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A meta-analysis of the efficacy and safety of aspirin in the treatment of elderly patients with sepsis

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Abstract: This study aimed to use meta-analytic techniques to evaluate aspirin's safety and effectiveness in treating elderly patients with sepsis. We searched PubMed, Embase, The Cochrane Library, Web of Science, and Medline databases for relevant literature, screened and extracted key data and Stata 12.0 was used for comprehensive analysis. From library establishment to June 2024, relevant literature on aspirin for elderly sepsis patients was retrieved from PubMed, Web of Science, Embase, Medline and The Cochrane Library. Literature for meta-analysis was screened by inclusion and exclusion criteria and valid data was extracted. Stata 12.0 software was then used for integrated analysis. Finally, a total of 12 relevant pieces of literature were included in this study, involving 136,931 research subjects. The results of the meta-analysis showed that aspirin can reduce ICU mortality, in-hospital mortality, 30-day and 90-day mortality and the incidence of bleeding events in elderly patients with sepsis. It can also shorten the length of ICU stay but can not improve the incidence of organ failure. These suggest that aspirin has good efficacy and safety in the treatment of elderly patients with sepsis.

Keywords: Aspirin, sepsis in the elderly, efficacy, meta-analysis.

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INTRODUCTION

A dysregulated host response to infection can produce sepsis. For example, pneumonia (e.g., caused by *Streptococcus pneumoniae*), urinary tract infections (e.g., caused by *Escherichia coli*) and bloodstream infections (e.g., caused by *Staphylococcus aureus*) can all lead to sepsis. Sepsis can cause multiple organ failures, such as acute kidney injury and respiratory failure. In severe cases, sepsis can also affect cardiac function and hepatic metabolism, further exacerbating the severity of the condition (Jacobi, 2022). Sepsis is highly prevalent, with complex pathogenic mechanisms and is a major cause of critical death, especially in elderly patients. A survey analysis report covering data from multiple countries shows that there are approximately 50 million cases of sepsis worldwide each year, with a case fatality rate as high as 46.4%. The incidence of sepsis peaks in early childhood and there is a second peak in the elderly population (Rudd *et al*., 2020). Some scholars believe that the main components of its pathophysiology are excessive inflammation, coagulation dysfunction and the involvement of platelets in both components (Chiu and Legrand, 2021; Nedeva, 2021). Platelets play a key role in hemostasis and thrombosis; in addition, when activated, platelets help host defense against infection by producing neutrophil extra cellular traps to capture bacteria (such as *Streptococcus pneumoniae* and *Staphylococcus aureus*). Platelet activation at sites of inflammation impairs microcirculatory flow, causes mild coagulation disorders or even severe disseminated intravascular coagulation, and is involved in the development of multiple organ dysfunction syndrome (Li *et al*., 2024). Decreased microcirculation platelet counts are frequently observed in patients with sepsis, which is a strong predictor of morbidity and mortality. The antiplatelet agent aspirin inhibits platelet over activation and attenuates uncontrolled inflammatory and coagulant responses in sepsis, making it a potential prophylactic and therapeutic tool (Gonzalez *et al*., 2022; Santos-Gallego and Badimon, 2021). A series of preclinical animal and human studies have now affirmed the beneficial effects of aspirin; e.g., Halushka *et al* (1981) demonstrated a significant 24-hour survival benefit when different concentrations of aspirin were given as pretreatment 30 minutes prior to the injection of Salmonella endotoxin to induce septic shock in rats. The findings from a randomized controlled trial conducted by Leijet *et al*. (2019) showed that low-dose aspirin therapy increased the body's tolerance to endotoxin. However, there has been debate concerning the effectiveness of aspirin in treating sepsis patients. Moreover, a systematic assessment of aspirin's impact on the treatment of elderly inpatients with sepsis is currently lacking. Therefore, to give a reference for clinical medical care, this study used meta-analysis to assess the effect of aspirin on elderly patients with sepsis.

Information and methods

Patient selection and exclusion criteria

Patient selection criteria: (1) Type of study: Cohort studies, case-control studies and randomized controlled trials (RCTs) with the restriction that the language be English; (2) Study subjects: Meeting the diagnostic criteria for sepsis in the International Sepsis Guidelines (Evans *et al*., 2021) and aged ≥60 years; (3) Interventions: Interventions were explicitly defined as the

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use of aspirin and controls were defined as the absence of aspirin or the use of placebo; (4) Outcome indicators: ICU mortality, in-hospital mortality, 30d mortality, 90d mortality, incidence of organ failure, length of ICU stay, and incidence of bleeding events.

Criteria for Exclusion: (1) literature such as reviews, dissertations, conference articles, clinical cases, systematic evaluations, and animal experiments; (2) literature that did not explicitly indicate that the drug used was aspirin; and (3) literature with incomplete or unavailable data that could not be extracted and converted and for which contacting the authors was unsuccessful; (4) duplicate publications; (5) literature that did not contain relevant outcome metrics or had poor outcome metrics; and (6) non-English language literature with poor article quality (score <4).

Literature retrieval

Electronic search of Medline, Web of Science, Embase, Cochrane Library and PubMed. Year of search: Built to June 2024. Using a combination of MeSH terms and free-text words, including "Sepsis," "Bloodstream Infection," "Aspirin," "Acetylsalicylic Acid" and so on. "Acetylsalicylic Acid" and so on. Taking the PubMed database as an illustration, the specific search strategy is presented below:

(Bloodstream Infection [Title/Abstract]) OR (Bloodstream Infections[Title/Abstract])) OR (Infection, Bloodstream[Title/Abstract]) OR (Septicemia [Title/ Abstract]) OR (Septicemias[Title/Abstract]) OR (Blood Poisoning[Title/Abstract])) OR (Blood Poisonings [Title/ Abstract]) OR (Poisonings, Blood[Title/Abstract]) OR (Poisoning, Blood[Title/Abstract]) OR (Severe Sepsis [Title/ Abstract])) OR (Sepsis, Severe [Title/Abstract]) OR (Pyemia [Title/Abstract]) OR (Pyemias [Title/Abstract]) OR (Pyaemia[Title/Abstract]) OR (Pyaemias [Title/ Abstract]) OR (Pyohemia [Title/ Abstract]) OR (Pyohemias[Title/Abstract]) OR ("Sepsis"[Mesh]) AND (("Aspirin"[Mesh]) OR (2-(Acetyloxy)benzoic Acid) OR (Acetylsalicylic Acid) OR (Acid, Acetylsalicylic) OR (Solprin) OR (Polopirin) OR (Solupsan) OR (Easprin) OR (Zorprin) OR (Acetysal) OR (Acylpyrin) OR (Colfarit) OR (Ecotrin)) OR (Endosprin) OR (Magnecyl) OR (Micristin) OR (Polopiryna) OR (Aloxiprimum) OR (Dispril)

Literature screening and data extraction

Two researchers extracted the literature that satisfied the requirements based on the inclusion and exclusion criteria, and the screening results were cross-checked. In cases of disagreements, a third researcher was consulted to decide whether the disputed literature should be included in the study following the discussion. Data were extracted from the final included literature, including (1) study information: the name of the first author, the date of publication, the design of the study and study duration; (2) baseline information: Number of participants, gender, and age and (3) outcome data such as mortality, incidence of organ failure, length of ICU stay and incidence of bleeding events.

Literature quality assessment

Literature where the type of study was a cohort study was assessed for quality utilizing the Newcastle-Ottawa scale (NOS) (Stang, 2010). The NOS Evaluation Cohort Study consists of three areas: evaluation of the choice of cohorts with and without exposure, similarity between the two groups, and outcomes, with a total score of 9 on the scale, with scores of 0-4 denoting low-quality studies, 5-6 indicating moderate-quality and 7 or higher signifying high-quality literature. The quality of the included randomized controlled trial literature was evaluated using the Risk of Bias Assessment Tool developed by the Cochrane Collaboration. The scoring consisted of 7 aspects: (1) the method of generating the randomized sequence; (2) whether the allocation was concealed; (3) whether a double-blind method was used; (4) blinding in the assessment of outcomes; (5) completeness of the outcome data; (6) whether the reporting was selective; and (7) other bias, and the risk of bias was specifically assessed in terms of "low, high and uncertain." Specifically, assess the degree of risk of bias. The assessment was carried out separately by two researchers at the same time and in case of disagreement during the final check, a third researcher intervened in the discussion until the final harmonization of the literature scores.

STATISTICAL ANALYSIS

Data analysis was conducted using Stata 12.0. Standardized mean deviation (SMD) and associated 95% confidence intervals (95% CI) were used to express continuous variables, while the ratio of ratios (OR) and its 95% CI were used to express categorical variables. Prior to meta-analysis, the existence of heterogeneity among the included literature was first determined by using the I^2 value and the x^2 test; if $P>0.10$ or $I^2<50\%$, it suggests a lack of significant statistical heterogeneity, and the fixed-effects model could be applied; if $P\leq0.10$ and $I^2\geq50\%$, it suggests that heterogeneity was large among the enrolled publications, and the random effect model was used for analysis, and the sources of heterogeneity were further analyzed. Sensitivity analyses assessed the stability of the combined results by subtracting one study at a time to determine the potential impact of individual studies on overall risk. To check for publication bias, Egger's linear regression and Beggs' test were employed. $P<0.05$ was used to determine the statistical significance of differences.

RESULTS

Results of literature screening

Overall 5608 documents were retrieved through relevant databases and after screening and elimination in

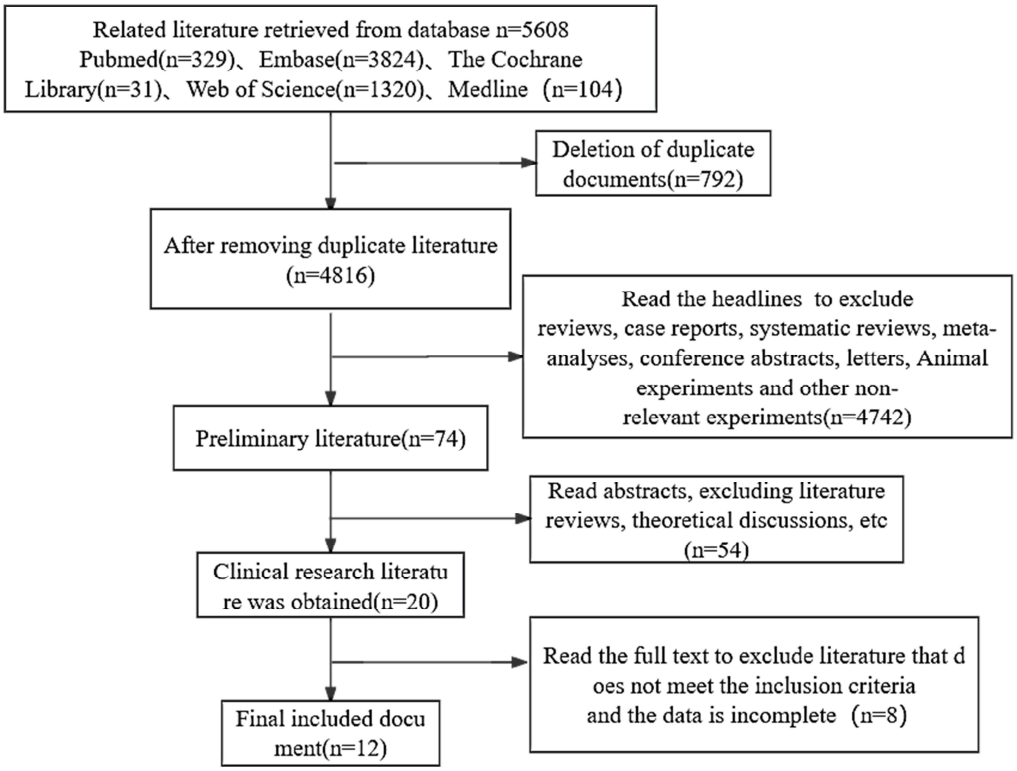

Fig. 1: Literature screening process

accordance with the inclusion as well as exclusion criteria, 12 eligible documents were ultimately included [10-21] and fig. 1 illustrates the literature screening procedure.

Basic information on included studies

An overall of 12 papers (Wiewe *et al*., 2016; Valerio-Rojas *et al*., 2013; Hsu *et al*., 2022; Chen *et al*., 2023; Wang *et al*., 2023; Campbell *et al*., 2015; Eisen *et al*., 2012; Otto *et al*., 2013; Tsai *et al*., 2015; Al Harbi *et al*., 2016; Sossdorf *et al*., 2013; Eisen *et al*., 2021) were incorporated for meta-analysis after searching and screening, including one from the Netherlands (Wiewe *et al*., 2016), one from the United States (Valerio-Rojas *et al*., 2013), two from China (Chen *et al*., 2023; Wang *et al*., 2023), two from Taiwan, China (Hsu *et al*., 2022; Tsai *et al*., 2015), one from the United Kingdom (Campbell *et al*., 2015) , two from Australia (Eisen *et al*., 2012; Eisen *et al*., 2021), two from Germany (Otto *et al*., 2013; Sossdorf *et al*., 2013) and one from Saudi Arabia (Al Harbi *et al*., 2016). A total of 136,315 study subjects were enrolled, of which 43,210 were treated with aspirin and 93,105 were not treated with aspirin. Eleven of the 12 papers had the type of study as a cohort study and one paper (Eisen *et al*., 2021) was a randomized controlled study. The fundamental features of the incorporated studies are presented in table 1.

Literature quality assessment

The literature chosen for this study is of medium to high quality, according to the results of each literature's quality rating, as indicated in tables 2 and 3.

Meta-analysis results and forest plot

ICU mortality rate

Four studies (2816 samples) (Valerio-Rojas *et al*., 2013; Otto *et al*., 2013; Sossdorf *et al*., 2013; Wiewel *et al*., 2016) mentioned the effect of aspirin on ICU mortality among elderly patients with sepsis; the test for heterogeneity showed P=0.152 and I^2=43.2%, indicating acceptable heterogeneity among the studies; thus a fixed-effects model was utilized for the meta-analysis. The findings indicated that aspirin could decrease the ICU mortality rate among elderly patients with sepsis [OR=0.65, 95% CI: (0.52-0.82)], as depicted in fig. 2. The sensitivity analysis's findings revealed that (fig. 3), the results did not change in direction after the exclusion of any of the literature, which indicated that the results were more stable and reliable.

In-hospital mortality rate

Six studies (41,875 samples) (Eisen *et al*., 2012; Valerio-Rojas *et al*., 2013; Otto *et al*., 2013; Campbell *et al*., 2015; Tsai *et al*., 2015; Al Harbi *et al*., 2016) mentioned the effect of aspirin on in-hospital mortality among elderly patients with sepsis (as the study in Eisen *et al*.

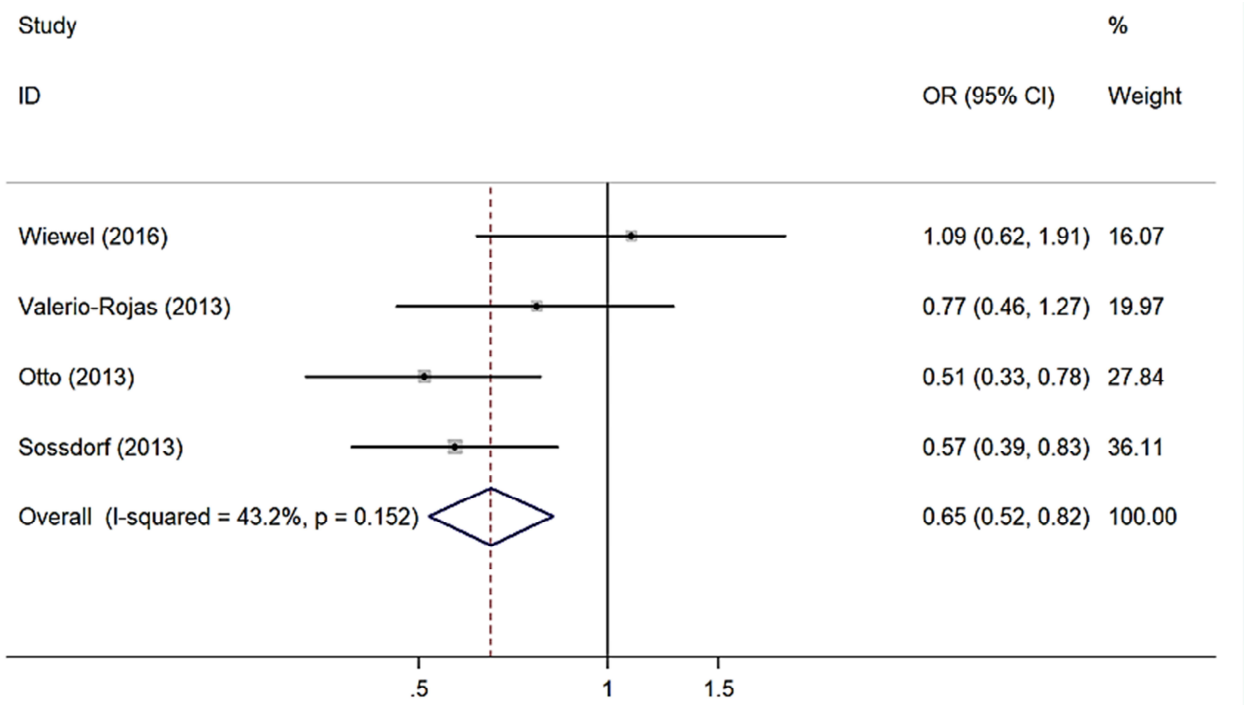

Fig. 2: Aspirin for elderly patients with sepsis forest graph of the influence of ICU mortality

(2021) was a randomized controlled trial, whereas the other studies were cohort studies; they were not included in the results of Eisen *et al*. (2021) to be merged); the test for heterogeneity's results revealed that P=0.102 and I^2=45.5%, indicating acceptable heterogeneity among the studies; thus a fixed-effects model was utilized for the meta-analysis. The results revealed that aspirin was able to decrease in-hospital mortality among elderly patients with sepsis [OR = 0.78, 95% CI:(0.76-0.80)], as illustrated in fig. 4. The results of sensitivity analyses showed (fig. 5) that the results did not undergo a directional change after the exclusion of any of the literature, which indicated that the results were more stable and reliable.

30 d mortality rate

Three studies (37,757 samples) (Wiewel *et al*., 2016; Chen *et al*., 2023; Wang *et al*., 2023) mentioned the effect of aspirin on 30-d mortality among elderly patients with sepsis; the test for heterogeneity showed P = 0.003 and I^2 = 82.6%, suggesting a large heterogeneity among studies, and meta-analysis was conducted employing a random-effects model. The findings demonstrated that aspirin was effective in lowering the 30-day mortality rate among elderly patients with sepsis [OR=0.79, 95% CI:(0.67-0.93)], as illustrated in fig. 6. The results of the sensitivity analysis indicated (fig. 7) that the merged results of the remaining studies did not change after excluding any of the literature, indicating that the results had some stable reliability; however, the heterogeneity was relatively large regardless of which literature was excluded and it was not possible to exclude the source of heterogeneity and the heterogeneity between the three studies may have mainly originated from differences in the databases and methods of data collection, and different databases may have contained different patient populations and data collection criteria, which may lead to differences in results.

90d mortality rate

Three studies (37,757 samples) (Wiewel *et al*., 2016; Hsu *et al*., 2022; Chen *et al*., 2023) mentioned the effect of aspirin on 90-d mortality among elderly patients with sepsis; the test for heterogeneity showed P < 0.001 and I^2 = 92.2%, suggesting a large degree of heterogeneity among studies, and meta-analysis was conducted employing a random-effects model. The findings demonstrated that aspirin was able to decrease 90-day mortality among elderly patients with sepsis [OR=0.81, 95%CI: (0.67-0.99)], as illustrated in fig. 8. The sensitivity analysis's findings indicated (fig. 9) that the study by Hsu *et al*. (2022) was the primary source of the heterogeneity, which derived its data from the National Health Insurance Research Database (NHIRD) in Taiwan, spanning the years 2001 to 2011, with a larger sample size, and which contained detailed data on Taiwan's universal health insurance program, which may have provided a wider and more diversified patient population, unlike other studies where data were derived from hospital ICU records or specific databases. After removing the study of Hsu *et al*. (2022) from the forest plot, I^2=0.0%, P=0.514, there was no significant heterogeneity in the literature; therefore, the fixed effect model was chosen for analysis, while the results showed that aspirin could reduce the 90d morbidity and mortality rate of elderly patients suffering from sepsis [OR=0.73, 95% CI:(0.67-0.79)], as shown in fig. 10.

Table 1: Fundamental traits of the literatures that are included

Number	First author	Published year	Research time	Number of included studies/cases	Sample size (T/C, cases)	Gender (T/C, Male/female)	Mean age (T/C)	Timing of Intervention	Primary outcome
1	Wiewel	2016	2011-2013	300	150/150	(91/59)/(96/54)	66.1/65.7	Before admission to ICU	①③④⑤⑥
2	Valerio-Rojas	2013	2007-2009	651	272/379	(160/112)/(202/177)	74.3/65.8	Upon admission to ICU	①②⑤⑥
3	Hsu	2022	2001-2011	51857	12776/39081	(7419/5357)/(23110/15971)	74.42/65.35	Before admission	④⑤
4	Chen	2023	2008-2019	7694	3847/3847	(2174/1673)/(2157/1717)	69.54/69.04	During hospitalization	③④⑥⑦
5	Wang	2023	2001-2012	33610	8571/25039	(5334/3237)/(13897/11142)	68.65/61.56	Upon admission to the ICU	③
6	Campbell	2015	2013-2015	139	12/127	(6/6)/(60/67)	69.95/70.59	Before admission to ICU	②
7	Eisen	2012	2000-2009	970	165/805	(110/55)/(539/266)	65.65/66.32	24 hours after onset of illness	②⑦
8	Otto	2013	-	886	190/696	-	68.65/62.60	Duration of ICU stay (at least 2 days)	①②
9	Tsai	2015	2000-2010	39035	17087/21948	(9346/7741)/(12115/9833)	74.4/66.1	During hospitalization	②
10	Harbi	2016	2004-2008	194	47/147	-	65	Upon ICU admission	②
11	Sossdorf	2013	-	979	93/886	(76/17)/(573/313)	60.30/66.30	During hospitalization	①
12	Eisen	2021	2010-2014	616	-	-	≥70	Before admission	②

Note: ① ICU mortality, ② In-hospital mortality, ③ 30-day mortality, ④ 90-day mortality, ⑤Incidence of organ failure, ⑥Length of ICU stay, ⑦Bleeding Events, T: Aspirin group, C: non-Aspirin group。

Table 2: The NOS scores of the cohort study literature

Docu	Study population selection				Comparability between groups	Outcome measurement			Total points
	Representativeness of the exposed group	Selection of non-exposed groups	Identification of exposure factors	No outcome indicators were available before the study began	Comparability of the resulting cohort based on design and analysis	Methods of evaluating outcome events	Whether the follow-up time was sufficient	Integrity of follow-up	
Wiewel *et al.* (2016)	1	1	1	1	2	1	1	0	8
Valerio-Rojas *et al.*(2013)	1	1	1	1	1	1	1	1	8
Hsu *et al.* (2022)	1	1	1	1	1	1	1	1	8
Chen *et al.* (2023)	1	1	1	1	1	0	1	1	7
Wang *et al.* (2023)	1	1	1	1	1	1	1	0	7
Campbell *et al.* (2015)	0	1	1	1	0	1	1	1	6
Eisen *et al.* (2012)	1	1	1	1	1	1	1	0	7
Otto *et al.* (2013)	1	1	1	1	0	1	1	0	6
Tsai *et al.* (2015)	1	1	1	1	0	1	1	1	7
Harbi *et al.* (2016)	1	1	1	1	1	1	1	1	8
Sossdorf *et al.* (2013)	1	1	1	1	0	1	1	1	7

Table 3: Assessment of the quality in randomized controlled trials

Docu	Generation of random sequences	Allocation hiding	Participants and research method of blind	Results in the reviewers blinded	Completeness of outcome measures	Selective reporting	Other sources of bias
Eisen *et al.* (2021)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Not clear

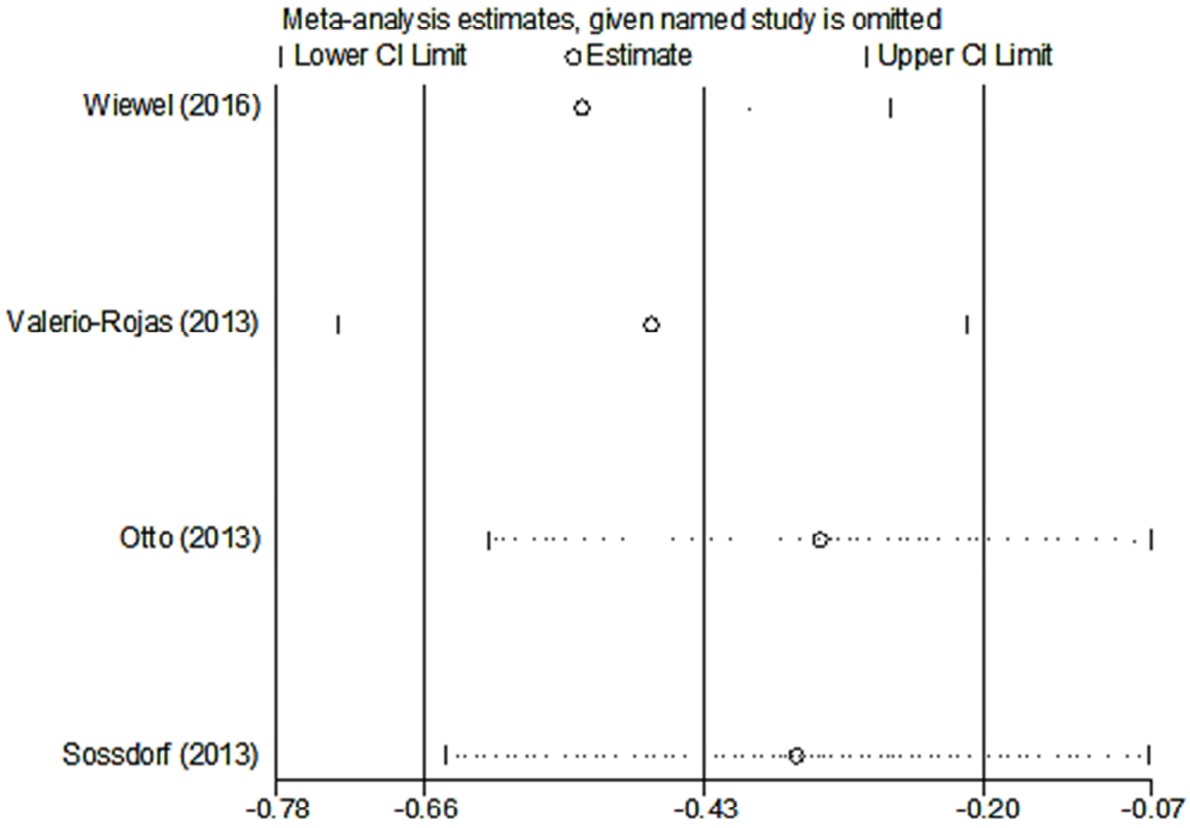

Fig. 3: Sensitivity analysis of pooled results of meta-analyses of the effects of aspirin on ICU mortality

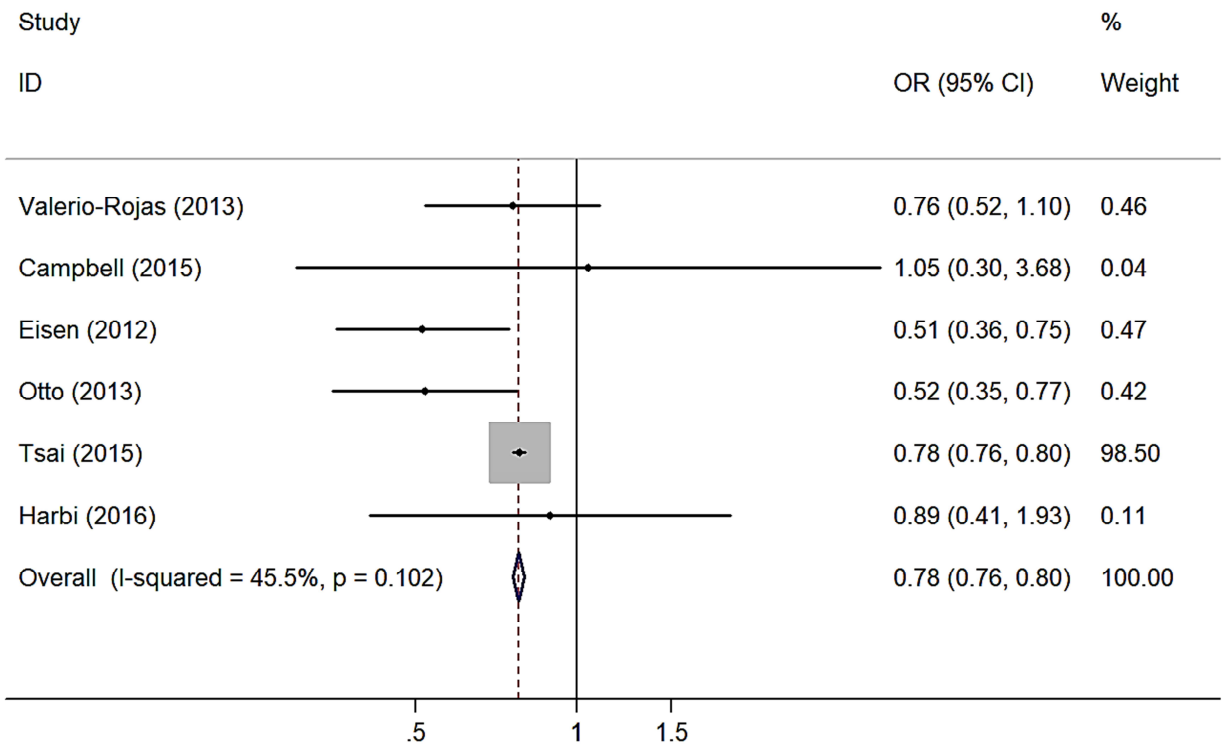

Fig. 4: Forest plot of the effect of aspirin on in-hospital mortality in elderly patients with sepsis

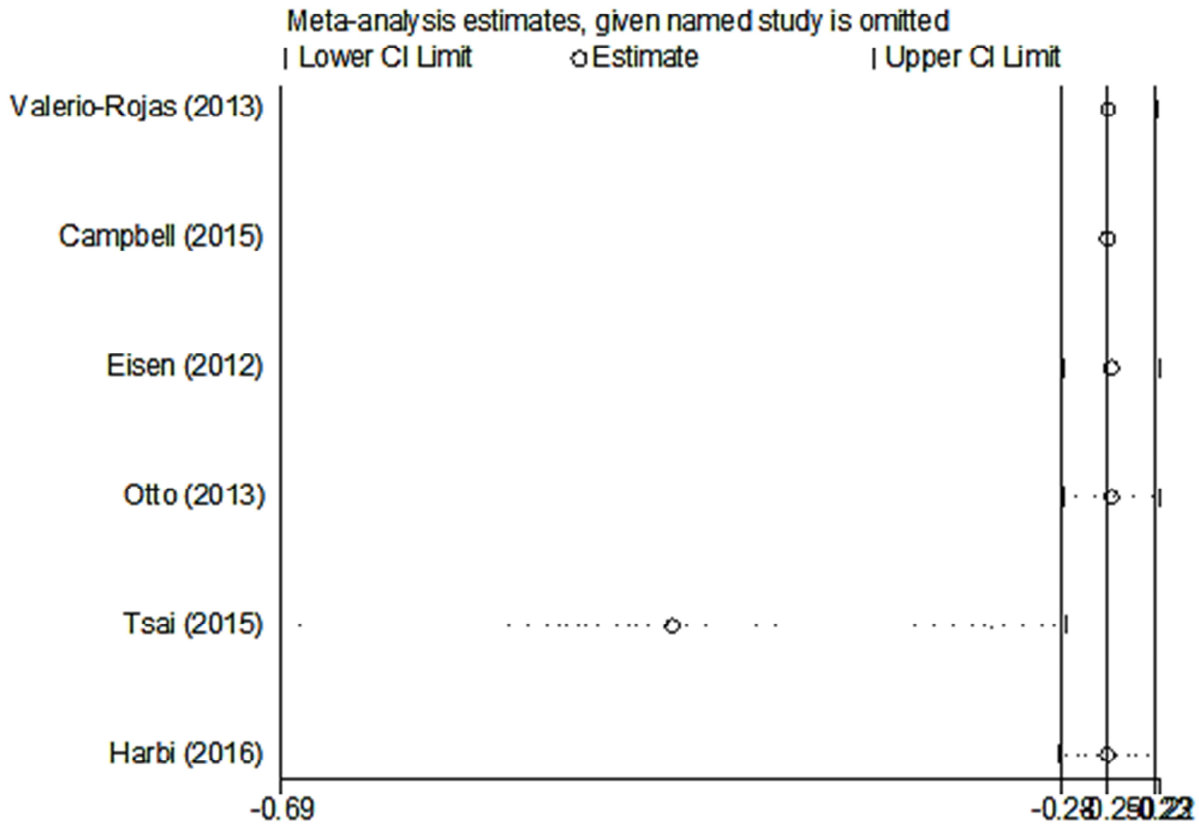

Fig. 5: Sensitivity analysis of pooled results of meta-analysis on the effect of aspirin on in-hospital mortality

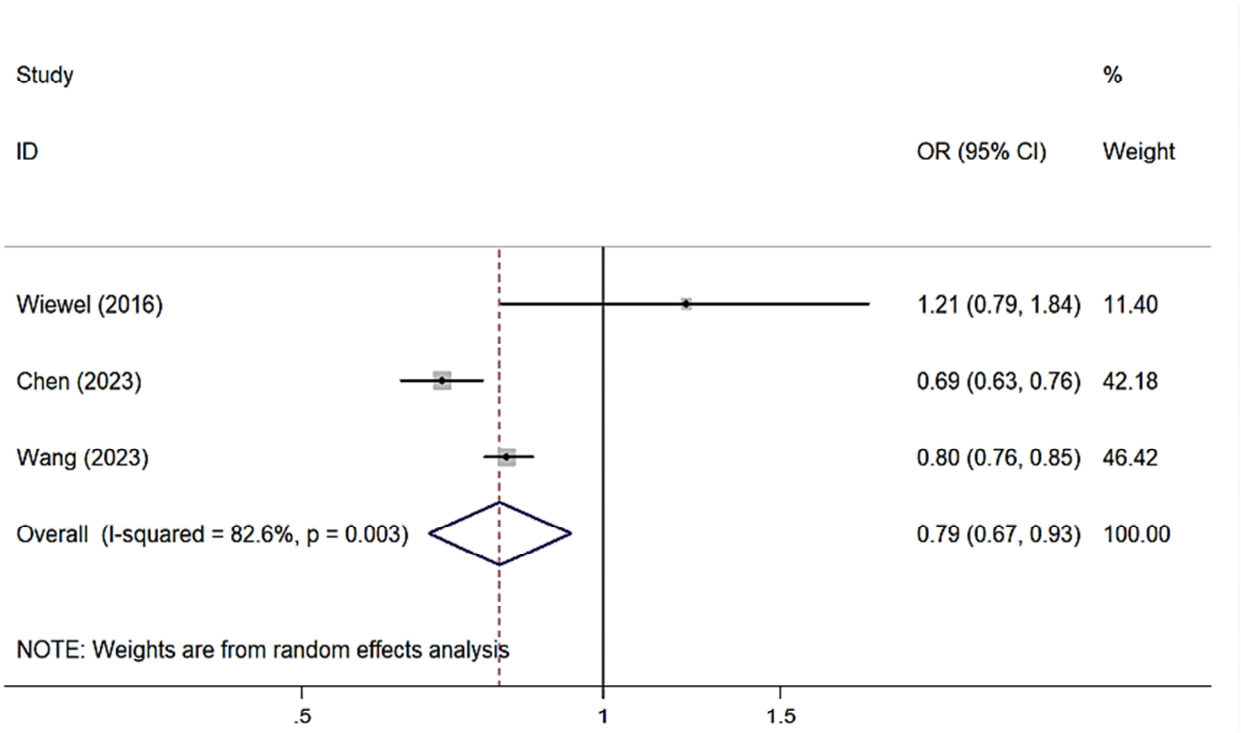

Fig. 6: Forest map of the effect of aspirin on 30-day mortality in elderly patients with sepsis

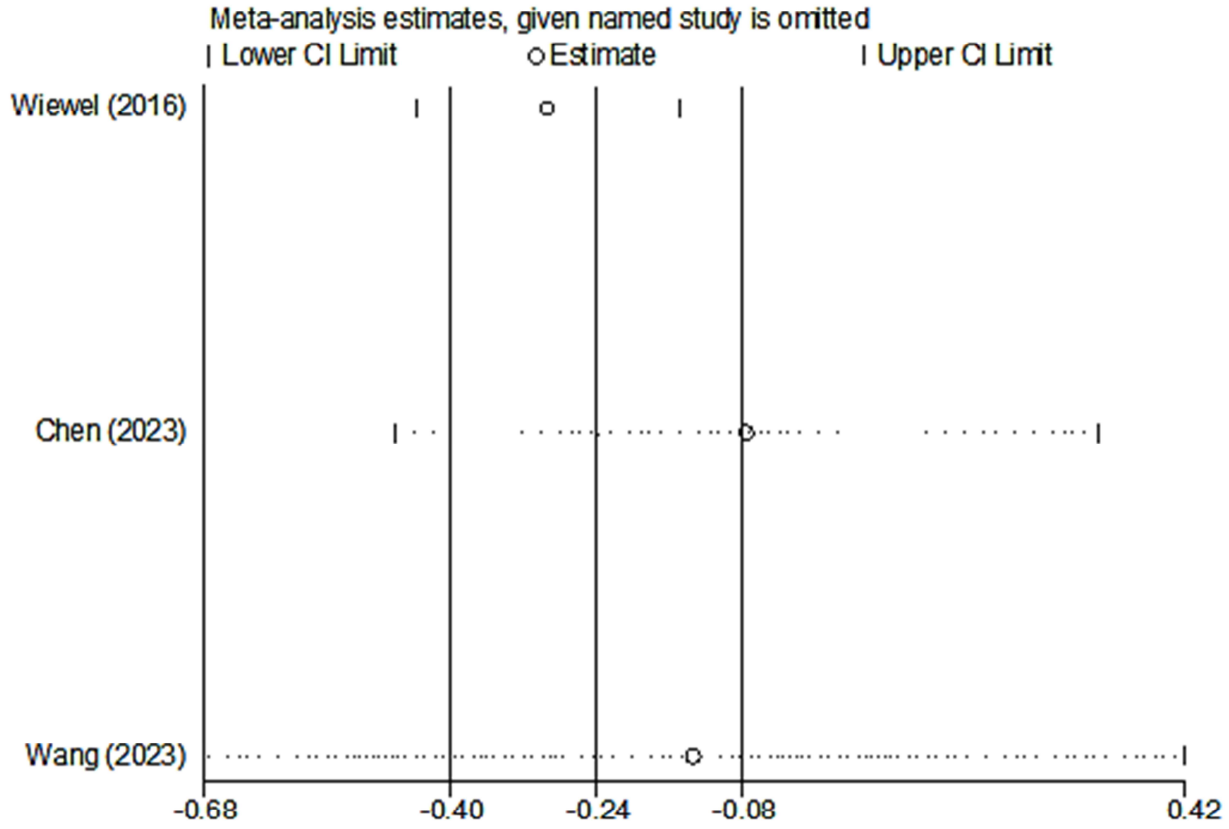

Fig. 7: Meta-analysis of the effect of aspirin on 30 d mortality Sensitivity analysis of combined results

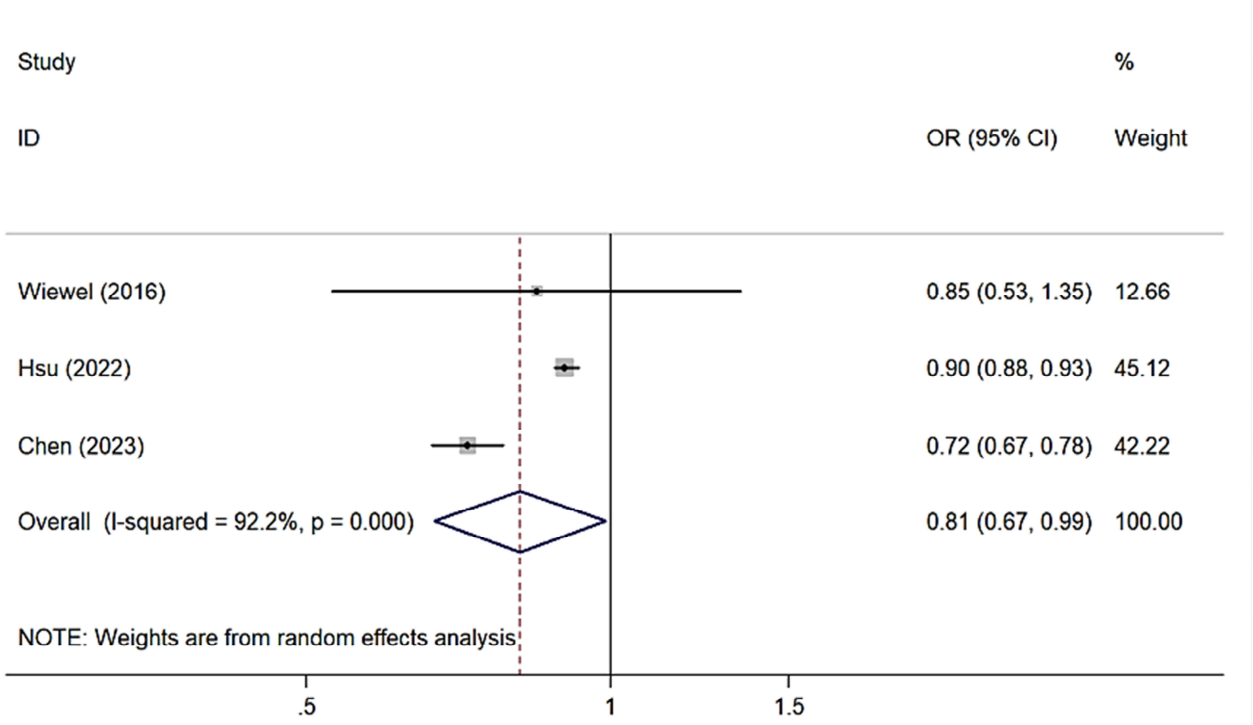

Fig. 8: Forest plot of the effect of aspirin on 90 d mortality in elderly septic patients

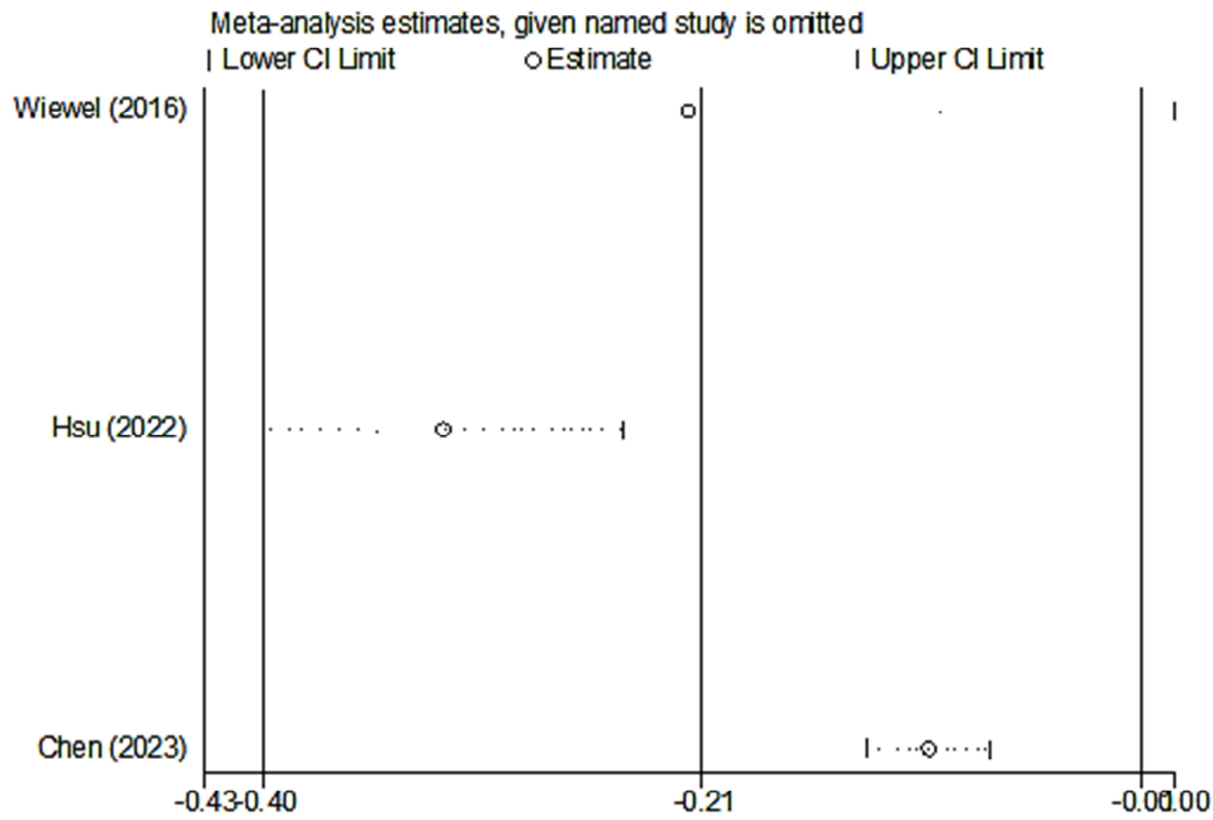

Fig. 9: Meta-analysis of the effect of aspirin on 90 d mortality Sensitivity analysis of combined results

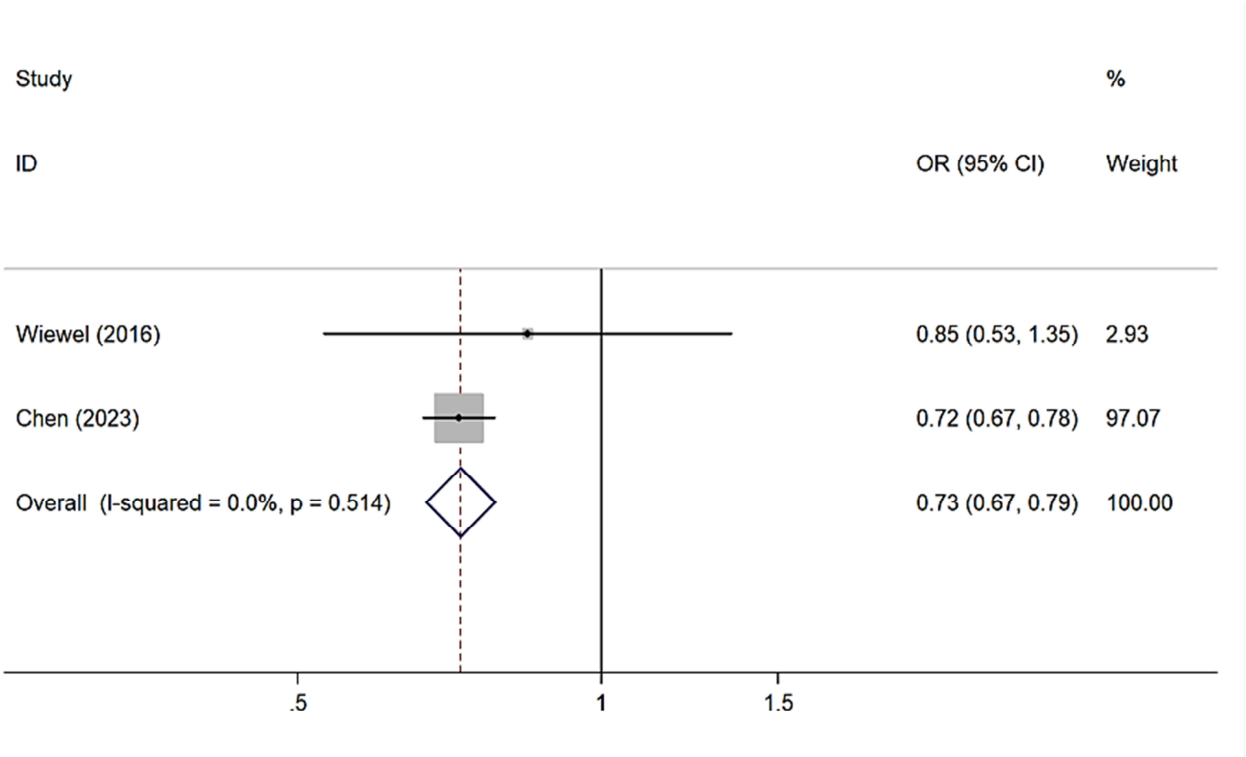

Fig. 10: Forest plot of the effect of aspirin on 90-d mortality in elderly septic patients after removal of the Hsu *et al.*

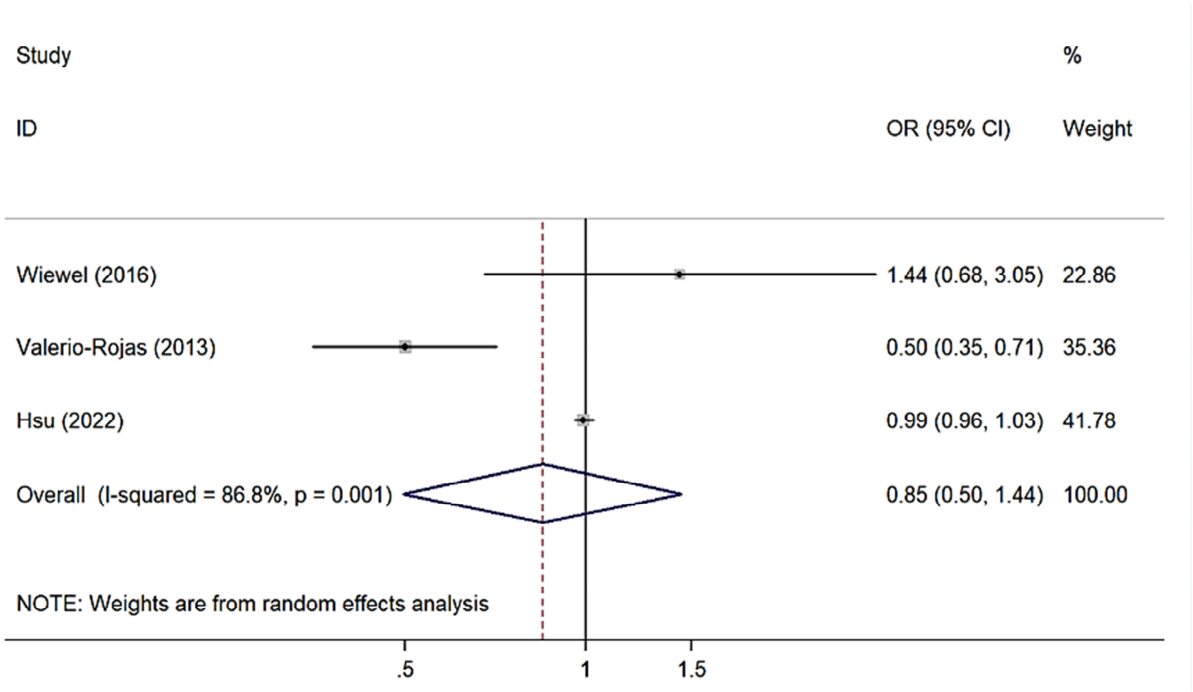

Fig. 11: Forest plot of the effect of aspirin on the incidence of organ failure in elderly septic patients

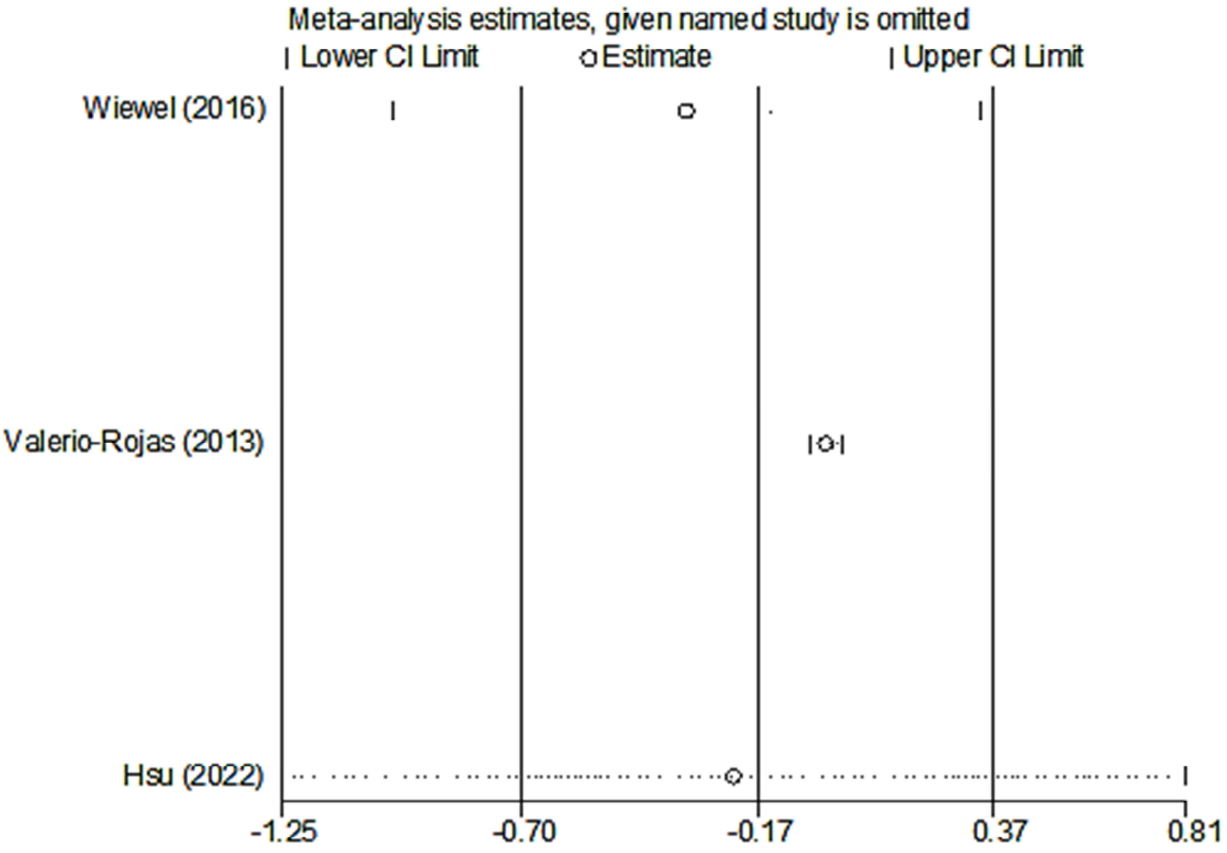

Fig. 12: Meta-analysis of the effect of aspirin on the incidence of organ failure Sensitivity analysis of the combined results

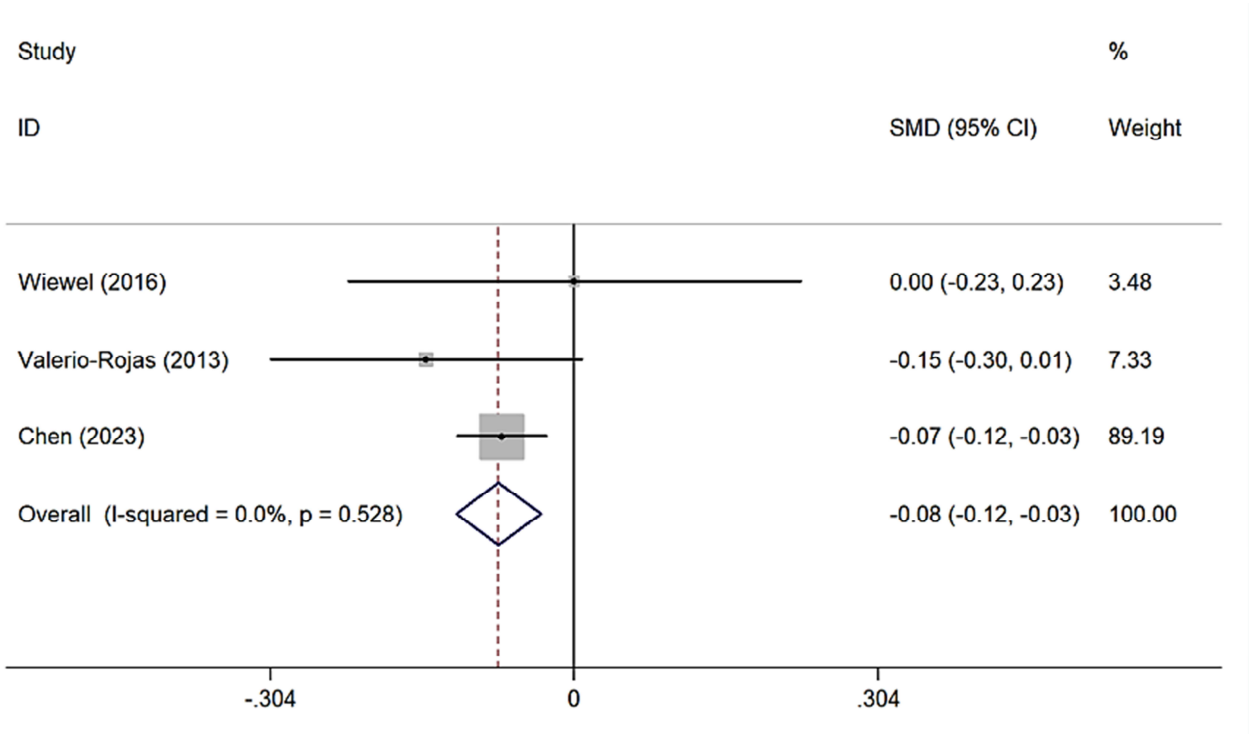

Fig. 13: Forest plot of the effect of aspirin on ICU length of stay in elderly septic patients

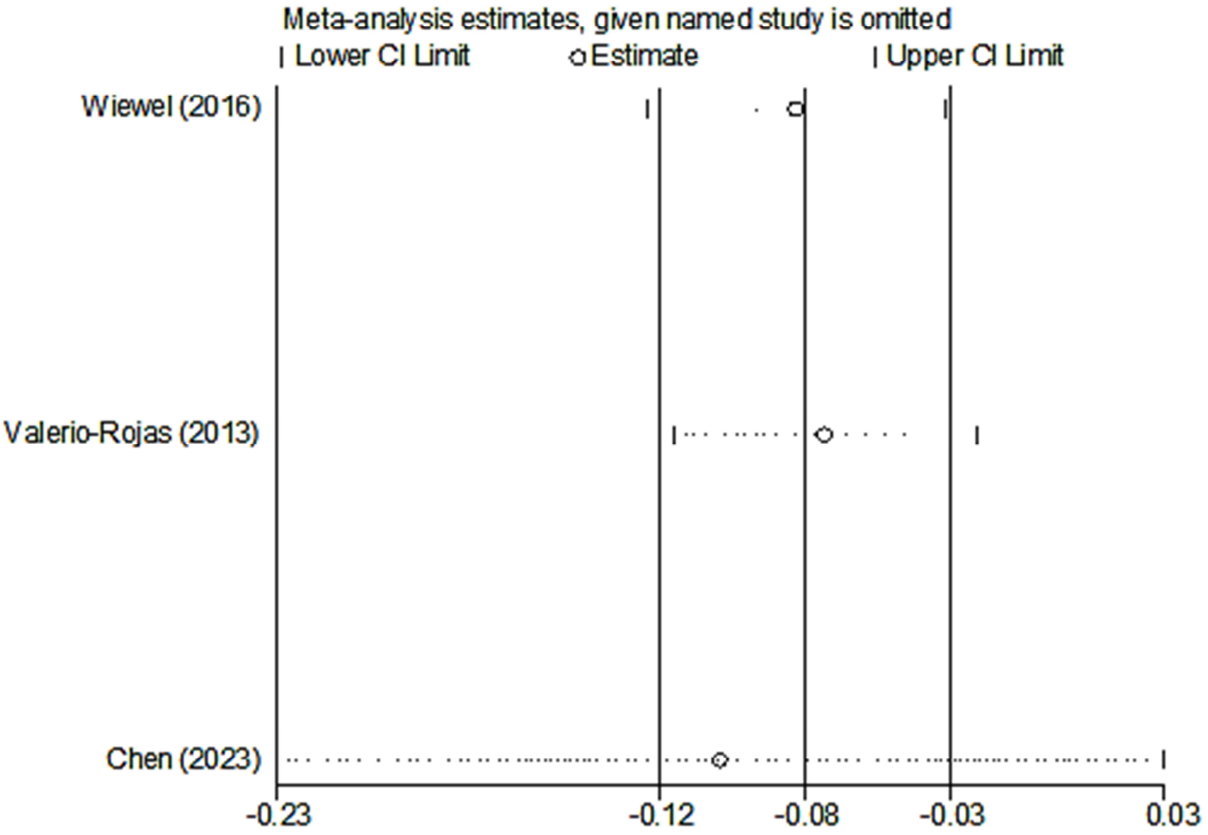

Fig. 14: Meta-analysis of the effect of aspirin on length of stay in the ICU Sensitivity analysis of combined results

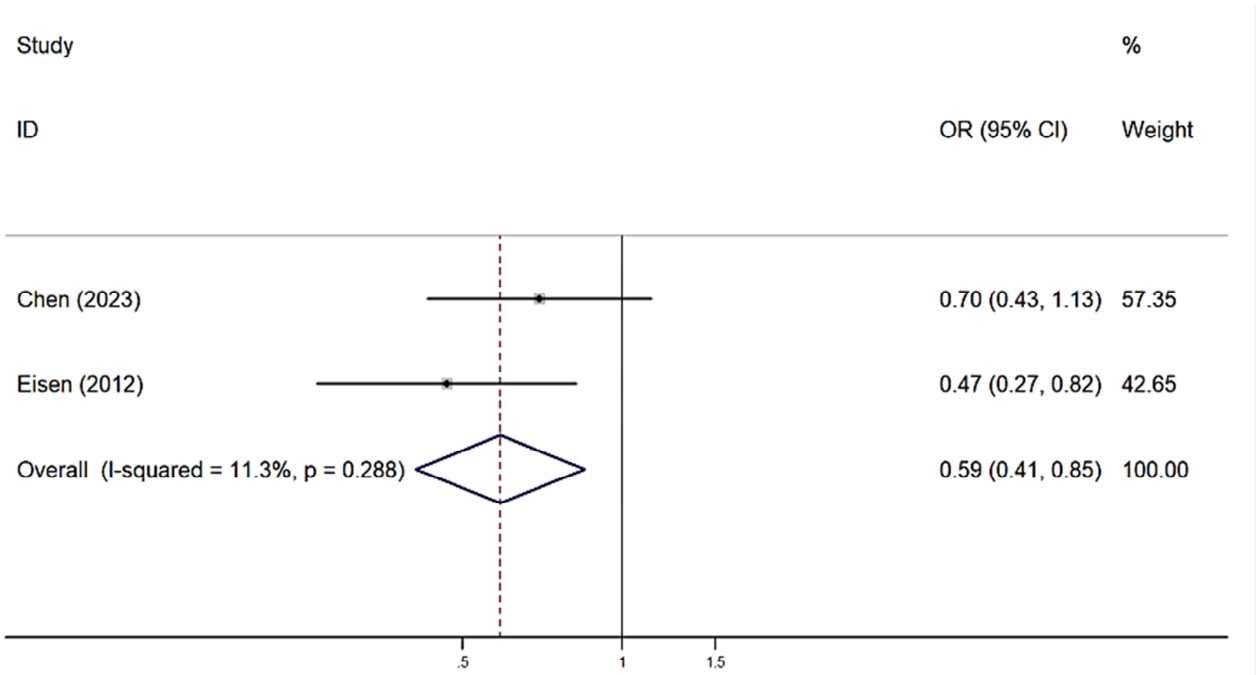

Fig. 15: Forest plot of the effect of aspirin on gastrointestinal bleeding in elderly septic patients

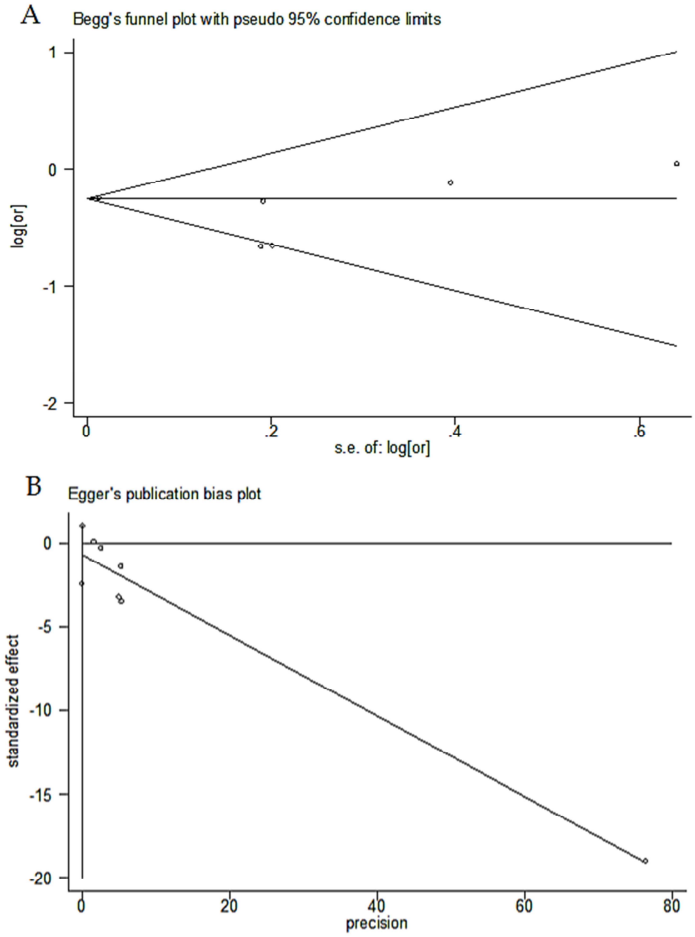

Fig. 16: Begg's anecdotal correlation test and Egger's linear regression test for the effect of aspirin therapy on in-hospital mortality in elderly patients with sepsis (A: results of Begg's anecdotal correlation test; B: results of Egger's linear regression test)

Incidence of organ failure

Three studies (52,808 samples) (Valerio-Rojas *et al*., 2013; Wiewel *et al*., 2016; Hsu *et al*., 2022) reported the impact of aspirin on the incidence of organ failure among elderly individuals with sepsis; the test for heterogeneity showed $P < 0.001$ and $I^2 = 86.8\%$, suggesting that there was a high degree of heterogeneity among studies, and meta-analysis was conducted employing a random-effects model. The findings demonstrated that aspirin therapy did not improve the incidence of organ failure in elderly patients with sepsis [OR=0.85, 95% CI: (0.50-1.44)], as detailed in fig. 11. The sensitivity analysis's findings indicated (fig. 12) that after removing any of the literature, the results did not change in direction, which indicated that the results were more stable and reliable.

Length of stay in ICU

Three studies (2816 samples) (Valerio-Rojas *et al*., 2013; Wiewel *et al*., 2016; Chen *et al*., 2023) reported the effect of aspirin on ICU length of stay in elderly patients with sepsis; the test for heterogeneity showed P=0.528 and I^2=0.0%, indicating no heterogeneity among the studies, thus a fixed-effects model was used for the meta-analysis. The findings demonstrated that aspirin could shorten the length of ICU stay in elderly septicemic patients [SMD=-0.08, 95% CI: (-0.12 to -0.03)], as specified in fig. 13. The sensitivity analysis's findings revealed (fig. 14) that after most of the literature had been excluded, the results did not change in direction, suggesting a certain degree of stability and reliability in the results.

Incidence of bleeding events

Two studies (8664 samples) (Eisen *et al*., 2012; Chen *et al*., 2023) reported the impact of aspirin on the incidence of bleeding events among elderly individuals with sepsis; the test for heterogeneity showed P =0.288 and I^2 =11.3%, indicating acceptable heterogeneity among the studies; thus a fixed-effects model was utilized for the meta-analysis. The findings demonstrated that aspirin could reduce the incidence of bleeding events among elderly patients with sepsis [OR=0.59, 95% CI: (0.41-0.85)], as shown in fig. 15.

Publication bias analysis

The articles' risk of bias was assessed using Begg's test and Egger's test. The results showed that the P value of the Egger's and Begg's test results for all outcome indicators was greater than 0.05, which indicated that there was little chance of publication bias and the results were more stable, and the results of the Begg's test (fig. 16A) and the Egger's test (fig. 16B) of the nosocomial mortality rate in the following fig. were used as an example to analyze the article bias.

DISCUSSION

This study comprehensively analyzed the effect of aspirin on elderly sepsis, and the results showed that aspirin not only reduced the mortality rate (including ICU, in-hospital, 30d and 90d mortality) of elderly sepsis patients but also reduced the length of stay in the ICU. The findings of this paper are also supported by a systematic evaluation that included 10 observational studies (Ouyang *et al*., 2019). The possible mechanisms for the benefit of aspirin therapy in elderly patients suffering from sepsis are (1) inhibition of cyclooxygenase (COX). COX-1 promotes platelet activation and aggregation through the production of thromboxane A2, which is a feature of sepsis (Bruno *et al*., 2023). COX-2 expression is increased under the stimulation of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and lipopolysaccharide, leading to increased production of prostaglandin E2, which promotes the production of inflammatory factors and mediates edema formation (Pan *et al*., 2022). Aspirin acetylates COX, which in turn inhibits the conversion of membrane phospholipid-derived arachidonic acid to thromboxane A2 and prostaglandins (Kolawole *et al*., 2022). (2) Blocking the activation of the nuclear transcription factor -κB (NF-κB). Aspirin can inhibit the activation of NF-κB through NF-κB inhibitory protein kinase and decrease the transcription of TNF-α as well as IL-6, thereby attenuating the inflammatory response (Sokołowska *et al*., 2024). (3) Promotion of lipoxin production. In animal and human trials, low doses of aspirin were shown to increase the synthesis of aspirin-triggered lipoxins (ATLs) (Arita *et al*., 2005; Khoshbin *et al*., 2023). In sepsis, ATLs may promote inflammation reduction through mechanisms including inhibition of neutrophil activation and aggregation, reduction of inflammatory factor release and increased phagocytosis of apoptotic neutrophils by macrophages (Rood *et al*., 2023). (4) Promotion of nitric oxide (NO) synthesis. Aspirin acetylates endothelial-type nitric oxide synthase proteins, which in turn leads to endothelial production and release of NO. NO inhibits platelet aggregation and leukocyte adhesion, as well as vasodilates blood vessels and inhibits micro thrombosis in septic states (Dony *et al*., 2023).

Most of the current studies confirm the benefits of aspirin in the treatment of sepsis, but there are some studies with inconsistent results, such as the observational study by Wiewel *et al*. (2016), which was included in the studies analyzed in this paper, which reported that aspirin did not have an ameliorative effect in elderly sepsis patients. As for the timing of aspirin administration, because there weren't many studies included in this analysis, the pooled effect size of each outcome indicator was insufficient, so a "timing-effect analysis of administration" could not be conducted. However, the randomized controlled experiment results of Eisen *et al*. (2021) suggest that aspirin cannot be used as a primary prevention strategy for sepsis in people over 70 years of age. In line with this, the results of a study by Leijte *et al*. (2019) showed that treatment with low-dose aspirin rather than prophylaxis

reversed endotoxin tolerance in humans. At the same time, patients receiving antiplatelet therapy should be closely monitored for bleeding events. Chen *et al*. (2023) and Eisen *et al*. (2012) recorded bleeding events; however, they did not discover that the aspirin group experienced a higher frequency of bleeding events. Paradoxically, the results of this meta-analysis indicated that patients using aspirin had a reduced probability of bleeding, which Eisen *et al*. (2012) suggested might be due to the timely stopping of aspirin in patients with a propensity for bleeding. However, due to the paucity of studies reporting related bleeding events, further clinical studies are needed to explore whether receiving aspirin therapy has an impact on the occurrence of bleeding events in elderly septic patients.

Limitations of this study: (1) it is difficult to completely exclude influences other than aspirin; (2) the included studies differed in terms of interventions, which may add to the sources of heterogeneity; (3) only one clinical RCT was included, unable to be analyzed combined. Results need further confirmation due to a lack of large prospective RCTs.

CONCLUSION

In conclusion, aspirin treatment in elderly sepsis patients can reduce mortality (including ICU, in-hospital, 30-d, and 90-d mortality) and shorten ICU stay to some extent. It doesn't improve organ failure incidence. Bleeding events aren't increased, but further studies are needed on its impact on bleeding in elderly septic patients.

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