

# Updates on Outcomes of Elderly ICU Patients Admitted to ICU for Sepsis: A Systematic Review

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## Keywords:

Elderly; Sepsis; Intensive care unit; Systematic review.

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## ABSTRACT

There are more elderly people being admitted to intensive care units (ICUs) due to an increase in the prevalence of severe sepsis and septic shock. Sepsis is more likely to affect the elderly due to co-morbid conditions, frequent and lengthy hospital stays, lowered immunity, functional limitations, and, most importantly, the effects of ageing itself. This systematic review aims to study the recent updates regarding the outcomes of elderly patients admitted to the ICU for sepsis. PubMed, SCOPUS, Web of Science, and Science Direct were systematically searched for relevant literature. Rayyan QRCI was employed throughout this comprehensive process. Our results included eight studies with a total of 29754 patients, and 15681 (52.7%) were males. In ICU, patients with sepsis, older age and elderly patients were risk factors for mortality. Fever and significant function loss were these individuals' most prevalent symptoms. High levels of HCT-ALB are linked to an increased risk of hospital and intensive care unit deaths. There is a dearth of knowledge on severe sepsis in the very elderly, especially regarding variables influencing prognosis, quality of life, and functional success following sepsis therapy. Since it is often believed that they will not respond to treatment as well, the very elderly are typically excluded from antisepsis and antimicrobial agent trials. To create optimal healthcare plans as the population ages and sepsis cases increase, future studies should, however, also focus on this patient age group. The effectiveness of prophylactic measures and the use of bundled approaches in the care of elderly patients with severe sepsis should be evaluated in further research.



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## 1. Introduction

In the entire world, sepsis is the most common cause of death and serious disease. Sepsis hospitalizations had 437 cases per 100,000 person-years global incidence rate, with hospital mortality in the last ten years

being about 17% [1]. Sepsis is becoming increasingly common [2- 4] as populations get older and develop more comorbid conditions. Sepsis is also becoming more widely recognized [2], [5], [6] and, in certain countries, is coded in a way that is more likely to result in payment [2].

The American College of Chest Physicians and the Society of Critical-Care Medicine (SCCM) created the first definition of sepsis (also known as "Sepsis-1") in 1992. Thus, sepsis was described as a host's systemic inflammatory response syndrome (SIRS) to an infection. Later, terms like sepsis, severe sepsis, septic shock, and multiple organ failure syndrome started to be employed in clinical settings [7]. The diagnostic standards for sepsis were widened during the second consensus meeting in 2001. "Sepsis-2" was consequently created in 2003 [8]. 2016 saw the creation of the "Sepsis-3" definition, which was produced by the SCCM and the European Society of Intensive Care Medicine. Sepsis is now understood to be a potentially fatal organ failure brought on by a dysregulated host response to an infection [2].

With 17.3%-37.0% of ICU patients developing sepsis during their stays, the condition is a major and growing medical problem [9- 12]. Sepsis still has a dismal prognosis due to the limited therapeutic options available, with ICU death rates ranging from 36.0% to 55.2% [9]. As a result, it is the leading cause of death in adult intensive care units [13- 15].

The ageing population puts more strain on medical facilities, notably the intensive care unit (ICU), and has sparked discussion about resource restriction and stricter admittance requirements. Due to their comparatively higher mortality risk and shorter life expectancy, ICU admission for the elderly is frequently questioned by intensivists [16], [17]. Despite sophisticated diagnostic and cutting-edge treatment approaches, ICU care may lead to protracted suffering rather than survival past hospital release with a respectable quality of life [18], [19]. This systematic review aims to study the recent updates regarding the outcomes of elderly patients admitted to the ICU for sepsis.

## **2. Methodology**

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed in conducting this systematic review [20].

### **2.1 Study Design and Duration**

October 2023 marked the start of this systematic review.

### **2.2 Search strategy**

To discover the pertinent literature, a thorough search was conducted across four main databases: PubMed, SCOPUS, Web of Science, and Science Direct. We limited our search to English and considered each database's specific needs. The following keywords were transformed into PubMed Mesh terms and used to locate the pertinent studies; "Sepsis," "Elderly," "Old people," "Geriatric population," "Intensive care unit," "ICU," and "Outcomes." The Boolean operators "OR" and "AND" matched the required keywords. Publications with full English text, available free articles, and human trials were among the search results.

### **2.3 Selection criteria**

We considered the following criteria for inclusion in this review:

- Patients admitted in ICU for sepsis
- Only geriatric and elderly population.
- Studies conducted between 2018 and 2023.
- Only human subjects.

- English language.
- Free accessible articles.

#### ***2.4 Data extraction***

The search technique's output was double-checked using Rayyan (QCRI) [21]. By modifying the combined search results with a set of inclusion/exclusion criteria, the researchers evaluated the relevance of the titles and abstracts. Each paper that met the requirements for inclusion underwent a careful examination by the reviewers. The authors talked about methods for resolving disputes. The approved study was uploaded using a data extraction form already created. The authors extracted data about the study titles, authors, study year, country, participants, gender, and main outcomes. A separate sheet was created for the risk of bias assessment.

#### ***2.5 Strategy for data synthesis***

Summary tables were created using data from relevant studies to provide a qualitative assessment of the findings and study components. After the data for the systematic review were gathered, the most efficient approach for utilizing the data from the included study articles was chosen.

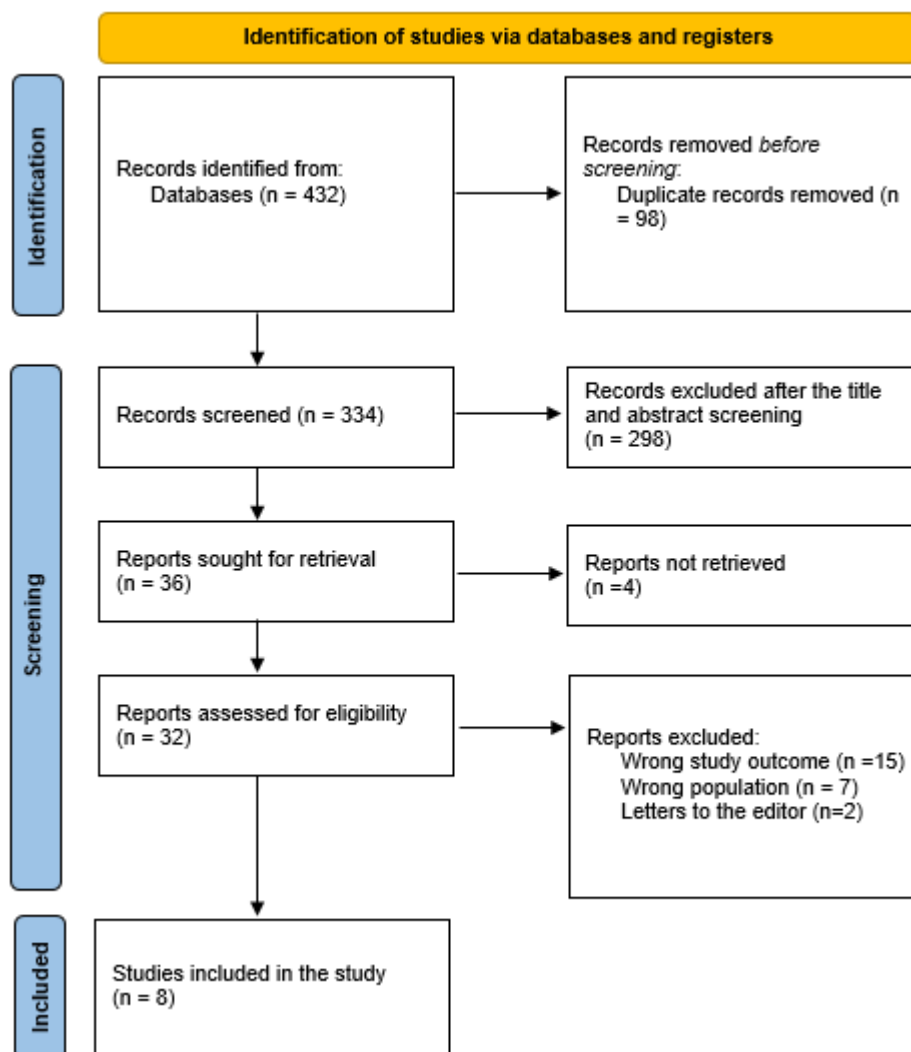
#### ***2.6 Risk of bias assessment***

The ROBINS-I risk of bias assessment technique for non-randomized trials of therapies was used to evaluate the caliber of the included studies [22]. The seven themes that were assessed were confounding, participant selection for the study, classification of interventions, deviations from intended interventions, missing data, assessment of outcomes, and choice of the reported result.

### **3. Results**

#### ***3.1 Search results***

A total of 432 study articles resulted from the systematic search, and 98 duplicates were deleted. Title and abstract screening were conducted on 334 studies, and 298 were excluded. 36 reports were sought for retrieval, and 4 articles were retrieved. Finally, 32 studies were screened for full-text assessment; 15 were excluded for wrong study outcomes, 7 for the wrong population type, and 2 articles were letters to the editors. Eight eligible study articles were included in this systematic review. A summary of the study selection process is presented in Figure 1.



**Figure (1):** PRISMA flowchart summarizes the study selection process.

### 3.2 Characteristics of the included studies

Table (1) presents the sociodemographic characteristics of the included study articles. Our results included eight studies with a total of 29754 patients, and 15681 (52.7%) were males. Three studies were retrospective in nature [23], [29], [30], three were prospective in nature [24], [27], [28], and two were cross-sectional studies [25], [26].

Table (2) presents the clinical characteristics. Elderly patients and older age constituted a risk factor for mortality in ICU patients with sepsis. Fever and significant function loss were the most frequent features in these patients. High hematocrit and albumin (HCT-ALB) are linked to 1.41 and 1.27 times the probability of ICU and hospital mortality.

Study	Study design	Country	Participants	Mean age (years)	Males (%)
[23]	Retrospective	Multi-centered	9385	6184 (aged 65–79 years), and 3201 (aged 80 years and older)	4859 (51.7)

[24]	Prospective	Italy	30	(80% ≥ 65 years and 53% ≥ 75 years)	18 (60)
[25]	Cross-sectional	India	76	50.07±18.15	32 (42.2)
[26]	Cross-sectional	The Netherlands	48	Median and IQR range 75 [72; 81]	35 (73%)
[27]	Prospective	Malaysia	30	70 ± 5	24 (80)
[28]	Prospective	Spain	3869	Median age 83 (81–86) years	2013 (52)
[29]	Retrospective	China	16127	Median age 76	8607 (53.4)
[30]	Retrospective	Turkey	189	Young-old (65-74 years), middle-old (75-84 years) and oldest-old (85 years and above).	93 (49.2)

**Table (2):** Clinical characteristics and outcomes of the included studies.

Study	Main outcomes	ROBIN-I
[23]	This study discovered a 2% absolute mortality difference between elderly and very elderly septic patients, which translates into a relative risk difference of about 20% in a patient population that is already at risk. Although statistically significant, this discovery is probably not clinically meaningful.	Moderate
[24]	Abdominal sepsis's high death rate in elderly patients. The majority of fatalities were seen in patients under the age of 65, underscoring the idea that age is a risk factor for abdominal sepsis. While qSOFA seems to be connected to 30-day mortality and could be useful in extra-hospital settings to distinguish patients with an increased risk of death for sepsis, SOFA is a reliable score of mortality, even in older sepsis patients.	Moderate
[25]	High mortality is correlated with sepsis. Older patients run a higher danger. The most frequent manifestation is fever, and the source is typically unknown.	High
[26]	ICU admission should be carefully considered because elderly patients with abdominal sepsis have a significant mortality rate. Despite significant functional loss in survivors, these conditions do not always result in self-perceived poor functioning, low HRQoL, or a reluctance to receive life-sustaining therapy.	Moderate
[27]	Age is a separate risk factor for mortality from sepsis, with mortality rates from sepsis being significantly greater in senior people.	Moderate
[28]	Very old patients treated with sepsis have a higher mortality rate 30 days after ICU admission. They did not discover sepsis admission to be a standalone risk factor for lowered survival, nevertheless. In this population, a lower 30-day survival rate was significantly correlated with frailty, advanced age, and a higher SOFA score upon admission. Therefore, whether a patient is admitted to the ICU or LST is established in extremely elderly patients, sepsis at admission should not be the main deciding criterion.	Moderate
[29]	In elderly sepsis patients, high HCT-ALB (6.7) is linked to 1.41 and 1.27 times the probability of ICU and hospital mortality, respectively. A promising clinical predictor of	High

	early risk stratification for elderly sepsis patients in ICU, HCT-ALB is straightforward and simple to obtain.	
[30]	Geriatric patients admitted to the ICU have a very high prevalence of sepsis and a very high 30-day death rate. Elixhauser Comorbidity Index >10 patients with geriatric sepsis had a death risk of >70%. Age has no impact on 30-day mortality in geriatric patients with sepsis, however, the length of ICU stay does rise with age in these individuals.	Moderate

#### 4. Discussion

Sepsis is more common as people age and is sharper in those over 80 [31]. Sepsis is also linked to extraordinarily high fatality rates. A decade ago, [32] showed that age was an independent predictor of mortality in patients admitted with sepsis [33]. Due to this, even if there are clinical indicators that suggest older patients should be admitted to the ICU, ICU doctors are typically hesitant to do so [34]. Data on the prognosis of elderly people with sepsis and septic shock are scarce. A few studies that were done on this particular patient population have indicated that older patients frequently develop severe sepsis and septic shock and that their mortality is higher than that of their younger counterparts [32- 34].

This study reported that elderly patients and older age constituted a risk factor for mortality in ICU patients with sepsis. Fever and significant function loss were the most frequent features in these patients. This was in line with [35], who stated that there is little information in the literature about elderly patients admitted to ICU for sepsis. The reported mortality rate is significant; about half of patients passed away in hospitals, and more than two-thirds of patients passed away within one year. Even though HRQoL is frequently preserved, elderly patients admitted to the ICU who survive suffer from severe impairment.

In addition to immunosenescence, which predisposes the elderly to sepsis at a higher incidence, there are changes in the body's reaction to sepsis as well, which results in a more severe presentation of infection. The pathophysiology of sepsis is greatly influenced by the activation of the coagulation cascade by severe sepsis. The increased risk of thrombosis and thromboembolism found in the elderly is explained by an aging-related rise in plasma levels of fibrinogen, factor VII, factor VIII, factor IX, and other clotting factors that are further potentiated during sepsis. Additionally, older people have a higher rate of plasminogen activator inhibitor type 1 production, which affects how well fibrin is removed from the circulation [36]. The greater short survival rates with drotrecogin (activated) in the Protein C Worldwide Evaluation of Severe Sepsis (PROWESS) experiment are partially explained by the combined effects of ageing and sepsis on the coagulation cascade [37].

The elderly also have aberrant cytokine responses [36]. Interleukin (IL)-2 and tumour necrosis factor (TNF)- production of type 1 cytokines is shifting to type 2 cytokines (IL-4, IL-10) [38]. But in the age, production of IL-1, IL-3, TNF, interferon, IL-8, and IL-12 is typically unaltered or even elevated [36]. The elderly are more vulnerable to systemic infection by microbial pathogens as a result, and their proinflammatory reactions are typically more persistent than in younger patients. This also reflects the aberrant removal of microbial pathogens by counter-regulatory cytokines such as IL-10 [36].

Numerous variables, including TNF, nitric oxide, and maybe additional inflammatory cytokines with a detrimental inotropic effect, such as IL-1 and IL-6, contribute to the idea of sepsis-associated cardiac depression [39]. Ageing can make this worse, which can result in a worse outcome for older septic patients. As compared to younger people, the geriatric reaction to endotoxins is likewise more severe, characterized by more profound hypotension, excess epinephrine response, delayed blood pressure recovery, and more substantial cytokine response [40].

If not anticipated, the clinical diagnosis of infection in the elderly is difficult and prone to error. Sepsis may manifest more severely and differently in elderly people than it does in younger ones [41]. In the elderly, the first inflammatory response to infection, which generally results in sepsis symptoms and signs, is muted or may perhaps not occur [36], [42]. However, the later presentation may be quite severe with a rapid development to septic shock.

The International Surviving Sepsis Guidelines should be followed for treating elderly patients with severe sepsis and septic shock [43]. Early implementation of the sepsis resuscitation and management bundles has been proven to increase survival with strong adherence across a range of age groups [44]. The same management guidelines that are used for young adults should be implemented in this situation, including early source control, early goal-directed therapy, and the use of low tidal volumes during mechanical ventilation. However, there are a few unique factors to keep in mind while treating elderly patients with severe sepsis and septic shock.

We also found that high HCT-ALB is linked to 1.41 and 1.27 times the probability of ICU and hospital mortality. Vasoactive substances, cytokines, chemokines, oxygen free radicals, and acute-phase reaction chemicals are just a few of the inflammatory mediators that the monocyte-macrophage system and other inflammatory response cells can make and release when infectious stimuli activate them. Increased capillary permeability and severe injury to some human organs and systems cause leakage of ALB and HCT variations, which changes their ratios [45]. Along with the above-mentioned effects of infection, patients' hypermetabolic states increase albumin consumption, intestinal dysfunction increases albumin loss, patients with chronic hypoxic diseases can increase HCT, and blood loss and anemia all affect HCT-ALB in different ways. A promising indicator for the differential diagnosis of infections is the numerical difference between HCT (%) and ALB (g/L) levels (HCT-ALB), which is highly sensitive and specific among patients with infectious disorders [46].

## 5. Conclusion

Older age and elderly patients were risk factors for mortality in sepsis-related ICU patients. The most common symptoms in these patients were fever and severe function loss. High levels of HCT-ALB are associated with a higher probability of ICU and hospital death. There is a lack of information on severe sepsis in the extremely elderly, particularly when it comes to factors affecting outcome, quality of life, and functional outcome after sepsis therapy. The very elderly are frequently excluded from antisepsis and antimicrobial agent trials since it is commonly thought that they will not respond as well to therapy. Future studies should, however, also concentrate on this age range of patients in order to develop the best healthcare strategies as the population ages and sepsis cases rise. Additional research should evaluate the effects of preventative interventions and the application of bundled techniques in the treatment of older patients with severe sepsis.

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