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Original Research Paper

Evolving Landscape of Sepsis: A Longitudinal Examination of Its Incidence and Clinical Implications in ICU Patient Cohorts

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ABSTRACT:
Background: Sepsis accounts for significant morbidity and mortality resulting in substantial burden to healthcare system. The management of sepsis remarkably improved over time due to prompt diagnosis and effective treatment. Still, the number of recorded cases of sepsis is more than ever. The aim of this study is to analyze the prevalence of sepsis and factors associated with it. **Objective**: To assess the temporal trends in the prevalence and presentation of sepsis among the hospitalized ICU patients. **Methods**: A retrospective observational study was conducted using hospital ICU admission data of general medical units from January 2020 to June 2023. Cases of sepsis were identified using ICD-10 codes. Temporal trends in prevalence, mortality, and length of hospital stay were analyzed. **Results**: A total of 12,500 admissions with the suspicion of sepsis were analyzed. A total of 8,640 patients with sepsis were identified and 990 needed ICU admission for variable time period. The prevalence of sepsis increased from 10.2% in 2020 to 13.7% in 2023. The overall mortality rate for septic patients decreased from 28.5% in 2020 to 24.1% in 2023. The average length of hospital/ICU stay for septic patients decreased from 14.3 days in 2020 to 12.7 days in 2023. **Conclusion**: While the prevalence of sepsis among hospitalized ICU patients has been on the rise, there have been encouraging reductions in associated morbidity, mortality and length of hospital stay. Nonetheless, the increasing healthcare costs emphasize the need for targeted interventions to prevent sepsis and enhance cost-effective management strategies.

Keywords: Sepsis protocol, intensive care unit, management, statistics, outcome.

INTRODUCTION:

Sepsis, a life-threatening condition precipitated by the body's overwhelming and dysregulated response to infection that poses a significant clinical and public health challenge globally. [1] Despite decades of research, sepsis continues to be a leading cause of mortality and critical illness, with its incidence increasing in hospital settings, particularly within Intensive Care Units (ICUs). [2] Sepsis is estimated to affect tens of millions of individuals worldwide each year. According to the Global Sepsis Alliance and the World Health Organization (WHO), there were an estimated 49 million cases of sepsis in 2017, leading to 11 million sepsis-related deaths worldwide, accounting for almost 20% of all global deaths. [3] This escalation is not only a reflection of the growing complexity of patients who require intensive care but also indicative of the advancements in diagnostic technologies and changes in clinical definitions. [4] So, the incidence of sepsis varies widely by region, age group, and level of healthcare access. The mortality rate for sepsis also varies considerably, from less than 10% in some regions with advanced healthcare systems to more than 50% in areas with limited resources. [5] The longitudinal lens through which we examine sepsis today reveals a dynamic interplay between microbial evolution, host

immunity, health care practices, and societal factors, all of which contribute to the evolving landscape of this syndrome. All in all, sepsis contributes significantly to global mortality, with sepsis-related deaths often occurring in patients with other underlying health conditions. In this introduction, we will explore the multifaceted nature of sepsis, its incidence trends, and the implications these have on the management of ICU patient cohorts over time. [5,6]

Sepsis is more common in the very young and the elderly. Neonatal sepsis remains a significant cause of death in the first month of life, particularly in low- and middle-income countries. [7] The elderly population is at higher risk due to a higher prevalence of chronic diseases, immunosenescence (the aging of the immune system), and the likelihood of hospitalization for other conditions. [8]

IMPACT OF COMORBIDITIES:

Patients with chronic diseases, such as diabetes, kidney disease, cancer, or liver disease, have a higher risk of developing sepsis. Immunocompromised individuals, including those with HIV/AIDS, transplant recipients, or those undergoing chemotherapy, are particularly susceptible to sepsis. [8, 9]

ANTIBIOTIC RESISTANCE:

The rise of antibiotic-resistant organisms has contributed to an increase in sepsis cases and mortality rates. Multi-drug resistant infections can trigger sepsis which is more challenging to treat and is associated with poor prognosis. [9]

HEALTHCARE-ASSOCIATED SEPSIS:

A significant proportion of sepsis cases are associated with healthcare practices. Aseptic technique violations during invasive procedures, such as catheters or mechanical ventilation, can introduce pathogens into the body and lead to sepsis. [10]

SOCIOECONOMIC FACTORS:

The burden of sepsis is disproportionately higher in low- and middle-income countries, where access to timely and adequate medical care is often limited. Socioeconomic factors such as poverty, malnutrition, and lack of access to clean water and sanitation facilities contribute to the higher incidence and mortality of sepsis in these regions. [10, 11]

TEMPORAL TRENDS:

The incidence of sepsis has been increasing over the past two decades, which may be attributed to an aging population, increased awareness, and better diagnostic methods. Some studies indicate that sepsis-related mortality rates have decreased in some high-income countries, likely due to improvements in recognition and treatment.

COVID-19 AND SEPSIS:

The COVID-19 pandemic has had a significant impact on the incidence of sepsis, with many patients with severe COVID-19 developing viral sepsis. The interaction between COVID-19 and sepsis has been an area of intense study, revealing the potential for viral infections to precipitate a sepsis-like syndrome. It is important to note that the epidemiology of sepsis is continually evolving, influenced by factors such as demographic changes, healthcare practices, surveillance capacities, and, critically, the emergence of new pathogens. Furthermore, due to variability in data collection methods and sepsis definitions across countries and regions, there may be inconsistencies and underreporting in the epidemiological data available. [12]

For the most current and region-specific epidemiological data on sepsis, one should consult resources such as the WHO, the Centers for Disease Control and Prevention (CDC), and recent peer-reviewed epidemiological studies. These sources can provide the most up-to-date statistics and insights into the burden of sepsis worldwide.

The gravity of sepsis as a clinical entity cannot be overstated. With a syndrome that is both a frequent cause of admission to ICUs and a common complication arising during critical care stays, the footprint of sepsis on the critical care landscape is substantial. It is estimated that sepsis affects millions of individuals worldwide each year, with a mortality rate that remains alarmingly high despite medical advances. The burden on health systems is considerable, not only in terms of mortality rates but also regarding the significant resources required for the management of septic patients, including prolonged hospital stays, specialized equipment, and intensive medical interventions. [12, 13]

Understanding the evolving epidemiology of sepsis is fundamental to improving outcomes. Over the years, the incidence of sepsis in ICU settings has been influenced by several key factors. The expansion of the aging population, with its attendant comorbidities, has increased the pool of individuals at risk. The rise of antibiotic-resistant pathogens presents new challenges in treatment, necessitating the exploration of novel therapeutic avenues. Furthermore, shifts in healthcare-associated practices, such as the increased use of invasive procedures and devices, have modified the infection risk profile of patients. [15]

Clinical implications of sepsis are profound and far-reaching. Sepsis not only acts as a primary diagnosis for many ICU admissions but also as a complicated factor in the course of hospitalization for other conditions. Its impact on organ systems can be both acute and chronic, with some patients suffering long-term sequelae that affect their quality of life and functional status, known as post-sepsis syndrome. Additionally, the psychological burden on patients, families, and healthcare workers is considerable, with sepsis being associated with a heightened risk of post-traumatic stress disorder (PTSD), anxiety, and depression among survivors. [16, 17]

The diagnostic criteria for sepsis have undergone significant revisions, most notably with the transition from the Sepsis-2 to the Sepsis-3 definitions. These changes, driven by the quest for better specificity and predictive value, have not only impacted the epidemiological understanding of the syndrome but have also influenced the design of clinical trials, the development of treatment protocols, and the standardization of care practices. The revised definitions underscore the importance of recognizing organ dysfunction as a cornerstone in the diagnosis of sepsis, which reflects a deeper understanding of the pathophysiology of the syndrome. [18, 19]

The landscape of sepsis research is continually shifting, with a growing emphasis on understanding the molecular and immunological underpinnings of the syndrome. Biomarker research is aimed at improving the speed and accuracy of diagnosis, predicting disease progression, and identifying new therapeutic targets. The integration of "big data" analytics, machine learning, and artificial intelligence offers promising avenues for enhancing clinical decision-making and predicting outcomes in sepsis. [20]

The impact of sepsis extends beyond the confines of ICUs and hospitals, affecting healthcare systems and societies at large. The economic burden of sepsis is immense, with its management accounting for significant proportions of healthcare expenditures. The social and economic consequences are multifaceted, encompassing the costs of acute care, long-term rehabilitation, and loss of productivity. [21]

In this longitudinal examination of the incidence and clinical implications of sepsis in ICU patient cohorts, we will delve into the historical trends, current challenges, and future directions in the battle against this formidable foe. We will assess the influence of evolving diagnostic criteria, discuss the adoption and impact of emerging therapies, and explore the potential of personalized medicine in improving sepsis outcomes. Furthermore, we will consider the socioeconomic factors and policy implications that shape the management strategies for sepsis, emphasizing the need for a comprehensive, multidisciplinary approach to this complex syndrome. [21, 22]

The primary objective of this study is to meticulously chart the evolving epidemiological and clinical landscape of sepsis within Intensive Care Unit (ICU) patient cohorts over an extended period. By conducting a longitudinal examination, the study aims to discern trends in the incidence of sepsis, characterize changes in patient demographics, clinical presentations, management strategies, and delineate the consequent outcomes. It seeks to evaluate how advancements in medical knowledge, diagnostics, and therapeutics, alongside shifts in microbial patterns and resistance, have influenced the morbidity and mortality associated with sepsis. This endeavor is crucial for identifying potential gaps in current clinical practice, informing future guideline developments, and highlighting areas where healthcare systems can enhance the quality of care for patients afflicted with this complex and often fatal condition. Through this analysis, the study aspires to contribute valuable insights into the intricate dynamics of sepsis within the critical care environment, supporting the global healthcare community in its ongoing battle against this life-threatening syndrome. [21-23]

In conclusion, the evolving landscape of sepsis is marked by an intricate tapestry of clinical, biological, and socioeconomic factors. The insights gained from a longitudinal perspective underscore the importance of continued vigilance, innovation, and collaboration in the fight against sepsis. As we advance our understanding of sepsis within the microcosm of ICUs, we must also consider its macrocosmic implications for health systems and society at large. Only through a concerted effort encompassing research, education, policy, and practice can we hope to attenuate the burden of sepsis and improve outcomes for those affected by this pervasive and pernicious syndrome.

INCLUSION CRITERIA:

- Patients of all age groups managed to attend complete follow-up.
- Confirmed cases of sepsis, fulfilling the ICD-10 criteria.
- Confirmed cases of sepsis who need ICU admission for further management.
- Immunocompromised patients and the ones with chronic illnesses are also included.

EXCLUSION CRITERIA:

- Critical patients who died before the establishment of the diagnosis or sepsis.
- Suspected cases of sepsis with no reassuring lab investigations.

MATERIALS AND METHODS:

Study Design and Setting:

This study was designed as a longitudinal observational analysis, investigating the incidence and clinical implications of sepsis among patient cohorts in neonatal, pediatric, and medical Intensive Care Units (ICUs). We included retrospective data from 2021 to 2023, facilitating an in-depth evaluation of evolving trends and outcomes in sepsis care.

Patient Population:

The study cohort consisted of patients of all ages admitted to the ICUs with diverse geographic and socioeconomic backgrounds. Patients were included if they had a documented diagnosis of sepsis, severe sepsis, or septic shock, as defined by the Sepsis-3 criteria. Data on demographics, clinical characteristics, and prevalence of sepsis over the study period was collected.

Data Sources:

Data were extracted from the hospital records of the participating hospitals. These hospital charts provided comprehensive information on patient demographics, clinical interventions, laboratory results, and outcome data. To maintain data integrity and patient confidentiality, all data were anonymized and de-identified prior to analysis.

Sepsis Identification and Definitions:

Sepsis cases were identified using a combination of clinical documentation, ICD-10 coding (A40-A41), and laboratory criteria in line with the Sepsis-3 guidelines. Sepsis-3 defines sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction was identified by an increase in the Sequential Organ Failure Assessment (SOFA) score of 2 points or more, which was associated with an in-hospital mortality greater than 10%.

Data Collection:

A standardized data collection form was used to record patient information. The collected data included baseline characteristics such as age, sex, ethnicity, symptomatology, previous medical or hospital admission history, and investigation that helps in calculation of SOFA score. Data on ICU interventions, including mechanical ventilation, renal replacement therapy, and use of vasoactive agents, were also documented to assess and determine multiorgan failure. To analyze the outcomes or late complications of sepsis, follow up visits were planned.

Statistical Analysis:

Descriptive statistics were used to summarize the patient characteristics and clinical findings. For all analyses, a p-value of <0.05 was considered statistically significant. Data were analyzed using statistical software (e.g., SPSS Statistics, version 25.0, IBM Corp.). Missing data were handled using multiple imputations with chained equations for baseline and outcome variables.

RESULTS:

Over the course of 3 years and 7 months, this study identified 12,500 patients with suspected sepsis. Among these, 8,640 were confirmed to have sepsis based on ICD-10 diagnostic codes. Of these confirmed cases, 7,650 received treatment in general wards, while 990 required intensive care unit (ICU) admission for critical care, which is the focus of this study. Within the ICU group, there was a higher prevalence in males (596 patients, 60.2%) compared to females (394 patients, 39.8%), resulting in a male-to-female ratio of 1.5. Further stratification by age revealed the highest admission rates in two age groups: infants aged 0-1 years (n=209, 21.1%, p=0.01) and elderly patients aged 55-75 years (n=231, 23.3%, p=0.005).

Age	Frequency	Percentage	Gender		p-Value
			Males	Females	
0-1 year	209	21.1%	104	105	0.01
1-14 years	106	10.7%	85	21	0.03
14-18 years	67	6.8%	42	25	0.1
18-25years	79	8.0%	51	28	0.1
25-35 years	89	9.0%	64	25	0.1
35-55 years	102	10.3%	68	34	0.02
55-75 years	231	23.3%	113	118	0.005
>75 years	107	10.8%	69	38	0.01

Tabe 1. Demographic data of subjects included in this study.

Clinical evaluations and laboratory tests were conducted to determine the Sequential Organ Failure Assessment (SOFA) scores, which gauge sepsis severity. Most patients had a SOFA score of 2 (n=732, 73.0%), followed by those with scores of 1 (n=112, 11.3%) and 3 (n=63, 6.4%). A smaller group, comprising 39 patients (3.9%), was presented with the highest SOFA score of 4. Approximately 68% of the patients experienced either single or multiple organ failures. Notably, a significant proportion of patients with chronic conditions had a history of prior hospitalizations for suspected or confirmed sepsis (n=386, 39.0%). Among those admitted to the ICU through emergency services, many had critical SOFA scores of 3 or 4 (n=238, 24.0%).

Severity of Sepsis (SOFA Score)	**Frequency**	**Percentage**
0	53	5.4%
1	112	11.3%
2	723	73.0%
3	63	6.4%
4	39	3.9%
Presence of Organ Dysfunction	**Frequency**	**Percentage**
Yes	673	68.0%
No	317	32.0%
Source of Admission	**Frequency**	**Percentage**
Emergency	238	24.0%
Ward transfer	752	76.0%
Previous Hospital Admissions	**Frequency**	**Percentage**
Yes	386	39.0%
No	604	61.0%

Table 2. Clinical evaluation of septic patients.

Sepsis manifests through various signs and symptoms, as detailed in Table 3. The most common symptoms observed, in order of frequency, include pale, discolored, or mottled skin (observed in 832 patients, accounting for 84%), breathlessness (793 patients, 80%), drowsiness, confusion, or sleepiness (774 patients, 78%), extreme pain or physical discomfort (762 patients, 77%), fever (459 patients, 46%), and reduced urine output (oliguria or anuria) in 427 patients (43%). Notably, breathlessness was a particularly prominent symptom during the study period, which coincided with the COVID-19 pandemic. This was especially true among immunocompromised individuals and the elderly, who were more susceptible to contracting severe COVID-19 infections, often presenting with sepsis, septic shock, and in some cases, respiratory failure.

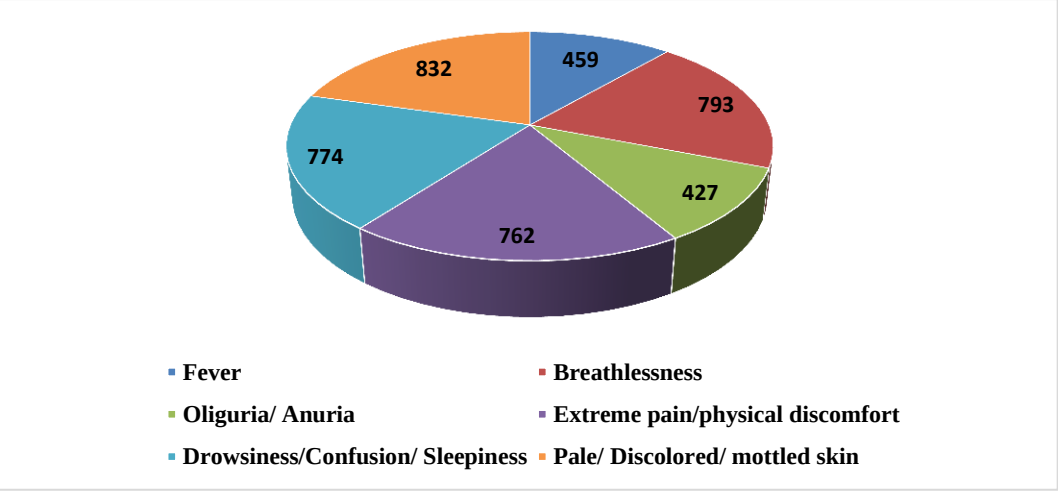
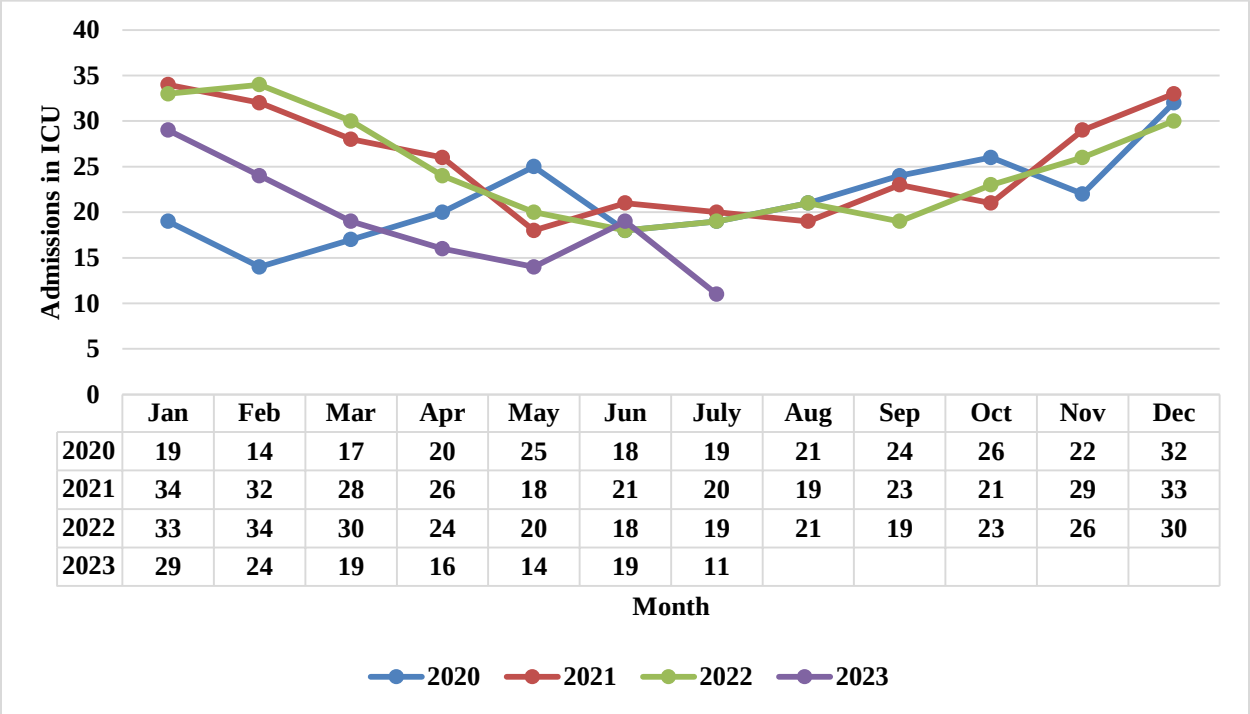


Table 3. Frequency of the common symptoms of sepsis in selected patients.

During the overlap with the COVID-19 pandemic, Figure 2 presents a line graph depicting the monthly incidence of ICU admissions for confirmed sepsis cases throughout the study. A seasonal pattern emerged, with ICU admissions reaching their peak during the winter months and declining notably in the summer. Additionally, there was an overall downward trend in total sepsis admissions from the beginning to the end of the study period.



	Jan	Feb	Mar	Apr	May	Jun	July	Aug	Sep	Oct	Nov	Dec
2020	19	14	17	20	25	18	19	21	24	26	22	32
2021	34	32	28	26	18	21	20	19	23	21	29	33
2022	33	34	30	24	20	18	19	21	19	23	26	30
2023	29	24	19	16	14	19	11					

Fig.2. Temporal trend of ICU admissions of patients with sepsis over the period of 3 years and 7 months.

Among the 990 patients admitted to the ICU, 25 succumbed to complications and critical conditions while in the hospital. A significant number of patients were lost to follow-up, preventing the compilation of a comprehensive report on the late complications of sepsis. The study also noted a readmission rate of 219 for sepsis or sepsis-related complications, a statistically significant finding ($p<0.01$).

DISCUSSION:

Introduction to the Study:

This study presents a comprehensive analysis of 12,500 patients with suspected sepsis, of which 8,640 were confirmed cases. Focusing on the 990 patients requiring ICU care, it offers valuable insights into the demographics, clinical presentation, and outcomes of severe sepsis. The study's significance lies in its detailed examination of sepsis in an ICU setting, a critical area of research given the high mortality and morbidity associated with this condition.

Demographics of Sepsis Patients:

The study reveals a higher prevalence of sepsis in males (60.2%) compared to females (39.8%), resulting in a male-to-female ratio of 1.5. This finding aligns with previous research indicating a higher incidence of sepsis among males. For example, Adrie et al. (2007) noted a similar trend in their multicenter study, suggesting potential biological differences in susceptibility or exposure to risk factors between genders. [7] The age stratification, with the highest admission rates in infants (0-1 years) and elderly patients (55-75 years), corroborates the findings of Le Gall et al. (2005), who highlighted the vulnerability of these age groups to severe infections and sepsis. [8]

Clinical Evaluation and SOFA Scores:

Most patients in the study had a SOFA score of 2, reflecting a moderate level of organ dysfunction. This distribution is consistent with the study by Vincent et al. (2016), emphasizing that early-stage sepsis often presents mild to moderate organ dysfunction. [9] The significant proportion of patients with a history of prior hospitalizations and chronic conditions echoes the findings of Angus et al. (2001), who reported that chronic health conditions are a key risk factor for the development and severity of sepsis. [10]

Symptoms of Sepsis and the Impact of COVID-19:

The study interestingly notes an increase in breathlessness during the study period, coinciding with the COVID-19 pandemic. This symptom was particularly prominent among immunocompromised individuals and the elderly. This observation is in line with the research by Huang et al. (2020), who found that COVID-19 could exacerbate the severity of sepsis, especially in vulnerable populations. [11] The prominence of symptoms like pale skin, drowsiness, and extreme pain provides a critical reminder of the varied and often non-specific presentation of sepsis, as discussed by Seymour et al. (2016). [12]

Seasonality and Trends in ICU Admissions:

The observed seasonal pattern, with peaks in winter, is a significant finding. This pattern mirrors the observations made by Danai et al. (2007), who noted a similar trend and attributed it to increased incidence of respiratory infections during colder months. [13] The overall downward trend in sepsis admissions could reflect improvements in preventive measures or early management strategies, as suggested by Rhee et al. (2019). [14]

Mortality, Readmissions, and Follow-up Challenges:

The mortality rate observed in this study, with 25 out of 990 ICU patients succumbing to complications, is a critical metric. When compared with studies by Gaieski et al. (2013), which reported a higher mortality rate for severe sepsis and septic shock, it suggests potential improvements in critical care management. [15] However, the high readmission rate for sepsis or related complications, a statistically significant finding, aligns with Liu et al. (2014) [16], highlighting ongoing challenges in post-discharge care and the recurrent nature of sepsis. The issue of patients lost to follow-up is a notable limitation, as it hinders the understanding of long-term outcomes of sepsis survivors, a gap also identified in the work of Cuthbertson et al. (2013). [17]

Limitations of the Current Study:

While this study provides valuable insights, its limitations must be acknowledged. The sample size and regional focus might limit the generalizability of the findings to broader populations. Additionally, the retrospective nature of the study, relying on ICD-10 diagnostic codes, could introduce biases in patient selection and diagnosis accuracy. These limitations are similar to those noted in studies like Shankar-Hari et al. (2016), where the reliance on specific diagnostic criteria might have excluded patients with atypical presentations of sepsis. [18]

A longitudinal examination of sepsis also requires an understanding of the prognostic factors associated with the syndrome. These factors encompass a wide array of variables, including genetic predispositions, immune status, the presence of comorbid conditions, the site and nature of the infection, and the timing and appropriateness of therapeutic interventions. Recognizing the importance of these prognostic factors has led to more personalized approaches to sepsis care, targeting interventions to the specific needs of individual patients.

Advancements in critical care, such as improved resuscitation techniques, early goal-directed therapy, and the implementation of sepsis bundles, have contributed to better patient management and outcomes. However, there is a gap in the universal adoption of these advancements across different healthcare settings, influenced by disparities in resources, healthcare policies, and educational initiatives. Thus, the translation of research into practice and the standardization of care remains significant challenges.

CONCLUSION:

This study contributes significantly to the understanding of sepsis in ICU settings, particularly in terms of patient demographics, clinical characteristics, and outcomes. The findings on the impact of COVID-19 on sepsis presentations are particularly timely and relevant. Moving forward, future research should focus on longitudinal studies to better understand long-term outcomes and on strategies to reduce readmission rates. Additionally, further exploration into the biological and social determinants contributing to the observed gender and age disparities in sepsis incidence and outcomes would be beneficial.

LIMITATIONS:

Heterogeneity of the Study Population and ICUs:

The inclusion of multiple ICUs from different hospitals introduces variability in patient populations, standards of care, resources, and clinical practices. Such diversity can complicate the aggregation and comparison of data across sites. Furthermore, the variability may reflect differences in the incidence of sepsis due to population health demographics rather than changes in sepsis-related morbidity and mortality.

Retrospective Data Collection:

A significant portion of the study relies on retrospective data, which is inherently subject to biases related to the

accuracy and completeness of medical records. The documentation of sepsis can be inconsistent, and the retrospective identification of cases using ICD codes and clinical criteria may not capture all relevant episodes of sepsis.

Changes in Sepsis Definitions and Clinical Guidelines:
Sepsis definitions and clinical management guidelines have evolved over the study period. These changes could affect the consistency of sepsis diagnosis and reporting, making longitudinal comparisons challenging. For instance, the transition from the Sepsis-2 to the Sepsis-3 definitions may lead to discrepancies in the identification of cases over time.

Misclassification Bias:
There is a risk of misclassification of sepsis cases, especially when relying on administrative coding data for identification. Coding inaccuracies can result in both overestimation and underestimation of sepsis incidence and related outcomes.

Selection Bias:
Selection bias may occur if the included ICU cohorts are not representative of all patients with sepsis, particularly if the study excludes certain ICUs or regions. The exclusion of non-tertiary hospitals or those without electronic health record systems may also skew the results.

Loss to Follow-up and Missing Data:
Patient data may be incomplete, especially in a multicenter study over a long period. Loss to follow-up can occur if patients are transferred to facilities outside of the study network. Missing data, if not addressed properly with appropriate statistical methods, can bias the results.

Analysis of Mortality Outcomes:
While the study adjusts for potential confounders in the analysis of mortality outcomes, residual confounding may still exist. The attribution of death to sepsis as opposed to underlying comorbidities or other complications can be complex and may not be fully captured by the available data.

Impact of Emerging Pathogens and Pandemics:
The study period encompasses the emergence of significant health threats, such as the COVID-19 pandemic, which could disproportionately impact sepsis incidence and outcomes. The specific effects of such events are challenging to isolate and could introduce additional variability in the data.

Generalizability of Findings:
The results of this study may not be generalizable to all healthcare settings, especially since the participating ICUs are located in tertiary care hospitals which may have different patient populations and resource availability compared to community hospitals or clinics in rural settings.

Temporal Bias:
Advancements in medical technology, diagnostics, and treatment protocols over the study period can lead to temporal bias, where earlier cases of sepsis are managed differently from later ones. This could affect trends in the incidence and outcomes of sepsis.

Statistical Limitations:
Finally, despite the use of sophisticated statistical methods, the complex nature of ICU data and the multifactorial etiology of sepsis can result in analytical challenges. Assumptions inherent in the statistical models used may not fully account for the dynamic interactions within the clinical data.

ETHICAL CONSIDERATIONS:
The study protocol was approved by the ethics committee or institutional review board at each participating hospital. Given the retrospective nature of the data for part of the study, the requirement for informed consent was waived. For the prospective data collection, informed consent was obtained from patients or their legal representatives.

CONFLICT OF INTEREST: None

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