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Effects of antiplatelet therapy on the mortality rate of patients with sepsis: A meta-analysis

Yaqi Ouyang [a], Yuhui Wang [b], Baoyan Liu [b], Xiaochun Ma [b,*], Renyu Ding [b,*]

[a] Department of Intensive Care Unit, Xiehe Hospital affiliated to Tongji Medical College, Huazhong University of Science and Technology,Jiefang Avenue 1277, Wuhan 430000, , Hubei Province, PR China

[b] Department of Intensive Care Unit, The First Hospital of China Medical University, Nanjing Bei Street 155, Shenyang 110001, Liaoning Province, PR China

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ABSTRACT

Purpose: Abnormal platelet activation plays an important role in the development of sepsis. The effect of antiplatelet drugs on the outcome of patients with sepsis remains unclear. This meta-analysis aimed to determine the effect of antiplatelet drugs on the prognosis of patients with sepsis.

Materials and methods: PubMed, Cochrane Library, CBM, and Embase were searched for all related articles published from inception to April 2018. The primary end point was mortality. Adjusted data were used and statistically analysed.

Results: Ten cohort studies were included. The total number of patients with sepsis was 689,897. Data showed that the use of antiplatelet drugs could effectively reduce the mortality of patients with sepsis (odds ratio (OR) = 0.82, 95% CI: 0.81–0.83, $p < 0.05$). Seven studies used aspirin for antiplatelet therapy, and subgroup analysis showed that aspirin effectively reduced ICU or hospital mortality in patients with sepsis (OR = 0.60, 95% CI: 0.53–0.68, $p < 0.05$). A subgroup analysis on the timing of anti-platelet drug administration showed that antiplatelet drugs can reduce mortality when administered either before (OR = 0.78, 95% CI: 0.77–0.80) or after sepsis (OR = 0.59, 95% CI: 0.52–0.67).

Conclusions: Antiplatelet drugs, particularly aspirin, could be used to effectively reduce mortality in patients with sepsis.

1. Introduction

Sepsis is among the main causes of intensive care unit (ICU) admission [1] and leads to multiple organ dysfunction and death [2,3]. The worldwide incidence of sepsis is gradually increasing [4], with millions developing sepsis annually. The mortality rate of patients with sepsis is ≥25% [1,5,6], and sepsis treatment in the United States costs approximately 17 million dollars annually [5].

Studies have shown that uncontrolled inflammatory responses and pro-coagulant effects are important mechanisms during the development of sepsis, and disorders of the coagulation system may cause disseminated intravascular coagulation that leads to the formation of intravascular microthrombus [7-9]. In this series of processes, platelet-endothelial cell interactions and platelet-neutrophil interactions due to platelet activation play an important role in microthrombus formation and the release of inflammatory factors [10-14]. Therefore, the use of antiplatelet agents to suppress platelet function in patients with sepsis may improve outcomes.

However, research on the effect of antiplatelet agents on the outcomes of patients with sepsis yielded conflicting results. Some studies have shown that antiplatelet agents may inhibit systemic inflammation by reducing platelet activity and inhibiting platelet aggregation [15,16], thus ultimately reducing the mortality rate [17-20] in patients with sepsis or infectious diseases and those who are critically ill [21-23]. Animal models have also shown supporting evidence on the benefit of antiplatelet agents in patients with sepsis [24,25]. However, other studies have shown that the use of antiplatelet drugs has no effect on patients with sepsis and those who are critically ill [23,26,27]. Thus, the effect of antiplatelet therapy on sepsis remains unclear. In this regard, this meta-analysis aimed to explore the effect of antiplatelet drugs on the prognosis of patients with sepsis.

2. Methods

This study was conducted according to the Preferred Reporting Project for Systematic Reviews and Meta-Analysis guidelines [28,29]. We used data derived from published articles, and therefore, the study

Abbreviations: ARDS, acute respiratory distress; CI, confidence interval; ICU, intensive care unit; NOS, Newcastle-Ottawa Scale; OR, odds ratio.

* Corresponding authors at: Department of Intensive Care Unit, The First Hospital of China Medical University, Nanjing Bei Street 155, Shenyang 110001, Liaoning Province, PR China.

E-mail addresses: xcma2972@sina.com (X. Ma), renyuding@126.com (R. Ding).

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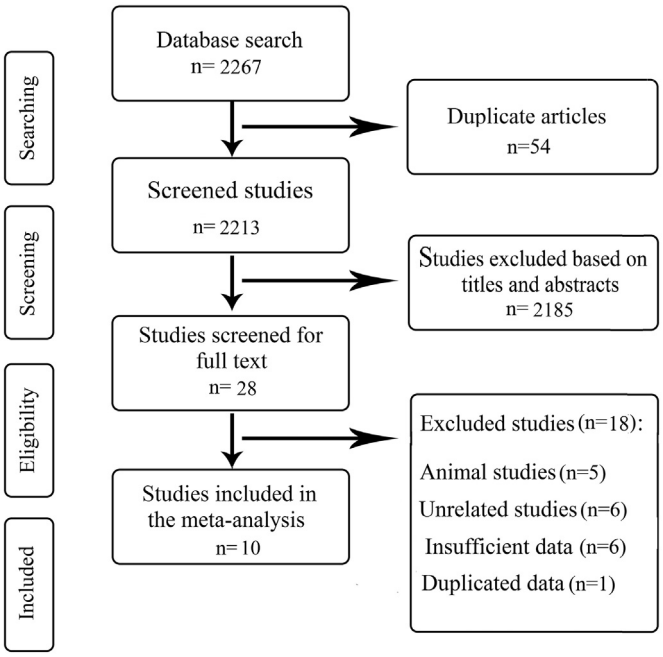

Fig. 1. Flow diagram of study selection.

does not require ethical approval and patient consent. Briefly, we searched the PubMed, Cochrane Library, CBM, and Embase databases for all relevant articles published in English from their inception to April 2018 using the following keywords: infection, sepsis, severe sepsis, septic shock, platelet inhibitors, antiplatelet, acetyl-salicylic acid, aspirin, clopidogrel, mortality, and death.

The inclusion criteria were as follows: (1) the patients in the experimental group and the control group were all adult patients aged ≥18 years; (2) there is a clear reference to the diagnosis of sepsis in the patient; (3) interventions were clearly defined as antiplatelet drugs including aspirin and clopidogrel and the control measures were defined as no use of antiplatelet drugs; (4) the main outcomes for mortality, including ICU mortality, in-hospital mortality, 30-day mortality, 60-day mortality, and 90-day mortality, were evaluated, and the longest observed mortality rate was adopted when there are multiple death rates; (5) clinical randomized controlled trials, cohort studies, case-control studies, or descriptive studies; and (6) the odds ratio (OR) and its 95% confidence interval (CI) are provided, or there are adequate data to calculate the OR and its 95% confidence interval.

Meanwhile, the exclusion criteria were as follows: (1) duplicate reports; (2) the data source and the experimental group were also duplicates; (3) the study included pregnant or lactating women; (4) patients who were only diagnosed with bacteraemia (not sepsis) were excluded; (5) there is no explicit mention of interventions of antiplatelet drugs including aspirin and clopidogrel; (6) it was unclear whether antiplatelet drugs were not used in the control group; (7) issues in research design

Table 1
Study information.

Author	Year	Patient type	Number of patients (total/antiplatelet)	Interventions	Outcomes	Timing, dosage, and duration of antiplatelet drugs
Valerio-Rojas et al.	2012	ICU patients with severe sepsis or septic shock	651/272	Acetyl salicylic acid-containing medication, clopidogrel, ticlopidine, or dipyridamole	Hospital mortality, length of ICU stay, incidence of ARDS, incidence of AKI, duration of mechanical ventilation, use of CRRT	At the time of ICU admission
Otto et al. (a)	2013	ICU patients with severe sepsis or septic shock	886/187	Aspirin	ICU mortality, hospital mortality	At least 2 days during the ICU at a dose of 100 mg/d
Otto et al. (b)	2013	ICU patients with severe sepsis or septic shock	886/8	Clopidogrel	ICU mortality, hospital mortality	At least 2 days during the ICU at a dose of 75 mg/d
Otto et al. (c)	2013	ICU patients with severe sepsis or septic shock	886/50	Aspirin combined with clopidogrel	ICU mortality, hospital mortality	At least 2 days during the ICU stay, with a dose of 100 mg/d aspirin and 75 mg/d clopidogrel
Lösche et al.	2012	ICU patients with severe sepsis or septic shock	834/187	Aspirin	ICU mortality	Low-dose aspirin during ICU stay
Eisen et al.	2012	ICU patients with sepsis	970/165	Aspirin	Hospital mortality, incidence of AKI, incidence of haemorrhage	Within 24 h of SIRS onset (common dose was 150 mg)
Wiewel et al.	2016	ICU patients with sepsis	972/267	Acetylsalicylic acid, Clopidogrel, Dipyridamole, Prasugrel	30-day mortality, length of stay ICU, organ failure during admission, shock during admission, ICU mortality, 60-day mortality	Pre-existing antiplatelet therapy
Campbell et al.	2015	ICU patients with sepsis	218/12	Aspirin	Hospital mortality	Prior to ICU admission
Harbi et al.	2016	ICU patients with sepsis	194/47	Aspirin	Hospital mortality, length of ICU stay, duration of mechanical ventilation, ICU-acquired severe sepsis	Continuation of a pre-ICU or a new medication in the ICU
Tsai et al.	2015	Patients with sepsis	683421/117447	All oral antiplatelet agents, including aspirin, clopidogrel, and ticlopidine	Hospital mortality	Current use
Maik et al.	2013	ICU patients with sepsis	979	Aspirin	Hospital mortality	Low-dose aspirin during ICU stay
Hsu et al.	2018	In-hospital patients with sepsis	1526	Aspirin	Hospital mortality, risk of organ dysfunction	Current maintenance of antiplatelet drugs taken at least twice a week

ICU: intensive care unit, ARDS: acute respiratory distress syndrome, SIRS: systemic inflammatory response syndrome, CRRT: continuous renal replacement therapy, AKI: acute kidney injury

Table 2
Study quality as assessed via the Newcastle-Ottawa Scale.

Author	Year	Selection	Comparability	Outcome
Valerio-Rojas et al.	2012	***	*	**
Otto et al.	2013	****	*	**
Lösche et al.	2012	***	*	**
Eisen et al.	2012	***	*	**
Wiewel et al.	2016	***	*	**
Campbell et al.	2015	***	*	**
Harbi et al.	2016	***	*	**
Tsai et al.	2015	***	*	***
Maik et al.	2013	**	*	**
Hsu et al.	2018	***	*	***

and poor quality of the article (<4 points); (8) incomplete data and the main outcomes are unclear or not provided; (9) the statistical methods are erroneous and cannot be corrected or data on OR and its 95% CIs or for their calculation are not provided.

The literature search and preliminary screening were carried out by YO and BL, respectively. The articles were screened according to their titles and abstract, and the full texts of the eligible articles were then reviewed. Those that met the criteria were evaluated. The references were also browsed to further search for related articles and avoid missing data. Data from the eligible studies, including authors, year of publication, number of patients, type of study, type of patient included, antiplatelet therapy used, and patient outcomes, were collected by YW. The quality of the literature was assessed by RD using the Newcastle-Ottawa Scale (NOS) [30]. Disagreements in the eligibility and quality of the studies were resolved through a group discussion and summarized by XM. The final decision was made based on votes from all five authors.

The primary outcome measure was mortality. Statistical analysis was performed using the STATA 10.0 (StataCrop, Texas, USA). All the articles used the adjusted OR and 95% CI. If the OR value was not directly provided, the relevant data were extracted to calculate the OR value. The chi-square test was used to determine heterogeneity among the studies, with $p > 0.1$, $I2 < 50\%$ indicating no heterogeneity, while $p < 0.1$, $I2 > 50\%$ indicating heterogeneity. Studies with no heterogeneity were analysed using a fixed-effects model. Meanwhile, a random effects model was used for the analysis of studies found to be heterogenous after determining the reasons for heterogeneity. Publication bias was evaluated using the funnel plot method. A *p*-value of ≤0.05 was considered significant.

3. Results

A total of 2267 articles were retrieved; of these, 10 articles were included in the meta-analysis [2,7,14,20,22,31-35]. All included articles were in English and were cohort studies published between 2012 and 2018. Fig. 1 shows the search and screening process.

Table 1 shows the main information of the 10 included studies. A total of 689,897 sepsis patients were included. All 10 studies included outcome mortality [2,7,14,20,22,31-35]. The definitions of sepsis varied among the studies, and some reports did not specify clear diagnostic criteria for sepsis [7,22,31,32,34]. Meanwhile, the diagnostic criteria for sepsis in the other studies were similar, but the choice of antiplatelet therapy varied [2,14,20,33,35]. Aspirin was the only antiplatelet intervention in seven studies [2,7,22,31-33,35].

The quality of the literature as assessed using the NOS is shown in Table 2 [30]. In terms of selection, comparability, and outcome, the studies by Otto et al., Hsu et al., and Tsai et al. were of higher literature quality, while that by Maik et al. was of lower literature quality. Except for the study by Hsu et al. and Tsai et al., the studies did not provide a detailed description of the rate of patients lost to follow-up.

Random effects model showed that the use of antiplatelet drugs can effectively reduce the mortality of patients with sepsis (OR = 0.82, 95% CI: 0.81–0.83, $p < 0.05$; Fig. 2). It showed significant heterogeneity among the 10 studies ($I2 = 74.1\%$, $p < 0.05$). Meanwhile, the seven studies that used aspirin alone for antiplatelet therapy were found to be homogenous ($I2 = 0\%$, $p = 0.504$). Analysis of these studies showed that aspirin effectively reduced mortality in patients with sepsis (OR = 0.60, 95% CI: 0.53–0.68, $p < 0.05$; Fig. 3). Five studies provided data on the mortality of patients with severe sepsis or septic shock and provided evidence that antiplatelet therapy helped reduce mortality (OR = 0.72, 95% CI: 0.49–0.95, $p < 0.05$; Fig. 4). A subgroup analysis on the timing of anti-platelet drug administration showed that antiplatelet drugs can reduce mortality when administered either before (OR = 0.78, 95% CI: 0.77–0.80, Fig. 5) or after sepsis (OR = 0.59, 95% CI: 0.52–0.67, Fig. 5).

On sensitivity analysis, the sensitivity of Tsai et al.'s study was markedly higher than that of the other studies (Fig. 6). This may be because

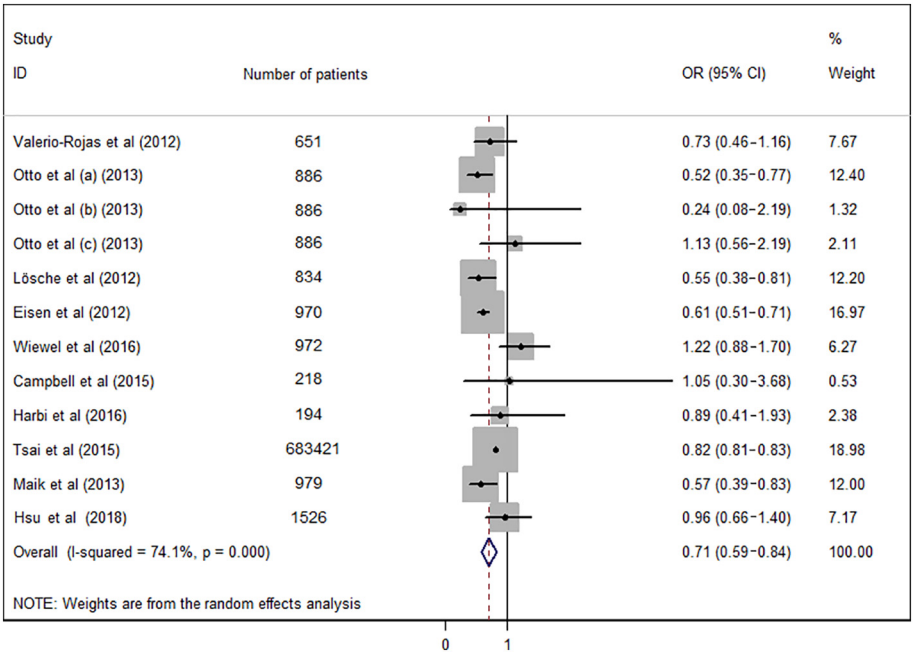

Fig. 2. Forest plots showing the effect of antiplatelet therapy on the mortality rate of patients with sepsis.

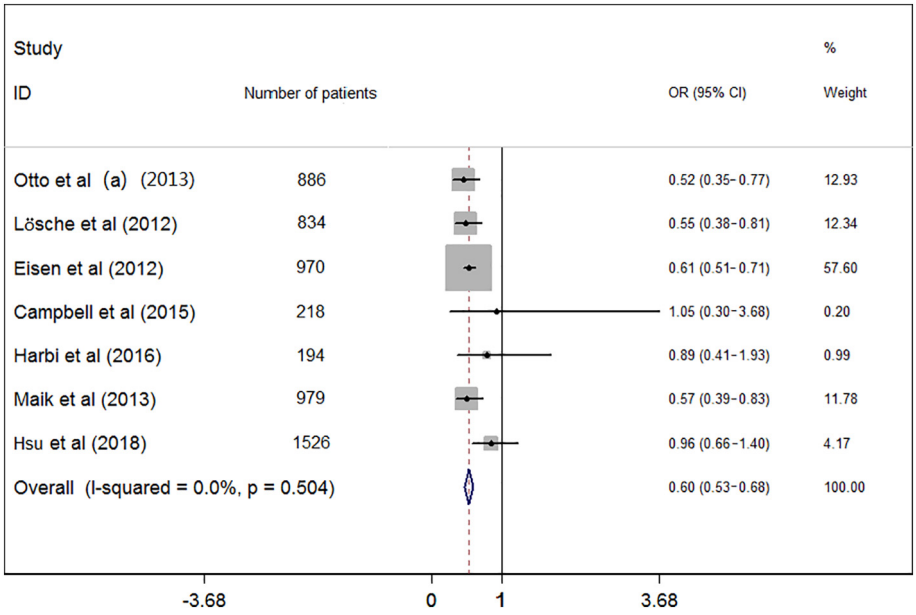

Fig. 3. Forest plots showing the effect of aspirin on the mortality rate of patients with sepsis.

the study comprised a large sample cohort, and the data were all sourced from the National Health Insurance Database in Taiwan, which lead to a 95% CI that was close to the OR value. When this study was excluded from the analysis, antiplatelet drugs continued to have a positive effect on the mortality of patients with sepsis (OR = 0.63, 95% CI: 0.56–0.70, $p < 0.05$), but the quality of the results declined ($I2 = 37.8\%$, $p = 0.168$). In summary, Tsai et al.'s study included a large sample size and was of high-level quality. The overall reliability was relatively high, and thus, it was included in the meta-analysis.

The funnel plot showed no publication bias in the included studies (Fig. 7).

4. Discussion

Animal models of antiplatelet therapy for sepsis have recently shown that aspirin reduces the synthesis of platelet thromboxane A2 and increases the survival rate of mice and dogs [36,37]. In a study using P2Y12 inhibitors in mice, clopidogrel did not significantly improve survival and haemodynamics in the first 24–48 h but tended to reduce mortality in the later period in the experimental group [38]. In a study on GPIIb/IIIa antagonists using a rabbit model of septic shock, the experimental group had lower mortality than the control group. It was hypothesized that GPIIb/IIIa antagonists inhibit coagulation activation via the inhibition of platelet aggregation and monocyte tissue factor expression and protection against endothelial dysfunction [39].

Based on the above findings, we hypothesized that antiplatelet drugs affect the development of sepsis through its inhibition of platelet function. It may also be due to the anti-inflammatory effects of aspirin [40] or other antiplatelet agents such as P2Y12 receptor inhibitors that reduce the effect of lipopolysaccharide-induced platelet aggregation [41]. Some studies suggest that aspirin decreases mortality in patients with sepsis via the increase in pathogen clearance resulting from the increased inflammation that is in turn due to the downregulation of prostaglandins and the activation of pro-oxidants [42,43].

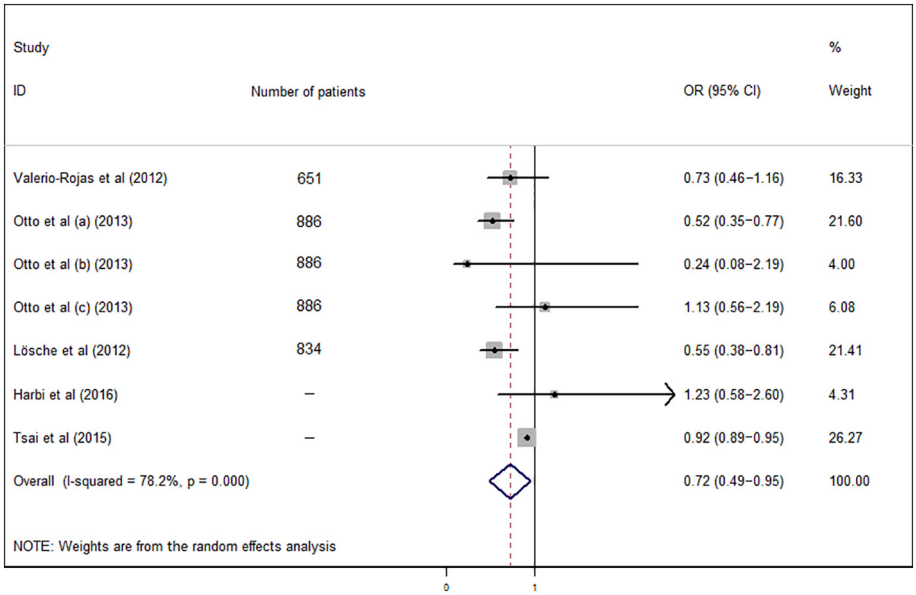

Fig. 4. Forest plots showing the effect of aspirin on the mortality rate of patients with severe sepsis or septic shock.

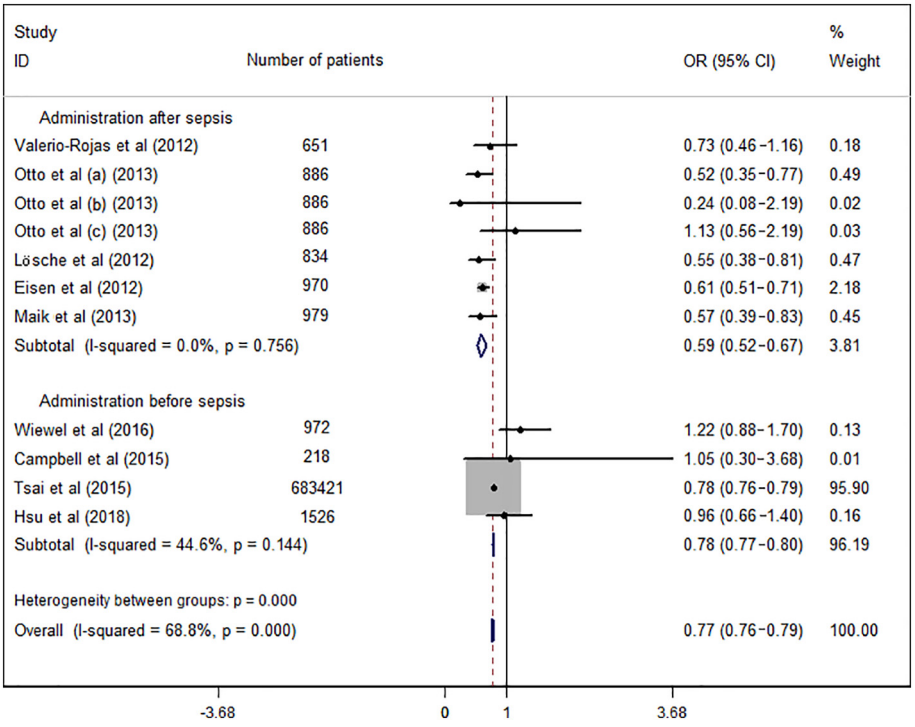

Fig. 5. Forest plots depicting the subgroup analysis of the effect of timing of antiplatelet therapy on the mortality rate of patients with sepsis.

The data extracted from the 10 papers included in this meta-analysis showed that the anti-platelet drugs effectively reduced the mortality of patients with sepsis (OR = 0.82, 95% CI (0.81–0.83), $p < 0.05$). Of the 10 studies, seven used aspirin for antiplatelet therapy. After analysis, it was concluded that the use of aspirin can effectively reduce mortality of patients with sepsis (OR = 0.60, 95% CI (0.53–0.68), $p < 0.05$). When studies that used aspirin were excluded in the analysis, the results of the remaining studies, except that of Tsai et al., showed no significant difference in outcomes. Maik et al.'s study used aspirin, clopidogrel, and non-steroidal anti-inflammatory drugs individually and showed that only aspirin affected mortality [22].

Aspirin is different from other antiplatelet drugs because it also has an anti-inflammatory effect that it exerts by inhibiting the synthesis of cyclooxygenase and the activation of nuclear factor-κB caused by inflammatory effector cells during pathologic conditions [44]. Therefore, a separate study is needed to determine the appropriate antiplatelet drugs for sepsis. However, because data are limited, it is hard to conduct further research.

All 10 studies provided data on mortality, including in-hospital mortality or ICU mortality. However, the secondary outcomes of the studies varied and included the duration of mechanical ventilation, incidence of acute respiratory distress (ARDS), incidence of acute kidney injury, need for renal replacement therapy, and length of stay ICU. Three articles [7,14,34] reported the duration of ICU stay (WMD = −0.066, 95% CI: -0.490–0.357, p = 0.38), and two articles [7,34] reported mechanical ventilation duration (WMD = 0.274, 95% CI: -0.298–0.845), (p = 0.289), with no significant difference. The study by Valerio-Rojas et al. showed that the use of aspirin can reduce the duration of mechanical ventilation and the incidence of ARDS [34]. By contrast, the study by Harbi et al. reported that the use of aspirin increases the duration of mechanical ventilation and the incidence of severe sepsis [7]. These differences in secondary outcomes between the studies by Valerio-Rojas et al. and Harbi et al. may be due to the difference in the illness severity of the patients [7,34]. However, we could not conduct a comparative analysis. Regarding the timing of antiplatelet drug administration, we found that antiplatelet therapy can effectively reduce mortality in patients with sepsis when administered either as a preventive (before sepsis) or an additional (after sepsis) treatment. However, Tsai et al. found an interesting phenomenon: when antiplatelet drugs as a preventive treatment are stopped for >30 days, their impact on reducing mortality would be unclear [20].

Due to the lack of large prospective randomized clinical trials, the above findings should be interpreted cautiously. Also, patients on antiplatelet therapy should be carefully monitored for adverse events such as bleeding. Otto et al. and Eisen et al. reported cases of bleeding events but did not find a higher incidence of bleeding events in the antiplatelet group. Eisen et al. believe this may be because of the discontinuation of aspirin in patients with bleeding tendency [2,33].

The strengths of this study include the high quality of the included reports. Meanwhile, this study also had some limitations. First, clinical randomized controlled trials were not included in the analysis. In addition, the timing of administration along with the duration and dosages of antiplatelet drugs varied among the included studies. This makes the generality of the conclusions difficult. Second, the definition of

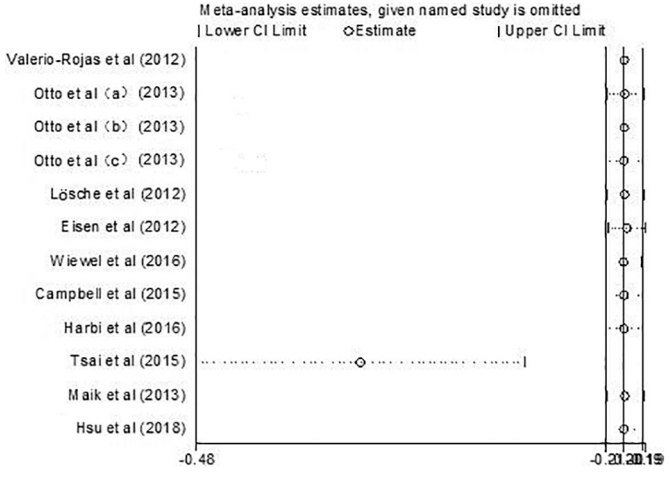

Fig. 6. Sensitivity analysis.

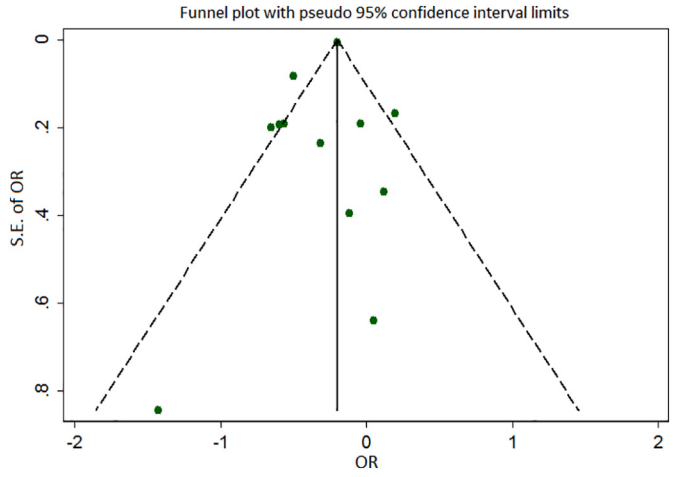

Fig. 7. Publication bias funnel map.

sepsis varied in the articles because the diagnostic criteria for sepsis is continually updated. Lastly, although there was no publication bias, unpublished studies with important results may have been missed; this limitation may be addressed in future studies by expanding the search for references.

5. Conclusion

The use of antiplatelet drugs can reduce the mortality rate in patients with sepsis. Particularly, aspirin can effectively reduce mortality in patients with sepsis. However, these findings need to be verified in large, multi-centre clinical randomized controlled trials.

Declarations of interest

None.

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