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Severe mental illness and mortality in sepsis and septic shock: a systematic review and meta-analysis

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Abstract

Background:

There have been conflicting reports regarding the case-fatality outcomes associated with sepsis and septic shock in patients with severe mental illness (SMI).

Methods:

We searched Medline®, Web of Science® and the Cochrane Library® databases (from inception to 4-July-2023) for papers reporting outcomes associated with sepsis and septic shock in adult with (cases) vs. without SMI (controls). The main study outcome was the unadjusted case-fatality rate at hospital discharge, or 30 days if unavailable. Secondary outcomes included the rates of adjusted case-fatality at hospital discharge.

Results:

A total of six studies were included in the systematic review, of which four provided data for meta-analysis involving 2,124,072 patients. Compared to controls, patients with SMI were younger and more frequently women. Unadjusted analyses showed that SMI patients had a lower case-fatality rate associated with sepsis and septic shock than their non-SMI counterparts (OR 0.61, 95% CI [0.58-0.65], PI 95% CI [0.49-0.77], $I^2 = 91\%$). Meta-regression and subgroup analyses showed that the denominator of the study population (i.e. septic shock or sepsis) was associated with the outcome with an R^2 of 59.7%.

Conclusion:

In conclusion, our study reveals a survival advantage of SMI patients over their non-SMI counterparts. Further research is needed to fully elucidate the mechanisms involved and to develop targeted interventions that can improve the prognosis of both SMI and non-SMI patients facing sepsis.

INTRODUCTION

Patients with severe mental illness (SMI) have been reported to have excess mortality from sepsis (the number of deaths due to sepsis in the whole population)[1, 2]. However, it remains unclear whether SMI is associated with a higher or lower sepsis-associated case fatality (the number of deaths due to sepsis in the population with sepsis). Indeed, conflicting data have been reported regarding the case-fatality outcomes associated with sepsis and septic shock in patients with SMI [3–5]. Historically, observational studies suggested that SMI patients had higher case-fatality rates from somatic diseases than their non-SMI counterparts [6–8], notably for cardiovascular and infectious diseases [9–11] and some studies have reported worse outcomes associated with septic shock in SMI patients compared to non-SMI patients [5, 9]. In contrast, both our group and others have recently published data extracted from large nationwide databases suggesting that in-hospital case fatality rates associated with septic shock were lower in SMI patients than in non-SMI patients [1, 4]. Several hypotheses may explain this survival advantage of SMI patients with septic shock, ranging from immunological and inflammatory profiles associated with SMI to the potential implication of psychotropic medications [1, 4].

In summary, it is crucial to determine whether patients with SMI have a decreased or increased case-fatality rate in sepsis and septic shock. This knowledge can contribute to improving their management and understanding the underlying pathophysiology responsible for these differences. Despite the increasing number of studies on this topic, to our knowledge, no systematic reviews or meta-analyses have been conducted.

The objective of this systematic review and meta-analysis is to investigate whether there are differences in case-fatality rates associated with sepsis and septic shock between SMI and non-SMI patients.

METHODS

The study was conducted following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses database on March 4, 2023 (CRD 42023400648).

Search strategy

We conducted a systematic search of the Medline through PubMed, Web of Science databases covering the period from inception to July 4, 2023, to identify papers reporting outcomes at the time of hospital discharge or any short-term time in adults (aged 16 years or older) with severe mental illness (SMI) and without SMI after sepsis and septic shock. We did not apply any language restrictions. The complete search strategy is detailed in Supplement 1.

Inclusion criteria

All studies comparing mortality rates from sepsis or septic shock between patients with and without SMI were included in the present systematic review and meta-analysis.

Exclusion criteria

We excluded case reports, case series and research involving pediatric patients (aged 15 or younger).

Paper selection

The titles and abstracts of all identified papers were screened independently by two authors (IL, EM) using the Covidence software tool. The selected papers were then downloaded in full and independently reviewed by the same two authors to ensure they met the inclusion criteria. Additionally, the reference lists of relevant articles were searched to identify any additional potentially relevant articles, using a snowballing method.

Any articles for which there was a discrepancy in ratings by the two screening authors in the Covidence software were reviewed and discussed individually by both authors. Articles were subsequently included only if both authors reached a consensus on their eligibility, and in case of non-consensus, a third author was contacted (GF).

Given that many of the included studies were based on national databases, there was a risk of overlapping patient data when multiple studies were from the same country and period. To prevent such overlap, we excluded any study that presented data from a country whose national database had already been used in another included study during the same period. In such cases, the study with the most detailed data was retained.

If any questions regarding eligibility or data presentation arose, we contacted the corresponding authors of the screened studies for clarification. The details of the inclusion/exclusion process are depicted in the PRISMA diagram (Fig. 1).

Data extraction

Two authors (IL, EM) independently extracted the data in duplicate using a standardized data extraction form within the Covidence software. Any discrepancies in the extracted data were resolved through consensus between the two authors, and in case of no consensus with a third author (GF). The data extracted encompassed various aspects, including study characteristics (such as the source country, study type, and whether it was a single or multicenter study), patient demographics (age and sex), medical history, treatments administered, and outcomes assessed. Additionally, we collected data regarding the types of adjusted analyses performed and the specific variables that were adjusted for in those analyses.

The final version of the database underwent validation by all the investigators involved in data collection (IL, EM) and is available as Supplement 2.

Assessment of risk of bias

For the primary outcome, two of the authors (IL, EM) assessed the risk of bias (RoB) of the included studies independently and in duplicate using the Newcastle and Ottawa scale [14]. Disagreements over RoB were resolved by consensus, and in case of no consensus with a third author (GF).

Outcomes

The primary study outcome for our research focused on determining the unadjusted case-fatality rate, which reflects the proportion of deaths among identified cases of sepsis and septic shock up to the point of hospital discharge. In cases where discharge data were not available, we also considered outcomes at 30 days post-admission.

Additionally, we explored several secondary outcomes, including:

- Adjusted case-fatality rate to hospital discharge or, if not available, at 30 days.
- Unadjusted and adjusted long-term case-fatality rates. These outcomes considered mortality rates beyond the immediate hospital stay, providing insights into the longer-term impact of sepsis and septic shock.
- Intensive care unit (ICU) and hospital length of stay. We examined the duration of ICU and overall hospital stays for patients with sepsis and septic shock, which can provide valuable information about the burden of these conditions.
- Rates of rehospitalization. Understanding the likelihood of patients being readmitted to the hospital after an initial episode of sepsis or septic shock is crucial for assessing the ongoing healthcare needs of these individuals.

In our analysis, the term “case-fatality rate” refers to an epidemiological metric that quantifies the percentage of deaths among individuals diagnosed with sepsis or septic shock. This calculation involves dividing the number of deaths associated with these conditions by the total number of diagnosed cases. This metric is valuable for assessing the severity and impact of sepsis and septic shock on patient outcomes.

Certainty of the evidence

The certainty of the evidence (i.e. the overall effect estimates) was assessed for the primary outcome and the secondary outcomes using Grading of Recommendations Assessment, Development and Evaluation (GRADE) [15].

Statistical analysis

The population characteristics were described as weighted means and weighted standard deviation (SD) for continuous variables and weighted means of percentages and weighted standard deviation from percentages for categorical variables. For adjusted analyses and for the studies providing odds ratios (OR) only, with no report of raw data on sepsis associated case-fatality, we used the generic inverse variance method to pool estimates and standard errors (SEs) as per Cochrane guidance [16, 17]. The results were reported as OR with their 95% confidence intervals (CI) for dichotomous outcomes. A prediction interval (PI) was calculated for the primary outcome and for any outcome with an OR excluding the value of no difference. Meta-analyses were performed using raw data for the primary outcome and adjusted estimates from multivariate models for the secondary adjusted outcomes. In the case of adjusted estimates, ORs and CIs were transformed to natural log and SEs using standard formulas. Both fixed and random effects models were calculated but only random effects were used for all analyses.

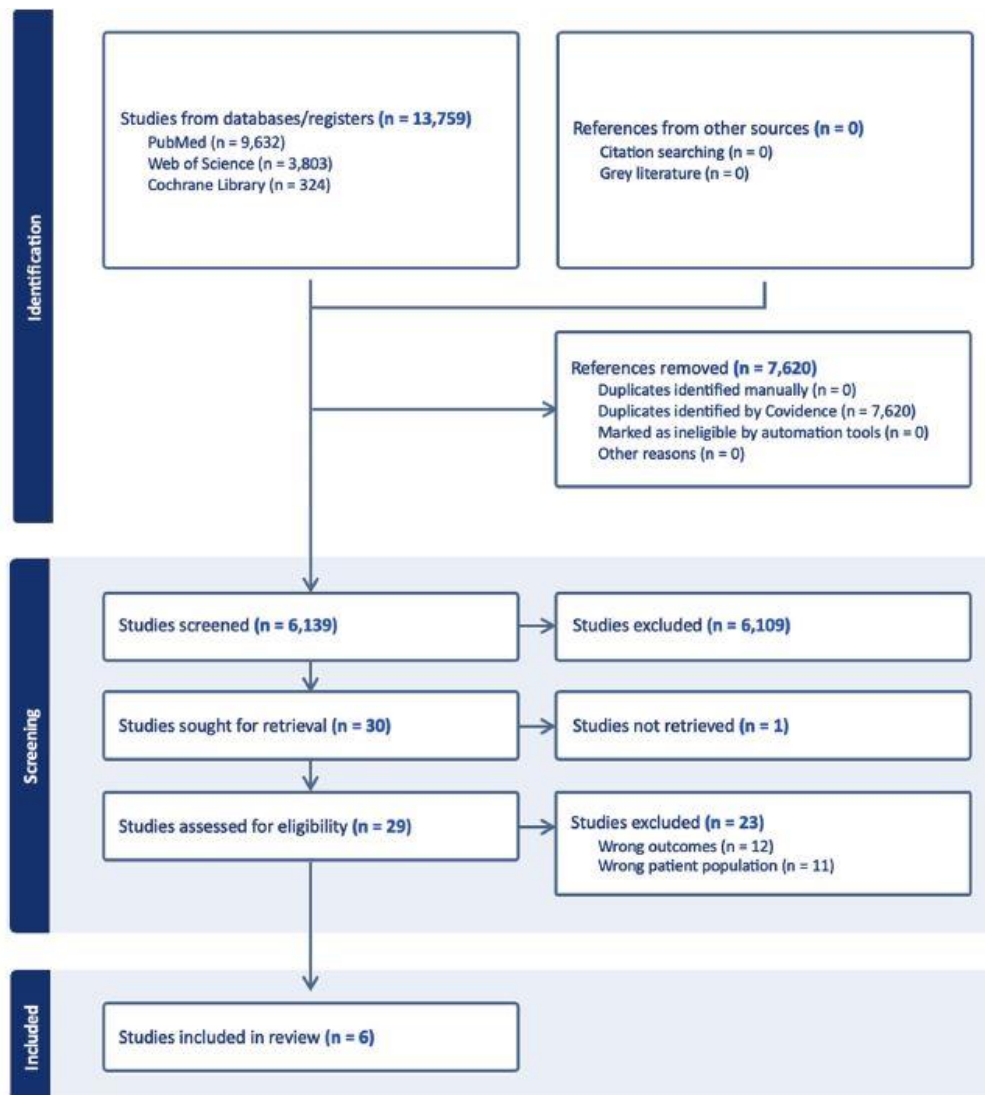


Fig. 1 Flow chart of the study.

Preplanned subgroup analyses were performed in order to assess possible heterogeneity stemming from the denominator (septic shock vs. sepsis), the type of SMI (schizophrenia alone vs. schizophrenia mixed with other mental illness) and the RoB of the included studies. For subgroup analyses, we calculated a pooled version of τ^2 to be used across all subgroups as the number of studies per group was <five studies, thereby decreasing reliance on an imprecise estimate of between-study heterogeneity in one subgroup [18].

As statistical heterogeneity was high, we included a Baujat plot analysis to identify outlier studies. Inspection of the plot prompted further sensitivity analyses through the omission of these outliers. Additionally, the analysis was further completed with metaregression analyses to identify potential confounders affecting our results.

For the Trial Sequential Analysis (TSA) within our meta-analysis, we utilized conventional boundaries to assess statistical significance. The use of conventional boundaries was considered appropriate for our context, where the volume of accumulated data was deemed sufficient to achieve the necessary power without necessitating the application of alpha-spending boundaries.

All P values were two-tailed. P values less than 0.05 were considered statistically significant. Statistical heterogeneity (i.e. chance variation between studies) was sought by visual inspection of forest plots and with the nonparametric Cochran's Q test and the I² statistic [17]. Heterogeneity was considered likely if $Q > df$ (degrees of freedom) and was considered confirmed if the p value was 0.10 or less. The possibility of small-study effects was first explored through inspection of funnel plot. The Harbord's and Peter's tests were planned to be performed to investigate small study effects, except in the case of significant heterogeneity between studies where an arcsine test using Rücker's random effects was to be preferred, assuming no publication bias [19–21]. These tests were chosen over the Egger's test, given the dichotomous nature of the outcome of interest [22, 23].

All analyses were performed using R software (R Core Team 2013, R Foundation for Statistical Computing, Vienna, Austria, URL (<http://www.R-project.org/>) with the package meta [24].

RESULTS

A total of 6139 studies were screened and six were included in the systematic review [1, 3–5, 9, 25]. The flow diagram is presented in Fig. 1. Four out of these six studies provided raw data suitable for a meta-analysis on the primary outcome, encompassing a total of 2 124 072 patients (335,506 with SMI and 1,788,566 without SMI).

Included studies

All the identified studies were observational, retrospective analyses of data from national databases [1, 4, 5, 9, 25] and one monocentric study [3]. The data covered three continents (Europe, Asia and North America) over a period of 14 years (2005–2019). No overlap was found between the articles, as all the databases used were different from each other. Four studies reported the outcomes of interest only for patients with sepsis [3, 5, 9, 25] while two studies included only patients with septic shock [1, 4]. Two studies had broad inclusion criteria (hospitalized patients with infection) and did not provide raw data on the subgroup of patients with sepsis, reporting either unadjusted OR on long-term case-fatality [5] or adjusted OR on 30-day case-fatality [9]. The authors of these studies were contacted, one of them replied that the data were not accessible [9] and the other did not respond after repeated requests [5]. The type of SMI among the included patients is presented in Table 1.

Baseline data

Among the four studies comparing SMI and non-SMI patients with sepsis as the primary outcome, the patients in the SMI group were younger than their non-SMI counterparts, with a weighted mean age (\pm weighted SD) of 65 (\pm 2.1) years and 69 (\pm 2.7) years, respectively ($p < 0.005$). The rate of women was higher in the SMI group (49.7%) than in the non-SMI group (45.6%) ($p < 0.005$). Comorbidities were described unevenly in the included studies: the Charlson score was broken down into its individual components in two studies [1, 25], while one study provided only the total Charlson score results [4] (Supplement 2). Psychiatric comorbidities such as alcohol abuse or tobacco consumption were scarcely reported. None of the studies reported on the usage or prevalence of psychiatric treatments.

Risk of bias

Using the Newcastle Ottawa score, the majority of studies achieved a score of 7/8 (Table 1). The monocentric study selected a cohort of patients based on an SMI diagnosis documented in the patient file without further validation against established criteria, resulting in one point deduction in ‘ascertainment of exposure’ domain [3].

The two studies which included patients with infection without describing subgroups of patients with sepsis and septic shock, were considered to be at a high risk of bias in the ‘representativeness of the exposed cohort’ domain [5, 9]. The Rucker’s test did not suggest publication bias ($p = 0.91$).

Primary outcome

Only four studies provided raw data on the unadjusted case-fatality rate at hospital discharge, which, when aggregated, showed a lower case-fatality rate in SMI patients compared to non-SMI patients, with an odds ratio (OR) of 0.61 and a 95% confidence interval (CI) of [0.58–0.65], with prediction interval (PI) 95% CI [0.49–0.77] (Fig. 2). One study did not provide raw data on case-fatality rates in patients with sepsis but provided an OR, which was included in the aggregated data without significantly altering the results (OR 0.73, 95% CI [0.65–0.81], PI 95% CI [0.49–1.08]) (Fig. 3).

Regarding our primary outcome, the variability due to between study heterogeneity was high ($I^2 = 91\%$). The variability increased to $I^2 = 98\%$ when the analysis was performed on all the studies providing raw data and unadjusted OR. Thus, Baujat, subgroup and meta-regression analyses were performed. Baujat analysis identified one outlier study [4] but its omission from the analysis did not change the value of I^2 (Supplement 3). Meta-regression analyses showed that the denominator of the study population (i.e septic shock or sepsis) was associated with outcome with a R^2 of 59.7% (Table 2). Subgroup analyses on the population denominator (i.e septic shock or sepsis) confirm the results of the meta-regression, with significant differences between septic shock and sepsis groups, $p = 0.03$ (Fig. 4). Meta-regression and subgroup analyses on RoB (studies rated 7/8 vs. 6/8) did not yield significant results ($R^2 = 0\%$ and no significant differences between the subgroups, $p = 0.95$). We could not perform subgroup analyses on the type of SMI (schizophrenia, bipolar disorder or unipolar depression) due to lack of data.

Secondary outcomes

Three studies included the adjusted OR for case-fatality rates to hospital discharge or, if not available, at 30-day. Adjustment variables, including age and sex, are detailed in Supplement 3. Aggregated data showed no differences between SMI patients and non-SMI patients regarding the case-fatality rates with an OR at 0.89 and 95% CI [0.75–1.06], PI 95% CI [0.10–8.06], $I^2 = 98\%$ (Fig. 5).

Long term case-fatality rates were reported in only one study [1] therefore no aggregated analysis was performed on this outcome.

Table 1. Study characteristics.

Study	Location	Inclusion period	Type of cohort	Inclusion criteria	Exclusion criteria	Type of SMI included	NOS
Soubani et al. [4]	US ^a	2016–2019	Population-based	Septic shock, Age ≥18 years	NP	Schizophrenia and affective disorders	8/8
Lakbar et al.[1]	France	2014–2018	Population-based	Age ≥18 years, Admitted to the ICU, Had a diagnosis of septic shock	ICU LOS < 48 h	Schizophrenia, bipolar disorder, major depressive disorder	8/8
Ishida et al. [3]	Japan	2012–2017	Retrospective Monocentric	Sepsis	Presence of psychiatric disorders other than affective disorders and schizophrenia, Unclear diagnosis of SMI or sepsis	Schizophrenia or affective disorders	6/8
Nilsson et al. [5]	Sweden	2018–2019	Population-based	Every person in the Swedish population, Age ≥ 20 years	NP	Psychotic disorder or bipolar disorders/ single manic episodes	6/8
Oud and Garza [25]	US, Texas ^a	2014–2017	Population-based	Age ≥ 18 years, Sepsis	Missing data on hospital disposition	Anxiety, mood disorders, personality disorders, schizophrenia and other psychotic disorders	8/8
Davydow et al.[9]	Denmark	2005–2013	Population-based	All living persons ≥ 15 years, Residing in Denmark for at least 10 years, hospitalized for an infection at least once	Individuals with a diagnosis of schizophrenia, schizoaffective disorder or bipolar disorder death in the first 24h of hospitalization	Unipolar depression	7/8

^aDatabases were considered as non overlapping or with a marginal and negligible overlap on the one year between 2016 and 2017 because Oud used a state database from Texas, while Soubani used the national inpatient sample (NIS), reporting 20% stratified sample of all discharges from U.S. community hospitals.
NOS Newcastle-Ottawa scale

The data on ICU and hospital lengths of stay and on rates of rehospitalization were not aggregated because of the heterogeneity of data reported, including both medians and means. Transformation of these data was not feasible owing to their skewed distribution.

The TSA revealed a conclusive finding with the cumulative Z-score surpassing the conventional significance boundary. Therefore, the substantial number of patients included in our meta-analysis was considered as sufficient, reinforcing the robustness and reliability of our findings (figure in Supplement 3).

Certainty of evidence

The results of the GRADE assessment with regard to primary and secondary outcomes are reported in Table 3. Certainty was rated as low for the estimated OR of unadjusted and adjusted case fatality rates to hospital discharge (or 30-day survival).

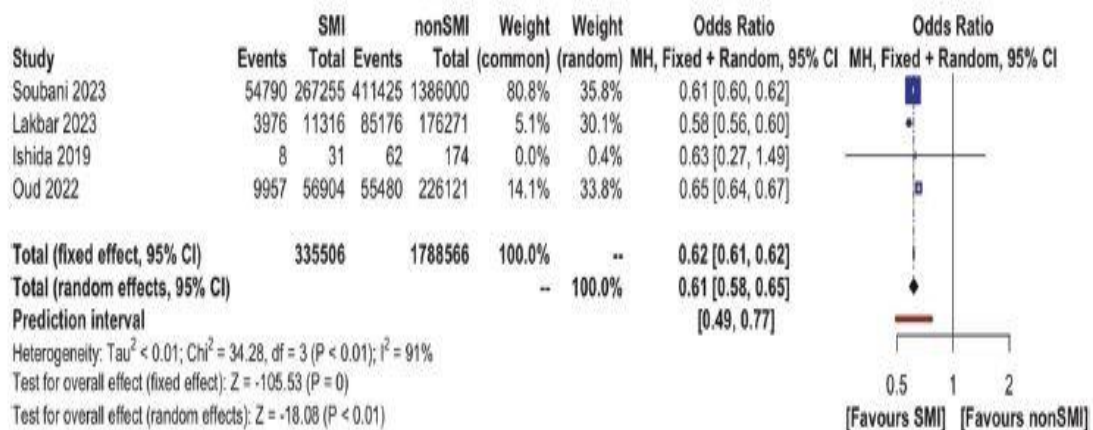


Fig. 2 Meta-analysis of studies providing raw data on unadjusted case-fatality rates to hospital discharge.

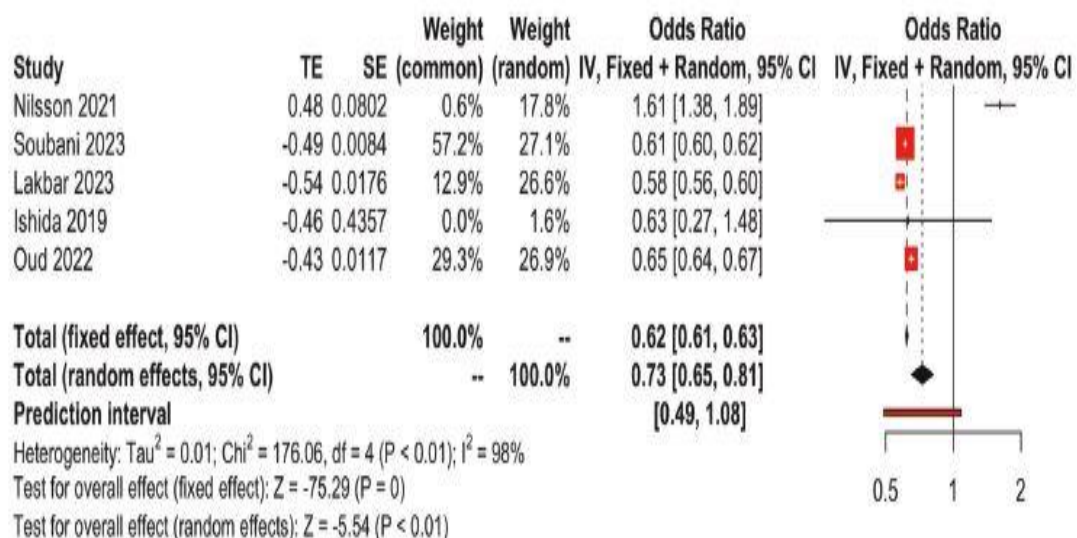


Fig. 3 Meta-analysis of studies providing raw data and unadjusted results (OR) on case-fatality rates at any time. Of note, Nilsson et al. provided data on long term mortality (within the two years following the index hospital stay).

Table 2. Meta-regression analyses results.

	Quality of the covariates adjusted for	Denominator of the population (i.e sepsis or septic shock)
R^2 (%)	0	59.7
p	0.95	0.029

DISCUSSION

Our meta-analysis identified a difference between SMI and non-SMI patients in terms of their outcomes following hospitalization for sepsis or septic shock. It appeared that SMI patients had a survival advantage over non-SMI patients, confirming the primary hypothesis derived from our previous study. Importantly, this meta-analysis, which included data from more than two million patients worldwide, represents the first systematic review and meta-analysis reporting on SMI patients with sepsis and septic shock, to the best of our knowledge.

The two Danish studies identified in our search lacked comprehensive patient-specific data regarding sepsis. In one of these studies, only an unadjusted OR for long-term mortality, covering a period of nearly two years, was available [5], whereas the other one solely reported an adjusted OR pertaining to 30-day mortality [9]. Despite our repeated efforts to consolidate these data, we were unable to obtain the necessary level of detailed data for inclusion in our meta-analysis. This variability in the data provided likely accounts for the lack of difference in case-fatality rates between SMI patients and those without SMI when adjusted data were aggregated. Only three studies met the criteria for this adjusted analysis, with one being a Danish study that excluded patients with schizophrenia and reported limited outcomes.

The mortality rate associated with infections has been reported to be higher in patients with SMI compared to non-SMI individuals [10]. However, our study indicates that SMI patients have a lower case-fatality rate from septic shock than their non-SMI counterparts. This suggests that the incidence of infections is likely higher among SMI patients, thereby increasing their overall mortality from infections. Yet, when experiencing a severe form of infection, such as septic shock, these patients exhibit a reduced case-fatality rate. These findings imply that there is a critical need to enhance infection prevention measures for SMI patients, for instance through improved vaccination strategies, and to ensure better management in primary care settings [26, 27]. Research on vaccination among individuals with SMI remains limited, despite the potential impact of their chronic inflammatory state and altered immune regulation on vaccine responsiveness [28].

In our meta-analysis, the reasons for survival differences between SMI patients and non-SMI patients were unclear, but potential factors included variations in immunological profiles and psychotropic medication effects [29, 30]. The SMI patients exhibit dysregulated cytokine responses, possibly offering protection in septic shock [31], as it was reported for autoimmune diseases [32]. Overexpression of specific pro-inflammatory cytokines like IL-12 and IFN- γ in SMI may counteract the sepsis-induced immunosuppression [31, 32].

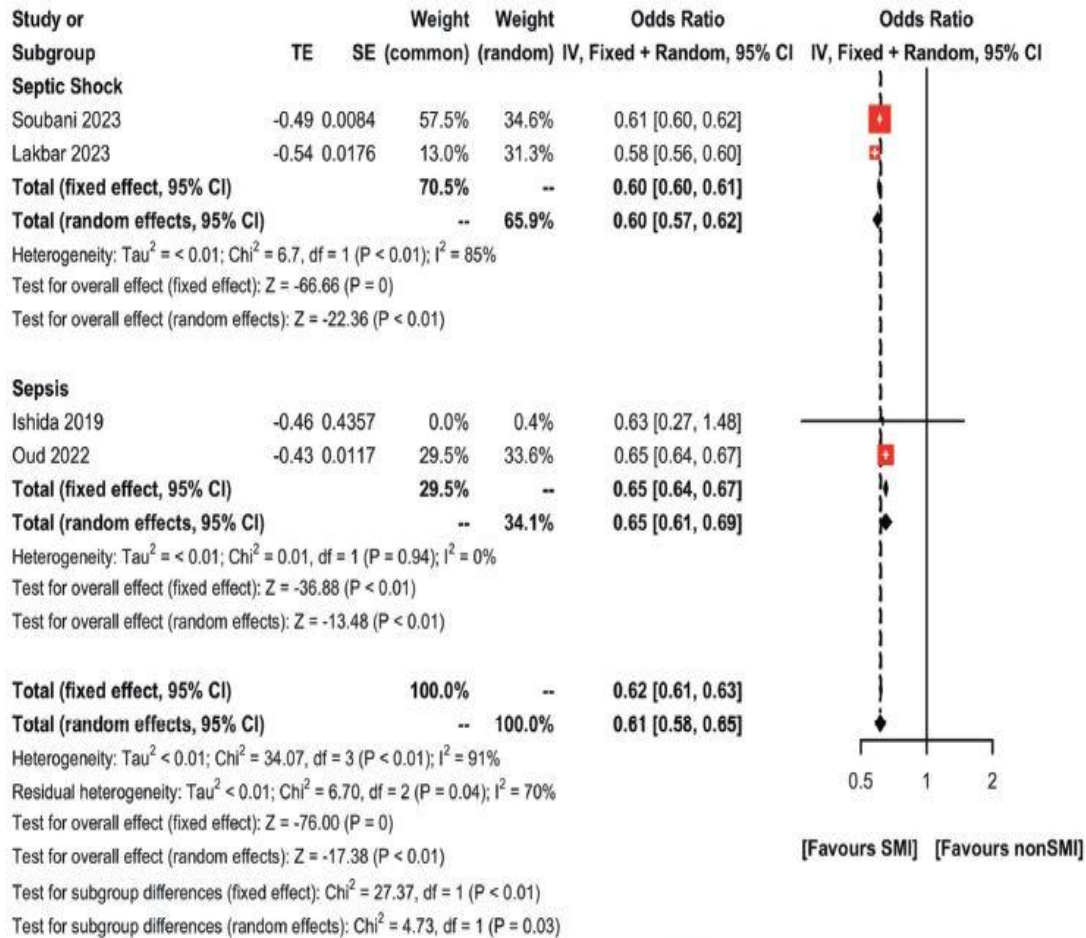


Fig. 4 Subgroup analyses on the population denominator: septic shock and sepsis subgroups.

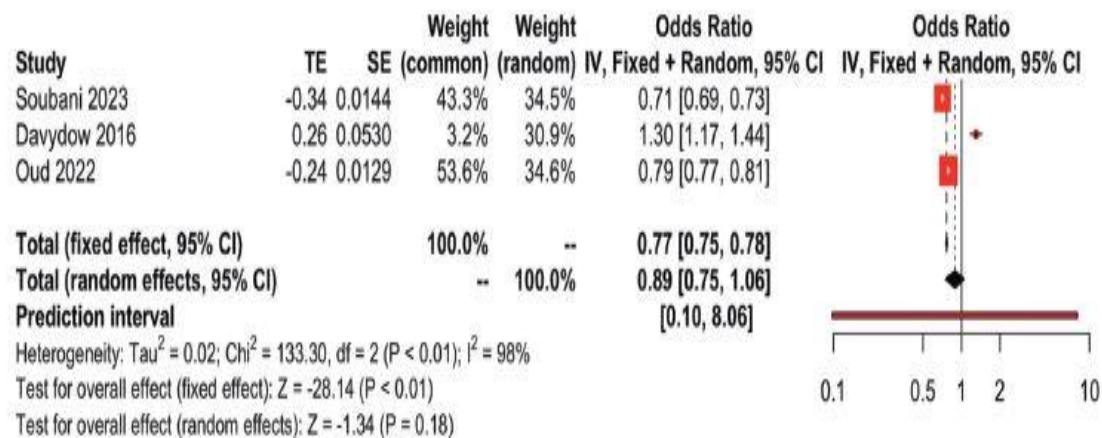


Fig. 5 Meta-analysis of studies providing adjusted results (OR) on case-fatality rates to hospital discharge or, if not available, at 30-day.

Psychotropic drugs, including antidepressants, lithium, and antipsychotics, modulate the inflammatory response [33]. Recent evidence suggests psychotropic medications like fluoxetine have antiviral and anti-inflammatory effects [34], potentially through acid sphingomyelinase inhibition.

Table 3. Certainty estimates of different outcomes using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods.

Certainty assessment		Effect (Odds ratio 95% CI)	Certainty	Importance		
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Unadjusted case-fatality rates to hospital discharge						
4	Observational studies	Not serious	Serious ^a	Not serious	Not serious	None
						OR = 0.62 (0.58-0.65)
						⊕⊕○○ LOW
						Critical
Adjusted case-fatality rates to hospital discharge						
3	Observational studies	Not serious	Serious ^a	Not serious	Not serious	None
						OR = 0.89 (0.75-1.06)
						⊕⊕○○ LOW
						Critical

^aHigh I² and discrepant results.

Identifying factors contributing to differential case fatality rates in SMI patients with sepsis compared to the general population is crucial. Our study, consistent with prior research [1, 4, 25], revealed that specific yet unidentified factors related to SMI have a mitigating effect on the expected negative outcomes, resulting in a significant reduction in case fatality rates. This underscores the need for research on immune system differences between SMI and non-SMI patients to identify intervention targets. However, other hypotheses as a recruitment bias due to prior hospitalization triage of SMI patients, as compared to the non-SMI patients, cannot be excluded.

Our study has several strengths. We prospectively registered the study protocol, performed analysis of adjusted data, assessed the RoB of the included studies and applied GRADE to assess the certainty of the evidence. We included nation-wide studies with large samples of patients and data, leading us to perform an analysis on more than two million patients.

However, our study also has limitations due to the nature of the question being investigated, as the included studies were observational in nature. Consequently, the conclusions drawn from the meta-analysis, as assessed with the GRADE method, have a low certainty of evidence. Additionally, the results displayed a high level of heterogeneity, which is partly explained by our inclusion of patients with infection, sepsis, and septic shock. The definitions used were based on the authors' choices and may have varied depending on the publication date, as new definitions of sepsis were introduced during the search period. This is outlined by our meta-regression and subgroup analyses showing that the denominator, i.e sepsis or septic shock has an impact in our heterogeneity results. This could have contributed to the heterogeneity observed across these observational studies. Furthermore, it was not possible to clearly differentiate between SMIs due to the limited number of studies reporting outcomes for each SMI. Therefore, we do not know, for example, whether individuals with schizophrenia and bipolar disorder specifically benefit from the reported lower mortality, as suggested by the results of our previous study [1].

CONCLUSION

In conclusion, our study highlights a survival advantage among patients with SMI compared to their non-SMI counterparts when facing sepsis. However, the underlying mechanisms responsible for this difference require further investigation. Future research should aim to provide a more comprehensive understanding of these mechanisms and explore the development of targeted interventions that can enhance the prognosis of both SMI and non-SMI patients dealing with sepsis.

DATA AVAILABILITY

Data is available in the literature corpus and can be found using the search strategy defined in the manuscript.

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