Original Article

Association and predictive value of soluble thrombomodulin with mortality in patients with acute respiratory distress syndrome: systematic review and meta-analysis

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Background: Acute respiratory distress syndrome (ARDS) is a heterogeneous illness that has a high mortality rate. The role and predictive value of soluble thrombomodulin (sTM) in ARDS mortality is disputable, so the present study aimed to evaluate the association and predictive value of sTM for the in-hospital mortality of ARDS.

Methods: PubMed, Web of Science, Embase, Cochrane Library, Chongqing VIP, WanFang, China National Knowledge Infrastructure (CNKI), and Chinese Biomedical Literature databases were searched for relevant literature published before October 10, 2022. Relevant observable studies were included for analysis. The Newcastle-Ottawa Scale and QUAPAS (Quality Assessment of Prognostic Accuracy Studies) were employed to appraise the quality of the included studies.

Results: Thirteen articles were included in the present study. The eligible studies were of moderate to high quality [Newcastle-Ottawa Scale (NOS) 5-8 scores], and the high risk of bias in the included studieson predictive value was mainly distributed in participant and analysis domains of QUAPAS. There were 1,992 patients with ARDS, and 538 died. Our meta-analysis demonstrated that nonsurvivors had more significantly increased sTM levels than did survivors [standardized mean difference (SMD) =1.473; 95% CI: 0.874–2.072; P<0.001]. Elevated sTM levels had an independent correlation with higher mortality in patients with ARDS [pooled odds ratio (OR) =2.126; 95% CI: 1.548–2.920; P<0.001]. sTM showed satisfactory performance in predicting the mortality of ARDS [summary receiver operating characteristic curve (SROC) =0.78; 95% CI: 0.64–0.89]. The pooled sensitivity was 72% (95% CI: 66–77%), and the pooled specificity was 77% (95% CI: 72–82%). Subgroup analysis showed no significant difference in the sTM levels between nonsurvivors and survivors in terms of patients with direct ARDS (SMD =0.813; 95% CI: –0.673 to 2.229; P=0.253).

Conclusions: sTM is associated with hospital mortality in ARDS and shows moderate predictive performance. As a result, it is a potential candidate for predicting the mortality of ARDS. However, caution is needed when sTM is used to predict adverse outcomes in patients with direct ARDS.

Keywords: Acute respiratory distress syndrome (ARDS); thrombomodulin; mortality; meta-analysis

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Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening lung injury characterized by refractory hypoxemia and bilateral pulmonary infiltrates. This syndrome is different from cardiogenic pulmonary edema (1). ARDS accounts for 10.4% of intensive care unit (ICU) admissions, 23.4% of patients on mechanical ventilation, and 21% to 55.7% of hospital deaths (2,3). Early detection of the ARDS patients at a high risk of adverse outcomes is crucial for the risk-stratification and precise treatment of this heterogeneous syndrome (4).

The pathogenesis and progression of ARDS are attributed to pulmonary inflammation, damage to the alveolocapillary membrane, and dysregulation of the coagulation and fibrinolytic systems (5,6). Thrombomodulin (TM), which is highly expressed in pulmonary alveolar capillaries, is an endothelial membrane-bound protein that regulates inflammation and coagulation (7). When TM interacts with thrombin, a TM-thrombin complex is formed to activate protein C, thereby exerting anticoagulatory, anti-inflammatory, and profibrinolytic effects (8). As a major form of circulating TM, soluble TM (sTM) is produced when an intact protein is cleaved under pathologic conditions like cardiovascular diseases, inflammation, infection, and metabolic disorders (9). Hence, elevated sTM levels are associated with endothelial injury, impaired anticoagulation and fibrinolysis, and inflammatory status.

The correlation between sTM and ARDS has been investigated by some researchers, and the results are conflicting. Elevated levels of sTM were observed in nonsurvivors, and/or elevated levels of sTM were independently associated with ARDS mortality (10,11), but this finding was contradictory with other research (12,13). Furthermore, the predictive accuracy of sTM for ARDS hospital mortality was unclear, and mild to moderate predictive value was reported (14,15). The discrepancy may attribute to different measurement methods, study designs or limited sample sizes.

As a result, the present study aimed to probe into the relationship between sTM and hospital mortality in patients with ARDS and evaluate the role and predictive value of sTM in this unfavorable outcome. We present the following article in accordance with the PRISMA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-23-432/rc) (16).

Methods

Search strategy

This study was registered on PROSPERO (International Prospective Register of Systematic Reviews; CRD42022368632). We searched PubMed, Web of Science, Cochrane Library, Embase, Chongqing VIP, WanFang, China National Knowledge Infrastructure (CNKI), and Chinese Biomedical Literature databases for relevant literature published before October 10, 2022. No restrictions were imposed on language or region. Two reviewers (LZ and LY) independently identified all potentially eligible studies. Any disagreements were mediated through a third reviewer (ZQ) for a final determination. Both free words and medical headings were used, including "thrombomodulin", "ARDS", "acute respiration distress syndrome", "acute lung injury", and "acute respiratory failure". The detailed search procedure is depicted in Table S1.

Selection criteria

According to PECOS principle, the studies that met the criteria were eligible. Populations: patients were diagnosed with ARDS or had acute hypoxemic respiratory failure caused by ARDS, with no restrictions on age.ARDS was diagnosed based on the Berlin definition (1), American European Consensus Conference (17), or Pediatric Acute Lung Injury Consensus Conference (18); and international consensus criteria were used to define sepsis (19). Exposure: serum or plasma sTM levels were measured, and the high level of sTM was defined by the cutoff value in the original studies. Control: low level of sTM was defined according to the original studies. Outcome: (I) sTM level in survivors and nonsurvivors with ARDS; (II) the odds ratio (ORs) values of sTM associated with the ARDS mortality; (III) diagnostic four-grid table (true positive, false positive, false negative and true negative) for predicting the ARDS mortality. Study design: the types of included studies were cohort study, cross-sectional study, case control study, and propensity matching study.

We excluded (I) studies with unclear or unreasonable diagnostic criteria for ARDS; (II) studies exploring the association between sTM and outcomes only based on histopathological and genetic levels; (III) the levels of sTM

were not completely reported, or the correlation between sTM and the risk of ARDS mortality was investigated only by univariate analysis, or the diagnostic four-grid table could not be extracted directly or indirectly from the original studies; (IV) conference abstracts without full text, or animal-based studies.

Literature screening and data extraction

All searched studies were imported into the Endnote software (X9.2, Clarivate) for management. After removal of duplicates, we checked the titles and abstracts to eliminate unqualified studies. Finally, the full texts of the remaining articles were downloaded for eligibility assessment. A standard data extraction table was used to collect data from the included studies, including study design, patient characteristics, sTM levels, time-points of sTM measurement, and outcome. The results of data extraction were cross-checked.

Quality evaluation

The Newcastle-Ottawa Scale (NOS) (20) was adopted to evaluate the risk of bias in the included studies except the cross-sectional study by Benatti *et al.* (12), which was assessed by the modified NOS (21). For studies, a score of 7–9 indicated high quality, 4–6 moderate quality, and a 1–3 low quality. QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies), which was developed to evaluate the risk of bias in the studies on diagnostic accuracy, was unsuitable for the studies on prognostic predictive value. The risk of bias in the studies investigating the predictive value of sTM for ARDS mortality was evaluated by QUAPAS (Quality Assessment of Prognostic Accuracy Studies) tool, which is a modification of QUADAS-2 (22). Two reviewers (LZ, LY) independently performed the quality assessment, and a third reviewer (ZQ) was consulted to resolve the discrepancies in the assessment.

Statistical analysis

Due to the variability in detection methods and enzyme-linked immunosorbent assay (ELISA) kits, continuous variables are expressed as the standardized mean difference (SMD). The risk of mortality associated with increased sTM is presented as ORs with 95% confidence intervals (CIs) after adjustment for other confounding factors. Data were pooled by the inverse variance weighting method. The Cochrane Q and Higgins I^2 tests were carried out to assess the heterogeneity. When $P<0.05$ and $I^2>50\%$, there was high heterogeneity. Thus, a random-effects model was employed for statistical analysis, and forest plots were drawn to present the analysis results. Due to the high degree of heterogeneity observed in this study, we carried out subgroup and meta-regression analyses to probe into the cause of heterogeneity. Sensitivity analysis was conducted by excluding noncohort studies and removing one study at a time. A funnel plot and Egger test or Deeks test were employed to determine publication bias. If publication bias was present, the trim-and-fill method was adopted. R version 4.0.3 (The R Foundation for Statistical Computing) was employed for statistical analysis. Stata 13.0 (StataCorp) was adopted for bivariate meta-analyses of pooled sensitivity, specificity, and the summary receiver operating characteristic curve (SROC). A 2-sided $P<0.05$ indicated a statistically significant difference.

Results

Study selection

We retrieved 891 records. After removing 504 duplicates, we examined the titles and abstracts to exclude unqualified studies. Based on a full-text review of 63 articles, we further ruled out 50 articles. Finally, 13 studies were included. The study selection process is shown in *Figure 1*.

Characteristics of the eligible studies

Thirteen studies were included in the study (10-15,23-29). The characteristics of the included studies are presented in *Table 1*. Among the 1,992 patients with ARDS, 538 patients died, and the median mortality was 37.1% (quartile interval 24.3–42.7%). The follow-up duration in the eligible studies was between 28 and 90 days. Children and adults were both included in our study. There were 12 trials, in which sTM was measured using ELISA kits produced by different manufacturers, such as R&D System, Abcam, Diagnostica Stago, and Shanghai Future. Gando *et al.* (28) employed the enzyme immunoassay (EIA) method for sTM detection. The included studies were of moderate to high quality, with NOS scores ranging from 5 to 8.

Difference in the sTM level between survivors and nonsurvivors

Twelve studies reported the sTM levels in nonsurvivors

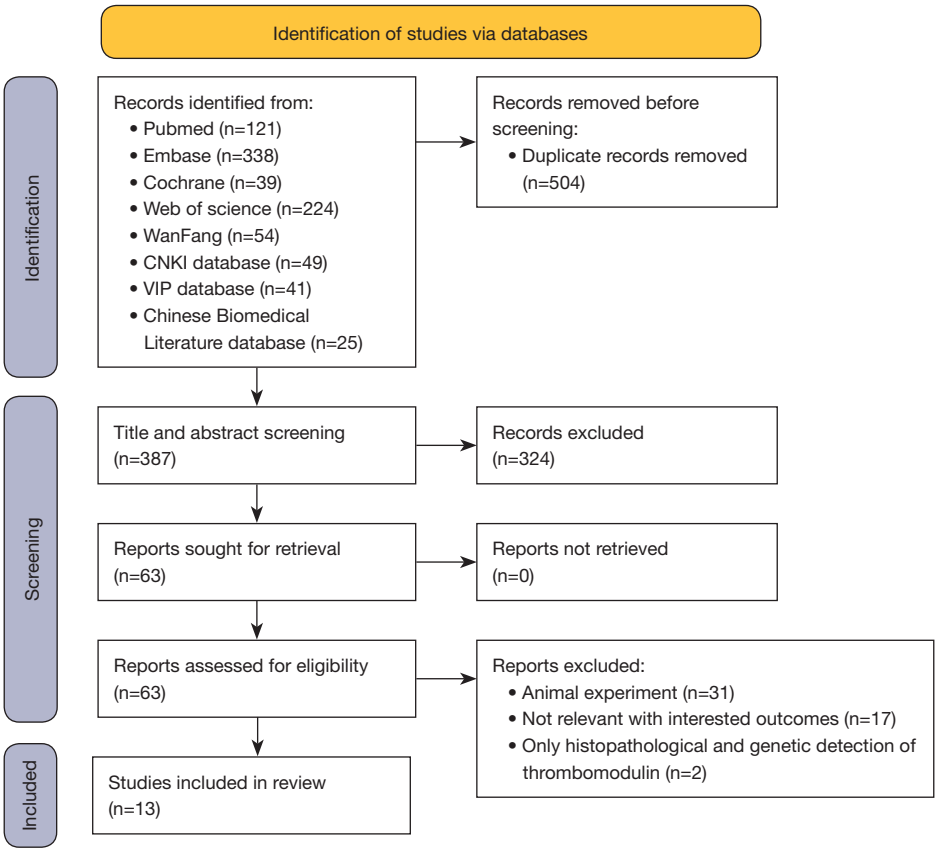

Figure 1 Flowchart of the search strategy.

and survivors. Our meta-analysis demonstrated that nonsurvivors had more significantly increased sTM levels than did survivors (SMD =1.473; 95% CI: 0.874–2.072; P<0.001; I^2=93%). The forest plot is illustrated in *Figure 2*. The difference in the sTM levels between nonsurvivors and survivors was significant in terms of patients with sepsis-related ARDS (SMD =1.057; 95% CI: 0.355 to 1.759; P<0.001; I^2=91%) and nonpulmonary sepsis-induced ARDS (SMD =1.473; 95% CI: 0.675–2.270; P<0.001; I^2=92%). In contrast, no significant difference was noted in the sTM levels in patients with direct ARDS (SMD =0.813; 95% CI: –0.673 to 2.229; P=0.253; I^2=93%), as shown in *Table 2*.

According to the meta-regression analysis, detection time (early or late), patient age (adults or children), type of ARDS (indirect, direct, or mixed), cause of ARDS (sepsis or mixed), detection method (ELISA or EIA), follow-up time (short-term or long-term), mortality level (high or low), samples (plasma or serum), and definition of ARDS were not the source of heterogeneity (P>0.05). The analysis of the source of heterogeneity is presented in *Table 2*.

A funnel plot and Egger test were employed to determine publication bias, which indicated 6 studies were outside the funnel plot, and 4 studies were symmetrically distributed. The funnel plot of publication bias is depicted in Figure S1. Meanwhile, the Egger test revealed that the publication bias was not significant (P=0.297). The results of the Egger test are shown in Figure S2. Furthermore, when 2 studies were added with the trim-and-fill method, a similar main effect was observed (SMD =1.120; 95% CI: 0.414–1.827; P=0.002, I^2=94%).

Elevated sTM and hospital mortality in patients with ARDS

Six studies analyzed the correlation between sTM and mortality in patients with ARDS by adjusted OR (10,13-15,24,26). Meta-analysis showed that elevated sTM levels had an independent correlation with higher

Table 1 Characteristics of the included studies associated with ARDS and in-hospital mortality

Study	Patients	Country	Male [%]	Age, years[a]	Design	Causes of ARDS	Diagnostic criteria	Detection assay	NOS
Benatti MN 2020	Adults	Brazil	17 [57]	44±16	Cross-section	Flu virus pneumonia	Berlin definition	ELISA	5[b]
Sapru A 2015	Adults	America	242 [54]	49.8±15.6	Retrospective cohort	Mixed	Berlin definition	ELISA	7
Orwoll BE 2015	Children	America	136 [56]	6.8±6.0	Prospective cohort	Mixed	AECC	ELISA	8
McClintock D 2008	Adults	America	28 [56]	55±16	Prospective cohort	Mixed	AECC	ELISA	7
Gando S 2004	Adults	Japan	40 [70]	50±5	Prospective cohort	Mixed	AECC	EIA	6
Sun HZ 2022	Adults	China	61 [59]	53±4	Retrospective cohort	Nonpulmonary sepsis	Berlin definition	ELISA	7
Tan YH 2021	Children	China	20 [51]	7.1±2.4	Case-control	Mixed	PALICC	ELISA	5
He CL 2021	Children	China	39 [70]	8.5±2	Case-control	Mixed	PALICC	ELISA	5
Li CC 2020	Children	China	36 [62]	0.5 (0.2–1.0)	Case-control	Pneumonia	Berlin definition	ELISA	5
Zhang Q 2020	Adults	China	106 [63]	51.9±3.7	Prospective cohort	Nonpulmonary sepsis	Berlin definition	ELISA	8
Song R 2021	Adults	China	56 [53]	53±3	Retrospective cohort	Mixed	Berlin definition	ELISA	7
Zheng YN 2022	Adults	China	93 [58]	65.9±5.3	Retrospective cohort	Nonpulmonary sepsis	Berlin definition	ELISA	7
Monteiro ACC 2021	Children	America	234 [54.2]	4.1 (0.7–11)	Retrospective cohort	Mixed	PALICC	ELISA	8

[a], the data were expressed as mean ± standard deviation or median (25th percentile–75th percentile); [b], risk of bias was evaluated by modified NOS. ARDS, acute respiratory distress syndrome; AECC, American European Consensus Conference; PALICC, Pediatric Acute Lung Injury Consensus Conference; ELISA, enzyme-linked immunosorbent assay; EIA, enzyme immunoassay; NOS, Newcastle-Ottawa Scale.

ARDS mortality (pooled OR =2.126; 95% CI: 1.548–2.920; P<0.001) after adjustments were made for various confounding variables, including gender, age, illness severity score, and sepsis status. There was a large heterogeneity across these studies (I^2=86%; P<0.01). The forest plot for the correlation between sTM and ARDS mortality is shown in *Figure 3*.

Predictive value of sTM for ARDS hospital mortality

Nine studies investigated the performance of sTM in predicting ARDS mortality (11,13-15,23-27). The risk of bias mainly centered on participant and analysis domains (*Table 3*). The sTM showed satisfactory performance in predicting ARDS hospital mortality (SROC =0.78; 95% CI: 0.64–0.89). The SROC of sTM in predicting ARDS mortality is shown in *Figure 4*. The pooled sensitivity was 72% (95% CI: 66–77%; I^2=30%), and the pooled specificity was 77% (95% CI: 72–82%; I^2=72.18%). The pooled sensitivity and specificity of sTM in predicting ARDS mortality are shown in *Figure 5*. No publication bias was found (Figure S3).

Sensitivity analysis

Cohort studies have less potential bias than do case-control and cross-sectional studies. Hence, this sensitivity analysis only included cohort studies. The results showed that

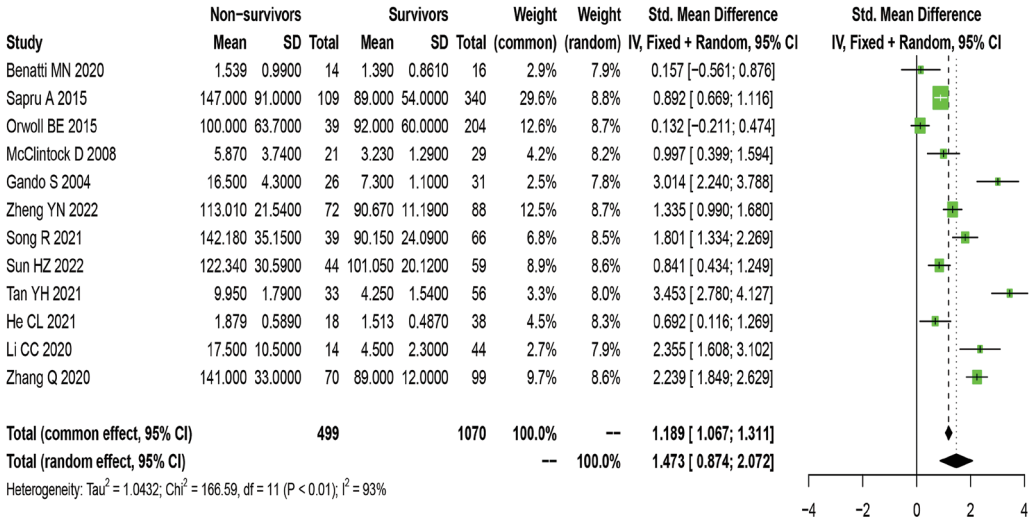

Figure 2 Forest plot for the difference of sTM between ARDS nonsurvivors and survivors. SD, standard deviation; CI, confidence interval; sTM, soluble thrombomodulin; ARDS, acute respiratory distress syndrome.

patients who died of ARDS had elevated sTM levels (SMD =1.377; 95% CI: 0.768–1.986; P<0.001; I^2=93%). The results of sensitivity analysis without noncohort studies is shown in Figure S4. The OR values were extracted from 6 cohort studies. Removing 1 study at a time in the sensitivity analysis indicated that our analysis results were stable (Figure S5).

Discussion

The mortality of ARDS is still very high (nearly 40%) due to the complex, diversified, and poorly known molecular mechanism, which impedes precise prognosis and treatments (2). For the diagnosis of ARDS, risk stratification, and outcome prediction, biomarkers may be useful. Previous meta-analyses (30,31) have reported that soluble receptor for advanced glycation end-products (sRAGE), a marker for lung epithelial injury, and N-terminal probrain natriuretic-peptide (NT-ProBNP), a cardiac stretch marker, have a close correlation with the mortality of ARDS. Nonetheless, no comprehensive meta-analysis has evaluated the association between sTM and the mortality of ARDS.

Our meta-analysis demonstrated that the nonsurvivor group showed more significantly increased sTM levels than did the survivor group, suggesting that patients who died from ARDS had aggravated vascular injury, severely impaired anticoagulation and fibrinolysis, and serious disruption of the alveolar-capillary barrier. Moreover, elevated sTM levels had an independent correlation with increased ARDS mortality.

The mechanism for TM shedding has been reported on. The sTM is formed due to the proteolytic cleavage of proteases, including neutrophil-derived proteases, rhomboids, and metalloproteinases, which are released during vascular damage-related diseases, including inflammation, infection, and sepsis (9). Furthermore, oxygen radicals can rapidly induce endothelial cells to chemically release sTM. Thus, elevated circulating sTM is an indicator of the severity of endotheliopathy, mirroring worse lung intravascular thrombosis, increased vascular permeability and extravascular leakage, impaired microcirculation, and organ dysfunction. The multifactorial mechanism leads to the progressive deterioration of ARDS.

Our subgroup analysis showed no significant difference in the sTM levels in patients with direct ARDS (primary or pulmonary ARDS) between nonsurvivors and survivors. Direct and indirect lung injuries are two distinct subphenotypes of ARDS. The former features alveolar epithelial injury and local alveolar inflammation, whereas the latter is characterized by inflammatory mediator-induced systemic vascular endothelial damage (32). Existing evidence has demonstrated that patients with indirect ARDS have more significantly elevated sTM levels than do those with direct ARDS (13), suggesting that circulating sTM cannot reflect the severity of lung injury in direct ARDS. Therefore, caution is needed in using sTM to predict adverse outcomes in patients with direct ARDS. Detection

Table 2 Subgroup analysis of the association between sTM and in-hospital mortality in ARDS

Subgroup	No.	Random-effects, SMD (95% CI)	I^2 (%)	Meta-regression (P value)[a]
Detection time[b]				
Early	9	1.578 (0.858–2.298)	95	0.135
Late	3	0.661 (0.320–1.004)	24	
Age group				
Adults	8	1.399 (0.808–1.970)	90	0.739
Children	4	1.638 (0.139–3.137)	96	
Type[c]				
Indirect	4	1.330 (0.688–1.972)	90	0.561
Direct	3	0.813 (–0.673–2.299)	93	0.334
Mixed	7	1.543 (0.063–2.454)	95	
Cause				
Sepsis	5	1.057 (0.355–1.759)	91	0.434
Mixed	7	1.543 (0.631–2.454)	95	
Detection method				
ELISA	11	1.186 (0.619–1.752)	93	0.080
EIA	1	1.328 (0.735–1.921)		
Follow-up days[d]				
≤30 days	8	1.386 (0.657–2.115)	92	0.801
>30 days	4	1.223 (0.051–2.395)	94	
Mortality[e]				
High	6	1.425 (0.633–2.217)	91	0.762
Low	6	1.237 (0.286–2.187)	94	
Sample				
Plasma	7	1.295 (0.302–2.288)	94	0.877
Serum	5	1.394 (0.830–1.957)	88	
Definition				
Berlin	6	1.464 (0.824–2.105)	91	0.723
PALICC	2	1.859 (1.421–2.297)	97	0.387
AECC	4	1.212 (0.029–2.395)	94	

[a], the last categorical variate of the subgroup was used as the reference in the meta-regression analysis; [b], an sTM level measured within 24 hours after the diagnosis of ARDS was define as early detection (baseline); otherwise, it was defined as late detection; [c], the study by Orwoll separately reported sTM values in indirect, direct, and mixed types of ARDS; [d], subgroup of follow-up >30 days comprised 60-day mortality and mortality in the intensive care unit or hospital; [e], the mortality was divided into high and low using a 40% cutoff value. sTM, soluble thrombomodulin; ARDS, acute respiratory distress syndrome; ELISA, enzyme-linked immunosorbent assay; EIA, enzyme immunoassay; PALICC, Pediatric Acute Lung Injury Consensus Conference; AECC, American European Consensus Conference; SMD, standardized mean difference; CI, confidence interval.

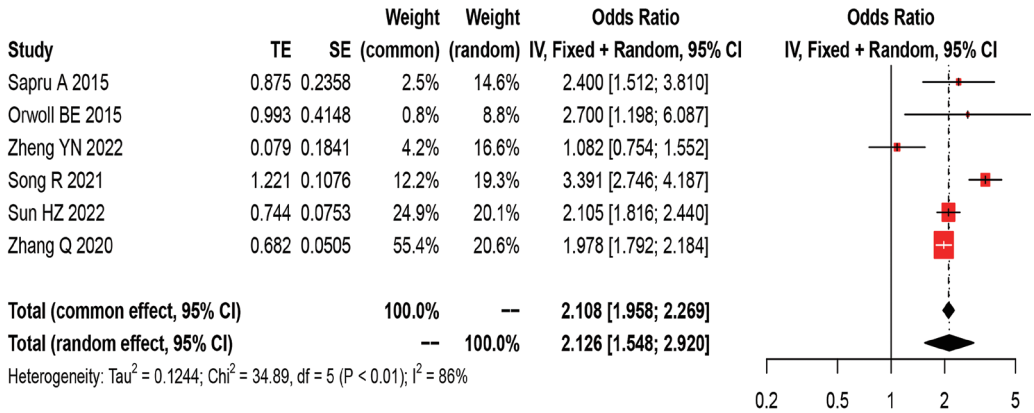

Figure 3 Forest plot for the association between sTM and mortality in patients with ARDS. TE, XXXXXXXXXXX; SE, XXXXXXXXXXX; CI, confidence interval; sTM, soluble thrombomodulin; ARDS, acute respiratory distress syndrome.

Table 3 Risk of bias assessment for included studies on prognostic accuracy of sTM by QUAPAS

Study	Participants	Index test	Outcome	Flow and timing	Analysis
Zhang Q 2020	Low	Low	Low	Low	Low
Li CC 2020	High	High	Low	Low	High
He CL 2021	High	High	Low	Low	Low
Tan YH 2021	High	Low	Low	Low	High
Song R 2021	Low	Low	Low	Low	High
Zheng YN 2022	Low	Low	Low	Low	High
Orwoll BE 2015	Low	Low	Low	Low	Low
Sapru A 2015	Low	Low	Low	Low	Low
Monteiro ACC 2021	Low	Low	Low	Low	Low

sTM, soluble thrombomodulin; QUAPAS, Quality Assessment of Prognostic Accuracy Studies.

time and the cause of ARDS are important considerations. The study by Sapru *et al.* (14) found an increased level of sTM on day 3 compared to day 1 and indicated that sTM had comparable performance in predicting ARDS mortality (AUC =0.72 for both baseline and day 3 sTM). Our meta-analysis revealed that the sTM levels, regardless of early or late measurement, are correlated with the mortality of ARDS and may be helpful for the early detection of ARDS in patients at a high risk of experiencing adverse outcomes from the perspective of clinical application. The major contributors to ARDS are pneumonia and nonpulmonary sepsis (3). Sepsis-related ARDS is characterized by a strong inflammation response to infection, substantial immune cell infiltration, and high mortality (33). Sepsis-related ARDS exhibits more significantly increased levels of sTM than those of ARDS induced by trauma or other causes (14). Our meta-analysis demonstrated that elevated sTM levels were correlated with higher mortality in sepsis-related and nonpulmonary sepsis-related ARDS. Furthermore, the multivariate logistic regression revealed that the association was independent of sepsis.

The bivariate analysis and SROC suggested that sTM had a moderate predictive performance for in-hospital mortality in ARDS. This finding highlights the fact that sTM alone cannot accurately predict the high risk of death in the mixed ARDS population. However, sTM, when combined with multidimensional variates such as clinical and multiomics data, is a potential candidate biomarker for predicting the prognosis of ARDS. Additionally, sTM may be a valuable indicator for subphenotyping ARDS because

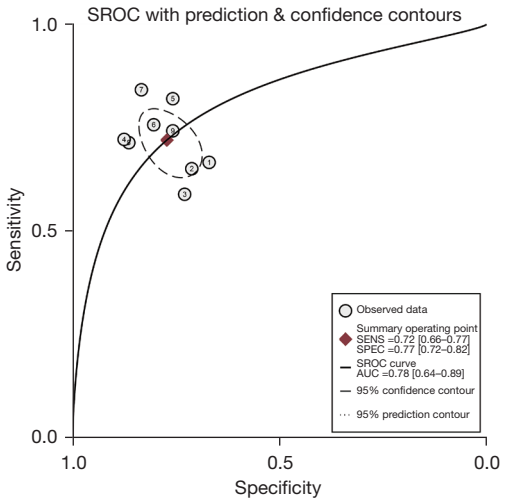

Figure 4 SROC of sTM predicting the ARDS mortality. SROC, summary receiver operating characteristic curve; SENS, sensitivity, SPEC, specificity; AUC, area under the curve; sTM, soluble thrombomodulin; ARDS, acute respiratory distress syndrome.

it significantly contributes to the pathogenesis of ARDS.

This study still has some limitations which should be noted. First, the heterogeneity among the studies was high, and this might be attributable to the variability in patient symptoms, lung injury types, measurement kits, and causes and severity of ARDS. However, except for the injury type, the subgroup analysis yielded consistent results across all groups and was corroborated by the sensitivity analysis. High intrasubgroup heterogeneity may imply a flawed grouping method based on clinical phenotype. Second, some included studies did not perform multivariate analysis or report the effect value of OR, so there was potential publication bias. Third, despite the fact that mortality rates often reflect the severity of diseases, the predictive value of sTM for mortality in patients with mild, moderate, or severe ARDS could not be fully elucidated due to a lack of available data. Finally, our meta-analysis did not include patients with COVID-19. COVID-19-related ARDS has longer-lasting

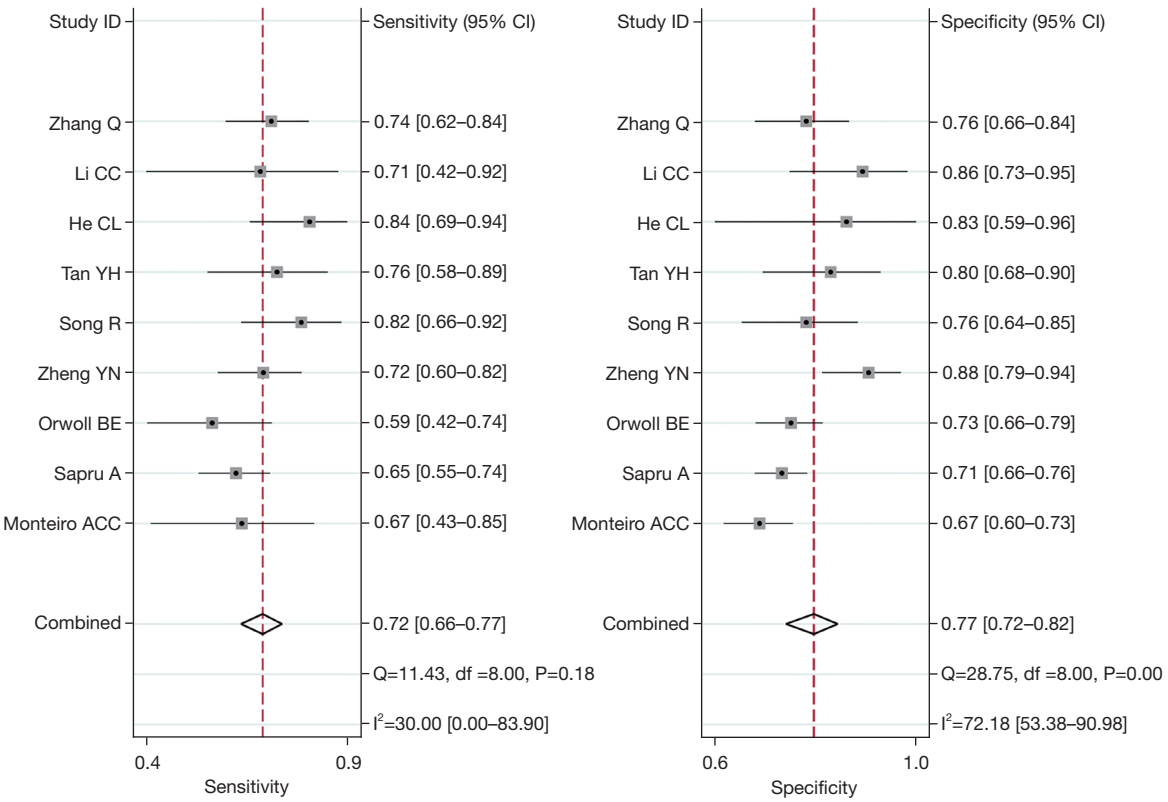

Figure 5 Pooled sensitivity and specificity of sTM in predicting ARDS mortality. CI, confidence interval; sTM, soluble thrombomodulin; ARDS, acute respiratory distress syndrome.

hyperinflammation and a greater incidence of thrombosis than does traditional ARDS (34). Elevated sTM levels were reported in patients with COVID-19 (35-37), but these studies did not focus on patients with ARDS. Therefore, they were deemed ineligible for this meta-analysis.

Conclusions

sTM is associated with in-hospital mortality in ARDS and shows moderate predictive performance. Hence, it is a potential candidate for predicting the mortality of ARDS. However, caution is needed when sTM is used to predict adverse outcomes in patients with direct ARDS. Future investigations targeted toward the subphenotype of ARDS or COVID-19-related ARDS may benefit this population.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-23-432/rc

Peer Review File: Available at https://atm.amegroups.com/article/view/10.21037/atm-23-432/prf

Conflicts of interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-23-432/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Literature search strategy

Search number	Query	Results
PubMed		
#1	"Hyaline Membrane Disease*"[tiab] OR "Hyaline Membrane Disease"[mh] OR "neonatal surfactant deficiency"[tiab] OR "surfactant deficiency disease*"[tiab] OR "surfactant deficiency disorder*"[tiab] OR "surfactant deficiency syndrome*"[tiab]	3217
#2	"shock lung"[tiab] OR "lung shock"[tiab] OR ARDS[tiab] OR "respiratory distress syndrome*"[tiab] OR "respiration distress syndrome*"[tiab] OR "Respiratory Distress Syndrome"[MH]	58390
#3	"Respiratory Depression"[tiab] OR "Ventilatory Depression"[tiab] OR "respiratory failure*"[tiab] OR "Respiratory Insufficiency"[MH]	99353
#4	"acute lung injury"[tiab] OR ALI[tiab] OR "acute lung injury" [mh]	8048
#5	thrombomodulin[tiab] OR thrombomodulin[mh]	5347
#6	#1 OR #2 OR#3 OR #4	156893
#7	#6 AND #7	121
Cochrane		
#1	MeSH descriptor: [Thrombomodulin] explode all trees	110
#2	thrombomodulin:ti,ab,kw	396
#3	#1 OR #2	396
#4	MeSH descriptor: [Hyaline Membrane Disease] explode all trees	100
#5	(Hyaline Membrane Disease:ti,ab,kw) OR (Hyaline Membrane Disease*:ti,ab,kw) OR (neonatal surfactant deficiency:ti,ab,kw) OR (surfactant deficiency disease*:ti,ab,kw) OR (surfactant deficiency disorder* :ti,ab,kw) OR (surfactant deficiency syndrome*:ti,ab,kw)	349
#6	#4 OR #5	349
#7	MeSH descriptor: [Respiratory Distress Syndrome] explode all trees	2785
#8	(shock lung:ti,ab,kw) OR (lung shock:ti,ab,kw) OR ARDS:ti,ab,kw OR (respiratory distress syndrome*:ti,ab,kw) OR (respiration distress syndrome*:ti,ab,kw)	8462
#9	#7 OR #8	8553
#10	MeSH descriptor: [Respiratory Insufficiency] explode all trees	3132
#11	(Respiratory Depression:ti,ab,kw) OR (Ventilatory Depression:ti,ab,kw) OR (respiratory failure*:ti,ab,kw)	18922
#12	#10 OR #11	20741
#13	MeSH descriptor: [Acute Lung Injury] explode all trees	587
#14	(acute lung injury:ti,ab,kw) OR ALI:ti,ab,kw	8986
#15	#13 OR #14	8986
#16	#6 OR #9 OR #12 OR #15	33274
#17	#3 AND #16	39
Embase		
#1	'respiratory failure'/exp OR 'lung insufficiency'/exp OR 'respiration deficiency':ab,ti OR 'respiration disturbance':ab,ti OR 'respiration failure*':ab,ti OR 'respiration insufficiency':ab,ti OR 'respiratory deficiency':ab,ti OR 'respiratory disturbance':ab,ti OR 'respiratory dysfunction':ab,ti OR 'respiratory insufficiency':ab,ti OR 'respiratory tract insufficiency':ab,ti OR 'lung failure':ab,ti OR 'pulmonary failure':ab,ti OR 'pulmonary insufficiency':ab,ti	135778
#2	'respiratory distress syndrome'/exp OR 'breathing distress syndrome*':ab,ti OR 'lung distress syndrome*':ab,ti OR 'pulmonary distress syndrome*':ab,ti OR 'respiration distress syndrome*':ab,ti OR 'respiratory distress syndrome*':ab,ti OR 'ards':ab,ti OR 'lung shock':ab,ti OR 'shock lung':ab,ti OR 'lung failure':ab,ti OR 'pulmonary insufficiency':ab,ti	110977
#3	'acute lung injury'/exp OR 'acute lung injury':ab,ti OR 'ali':ab,ti	33800
#4	'hyaline membrane disease'/exp OR 'hyalin membrane disease*':ab,ti OR 'hyalin membrane syndrome*':ab,ti OR 'hyaline membrane pneumonia':ab,ti OR 'neonatal surfactant deficiency':ab,ti OR 'surfactant deficiency disease*':ab,ti OR 'surfactant deficiency disorder*':ab,ti OR 'surfactant deficiency syndrome*':ab,ti	4927
#5	'thrombomodulin'/exp OR thrombomodulin:ab,ti	4914
#6	#1 OR #2 OR #3 OR #4	242963
#7	#5 AND #6	338
Web of science		
#1	TS=(thrombomodulin)	6847
#2	TS=(Hyaline Membrane Disease*) OR TS=(neonatal surfactant deficiency) OR TS=(surfactant deficiency disease*) OR TS=(surfactant deficiency disorder*) OR TS=(surfactant deficiency syndrome*)	3090
#3	TS=(shock Lung) OR TS=(lung shock) OR TS=ARDS OR TS=(respiratory distress syndrome*)	66415
#4	TS=(Respiratory Insufficiency) OR TS=(Respiratory Depression) OR TS=(Ventilatory Depression) OR TS=(respiratory failure*)	82935
#5	TS=(acute lung injury) OR TS=ALI	49801
#6	#5 OR #4 OR #3 OR #2	167897
#7	#6 AND #1	224

Table S1 (*continued*)

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Table S1 (*continued*)

Search number	Query	Results
WanFang database		
#1	AB= 血栓调节蛋白 OR TI= 血栓调节蛋白	1678
#2	AB= 透明膜病 OR TI= 透明膜病 AB= 表面活性物质缺陷 OR TI= 表面活性物质缺陷 OR AB= 表面活性物质缺乏 TI= 表面活性物质缺乏	2092
#3	AB= 休克肺 OR TI= 休克肺 OR AB= 肺休克 OR TI= 肺休克 OR AB= 呼吸窘迫综合征 OR TI= 呼吸窘迫综合征	39777
#4	AB= 呼吸功能不全 OR TI= 呼吸功能不全 OR AB= 呼吸抑制 OR TI= 呼吸抑制 OR AB= 通气抑制 OR TI= 通气抑制 OR AB= 呼吸衰竭 OR TI= 呼吸衰竭	73087
#5	AB= 急性肺损伤 OR TI= 急性肺损伤	13864
#6	#5 OR #4 OR #3 OR #2	121674
#7	#6 AND #1	54
VIP database		
#1	AB= 血栓调节蛋白 OR TI= 血栓调节蛋白	1371
#2	R= 透明膜病 OR T= 透明膜病 OR R= 表面活性物质缺陷 OR T= 表面活性物质缺陷 OR R= 表面活性物质缺乏 OR T= 表面活性物质缺乏	1990
#3	R= 休克肺 OR T= 休克肺 OR R= 肺休克 OR T= 肺休克 OR R= 呼吸窘迫综合征 OR T= 呼吸窘迫综合征	22790
#4	R= 呼吸功能不全 OR T= 呼吸功能不全 OR R= 呼吸抑制 OR T= 呼吸抑制 OR R= 通气抑制 OR T= 通气抑制 OR R= 呼吸衰竭 OR T= 呼吸衰竭	60769
#5	R= 急性肺损伤 OR T= 急性肺损伤	11518
#6	#5 OR #4 OR #3 OR #2	92145
#7	#6 AND #1	41
CNKI database		
#1	AB= 血栓调节蛋白 OR TI= 血栓调节蛋白	1687
#2	AB= 透明膜病 OR TI= 透明膜病 AB= 表面活性物质缺陷 OR TI= 表面活性物质缺陷 OR AB= 表面活性物质缺乏 TI= 表面活性物质缺乏	2091
#3	AB= 休克肺 OR TI= 休克肺 OR AB= 肺休克 OR TI= 肺休克 OR AB= 呼吸窘迫综合征 OR TI= 呼吸窘迫综合征	23435
#4	AB= 呼吸功能不全 OR TI= 呼吸功能不全 OR AB= 呼吸抑制 OR TI= 呼吸抑制 OR AB= 通气抑制 OR TI= 通气抑制 OR AB= 呼吸衰竭 OR TI= 呼吸衰竭	60312
#5	AB= 急性肺损伤 OR TI= 急性肺损伤	12855
#6	#5 OR #4 OR #3 OR #2	93607
#7	#6 AND #1	49
Chinese Biomedical Literature database		
#1	血栓调节蛋白 [标题] OR 血栓调节蛋白 [摘要]	1229
#2	透明膜病 [摘要] OR 透明膜病 [标题] 表面活性物质缺陷 [摘要] OR 表面活性物质缺陷 [标题] OR 表面活性物质缺乏 [摘要] 表面活性物质缺乏 [标题]	1655
#3	休克肺 [摘要] OR 休克肺 [标题] OR 肺休克 [摘要] OR 肺休克 [标题] OR 呼吸窘迫综合征 [摘要] OR 呼吸窘迫综合征 [标题]	19618
#4	呼吸功能不全 [摘要] OR 呼吸功能不全 [标题] OR 呼吸抑制 [摘要] OR 呼吸抑制 [标题] OR 通气抑制 [摘要] OR 通气抑制 [标题] OR 呼吸衰竭 [摘要] OR 呼吸衰竭 [标题]	49668
#5	急性肺损伤 [摘要] OR 急性肺损伤 [标题]	9101
#6	#5 OR #4 OR #3 OR #2	68129
#7	#6 AND #1	25

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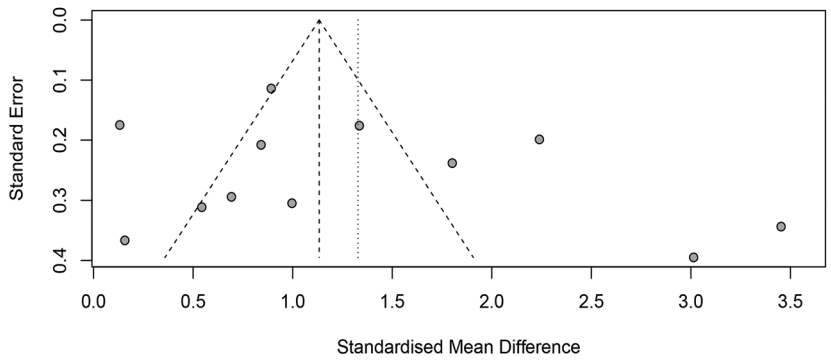

Figure S1 The funnel plot of publication bias for SMD (gray dots represent the SMD of studies). SMD, standardised mean difference.

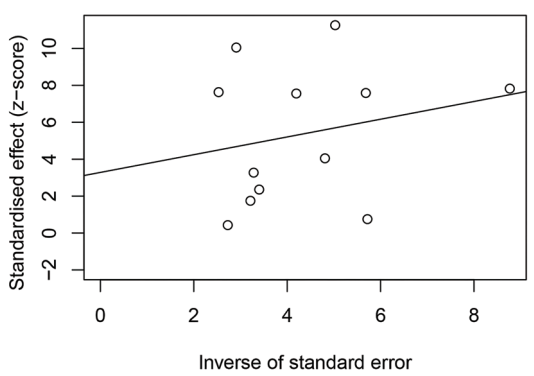

Figure S2 Effect plot of the Egger test (white dots represent the inverse of standard error of studies).

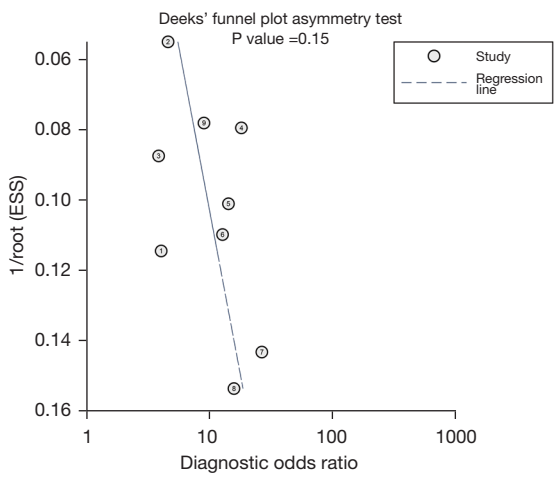

Figure S3 The funnel plot of publication bias for predictive value. ESS, effective sample sizes.

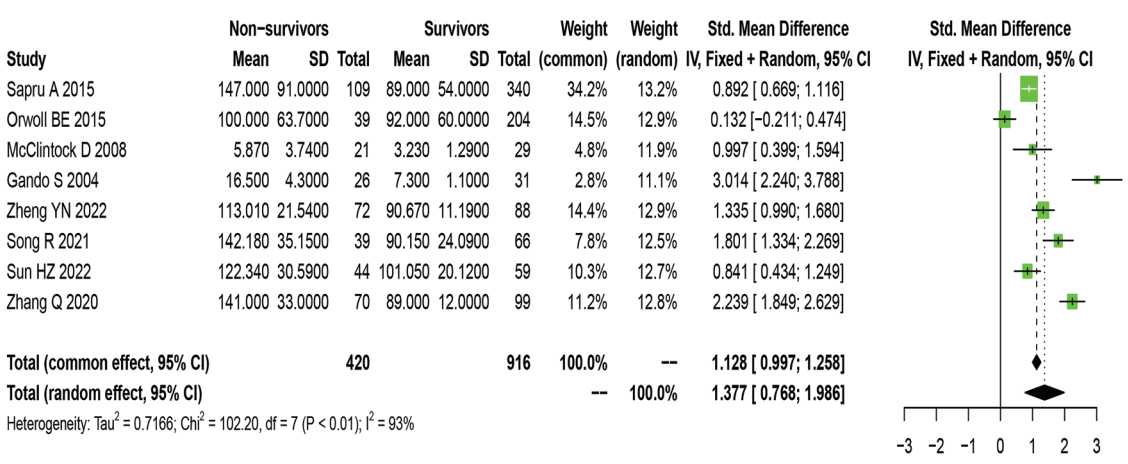

Figure S4 Forest plot for the association between sTM and ARDS mortality without noncohort studies. sTM, soluble thrombomodulin; CI, confidence interval; OR, odds ratio; ARDS, acute respiratory distress syndrome.

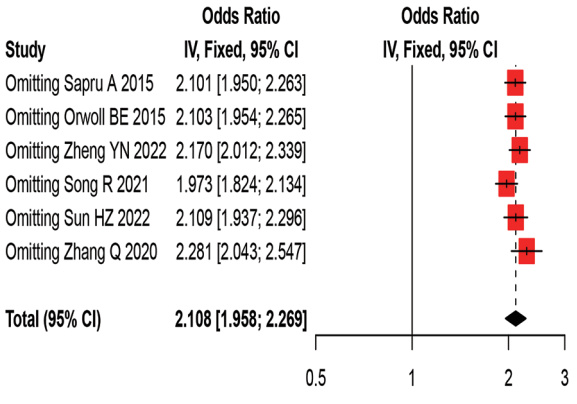

Figure S5 Forest plot for the sensitivity analysis of the association between sTM and ARDS mortality. sTM, soluble thrombomodulin; CI, confidence interval; OR, odds ratio; ARDS, acute respiratory distress syndrome.

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