Impact of premorbid use of beta-blockers on survival outcomes of patients with sepsis: A systematic review and meta-analysis

HUAN CHU, FENGMIN FEI, YAO SU and HUIFEI ZHOU

Department of Critical Care Medicine, Huzhou Third Municipal Hospital, The Affiliated Hospital of Huzhou University, Huzhou, Zhejiang 313000, P.R. China

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Abstract. It is unclear if premorbid use of beta-blockers affects sepsis outcomes. The present systematic review aimed to assess the impact of premorbid beta-blocker use on mortality and the need for mechanical ventilation in patients with sepsis. Embase, Scopus, PubMed and Web of Science were searched for studies comparing outcomes of patients with sepsis based on the premorbid use of beta-blockers. The primary outcome was mortality, and the secondary outcome was the need for mechanical ventilation. The results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). A total of 17 studies including 64,586 patients with sepsis were included. Of them, 8,665 patients received premorbid beta-blockers and 55,921 patients were not treated with premorbid beta-blockers and served as a control group. Pooled analysis of mortality rates revealed that premorbid use of beta-blockers did not affect in-hospital mortality (OR: 0.96; 95% CI: 0.78, 1.18; and I^2=63%) but significantly reduced one-month mortality rates (OR: 0.83; 95% CI: 0.72, 0.96; and I^2=63%). Combined analysis of adjusted data showed that premorbid beta-blockers were associated with a significant survival advantage in patients with sepsis (OR: 0.81; 95% CI: 0.72, 0.92; and I^2=70%). However, there was no effect of premorbid use of beta-blockers on the need for mechanical ventilation (OR: 0.93; 95% CI: 0.66, 1.30); and I^2=72%). The results of the present study indicated that premorbid use of beta-blockers is associated with improved survival in patients with sepsis. However, it does not impact the need for mechanical ventilation. The results should be interpreted with caution as the data is observational and unadjusted.

Correspondence to: Dr Huifei Zhou, Department of Critical Care Medicine, Huzhou Third Municipal Hospital, The Affiliated Hospital of Huzhou University, 2088 Tiaoxi East Road, Huzhou, Zhejiang 313000, P.R. China
E-mail: zhuifei098@163.com

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Introduction

Sepsis is a complex syndrome caused by pathophysiological and biochemical dysregulation triggered by autogenous factors in response to bacterial, viral, parasitic or fungal infections (1,2). According to the 1997-2017 Global Burden of Disease Study, there were 48.9 million sepsis cases and ~11 million sepsis-related deaths in the past two decades (3). Data from China demonstrated that in 2022 alone, a total of 25.5% of intensive care unit (ICU) patients were diagnosed with sepsis and in ~13% of these cases sepsis progressed to septic shock that is associated with severe circulatory, cellular, coagulation and metabolic abnormalities that lead to higher risk of mortality compared with uncomplicated sepsis (4). Diagnosis of sepsis is difficult due to the lack of signs and symptoms and absence of any gold standard test (1,2). It is considered a major public health concern, with high morbidity and mortality, and a heavy economic burden on the healthcare system (5-7).

Catecholamines, such as norepinephrine, have been widely used for restoring circulatory failure in sepsis. However, their use is associated with several adverse effects, such as non-compensatory tachycardia, insulin resistance and coagulopathy, all of which may lead to poor outcomes for the patient (8,9). Additionally, catecholamines may worsen hypermetabolism by causing hyperglycemia and hyperlactatemia that may result in further end-organ damage (10). Patients with sepsis also have activated adrenergic system which can be considered as an adaptive response to the disease (11). Recently, a concept of 'decatecholaminization' has been put forward for patients with sepsis. It aims to improve patient outcomes by blocking beta-adrenergic receptors, and limiting intrinsic adrenergic response by delivery of exogenous catecholamines (12,13). A previous randomized controlled trial (RCT) has shown that the use of short-acting beta-blockers can significantly reduce mortality rates in patients with sepsis (14). Another systematic review and meta-analysis of seven RCTs demonstrated that the use of beta-blockers in patients with sepsis indeed offers a significant survival advantage and is associated with a reduction in 28-day mortality (15). Therefore, understanding the effect of premorbid use of beta-blockers on the outcomes of septic patients is crucial. While several observational studies attempted to assess the role of premorbid beta-blockers on outcomes of sepsis, the results were inconclusive (16-18).

Moreover, a total of two prior meta-analyses included a limited number of studies (11,19).

The present study aimed to conduct the most comprehensive review on the effect of premorbid beta-blockers on the outcomes of patients with sepsis.

Materials and methods

Literature search and inclusion criteria. The present study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (20), and the review protocol was published on PROSPERO (https://www.crd.york.ac.uk/prospero/; protocol no. CRD42023491920).

The authors collaborated with an experienced medical librarian to search Embase (https://www.embase.com/search/quick), Scopus (https://www.scopus.com/home.uri), Web of Science (https://www.webofscience.com/wos/) and PubMed (https://pubmed.ncbi.nlm.nih.gov) for peer-reviewed articles or conference proceedings. The search included studies from inception of databases to 15th December 2023. A separate additional search was performed on Google Scholar (https://scholar.google.com) for any missed articles. All studies from the inception of these databases to the last search date were eligible. The language was restricted to English.

Literature was searched with different combinations of the following key words: Beta blockers, adrenergic beta antagonist, beta antagonist, beta-adrenoreceptor antagonist, beta-adrenergic receptor antagonist, beta-adrenergic blocking agent, adrenergic beta-1 receptor antagonists, sepsis, septic shock, septicaemia and systemic inflammatory response syndrome. Further details are provided in Table SI.

After the initial search of the databases, all search results were combined in a single reference manager software (EndNote version 20; Clarivate). All duplicate entries were removed. Two authors independently screened the studies based on the following inclusion criteria:

i) Studies on adult patients with sepsis or septic shock; ii) exposure was premorbid use of beta-blockers; iii) comparison was no premorbid use of beta-blockers; iv) outcomes of interest were mortality and the need for mechanical ventilation; and v) all study types were eligible. Studies on beta-blocker use after diagnosis of sepsis were excluded. Studies without a control group, and studies reporting data on all antihypertensive agents rather than on beta-blockers specifically were also not eligible.

After initial screening, relevant studies were identified and downloaded. Full texts of these studies were further independently reviewed by the two authors, and all differences were resolved by discussion with a third author. References of selected articles were scrutinized to discover other relevant papers missed by the primary search strategy.

Data extraction and study quality assessment. Extracted data included author, study type, location, sample size, sepsis definition, sample size, age and sex details, lactate levels, Sequential Organ Failure Assessment score (SOFA) score, septic shock, type of outcomes reported and follow-up. The primary outcome was mortality and the secondary outcome was the need for mechanical ventilation. Unadjusted and adjusted data for mortality were extracted separately.

Studies were assessed for their methodological quality by the two authors using the Newcastle Ottawa Scale (NOS) (21). Points were awarded for the representativeness of the study cohort, comparability of groups and measurement of outcomes with each receiving a maximum of four, two and three points respectively.

Statistical analysis. Continuous data were presented as the mean (standard deviation) or median (interquartile range). Binary outcomes (unadjusted data) were analyzed using the inverse-variance random-effects meta-analysis. The effect size was reported as odds ratios (ORs) with 95% confidence intervals (CIs). Adjusted data were combined using the generic inverse variation function using 'Review Manager' (RevMan, v.5.3; The Cochrane Collaboration). To quantify the inter-study variability, statistical heterogeneity was checked using the χ^2 test and I^2 statistic. P-value of <0.10 with the χ^2 test or an I^2 value of >50% was considered as substantial heterogeneity. Publication bias for the primary outcome was checked by funnel plots. The robustness of the meta-analysis for the primary outcome was further verified by a sensitivity analysis. Individual studies were excluded, and the final OR was recalculated.

Results

Search outcomes. Systematic search across four databases identified 9,410 studies. After deduplication, a total of 3,186 articles underwent the initial screening of titles and abstracts. Full texts of the remaining 37 studies were selected for further analysis. Of them, nine studies in total were excluded since they reported data on other antihypertensive drugs and an additional number of ten studies were excluded because they assessed the effect of ongoing or newly prescribed beta-blockers on patients with sepsis. Finally, a total of 17 studies (16-18,22-35), comparing premorbid beta-blocker use with controls in patients with sepsis, were selected for the analysis (Fig. 1).

Study characteristics. Data extracted by the authors are shown in Table I. A total of three studies were prospective while 14 were retrospective. In total, four studies (17,29-31) were reported as conference proceedings. The included studies were from the USA, France, Italy, Israel, Singapore, China, Taiwan, India and Saudi Arabia, and were published between the years 2012 and 2023. 'Sepsis-2' and 'Sepsis-3' were the most accustomed definitions in the included studies. The 17 studies included 64,586 patients. Of them, a total of 8,665 patients received premorbid beta-blockers, and the 55,921 patients that were not treated by the premorbid beta-blockers were used as a control group. The mean/median age of patients was >60 years across studies. Most studies reported a predominance of the male sex in both groups. The percentage of patients with septic shock ranged from 3.4 to 100%. In total, 16 studies reported unadjusted mortality rates, while one study reported only adjusted mortality data. Mortality was reported as the ICU or in-hospital mortality, or as 28- or 30-days mortality. For the meta-analysis, ICU and in-hospital data were pooled together as in-hospital mortality and 28- and 30-days mortality was pooled together as one-month mortality. The total NOS score of the studies was between 6 and 8.

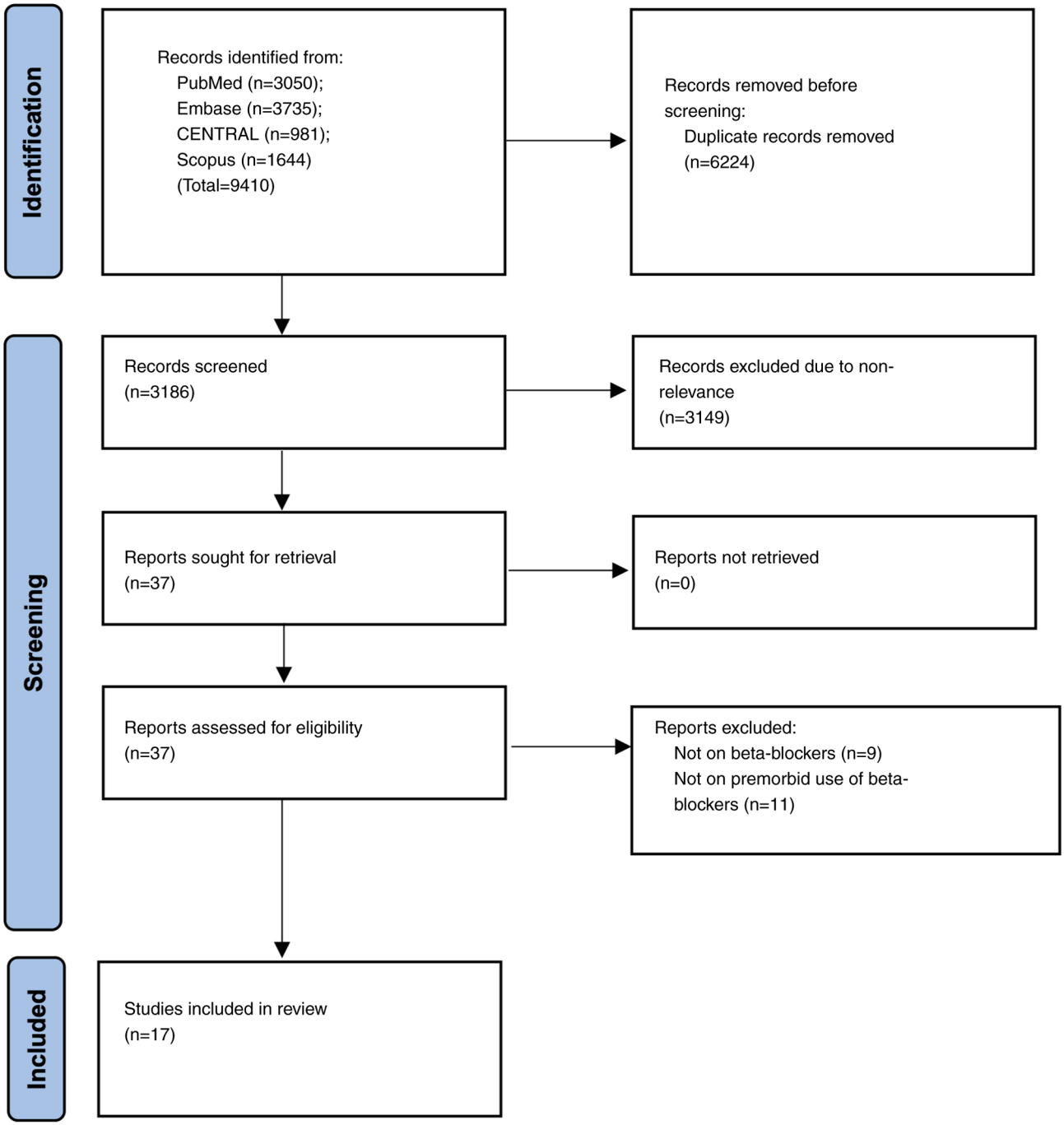

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart depicting selection of studies.

Meta-analysis. Pooled analysis of unadjusted mortality rates included 3,185 patients on premorbid beta-blockers and 8,899 patients in the control group and showed that premorbid beta-blocker use did not affect in-hospital mortality [OR: 0.96; 95% CI: (0.78, 1.18); and I^2=63%].

However, a meta-analysis of one-month mortality data of 4,440 patients on beta-blockers and 13,809 patients in the control group demonstrated that use of premorbid use of beta-blockers significantly reduced mortality (OR: 0.73; 95% CI: 0.64, 0.83; and I^2=19%). Overall, the combined data from 16 studies demonstrated that premorbid use of beta-blockers did offer a significant survival advantage in patients with sepsis (OR: 0.83; 95% CI: 0.72, 0.96; and I^2=63%) (Fig. 2). The funnel plot showed no publication bias (Fig. 3).

Adjusted mortality data was reported by only six studies. Combined analysis revealed that premorbid beta-blockers significantly reduced mortality rates in patients with sepsis (OR: 0.81; 95% CI: 0.72, 0.92; and I^2=70%) (Fig. 4).

The data of the need for mechanical ventilation was reported in six studies. Pooled analysis demonstrated no significant impact of beta-blocker use on the need for mechanical ventilation (OR: 0.93; 95% CI: 0.66, 1.30; and I^2=72%) (Fig. 5).

Sensitivity analysis. As presented in Table II, the results of the sensitivity analysis for the meta-analysis of unadjusted

Table I. Baseline details of included studies.

First author	Year	Type	Place	Definition of sepsis	Groups	Sample size	Age (years)	Male sex (%)	Septic shock (%)	Admission SOFA score	Lactate levels (mmol/l)	Outcomes	Follow-up	NOS score	(Refs.)
Kumar *et al*	2023	P	India	Sepsis-3	BB	38	NR	NR	0	7.3 (3)	1.4 (1.1)	Mortality	28 days	6	(28)
					No BB	38			0	7.4 (3.3)	1.5 (0.8)				
Ma *et al*	2022	R	China	Sepsis-3	BB	48	72.8 (12.3)	52.1	64.6	9.9 (4.4)	NR	Mortality, MV	28 days	7	(27)
					No BB	180	64.3 (16.1)	63.3	78.9	11.5 (4.6)					
Tan *et al*	2021	R	Multi-national	Sepsis-3/ ICD-9	BB	1556	70.3 (13.5)	54.9	9.8	10.5 (3.6)	1.5 (1-2.4)	Mortality, MV	In-hospital	8	(26)
					No BB	2530	63.9 (16.4)	54.1	13.8	10.8 (3.8)	1.6 (1.1-2.7)				
Pham *et al*	2021	R	Australia	Sepsis-2	BB	49	70.9 (NR)	75.5	69.4	NR	2.6 (2.1-3)	Mortality	In-hospital	6	(25)
					No BB	140	63.5 (NR)	50	70		3.6 (3.1-4.1)				
Kuo *et al*	2021	R	Taiwan	Sepsis-3	BB	209	71.3 (14.3)	66.5	34.4	NR	2 (1.9)	Mortality	ICU	6	(18)
					No BB	1053	68.9 (17.3)	66.5	46.1		1.8 (3.1)				
Guz *et al*	2021	P	Israel	Sepsis-2	BB	320	74 (62-82)	45.9	3.4	2 (1-3)	NR	Mortality, MV	30 days	7	(24)
					No BB	866	72 (57-83)	47.3	4.5	2 (0-3)					
Chan *et al*	2021	P	Singapore	Sepsis-3	BB	70	77.5 (62-85)	52.9	NR	3 (2-5)	1.7 (1.5)	Mortality	28 days	6	(35)
					No BB	125	70 60-79)	56		2 (1-3)	1.8 (1.7)				
Hsieh *et al*	2019	R	Taiwan	ICD-9	BB	1040	NR	NR	NR	NR	NR	Mortality	In-hospital	7	(23)
					No BB	33213									
DeMott *et al*	2018	R	USA	ICD-9	BB	46	67 (57-72)	52.2	100	14 (10-16)	NR	Mortality, MV	In-hospital	6	(22)
					No BB	51	62 (51-73)	62.7	100	12 (9-16)					
Charles *et al*	2018	R	France	NR	BB	230	72.9 (61.5-80)	66.1	NR	9 (6-12)	1.75 (0.9-3.4)	Mortality, MV	In-hospital	NE[a]	(29)
					No BB	708	66.9 (56-78)	63	NR	9 (6-13)	1.8 (0.8-4)				
Arnautovic *et al*	2018	R	USA	Septic shock defined as patients requiring vasopressors to maintain 65 mmHg despite adequate fluid resuscitation, as well as a serum lactate level >2.0 mmol/l	BB	49	NR	NR	100	NR	NR	Mortality	In-hospital	6	(16)
					No BB	60			100						

Table I. Continued.

First author	Year	Type	Place	Definition of sepsis	Groups	Sample size	Age (years)	Male sex (%)	Septic shock (%)	Admission SOFA score	Lactate levels (mmol/l)	Outcomes	Follow-up	NOS score	(Refs.)
Singer *et al*	2017	R	USA	ICD-9	BB	2838	NR	64.7	NR	NR	NR	Mortality	30 days	7	(34)
					No BB	4001	NR	62.9							
Alsolamy *et al*	2016	R	Saudi Arabia	NR	BB	623	NR	NR	NR	NR	NR	Mortality	ICU	NE[a]	(30)
					No BB	4006									
Sharma *et al*	2015	R	NR	NR	BB	48	71 (NR)	42	NR	NR	NR	Mortality	In-hospital	NE[a]	(17)
					No BB	75	65 (NR)	51							
Contenti *et al*	2015	R	France	Sepsis-2	BB	65	78 (11)	62.9	30.8	5 (2.8)	3.9 (2.3)	Mortality, MV	28 days	6	(33)
					No BB	195	75 (16)	54.4	32.3	5.3 (2.8)	5.6 (3.6)				
Al-Qadi *et al*	2014	R	USA	NR	BB	375	NR	NR	NR	NR	NR	Mortality	In-hospital	NE[a]	(31)
					No BB	276									
Macchia *et al*	2012	R	Italy	ICD-9	BB	1061	72 (12.8)	49.2	NR	NR	NR	Mortality	28 days	7	(32)
					No BB	8404	72 (13)	49.8							

[a]NE, not estimable as the study was reported as conference abstract. Continuous data are presented as the mean (standard deviation) or median (interquartile range). BB, beta-blockers; P, prospective; R, retrospective; SOFA, Sequential Organ Failure Assessment; NR, not reported; NOS, Newcastle Ottawa Scale; ICD, International classification of diseases; ICU, intensive care unit; MV, mechanical ventilation.

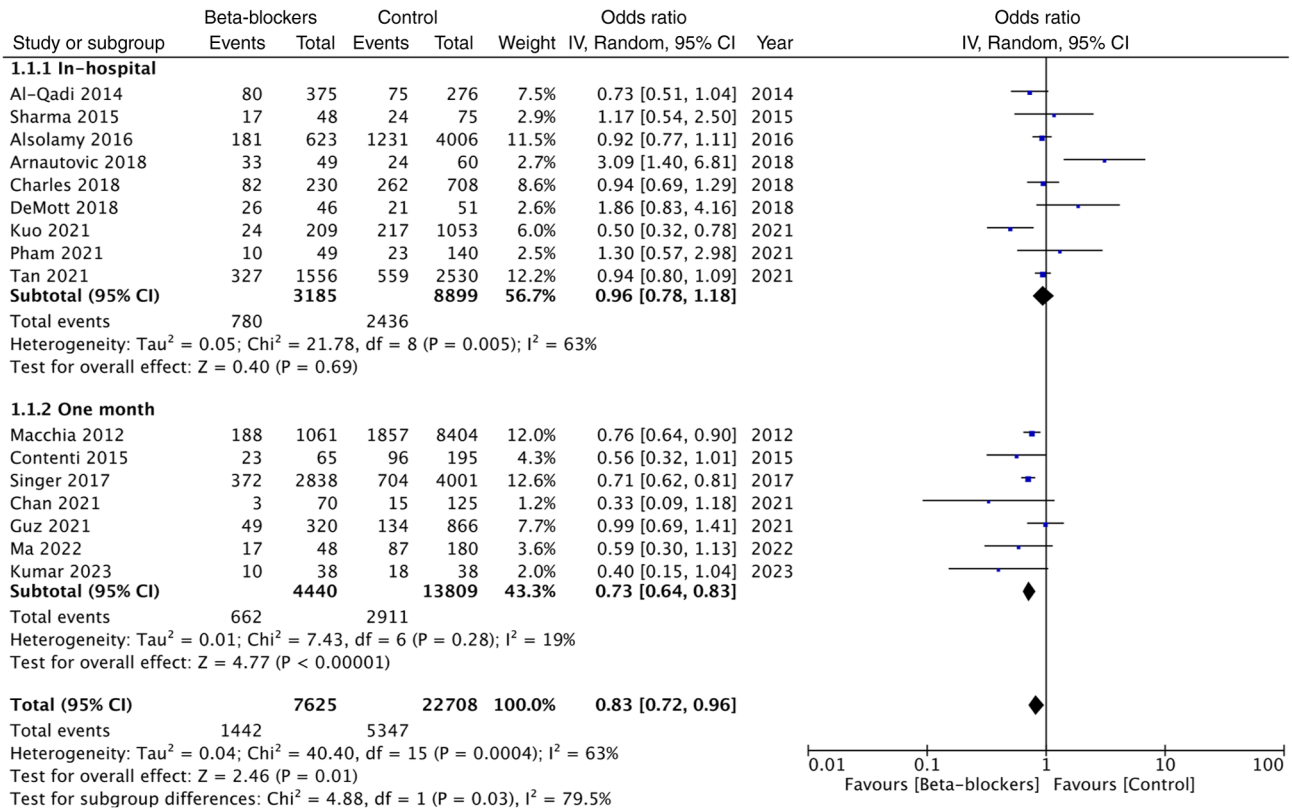

Figure 2. Forest plot showing the meta-analysis of crude mortality rates with subgroup analysis based on timing of mortality. Blue square and horizontal lines for each study denote the point estimate and the 95% CIs. Black diamond at the bottom of the graph indicates the pooled estimate. CI, confidence interval.

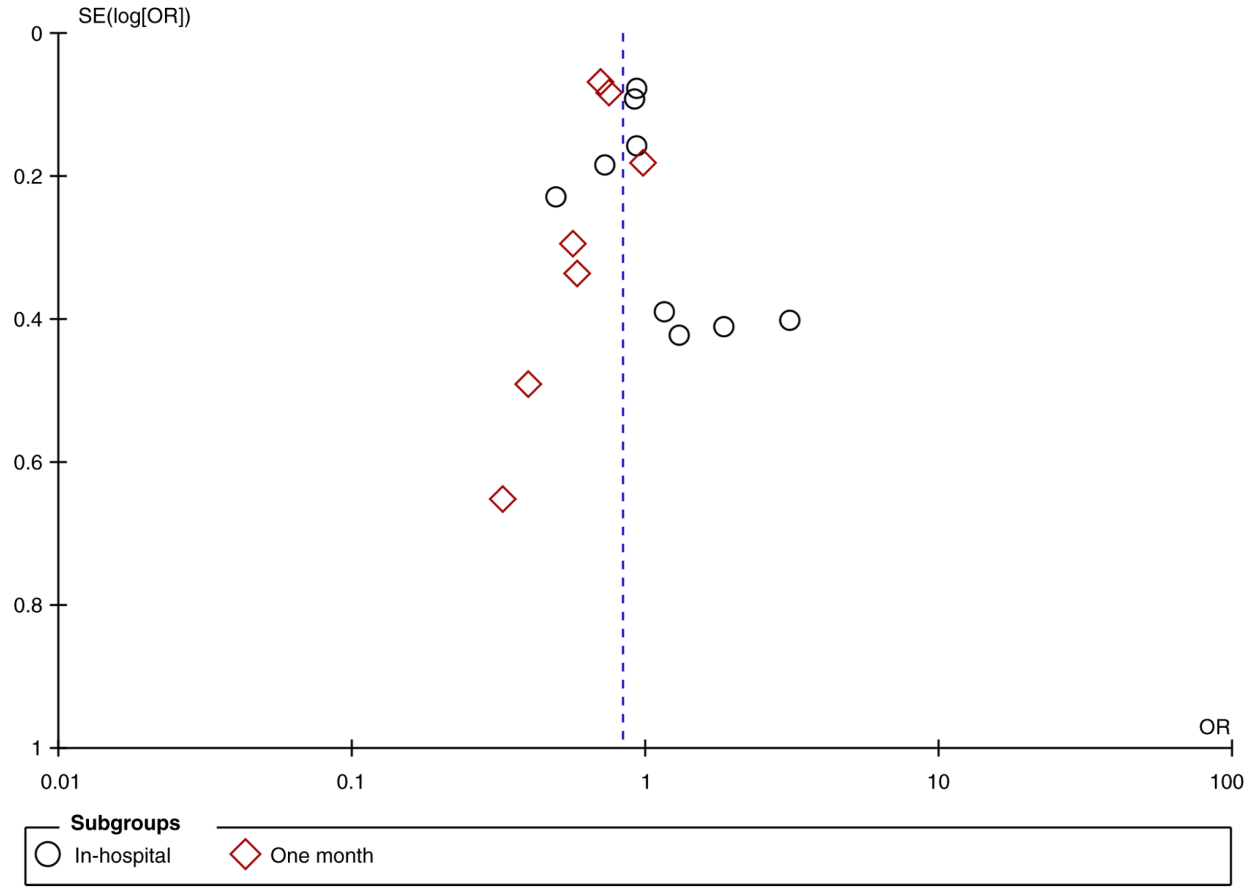

Figure 3. Funnel plot for assessing publication bias. Dotted line denotes the pooled effect size. Distribution of studies on either side of the line indicates no publication bias.

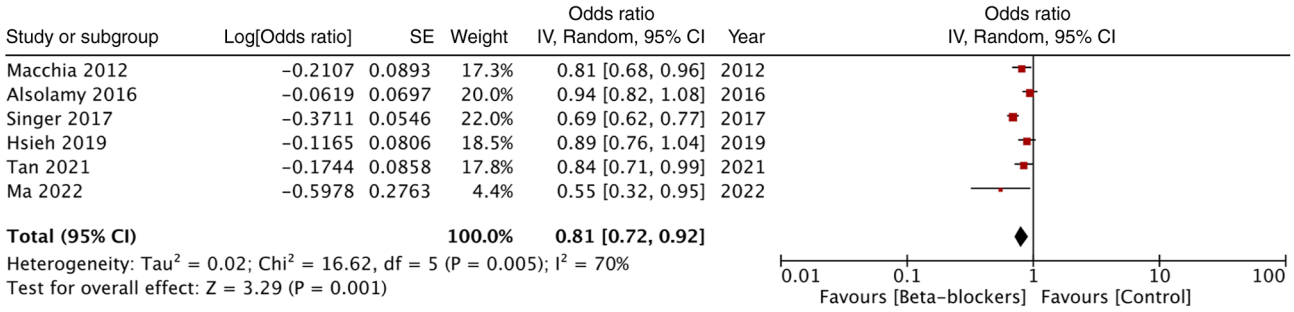

Figure 4. Forest plot showing the meta-analysis of adjusted mortality rates. Red square and horizontal lines for each study denote the point estimate and the 95% CIs. Black diamond at the bottom of the graph indicates the pooled estimate. CI, confidence interval.

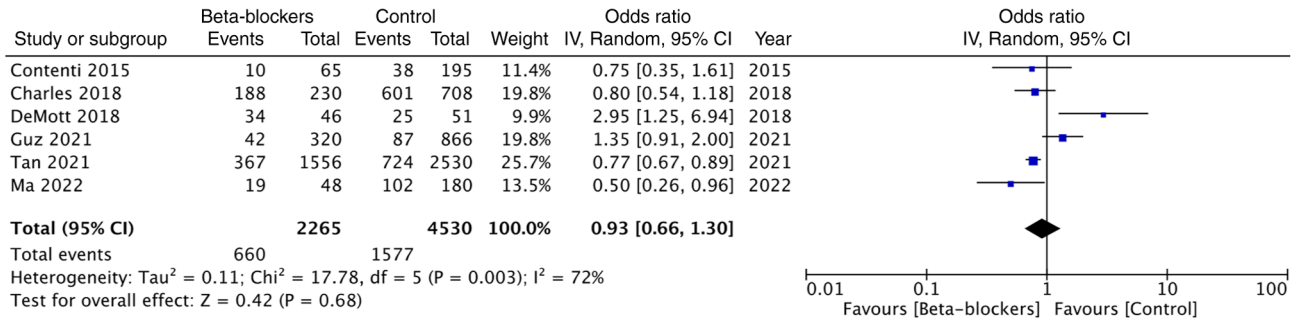

Figure 5. Forest plot showing the meta-analysis of the need for mechanical ventilation. Blue square and horizontal lines for each study denote the point estimate and the 95% CIs. Black diamond at the bottom of the graph indicates the pooled estimate. CI, confidence interval.

mortality rates demonstrated OR between 0.81 to 0.86. The upper limit of 95 CI% did reach the value of 1 on the exclusion of two studies indicating no significant impact of premorbid beta-blocker use on mortality after sepsis.

As demonstrated in Table III, the results of the sensitivity analysis for the meta-analysis of adjusted mortality rates remained statistically significant on sequential exclusion of all studies with the OR ranging from 0.78 to 0.87.

Discussion

This updated systematic review and meta-analysis examined the impact of premorbid use of beta-blockers on the outcomes of sepsis. Importantly, due to the limited data, only two outcomes, mortality and a need for mechanical ventilation, were included in the analysis. Analysis of 16 studies reporting unadjusted mortality rates demonstrated that premorbid use of beta-blockers had a protective role on patient survival after sepsis. However, mortality rates were reduced only at one-month follow-up with no impact on in-hospital mortality. Premorbid use of beta-blockers was found to reduce one-month mortality by 27% and overall mortality rates by 17%. The validity of the results is strengthened by the absence of publication bias, large sample size and no evidence of any outliner study. A detailed sensitivity analysis demonstrated minimal changes in the effect size on the exclusion of one study at a time.

The difference in in-hospital and one-month outcomes in the present meta-analysis is interesting. Forest plot analysis of the unadjusted mortality rates detected significant variation in the results of studies reporting in-hospital mortality with high heterogeneity in the meta-analysis. On the other hand, data for one-month mortality was more consistently in favor of beta-blockers, with the OR values of all the included studies being below 1. The interstudy heterogeneity of the meta-analysis was also low, with I^2=19%. It can be hypothesized that the difference in results could be explained by the quality of the studies, as the meta-analysis on in-hospital mortality included four studies (17,29-31) that were published as conference abstracts. Another reason could be the unaccountable baseline differences among studies in terms of patient population, sepsis severity, treatment protocols and so on, which could have skewed the results.

Unadjusted mortality rates are often confounded and may not be a correct measurement of the outcome (36). In the context of sepsis, several variables including age, sex, comorbidities, SOFA, Acute Physiology and Chronic Health Evaluation II score, baseline vital signs, lactate levels, creatinine levels, complications such as renal failure and intervention strategies (vasopressor use, mechanical ventilation, continuous renal replacement therapy) can all impact the prognosis (37-39). Beta-blockers are often prescribed to patients who are hypertensive or have chronic heart failure. Also, age of patients receiving beta-blockers was higher in all included studies, compared with the control group. Given such differences, adjusted mortality rates would represent an improved measurement of survival outcomes.

In the present review, a meta-analysis of a limited number of studies reporting adjusted data demonstrated a protective role of premorbid beta-blockers on sepsis-associated mortality. These results remained consistent after the sensitivity analysis, without any change in the significance of the results. Lastly, only few studies reported secondary outcome data, and the

Table II. Results of sensitivity analysis for crude mortality rates.

Excluded study, year	Resultant odds ratio	(Refs.)
Al-Qadi *et al*, 2014	0.84 (0.72, 0.98)	(31)
Sharma *et al*, 2015	0.83 (0.71, 0.96)	(17)
Alsolamy *et al*, 2016	0.82 (0.70, 0.97)	(30)
Arnautovic *et al*, 2018	0.81 (0.71, 0.92)	(16)
Charles *et al*, 2018	0.82 (0.71, 0.96)	(29)
DeMott *et al*, 2018	0.82 (0.71, 0.94)	(22)
Kuo *et al*, 2021	0.86 (0.74, 0.99)	(18)
Pham *et al*, 2021	0.82 (0.71, 0.95)	(25)
Tan *et al*, 2021	0.82 (0.70, 0.97)	(26)
Macchia *et al*, 2012	0.84 (0.72, 1.00)	(32)
Contenti *et al*, 2015	0.85 (0.73, 0.98)	(33)
Singer *et al*, 2017	0.85 (0.73, 1.00)	(34)
Chan *et al*, 2021	0.84 (0.73, 0.97)	(35)
Guz *et al*, 2021	0.82 (0.70, 0.96)	(24)
Ma *et al*, 2022	0.84 (0.73, 0.98)	(27)
Kumar *et al*, 2023	0.85 (0.73, 0.98)	(28)

Table III. Results of sensitivity analysis for adjusted mortality rates.

Excluded study, year	Resultant odds ratio	(Refs.)
Macchia *et al*, 2012	0.81 (0.69, 0.94)	(32)
Alsolamy *et al*, 2016	0.78 (0.69, 0.89)	(30)
Singer *et al*, 2017	0.87 (0.79, 0.95)	(34)
Hsieh *et al*, 2019	0.79 (0.68, 0.92)	(23)
Tan *et al*, 2021	0.80 (0.69, 0.94)	(26)
Ma *et al*, 2022	0.83 (0.73, 0.94)	(27)

meta-analysis did not reveal any effect of beta-blocker use on the need for mechanical ventilation.

While the results are consistent with previous reviews, the current analysis has significantly higher number of included studies. Tan *et al* (19) reviewed evidence from nine studies and conducted a meta-analysis with just three studies to demonstrate the protective effect of premorbid beta-blockers. Hasegawa *et al* (11) reported similar results, although, just ten studies were included in the review. The present review has added seven more studies with an overall sample size of 64,586 patients to present the most comprehensive evidence on the potential impact of premorbid beta-blockers on the outcomes of sepsis.

The role of beta-blockers in the management of patients with sepsis has received significant attention in the past decade with very controversial results. A previous study found that short-acting beta-blockers such as esmolol and landiolol are able to efficiently control tachycardia in patients with sepsis without any relative decrease in the mean arterial pressure, and improve patient survival (40). However, recently published STRESS-L RCT (41) has revealed that in patients with septic shock and tachycardia that were managed by norepinephrine for >24 h, the use of beta-blocker landiolol did not affect SOFA scores or mortality rates. The trial had to be stopped prematurely due to the possible adverse effects of beta-blockers. By contrast, a retrospective study has shown that that in patients who receive chronic beta-blockers, continuation of beta-blockers therapy was significantly associated with reduced in-hospital, 28 and 90-day mortality compared with drug cessation (42).

The effect of beta-blockers in sepsis is indeed as complex as the pathophysiology of the disease itself. Sympathetic response is an important initial phase of sepsis that leads to increased myocardial contractility, heart rate and vasoconstriction as a way of counteracting the effect of inflammatory response to infection (43). Current guidelines recommend the use of norepinephrine to treat vasoplegia and capillary leakage due to its vascular α1-agonist effect (9). However high catecholamine levels are associated with adverse effects such as tachycardia, dysautonomia and altered cardiac hemodynamics (10). Furthermore, they can increase cardiac dysfunction by inducing cardiomyopathy and cardiomyocyte necrosis (13). A RCT comparing norepinephrine and dobutamine with epinephrine alone, revealed that these regimens resulted in similar survival of septic shock patients. These results indicated a lack of benefit of beta-adrenergic simulation in septic shock (44). The concept of 'decatecholaminization' is based on the blockage of beta-receptors which are predominantly present in the heart, while allowing adrenergic stimulation of vascular alpha receptors that would lead to vasoconstriction (12,13). Premorbid use of beta-blockers can therefore reduce the adrenergic response of the heart, leading to a reduction in heart rate, improved diastolic time and higher coronary perfusion. They can also reduce myocardial oxygen consumption and lower the risk of myocardial ischemia (19). The use of beta-blockers would reduce tachycardia, improve stroke volume and ultimately reduce mortality (11). Beta-blockade can also blunt the hypercatabolic adrenergic response, often observed in sepsis, and can be associated with proteolysis, lipolysis and hyperglycemia. Beta-blockers have been shown to reverse muscle-protein catabolism and reduce catabolic states (45). Premorbid use of beta-blockers is also associated with higher mean arterial pressure and lower lactate levels at admission in patients with sepsis which could also lower mortality rates (11).

The strengths of the present systematic review lie in the detailed and updated literature search. The present analysis included a total of 17 studies examining the role of premorbid beta-blockers on outcomes of sepsis. The current study presented the most current and comprehensive evidence on the subject, thereby allowing clinicians to take informed decisions. Sensitivity analysis and separate meta-analysis for unadjusted and adjusted data further contributed to comprehensive evaluation of the evidence.

There are limitations to the present study. Firstly, most studies were retrospective. In addition, most studies did not report adjusted data. Hence, selection and confounding bias are important drawbacks of the current evidence. Secondly, studies did not report if beta-blockers were continued or withheld during the hospitalization period. Therefore, the current review was unable to comment on the role of continued therapy

on sepsis outcomes. Thirdly, most studies did not report separate data on non-selective and cardio-selective blockers. The type of beta-blocker was also not reported in most studies. Furthermore, no information was available on the duration and dosage of beta-blocker use in the study group. Further investigations are therefore needed to provide answers to these questions. Lastly, one cannot negate the heterogeneity in the patient population and sepsis severity among the studies. This could have primarily contributed to the high heterogeneity in the primary meta-analysis.

In conclusion, premorbid use of beta-blockers may contribute to improved survival in patients with sepsis. However, there was no impact on the need for mechanical ventilation. Given the observational nature of the data and the predominance of unadjusted data, the results should be interpreted with caution. Further prospective studies with large sample sizes and considering confounding factors should be conducted to provide improved evidence.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HC conceived and designed the study. FF, YS and HZ collected the data and performed the literature search. HC contributed to the writing of the manuscript. FF and YS confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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