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Study the clinical features, causative organisms, incidence, severity, evaluation of organ dysfunction and outcome of sepsis in ICU patients: A literature review

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Abstract
The purpose of this study was to compile the data we have and provide a concise summary of the risk variables linked with the incidence of sepsis in adult patients admitted to the ICUs while they were there. Demographic, critical care intervention, surgical, co-morbidity, organ injury severity, and biomarker and biochemical and molecular indicators were the sources from which the risk variables were derived. Patients hospitalised to the intensive care unit had a greater risk of sepsis whether they were older or male. Patients hospitalised to medical, surgical, neurologic, trauma, and general ICUs were all included in our research, which compiled risk variables for sepsis across all of these specialties. Non-modifiable risk factors included age, sex, and co-morbidities, while modifiable risk factors included critical care interventions and surgery-related factors. This suggests that better surgical patient care and effective management of critical care interventions may play an important role in reducing the development of sepsis in patients admitted to intensive care units.

Keywords: Sepsis, health care, risk factors, ICU

Introduction
Infection with sepsis is a common reason for hospitalization in critical care units (ICU). Patients in the intensive care unit (ICU) have a high risk of death and serious complications due to severe sepsis and septic shock. Sepsis has a mortality rate of 30%-40% [1-3]. No progress has been made in reducing sepsis mortality in the past two decades [4, 5]. Acute organ failure due to a known or suspected infection causes severe sepsis, which can then progress to septic shock (Severe sepsis and hypotension not reversed with fluid resuscitation). Sepsis is a complicated and multi-factored pathophysiology. Both pro- and anti-inflammatory responses are triggered in response to infection, and both help with infection management and tissue damage that can eventually cause organ failure. Both the host (such as preexisting conditions and immune suppression) and the infection have a role in how a patient reacts to sepsis (Virulence and organism load). Impairment in tissue oxygenation and coagulation disorders such as intravascular coagulation, fibrinolysis, and microvascular thrombi result from endothelial injury. When blood vessels dilate and blood pressure drops, oxygen supply to tissues is cut in half, which can cause organ failure.
Studies examining the prevalence and distribution of sepsis often target high-income nations. The guidelines for treating patients are based on research like those described in [6, 7]. More research from LMICs would better capture the actual global impact of sepsis by illuminating the challenges of treating the condition in areas with limited resources [8, 9].
Sepsis is a major health care issue because of the difficulty of studying and treating it from the perspectives of pathophysiology, clinical medicine, and therapeutics. Many have attempted to define this condition, but it is generally accepted that they all refer to the inflammatory response of the body's immune system to an infection or acute sickness. Even though these definitions have been put out, they are not widely recognised. Patients in the intensive care unit (ICU) have a far lower quality of life and a lower chance of survival if they are diagnosed with sepsis, severe sepsis, or septic shock. A wide range of organ dysfunction and failure is associated with these diseases [10].
The first three days of sepsis disease are linked with a pattern of developing neurologic, coagulation, and renal impairment, all of which contribute to an increased risk of death. Despite the ubiquitous nature of pulmonary dysfunction in patients with sepsis syndrome,

there is no association between initial pulmonary impairment and an increased risk of death. One or more variables, such as age, gender, immunity, and co-morbidities, contribute to the overall mortality rate. The causative microorganism of sepsis is another contributor to outcome [11]. Patients hospitalized to critical care units (ICUs) are increasingly at risk for developing sepsis, with incidences ranging from 17.3 percent to 7 percent [12, 13]. Still, the prognosis of sepsis is dismal, with ICU death rates ranging from 36.0% to 55.2% due to the lack of effective treatments [12]. Since this is the case, it is the leading cause of mortality in adult intensive care units. However, in recent years, more and more emphasis has been turned towards detecting patients at risk of sepsis upon admission [14, 15], which is important since the bulk of sepsis studies have primarily focused on acute therapy of the condition to minimise death rate [16-18]. A quick literature search reveals that understanding the causes of sepsis is becoming increasingly popular. Making educated medical decisions requires an awareness of potential dangers. Identifying patients at risk of sepsis is crucial for doctors to take preventative measures and allow patients to voice their treatment preferences. Chronic health problems, advanced age, being male, drinking too much alcohol, and being malnourished are all potential causes of sepsis [19-21]. Malignancy and its intensive treatment also lower the immune system, which increases the risk of sepsis [14]. Different studies have documented different risk factors for sepsis developing over the years because of the diverse nature of the critically sick patients admitted to ICUs.

As a country of 1.2 billion people, India has one of the world's highest rates of infectious illness deaths [23]. An estimated 12 percent of individuals (Range, 1-51 percent) who report with acute febrile sickness will have bacteremia, notwithstanding the absence of comprehensive data on the manifestations of such illnesses [24]. Although the term "sepsis" is sometimes used interchangeably with "blood stream infection," the focus of this study will be on sepsis as a condition. Diagnostic test availability varies across India [25, 26]. Thus complicating the challenge of correctly identifying these prevalent illnesses. Biomarker-based decision support systems for early detection of bacterial infections are an area of intense research and development. Additionally, due to the increasing prevalence of antibiotic resistance on the Indian subcontinent, biomarkers that aid in antibiotic stewardship are in high demand.

This review aimed to aggregate the available data and summarise the risk variables related with the incidence of sepsis in adult patients admitted to the ICUs during their ICU stay.

Demographic characteristic

Ten cohort studies looked at the impact of gender, but only three demonstrated a significant connection between sepsis and male gender in multivariable analysis (OR: 1.81 (p 0.001), OR: 1.55 (p 0.001), and OR: 1.20 (p 14 0.05), respectively) [20, 31, 39]. All eleven cohort studies also looked at how old individuals were when they contracted sepsis. One research found a negative or inverse correlation between age and incident sepsis (OR: 0.99 [p 0.001]), while two studies observed a significant connection between older age and incident sepsis in ICU admitted patients (OR: 1.62 [p 0.001] and OR: 1.09 [p 0.01]) [39].

Critical care interventions

Two cohort studies found a significant positive correlation between mechanical ventilation and length of intensive care unit (ICU) stay (OR: 1.20 [p 0.05] and OR: 5.51 [p 0.001]). One cohort analysis found that the use of urinary catheters (OR: 1.49 [p 0.001]) and central venous catheters (OR: 1.19 [p 0.001]) was positively linked with sepsis. Also, one case-control research found that giving critically sick patients parenteral feeding through nasogastric tubes was associated with an increased risk of developing sepsis (odds ratio [OR], 5.1; p 0.001). Therapeutic treatments such as fluid resuscitation and use of vasoactive medications were also found as risk variables (OR: 1.90 [p< 0.01] and OR: 2.58 [p< 0.001]) for the development of sepsis in a cohort study [19, 41].

Pre-existing comorbidities

Several studies have looked at how preexisting comorbidities influence sepsis progression in intensive care unit (ICU) admissions. Two separate studies-a cohort20 and a case control 32-found that preexisting conditions were risk factors [32]. Case-control research found that the presence of two or more intrinsic comorbidities was related with an elevated risk of sepsis (OR: 11.8, p 0.001) [32] and cohort research [20] found that individuals with preexisting medical disorders had an increased risk of sepsis (OR: 1.62, p 0.001). Other risk factors for developing sepsis include chronic obstructive pulmonary disease (COPD), immunosuppressive disorders14, and alcohol dependence37, each of which had an adjusted OR of 3.81 (p 0.05), 18.47 (p 0.05), and 1.54 (p 0.001), respectively. Two ICU scoring systems, the Glasgow Coma Scale20 and the Simplified Acute Physiology Score II14, have been evaluated in cohort studies to determine their prognostic value in determining a patient's central nervous system (CNS) and morbidity status. Both a Glasgow Coma Scale of 8 (odds ratio [OR] 1.32, p 0.001) and a one-unit rise in the Simplified Acute Physiology Score II (odds ratio [OR] 1.09, p 0.01) were observed to be positively associated with the occurrence of sepsis in those studies. In addition to CNS illness upon ICU admission [19], coma [32] was also identified as a risk factor, with an odds ratio (OR) of 1.14 (p 0.001).

Surgery-related factors

Both a case-control research and a cohort study (Coshort) found that emergency or urgent procedures increased the risk of sepsis [32, 40]. Both the unadjusted and adjusted ORs were 3.0 (p0.001), with the latter being 2.63 (p0.001). Adjusted odds ratios (ORs) of 2.5 (p 0.001) and 2.37 (p 0.001) were found between the incidence of sepsis and the number of surgical interventions [32] and the number of operational procedures [20], respectively. Two Case-control studies (OR: 2.6, p 0.001) and a cohort study (OR: 1.18, p 0.03) found that abdominal surgery [32] and laparotomy [20] were independent risk factors for the development of sepsis, respectively. One cohort analysis found that the quantity of transfused packed red blood cells between ER visit and intensive care unit admission was associated with worse outcomes (OR: 1.60, p 0.001) [20].

Severity of organ injury

One cohort study [20] found a statistically significant correlation between the severity of organ injury in trauma patients and the occurrence of sepsis, with the number of

injuries (OR: 1.09, p 0.001), injury severity score (OR: 1.01, p 0.001), and abbreviated injury scale (THORAX) score (OR: 1.30, p 0.001) serving as measures of this association.

Biomarkers and biochemical and molecular indicators

One case-control [36] study and two prospective studies have evaluated the biomarkers sP-selectin, sE-selectin, and Gcglobulin [30, 34]. Additionally, one case-control [32] study and two cohort studies have investigated three biochemical indicators: serum albumin, plasma cholesterol, and serum 25-hydroxyvitamin D [33, 39].

Blood cultures processed using standard microbiologic methods are a common diagnostic step, but whether or not they return with the pathogen of interest depends on a number of conditions, including whether or not the patient has recently been treated with antibiotics [41, 42].

An essential objective is to promptly recognize infection and initiate appropriate medication since delays in initial treatment for sepsis and bacteremia increase mortality [43], duration of stay [44], and cost. [45] Biomarkers may be useful for quick diagnosis and risk assessment, as findings from standard blood culture procedures might take up to 48 hours to become available. Diagnostic assays have been developed in an effort to improve the sensitivity and specificity of clinical decision making in the treatment of sepsis and bacteremia. Early studies used nonspecific measures like fever and leukocytosis to identify sepsis [46]. ESR and C-reactive protein (CRP) were the subject of further research to aid in the diagnosis algorithm, although they also had low specificity.

Discussion

In India, sepsis and its consequences account for a disproportionately high number of paediatric deaths [47]. This is consistent with the global trend [48, 49]. The first published consensus definitions of sepsis were in 199246; these definitions have since been revised [50]. The surviving sepsis campaign recommendations were reviewed and changed in light of advances in our knowledge of the pathogenesis, diagnosis, and treatment of sepsis [51].

Two of the cohort studies we reviewed had encouraging results [19, 20], and one study found an inverse relationship between age and the occurrence of sepsis [39].

In 2008, approximately two-thirds of all patients hospitalized with sepsis in the United States were older people [52]. Reduced physiologic reserve, immune senescence, subtle clinical manifestations, greater use of invasive devices, and hospitalization all contribute to the increased prevalence among the elderly [53]. Patients older than 65 years often have many co-morbid diseases that increase their risk of developing sepsis [52, 54], including coronary artery disease, congestive heart failure, and chronic obstructive pulmonary disease. Studies on the prevalence of sepsis in the general population show that it mostly affects those aged 65 and up by a significant margin (About 60%). The rising rate of sepsis in developed nations is likely due to the ageing of their populations [52].

After controlling for other factors, only three of the eleven cohort studies included in our evaluation indicated a significant link between male gender and sepsis [20, 31, 39]. The incidence of sepsis is higher in men, with estimates ranging from 54% to 66% based on several experimental and clinical research [55]. This link has been puzzling for a long time, but it may point to the impact of female sex hormones on the body's immune and cardiovascular systems [56]. Three studies looked into the link between invasive procedures performed during an ICU stay and the development of sepsis [19, 32, 40]. Mechanical ventilation was cited as a risk factor in two separate studies as one of these methods [19, 40]. This was likely linked to the common occurrence of ventilator-associated pneumonia as an infection site in critically sick patients [57]. Due to its modifiability, mechanical ventilation is a potential target for quality improvement initiatives aimed at reducing sepsis in surgical patients. Additionally, the three studies cited above revealed that the duration of catheterization and the kind of catheters used during the intensive care unit stay were risk factors. In the intensive care unit, bloodstream infections due to catheters are prevalent and can be fatal [58]. Between 1992 and 2004, the median rate of catheter-related bloodstream infection in all types of ICUs was between 1.8 and 5.2 per 1000 catheter-days, as reported by the National Nosocomial Infections Surveillance system [59]. Consequently, the infection rate can be lowered and the result improved by proper care of the tube system.

Our investigation revealed a number of potential dangers associated with the operation itself. There are a number of risk factors for surgical patients, including age, preexisting medical disorders, and extended hospital stays, which can lead to infection complications [40]. One large cohort study [40] and one case-control study [32] both found that emergency surgery was a strong and powerful predictor of sepsis in surgical patients admitted to the intensive care unit. Comorbidities such as chronic obstructive pulmonary disease (COPD) [14], immunosuppressive disorders [14], central nervous system infection (CNS) [19], and alcohol dependency all enhanced the incidence of sepsis in our assessment of five studies. More than half of patients with severe sepsis had at least one comorbid condition, according to recent research [60]. Sepsis has been linked to conditions including diabetes mellitus, heart failure, lung illness, immune suppression, liver disease, malignancy, and kidney failure [61].

Infection is a genetically complicated illness that results from the interplay of a person's genotype and the environment (Infectious micro-organisms). Methods like linkage analysis are used to investigate Mendelian, single-gene illnesses. An identifiable genetic marker is employed in linkage analysis to trace the inheritance pattern of a neighbouring disease gene whose precise position is unknown but whose location in the genome is known to be close by [62]. For complicated disorders that might include several genes, this strategy has been ineffective. Investigators have found several connections between genetic polymorphisms in these pertinent candidate genes and clinical outcome in disorders including diabetes, hypertension, and infection by leveraging the known pathophysiology of particular diseases to guide excellent predictions [63]. Examination of the frequency of a 'risk' allele in afflicted vs unaffected people is the primary goal of candidate gene association studies. Due to the low impact size of risk alleles in complex disease and low resolution, linkage studies are not as effective as candidate gene association studies in finding risk genetic variations for common, complicated diseases [62]. However, new insights are emerging from whole-genome genotyping in large patient groups with a few complicated disorders. Candidate genes in the inflammatory and immunological systems have

received a lot of attention in genetic association studies of infectious disorders because of their presumed importance in the body's response to infection. Inappropriate stimulation of the inflammatory response to invading microorganisms may result from polymorphisms in inflammatory and immune system genes. Because an incorrect coagulation response is significant in the pathophysiology of sepsis and is closely related to the immune response, researchers in critical care have also examined potential genes in the coagulation system [64, 65].

Patients with comorbidities such chronic obstructive pulmonary disease (COPD), immunosuppressive diseases, central nervous system infection (CNS), and alcohol dependency were more likely to develop sepsis after ICU admission, according to the results of five studies included in our meta-analysis. More than half of patients with severe sepsis had at least one comorbid condition, according to recent research [60]. Sepsis has been linked to conditions including diabetes mellitus, heart failure, lung illness, immune suppression, liver disease, malignancy, and kidney failure [61].

Several biomarkers that can help tell sepsis patients apart from those who don't have it based on the SIRS criteria have been getting a lot of press as of late. Soluble selectins are a class of cell adhesion molecules that enhance contacts between leukocytes and endothelium, which play a crucial role in the onset and progression of sepsis [66, 67]. Patients who developed sepsis within 1 week after cardiopulmonary resuscitation had greater sP-selectin levels than those who did not develop sepsis; however, the prospective controlled study [36] did not account for covariates. After controlling for other factors, another study [34] reported that patients admitted to a general ICU who had elevated levels of sE- and sP-selectin were more likely to develop sepsis.

Patients admitted to the ICU who were deficient in 25-hydroxyvitamin D were more likely to develop sepsis, according to one study included in our evaluation. Despite the small sample size, a recent systematic review and meta-analysis found a correlation between vitamin D insufficiency and an increased risk of sepsis [68]. Despite decades of study on the subject, no single, definitive biomarker for sepsis has been found as of yet.

Important genetic connections with sepsis outcomes have been found, but more work is needed to incorporate this knowledge into patient management. While the ability to forecast risk for unfavourable result based on genotype is somewhat valuable, the ability to predict response to therapy is certainly more relevant for doctors making treatment decisions. This highlights the need for genetic association studies to broaden their focus to incorporate therapeutic response as a measureable end-point. Secondly, in order to verify that genotypic information adds to predictions of response to therapy or outcome beyond what is attainable using traditional measurements, specificity and sensitivity studies must be incorporated into predictive genetic relationships (Age, severity of illness, and so on). To confirm the treatment-modifying findings and to quantify the effectiveness (Beyond efficacy) of judgements based on the predictive genetic test, third, prospective testing of these tests in large multicenter trials will be essential. These are significant challenges, but they are not insurmountable, especially when we work together on a global scale, as we must do today.

There were a few cracks in our research. Most of the studies we included were conducted at academic medical centres, so their patient groups may not be representative of those seen in other types of hospitals. Also, it was hard to compare studies since they used different ICU types, sepsis criteria, covariate adjustments, and sample sizes. Finally, as the purpose of this systematic review was to identify sepsis risk factors, all of the papers included were observational. Therefore, observational study bias may affect the results of this investigation. However, when evaluated with the Newcastle-Ottawa Scale, the vast majority of the studies were of high quality.

There needs to be well-designed studies in India to determine cutoff values for the diagnosis and deescalation of antibiotics in Indian patients with sepsis in order to move the area of biomarker research forward. More research is needed on specific demographics, such as those with certain syndromes, as well as subgroups such as paediatric vs adult patients, variable sepsis severity, medical versus surgical patients, and other populations. Investigational biomarkers that show promise for assessing sepsis either as a standalone test or in combination with other tests to increase sensitivity and specificity need to be studied further for their possible application in India.

Conclusion

Despite improvements in treatment and diagnosis, sepsis remains a leading cause of death and disability. Significant progress might be made in the diagnosis and treatment of sepsis and the prognosis of patients by using biomarkers for sepsis and, by extension, bloodstream infections. Unfortunately, despite many years of study, there is still no one biomarker that can be used as a standalone diagnosis. In terms of sepsis biomarkers, PCT continues to be the most studied and applied. Several sepsis risk factors have been found and studied in recent years; the majority of these have been confirmed in at least two studies and may thus be routinely implemented in clinical practise. Reducing the duration of mechanical ventilation in surgical patients, effective management of tube systems, and treatment of some metabolic disorders during ICU stay were identified as modifiable risk factors for sepsis, suggesting that a substantial percentage of sepsis cases may be prevented through widespread quality-improvement programmes.

Conflict of Interest

Not available

Financial Support

Not available

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