Predictive roles of D-dimer for mortality of patients with community-acquired pneumonia: a systematic review and meta-analysis

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ABSTRACT

Objective: To explore the predictive roles of D-dimer for the mortality of patients with community-acquired pneumonia (CAP). **Methods:** This was a systematic review and meta-analysis. We searched the following databases: PubMed, EMBASE, Web of Science, Ovid MEDLINE, and Cochrane Library from their inception to July 26, 2020. Studies exploring the relationship between blood D-dimer levels and CAP-related mortality were selected. In this meta-analysis, we calculated mortality rates, sensitivity, specificity, positive likelihood ratios, and negative likelihood ratios. **Results:** The search identified 1,073 articles, 8 of which (a total of 2,126 patients) were included in this meta-analysis. The pooled mortality rate of the overall sample was 0.10 (95% CI, 0.08-0.14). The levels of blood D-dimer in the nonsurvivors were significantly higher than those in the survivors (weighted mean difference = 1.03 mg/L [95% CI, 0.81-1.26]; $p < 0.00001$). The area under the summary ROC curve for the optimal cutoff value of D-dimer as a predictor of mortality was 0.848 (SE = 0.046), and the pooled negative likelihood ratio for D-dimer within the normal range was 0.24 (95% CI, 0.11-0.53). **Conclusions:** Blood D-dimer might be helpful for the initial assessment of mortality risk of patients with CAP. D-dimer levels within the normal range indicate low risk of mortality. Because of the small sample size in our study, our findings should be further explored and validated in future studies with larger sample sizes.

Keywords: Fibrin fibrinogen degradation products; Community-acquired infections/mortality; Pneumonia/mortality; Meta-analysis.

INTRODUCTION

As we all know, community-acquired pneumonia (CAP) has significant morbidity, mortality, and disease burden among adults ≥ 18 years of age.[1] Early assessment of CAP severity is very important for the management of CAP in adults.[2] The Pneumonia Severity Index (PSI) and the mental **C**onfusion, **U**rea, **Respiratory** rate, **B**lood pressure, and age ≥ **65** (CURB-65) score have been developed to predict CAP-related mortality in adults. Due to the lack of evidence of the effectiveness or safety of CURB-65, this score was conditionally recommended to determine whether hospitalization is required or not.[3] Although PSI is an effective and safe assessment tool, its rules are complicated and its application is time-consuming. Therefore, clinicians desire a simple test that could be helpful to predict CAP-related mortality. In addition, some studies suggested that proadrenomedullin, prohormone forms of atrial natriuretic peptide, cortisol, procalcitonin, copeptin, C-reactive protein, and IL-6 could also predict CAP-related mortality better.[4,5]

It is known that D-dimer is a specific product of fibrinolysis and can be tested quickly. Besides, D-dimer testing is commonly used. Some studies showed that the mean levels of D-dimer in nonsurvivors of CAP were significantly higher than were those in survivors of CAP and that D-dimer levels could be used to predict mortality in patients with CAP.[6-8] However, some investigators[9] suggested that the difference of mean D-dimer levels between CAP survivors and nonsurvivors was not statistically significant. So far, the effects of D-dimer levels on the prognosis of patients with CAP have yet to be systematically analyzed and discussed. Therefore, this systematic review and meta-analysis was conducted to explore the roles of D-dimer in predicting mortality in patients with CAP. It was hypothesized that elevated D-dimer levels might predict higher risk of mortality in patients with CAP.

METHODS

Protocol and registration

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, the study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; Record ID: CRD42020188254) before this systematic review and meta-analysis was performed.

Search strategy

The search strategy was based on the following search items: ("Pneumonia" OR "Pneumonitis" OR

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"Pneumonitides" OR "Pulmonary Inflammation" OR "Lung Inflammation") AND ("D-dimer Fibrin" OR "D-dimer Fragments" OR "Fibrin Fragment D1 Dimer" OR "Fibrin Fragment DD" OR "D-dimer" OR "Fibrin Fragment D-dimer" OR "Fibrin Fragment D"). Two of the authors searched the following databases: PubMed, Web of Science, EMBASE, Cochrane Library, and Ovid MEDLINE from their inception to July 26, 2020. In addition, manual retrieval of cross-references and related articles was performed as a supplement to the electronic search. When the same population was studied in twin studies, the most complete or the most recent one was included.

Inclusion and exclusion criteria

The inclusion criteria of studies were as follows: detecting blood D-dimer levels of adult patients with CAP; exploring the relationship between blood D-dimer levels and mortality of patients with CAP; and being published in English or Chinese.

The exclusion criteria of studies were as follows: overlapping or duplicate publications; article types such as abstracts, reviews, case reports, letters, or those based on animal experimental models; and studies involving children.

Data extraction

Data from the selected studies were extracted by the two of the researchers. If there were disagreements, they were resolved by a third researcher.

The extracted data included study characteristics (first author's name, year of publication, country, sample size, and mean age of the cohort), study design (retrospective or prospective), sample characteristics (sample collection time, type of specimen collected, and detection methods), mortality, and methods of D-dimer analysis (optimal cutoff threshold, normal range, and number of true positives, false positives, false negatives and true negatives, as well as mean D-dimer levels in survivors and nonsurvivors). We wrote to the authors of studies to ask for missing data when necessary. When no reply was received within four weeks, we used estimations based on the data available or the study was removed from the review.

Quality assessment

The same two researchers used the Newcastle-Ottawa Scale (NOS) to evaluate the methodological quality of the selected studies. Total scores of NOS range from 0 to 9; studies with scores ≥ 6 were considered high-quality studies.

Statistical analysis

D-dimer levels in survivors and nonsurvivors of CAP were quantitatively synthesized using the Review Manager program, version 5.0 (RevMan 5; Cochrane Collaboration, Oxford, UK). The weighted mean difference was used in order to compare continuous variables. Synthesized sensitivity, specificity, positive likelihood ratio (LR+), negative LR (LR−), diagnostic OR, and summary ROC (SROC) curve of cutoff and normal values for predicting CAP-related mortality (and their respective 95% CIs) were calculated using Meta-DiSc, version 1.4 (Cochrane Colloquium, Barcelona, Spain). When means and ranges were applied to continuous data, standard deviations were calculated in accordance with Hozo et al.[10] The chi-square test was used to assess statistical heterogeneity, which was quantified by *I2* between studies. Statistical significance was defined as $p < 0.1$ and $I2 > 50\%$. The fixed-effects model was applied to the studies without significant heterogeneity, and the random-effects model was applied to the studies with significant heterogeneity. Sensitivity analysis was performed after eliminating the articles one by one (Review Manager) to estimate whether pooled results were stable or not. Potential publication bias was assessed by funnel plots.

RESULTS

Study selection

The search of the selected databases retrieved 1,073 studies, whereas no cross-references or related articles were selected for analysis. After removing 174 duplicates, the titles and abstracts of 899 articles were reviewed, and 822 were considered irrelevant to the research topic and were excluded. Of the 77 remaining articles that were carefully reviewed, 8 were included in the study. The flow chart of the study selection process is shown in Figure 1.

Characteristics of the included studies

The major characteristics of the studies[6-9,11-14] included in this review are shown in Table 1. Publication year of the studies ranged from 2003 to 2018. There were 7 prospective studies[6-9, 11,13,14] and 1 retrospective study.[12] Mean D-dimer levels of survivors and nonsurvivors of CAP were reported in 5 studies.[6-9,14] In order to predict CAP-related mortality, true- and false-positives and negatives were calculated in 3 studies[6,7,12] reporting optimal cutoff values (Table S1) and in 3 studies[11,13,14] reporting normal ranges (Table S2). The methods of D-dimer testing were reported in 7 studies,[6-9,11,13,14] but none of these studies reported whether blinded or independent measurements were performed or not. Follow-up was carried out from discharge to 90 days afterwards.

Methodological quality assessment of the studies

The NOS scores of the studies included in this review are summarized in Table 1. None of the studies provided information regarding confounding factors (baseline data, i.e., age) in patients with and without elevated D-dimer levels. Only 1 study explicitly described the method of assessing mortality.[13] Details on methodological quality assessment are shown in Table S3.

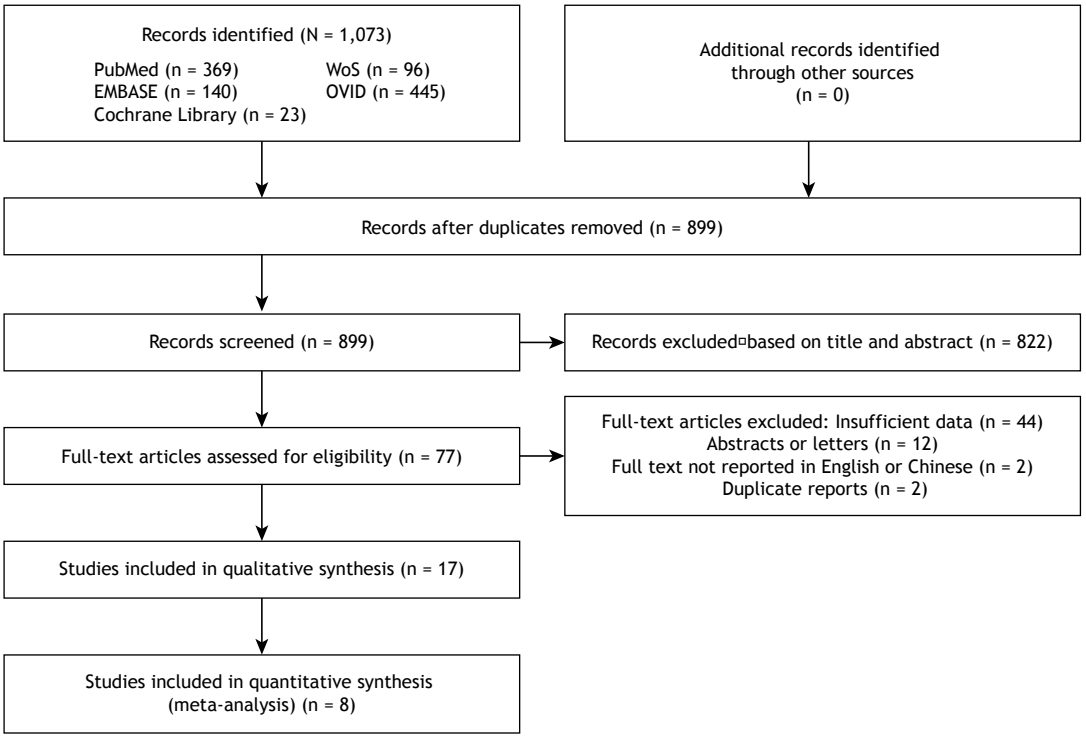

Figure 1. Flow chart of the study selection process. WoS: Web of Science.

Predictive value of D-dimer for CAP-related mortality

A total of 8 studies[6-9,11-14] involving 2,126 patients with CAP were included in this meta-analysis. The mortality of CAP patients ranged from 4.4% to 15.6%. The pooled mortality of the studies included was 0.10 (95% CI, 0.08-0.14; Figure S1). The pooled D-dimer levels in 507 patients from 5 studies[6-9,14] showed significant differences between survivors and nonsurvivors (weighted mean difference = 1.03 mg/L; 95% CI, 0.81-1.26; $p < 0.00001$; Figure 2). Three studies[6,7,12] reported optimal cutoff values of D-dimer for predicting CAP-related mortality: 2.0 mg/L[12]; 1.538 mg/L[7]; and 1.798 mg/L[6] (Table S1). Pooled results were as follows: sensitivity = 0.75 (95% CI, 0.63-0.85; Figure 3A); specificity = 0.82 (95% CI, 0.79-0.85; Figure 3B); LR+ = 3.88 (95% CI, 2.34-6.42; Figure 3C); LR− = 0.31 (95% CI, 0.20-0.47; Figure 3D); diagnostic OR = 12.65 (95% CI, 7.09-22.57; Figure 3E); and AUC = 0.848 (SE = 0.046; Figure 3F). Three studies[11,13,14] reported the normal range of D-dimer levels for predicting CAP-related mortality (Table S2). Pooled results were as follows: sensitivity = 0.96 (95% CI, 0.90-0.99; Figure 4A); specificity = 0.21 (95% CI, 0.19-0.24; Figure 4B); LR+ = 1.21 (95% CI, 1.10-1.33; Figure 4C); LR− = 0.24 (95% CI, 0.11-0.53; Figure 4D); and diagnostic OR = 4.97 (95% CI, 2.19-11.27; Figure 4E).

Sensitivity analysis and publication bias

A sensitivity analysis was conducted on the sequential exclusion of studies for each index, and none of these exclusions affected the results significantly, indicating that the results of the present study are relatively stable. The funnel plot of the 8 studies included in the analysis showed no obvious asymmetry (Figure 5), which suggests that publication bias was not significant.

DISCUSSION

Five studies[6-9,14] showed that, when compared with survivors of CAP, nonsurvivors had much higher blood D-dimer levels. The results showed that the optimal cutoff value of D-dimer had high pooled specificity and relatively low pooled sensitivity for predicting mortality. In contrast, normal D-dimer values in blood had very high sensitivity and very low specificity.

The CAP-related mortality of hospitalized patients was estimated to be between 6% and 20%,[15] which varied greatly depending on treatment setting, disease severity, and follow-up period. In our study, the pooled CAP-related mortality was 10% (95% CI, 0.08-0.14), which was basically consistent with the previous results.

D-dimer includes multiple specific peptide fragments produced by the degradation of cross-linked fibrin. It is commonly used for the diagnosis of pulmonary embolism. The procoagulant responses of the patient are closely associated with inflammatory reaction to infection.[16] A study[17] recruiting 684 ER patients with infection or sepsis, 19% of whom were diagnosed with CAP, revealed that high D-dimer levels were related to 28-day mortality. In addition, it has been reported that sepsis induced a coagulopathy score

Table 1. Characteristics of the studies included in the analysis.

Study	Year of publication	Country	Sample size	Age, years[a]	P/R	Clinical setting	Optimal cutoff value	Normal range	Blood collection	Type of specimen	Detection method	Hospital setting	Mortality rate, % (n/N)	Primary outcome	NOS score
Chalmers et al.[11]	2009	United Kingdom	314	61 [42-73]	P	CAP	N/A	0-0.5 mg/L	On admission	N/A	ELISA	Teaching hospital	7.0 (22/314)	30-day mortality	5
Dai et al.[12]	2018	China	230	82 [74-87]	R	CAP with COPD	2.0 μg/mL	N/A	N/A	N/A	N/A	A tertiary specialized teaching hospital and a secondary hospital	6.6 (19/290)	In-hospital mortality	6
			290	79 [67-86]		CAP without COPD							8.3 (19/230)		
Milbrandt et al.[13]	2009	USA	732	N/A	P	CAP	N/A	0-0.256 mg/L	ER admission	Plasma	Latex immunoassay	Academic and community hospitals	11.5 (84/732)	90-day mortality	7
Nastasijević Borovac et al.[7]	2014	Serbia	129	64.8 ± 13.3	P	CAP	1.538 mg/L	N/A	On admission	Plasma	Quantitative latex method	Teaching hospital	10.1 (13/129)	Mortality	4
Salluh et al.[6]	2011	Brazil	90	73.5 [57.7-83.0]	P	Severe CAP	1.798 mg/L	N/A	First day of ICU admission	N/A	Immunoturbidimetry	Tertiary hospital	15.6 (14/90)	In-hospital mortality	6
Shilon et al.[9]	2003	Israel	68	67.0 ± 20.8	P	CAP	N/A	0-0.375 mg/L	At admission	Plasma	Miniquant D-dimer assay	Primary care hospital	4.4 (3/68)	In-hospital mortality	7
Snijders et al.[14]	2012	The Netherlands	147	63.1 ± 17.8	P	CAP	N/A	0-0.5 mg/L	First day of admission	Serum	ELISA	A teaching hospital	5.4 (8/147)	30-day mortality	6
Xu et al.[8]	2017	China	126	62.5 ± 8.9	P	CAP	N/A	N/A	N/A	Serum	Immunoturbidimetry	A tertiary hospital	14.3 (18/126)	In-hospital mortality	6

P: prospective; R: retrospective; NOS: Newcastle-Ottawa Scale; and CAP: community acquired pneumonia. [a]aValues expressed as median [IQR] or mean ± SD, except where otherwise indicated.

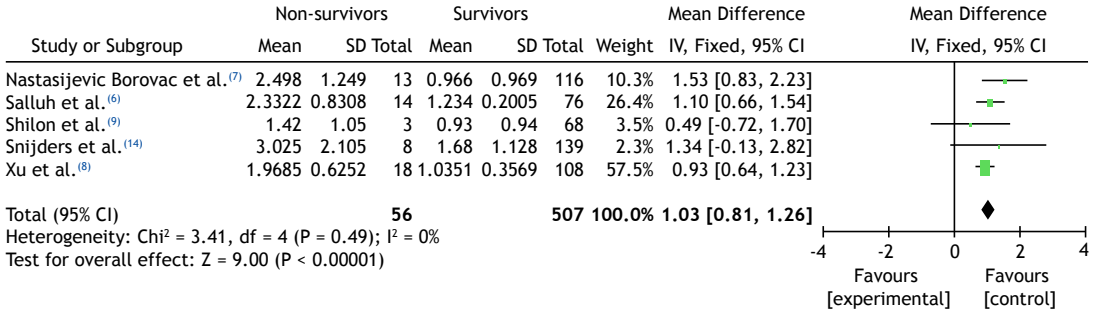

Figure 2. Meta-analysis and forest plot of D-dimer levels in the survivors and non-survivors.

> 4 and elevation of D-dimer levels (more than six times the reference value), which was associated with a worse prognosis of severe COVID-19.[18] What is more, another study suggested that an increase in D-dimer levels is the most significant change in coagulation parameters in patients with severe COVID-19, and progressively increasing values can be used as a prognostic parameter of a worse outcome.[19] D-dimer levels could be extremely useful to identify patients who could be potential targets for therapeutic interventions aimed at resolving coagulation disorders, such as heparin or recombinant activated protein C. Our pooled data showed that nonsurvivors of CAP had higher D-dimer levels than did survivors of CAP, which suggested that elevated D-dimer levels might be related to a higher risk of death in patients with CAP.

The most commonly used tools for the initial evaluation of CAP are CURB-65 and PSI. The use of PSI increased the proportion of low-risk patients who were safely treated on an outpatient basis.[3] Our meta-analysis found that D-dimer values within the normal range might help identify low-risk CAP patients. The prognostic models of PSI and CURB-65 were applied to immunocompetent patients with pneumonia from diagnosis in order to predict 30-day mortality.[3] A meta-analysis[20] found that the AUC of the SROC curve of PSI was 0.81 (SE = 0.008) for predicting CAP-related mortality and that the cumulative mortality rate was 8.3%. The present study pooled the optimal cutoff value of D-dimer and showed that the AUC was good (AUC = 0.848; SE = 0.046).

It was reported that the detection of D-dimer levels in CAP patients might affect diagnostic procedures for venous thromboembolism (VTE) and might even cause the use of unnecessary and expensive tests.[21] However, when VTE is excluded, D-dimer has much more significance in the comprehensive clinical evaluation.[22,23] Elevated levels of D-dimer might remind the clinician to assess the risk of VTE in those patients. Therefore, the addition of D-dimer testing to the diagnostic algorithm has the potential to make the diagnosis of deep vein thrombosis (DVT) in outpatients more convenient and economical. However, patients with D-dimer levels higher than reference levels are not systematically assessed to detect whether VTE is present or not. This means that undetected VTE might cause CAP-related mortality of patients.[21] On the other hand, since DVT cannot be diagnosed by clinical evaluation alone, when patients have D-dimer levels within the normal range, DVT can be excluded.[24] Therefore, "normal" D-dimer levels could be used to predict the prognosis of CAP, without being affected by DVT. In the present study, the pooled LR− of "normal" D-dimer level was 0.24 (95% CI, 0.11-0.53), which was similar to that of CURB-65 scores 0-1 (LR− = 0.21 [95% CI, 0.15-0.30]) in a previous study,[20] indicating that D-dimer levels within the normal range are useful to identify CAP patients with a low risk of mortality.

The heterogeneity between studies was significant regarding some variables. Different methods of D-dimer testing, blood sample collection, severity of CAP, and age distribution might bring about the obvious heterogeneity. Therefore, the random-effects model was applied to the pooled data, which could reduce the effect of heterogeneity, but not eliminate it.

Although our study cannot prove that D-dimer levels can be used as a single biomarker replacing the classical, well-validated scores, D-dimer can be quickly quantified, and using D-dimer levels together with PSI might help predict CAP-related mortality, improving the treatment and management of the disease more accurately and scientifically.

In the present study, there were several limitations. First, the major limitation was that the methodological quality of the studies included in the analysis was generally low, the comparability scores of all of which being equal to zero, and none provided information information about blinding methods. Second, there was high heterogeneity among the studies, and, thus, the results should be interpreted with caution. Third, pulmonary embolism or thromboembolism were not listed as an exclusion criterion in 5 of the studies.[6,9,12-14] Fourth, most of the studies were single center studies, which might have caused admission or selection bias. Last but not least, the small sample size and the small number of studies reduced the applicability of this meta-analysis. Nevertheless, multiple strategies were used for selecting studies, and strict criteria were adopted to evaluate their

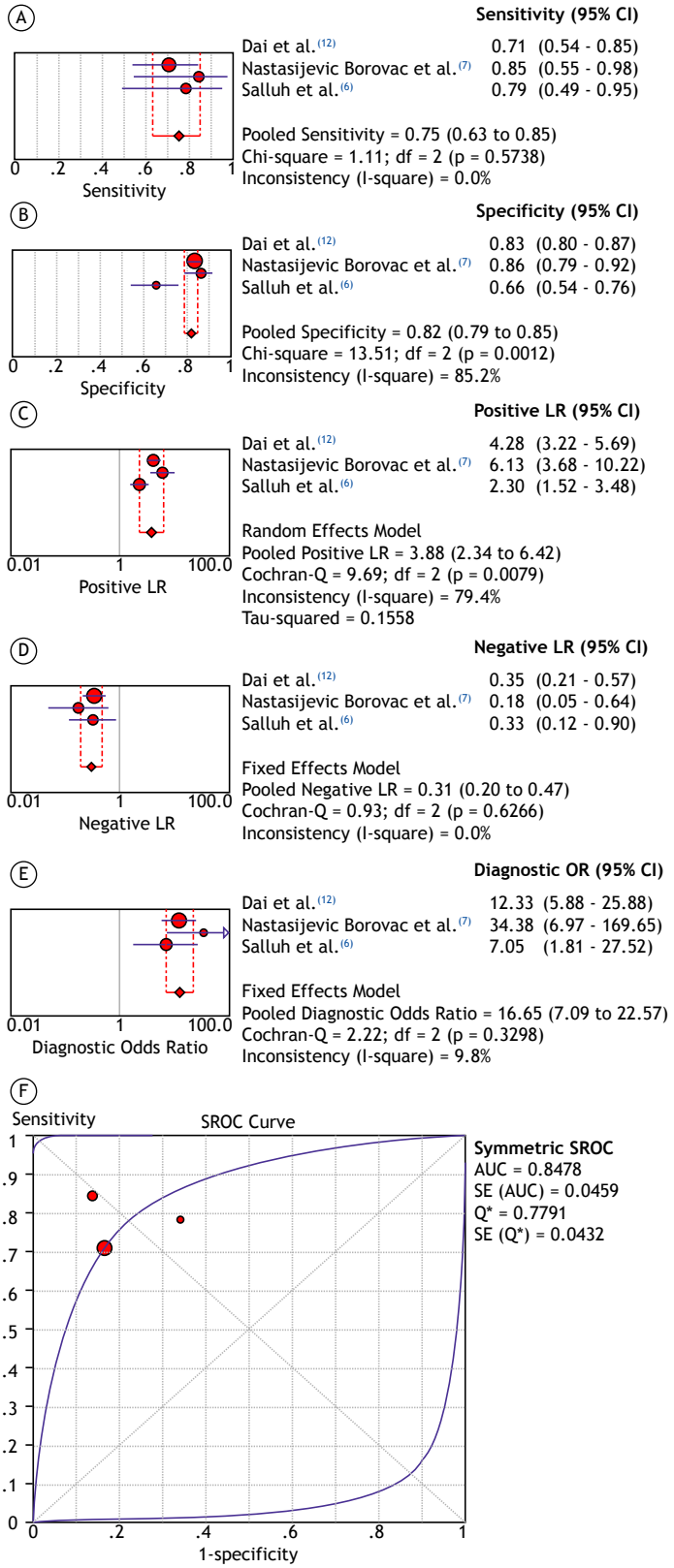

Figure 3. Optimal D-dimer cutoff values for predicting mortality. Forest plot and meta-analysis of sensitivity, in A; specificity, in B; positive likelihood ratio (LR) in C; negative LR, in D; diagnostic odds ratio, in E; and summary ROC curve, in F.

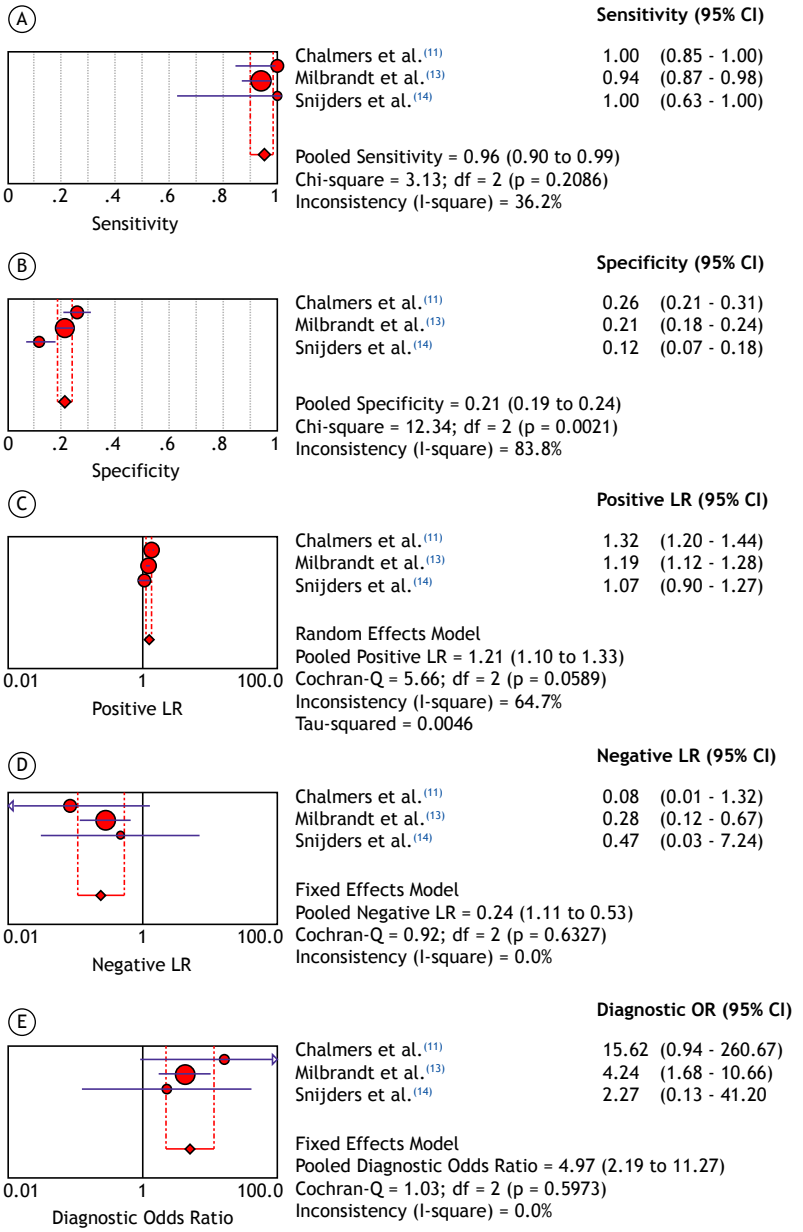

Figure 4. Normal D-dimer values for predicting mortality. Forest plot and meta-analysis of sensitivity, in A; specificity, in B; positive likelihood ratio (LR) in C; negative LR, in D; and diagnostic odds ratio, in E.

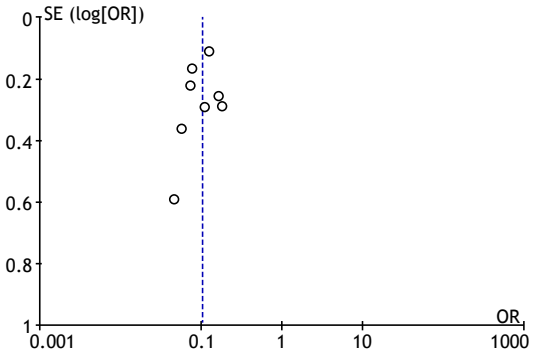

Figure 5. Funnel plot of publication bias.

methodological quality. The studies included in the analysis were carried out in seven countries from different continents, reducing publication bias. Thus, our results can be considered reliable.

In conclusion, as a biomarker, blood D-dimer may be helpful for the initial assessment of mortality risk of CAP patients, especially for identifying patients with a low risk of death when their D-dimer levels are within the normal range. However, well-designed prospective studies will be still necessary to explore the value of blood D-dimer levels for predicting CAP-related mortality in different clinical settings in the future.

AUTHOR CONTRIBUTIONS

CY: study conception and design; data collection; data analysis and interpretation; drafting and revision of the manuscript; and approval of the final version. HHZ, JH, and QYZ: data collection; data analysis and interpretation; and approval of the final version. KL: study conception and design; critical review for intellectual content; and approval of the final version.

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