or a true biological effect.

The role of nurses in the early recognition of sepsis is increasingly acknowledged. Lemoh et al. (55) highlighted that nurses are often the first to identify patient deterioration and initiate sepsis screening, emphasizing the need for clearer definitions and consistent training (55). Similarly, Zaboli et al. (56) demonstrated that nurse-led identification using qSOFA and lactate can effectively stratify high-risk septic patients (56). In our study, daily mSOFA assessments were performed by a dedicated researcher; however, integrating nurse-led screening

protocols could further improve early recognition in routine ICU practice.

The 30-day mortality rate in our cohort was 46.1%, consistent with rates reported in studies from Ethiopia (50.9%) (25) and Jordan (52.7%) (57). Similarly, a Brazilian multicenter study reported a 30-day mortality rate of 55.7%, attributed to severe illness and a high prevalence of hospital-acquired infections and antimicrobial resistance (45). Collectively, these findings underscore the persistent burden of sepsis-related mortality in resource-limited settings and the urgent need for early recognition and effective management strategies.

4.1. Limitations

This study has several limitations. First, the observational design precludes causal inference, and the identified associations should be interpreted as correlational. Second, the study was conducted in a single region (Northern Iran) in ICUs affiliated with a single university, which may limit the generalizability of our findings to other healthcare settings with different patient populations, resources, or antimicrobial resistance patterns. Third, the 30-day follow-up period may not fully capture the long-term outcomes of sepsis, such as late mortality or post-sepsis syndrome. Fourth, the exclusion of patients with an ICU stay of less than 48 hours and of those who developed sepsis within the first 48 hours may have introduced selection bias; specifically, patients with more fulminant presentations and different risk profiles may have been excluded, potentially limiting the applicability of our findings to this subgroup. Fifth, although the 48-hour exclusion criterion minimized the inclusion of infections that were clinically manifest at ICU transfer, we could not ascertain whether some infections manifesting after 48 hours were already incubating at the time of transfer; such cases would have been classified as ICU-acquired, potentially leading to a modest overestimation of ICU-attributable sepsis. Sixth, the lack of blinding during data extraction may have introduced information bias, particularly for subjective variables such as clinical jaundice. Seventh, microbiological investigations were performed at the discretion of the attending physicians without a standardized protocol across the nine ICUs, which may have led to variations in culture yield and pathogen identification. Eighth, because ICU length of stay, RRT, and vasopressor use occurred before sepsis onset in some patients and after it in others, these variables were excluded from the regression model to avoid immortal time bias and reverse causality. Ninth, the mSOFA score used in this study is a resource-adapted modification rather than a validated severity score. The mSOFA was originally developed for resource-constrained settings in which the full laboratory panel required by the original SOFA is not uniformly available (31), and its feasibility has been demonstrated in other low-resource ICU settings, such as Uganda (32); Mulatu et al. also used the mSOFA for sepsis assessment in Ethiopian ICUs (25). Because platelet count and serum bilirubin were not uniformly available, a sensitivity analysis comparing the mSOFA with the original SOFA could not be performed. The mSOFA was therefore used as a pragmatic screening tool for organ dysfunction. Although its discriminative ability in this study was good (AUC = 0.817), external validation in other Iranian ICU populations is required before its routine use can be recommended. Tenth, several descriptive variables that would have enriched the characterization of sepsis were not systematically available in a structured format across the participating ICUs. These include the precise timing of sepsis onset, a formal Sepsis-3 classification of septic shock (because lactate was not uniformly measured), organ support initiated specifically after sepsis onset (because support initiation was not time-stamped), and cause of death. Mortality was ascertained as all-cause 30-day mortality, which is the standard outcome in sepsis research. Finally, we could not perform a formal sensitivity analysis for prior antibiotic exposure because comparable data were not collected for non-septic patients; therefore, residual confounding by prior antibiotic exposure cannot be excluded.

4.2. Conclusions

In this prospective, multicenter study, ICU-acquired sepsis occurred in 12.1% of patients hospitalized for more than 48 hours, with a 30-day mortality rate of 46.1%. Independent risk factors included an age of 40 – 59 years, prior admission to infectious diseases wards, admission for renal disorders, mechanical ventilation, and combined enteral and parenteral nutritional support. These findings provide region-specific baseline data on the incidence, risk factors, and clinical outcomes of ICU-acquired sepsis in Northern Iran. The high mortality rate observed in this cohort highlights the persistent burden of sepsis in resource-limited settings. Identifying these high-risk subgroups may help clinicians prioritize closer monitoring of warning signs in these patients. However, because the observational design precludes causal inference, future prospective studies are needed to validate these risk factors and to develop targeted preventive strategies in this region.

Footnotes

AI Use Disclosure: The authors declare that no generative AI tools were used in the creation of this article.

Authors' Contribution: Conceptualization: Fatemeh Ahmadi, Hedayat Jafari, and Ravanbakhsh Esmaeili; Data curation: Fatemeh Ahmadi; Formal analysis: Mahmood Moosazadeh; Investigation: Fatemeh Ahmadi; Methodology: Fatemeh Ahmadi, Hedayat Jafari, Mahmood Moosazadeh, Roya Ghasemian, Fatemeh Heidari, and Ravanbakhsh Esmaeili; Project administration: Hedayat Jafari and Ravanbakhsh Esmaeili; Resources: Fatemeh Ahmadi and Ravanbakhsh Esmaeili; Software: Fatemeh Ahmadi and Mahmood Moosazadeh; Supervision: Hedayat Jafari, Mahmood Moosazadeh, and Ravanbakhsh Esmaeili; Validation: Fatemeh Ahmadi, Hedayat Jafari, and Ravanbakhsh Esmaeili; Visualization: Fatemeh Ahmadi; Writing—original draft: Fatemeh Ahmadi; Writing—review and editing: Fatemeh Ahmadi, Hedayat Jafari, Mahmood Moosazadeh, and Ravanbakhsh Esmaeili. All authors read and approved the final manuscript.

Conflict of Interests Statement: The authors declare no conflict of interests regarding the publication of this paper.

Data Availability: The data supporting the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available because of ethical restrictions and participant confidentiality.

Ethical Approval: This study was approved by the Ethics Committee of Mazandaran University of Medical Sciences (Ethics Code: IR.MAZUMS.REC.1403.355). Before the study began, written informed consent was obtained from the patients or their legal guardians after they had received adequate information about the study objectives and procedures.

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Informed Consent: Written informed consent was obtained from all participants or their legal guardians before enrollment in the study.

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