Efficacy of Monocyte Distribution Width in the Early Diagnosis of Sepsis: A Diagnostic Meta-Analysis

Jiahao Chen
The First Affiliated Hospital of Soochow University
Qiang Guo (guojiang@suda.edu.cn)
The First Affiliated Hospital of Soochow University

Research Article

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Abstract

Background: Delayed diagnosis of sepsis urgently requires a fast, convenient, and inexpensive method to improve the early diagnosis of sepsis. Increasing evidence showed that monocyte distribution width (MDW) could be used as a non-invasive biomarker with high sensitivity and specificity for the early diagnosis of sepsis. However, the accuracy and reliability of its diagnosis are still controversial in different studies.

Method: A meta-analysis of all available studies regarding the association between MDW and the diagnosis of sepsis was performed to systematically evaluate the diagnostic efficacy of MDW in the prediction of sepsis.

Results: The estimated results of all eight studies are as follows: sensitivity, 0.84 (95% CI 0.77, 0.90); specificity, 0.68 (95% CI 0.54, 0.80); PLR, 2.7 (95% CI 1.8, 4.1); NLR, 0.23 (95% CI 0.15, 0.35); DOR is 12 (95% CI 5, 25). The corresponding overall area under the curve is 0.85 (95% CI 0.82, 0.88).

Conclusion: In conclusion, this meta-analysis demonstrates that MDW has high accuracy in distinguishing patients with sepsis from healthy controls for early diagnosis of sepsis. However, large-scale prospective studies and joint diagnosis with other indicators are urgently required to confirm our findings and their utilization for routine clinical diagnosis in the future.

Background

Sepsis is the leading cause of death in hospitals[1], and it brings a huge economic burden to the global health care system. Recent research estimated that there are currently 30 million cases and 6 million deaths each year due to sepsis[2]. Researches demonstrated both the time from first healthcare contact to antibiotic administration and emergency department (ED) delay in antibiotic administration are associated with greater in-hospital mortality in patients with community-acquired sepsis[3]. Therefore, early identification of sepsis and grasping the timing of antibiotic use are the top priorities.

Some classic biomarkers, such as white blood cell count (WBC), c-reactive protein (CRP), and procalcitonin (PCT), have been used to assist in the diagnosis of sepsis[4]. Unfortunately, the diagnostic performance that these biomarkers can provide is not high[5]. This has prompted doctors and researchers in intensive care and emergency departments to re-think and search for more effective biomarkers in sepsis. Crouser, Ed et al. evaluated the value of monocyte distribution width (MDW) for the early diagnosis of sepsis for the first time in 2017[6]. There is increasing evidence that MDW has a great contribution to the early diagnosis of sepsis[6–13].

However, there is no consensus on the results of MDW diagnostic efficacy studies. Therefore, we conducted a systematic meta-analysis of these data to determine whether MDW can be used as a biomarker for the early diagnosis of sepsis.

Materials And Methods

Literature search

This meta-analysis was conducted based on the guidelines for diagnostic meta-analysis[14]. We systematically searched PubMed, Embase, Cochrane library to screen related articles published before May 2021. The search terms included: “sepsis or septic shock”, “monocyte distribution width or MDW”. We searched for articles that

were limited to human studies, and in all languages. Possible missing articles were supplemented by using the related article function in PubMed and manually searching for references in the identified articles. The search strategy used for this review is shown in **Supplementary File 1**.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) concerning the diagnostic value of MDW for sepsis; (2) using the diagnostic standard (Sepsis 2.0 or Sepsis 3.0) for sepsis; (3) providing adequate data for the construction of two-by-two tables, including true positive, false positive, true negative, and false negative. Exclusion criteria were the following: (1) not relevant to the diagnostic value of MDW for sepsis; (2) in the form of letters, editorials, conference abstracts, case reports or reviews. If the same patient population was reported in several articles, we selected only the most comprehensive articles after screening.

Data extraction and quality assessment of included studies

Two reviewers independently screened the articles and extracted the research data. Discussion and consensus were conducted to resolve disagreements between the reviewers. The extracted data included the following: first author names, year of publication, sample source, study design, sample size, specimen test method, cut-off value, diagnostic outcomes, including sensitivity, specificity, true positive, false positive, true negative, and false negative. For studies that only provide sensitivity and specificity, due to the lack of contact with the researchers, we use these two to calculate true positive, false positive, true negative, and false negative. The methodological quality of each study was assessed and scored according to the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) criteria[15].

Statistical analysis

All analyses in this meta-analysis were performed using STATA/SE 15.1 software. The bivariate meta-analysis model was applied to calculate the pooled parameters with their corresponding 95% confidence intervals (CIs), including sensitivity, specificity, positive and negative likelihood ratios (PLR, NLR), and diagnostic odds ratio (DOR)[16, 17]. The sensitivity and specificity of various studies were summarized to generate the summary receiver operator characteristic (SROC) curve, and the area under the SROC curve (AUC) was calculated to evaluate the accuracy of diagnosis. The Q test and I2 statistics were conducted to assess the heterogeneity between studies. If the heterogeneity is high (P-value < 0.10 for the Q test, I2 value > 50 %), we employed the random-effects model[18]. We further performed subgroup analyses and meta-regressions to figure out the potential sources of heterogeneity. For the test of publication bias, we performed the Deeks' funnel plot asymmetry test (P-value <0.10 shows significant publication bias)[17].

Results

Literature searching

The initial literature search retrieved 58 potentially applicable articles based on the predefined selection criteria, among which 18 duplicate publications were excluded, leaving 40 articles remaining to be evaluated. We excluded 22 articles after screening the titles and abstracts. After a detailed assessment of the full texts, 11 articles were excluded, including one with insufficient data, one that was the letter, and nine that were conference

abstract. Therefore, eight studies from seven articles were included in this meta-analysis[6–13]. A flowchart summarizing the selection of the included studies is shown in Figure 1.

Study characteristics and quality assessment

The major characteristics of these seven articles are shown in Table 1. In this meta-analysis, these eight studies evaluated the diagnostic value of MDW for sepsis, including a total of 1,162 sepsis patients and 6324 control individuals. The publication year of the selected papers is from 2017 to 2021. The quality assessment of these studies is shown by the QUADAS-2 score in Table 1.

Table 1
Characteristics of the included studies.

First author	Year	Sepsis		Non-sepsis	Source	EDTA	Cut-off	Diagnostic power		QUADAS-2
		Sepsis-2	Sepsis-3					Sen (%)	Spe (%)	
Elisa Piva	2021	N/A	112	394	ICU	K2	24.63	66.88	77.79	5
A la Woo	2021	NA	188	361	ED	K2	19.80	83.00	49.90	5
Chihhuang Li	2021	N/A	54	146	ED	K2	20.00	90.60	37.10	5
		202	N/A	146	ED	K2	19.30	86.40	54.20	
Ennio Polilli	2020	N/A	105	155	IDU	K3	21.90	94.30	69.70	5
Luisa Agnello	2020	88	N/A	2127	ED	K3	23.50	92.00	92.90	5
Elliott D. Crouser	2020	385	N/A	1773	ED	K2	20.00	74.00	72.00	6
Elliott D. Crouser	2017	98	N/A	1222	ED	K2	20.50	77.00	72.00	6

N/A: None; EDTA: Ethylene Diamine Tetraacetic Acid; ICU: Intensive Care Unit; ED: Emergency Department; IDU: Infectious Diseases Department; Sen: Sensibility; Sep: Specificity

Diagnostic accuracy of MDW in sepsis

Figure 2 shows the data forest plot of seven studies on the sensitivity and specificity of MDW in the diagnosis of sepsis. A random-effects model is applied to evaluate the accuracy due to the significant heterogeneity observed in the sensitivity and specificity data (I2 is 88.92% and 98.98%, respectively). The pooled results of all seven studies are as follows: sensitivity, 0.84 (95% CI 0.77, 0.90); specificity, 0.68 (95% CI 0.54, 0.80); PLR, 2.7 (95% CI 1.8, 4.1); NLR, 0.23 (95% CI 0.15, 0.35); DOR is 12 (95% CI 5, 25). Figure 3 shows the corresponding overall SROC curve and the AUC is 0.85 (95% CI 0.82, 0.88), demonstrating that MDW has high accuracy in distinguishing patients with sepsis from the control group.

Meta-regression and robustness tests

To further investigate the potential sources of inter-study heterogeneity, we conducted the meta-regression analyses, with results showing in Figure 4. Notably, the meta-regression results reveal that the selection of anticoagulants (P<0.001) and cut-off value (P<0.01) are the conspicuous sources of heterogeneity. God-of-fit and bivariate normality analyses (Figure 5a, b) are performed and prove the moderate robustness of the bivariate model. Only one outlier has been identified through influence analysis and outlier detection (Figure 5c, d). There is no significant change in the overall results after excluding this outlier (Table 2). Finally, the Deeks' funnel plot asymmetry test suggests statistically nonsignificant publication bias (P=0.39) (Figure 6). The above test results confirm that the results of our meta-analysis are reliable and robust. **Discussion**

Table 2
Diagnostic performance of MDW in patients with sepsis

Analysis	Overall	Outlier excluded
Number of studies	8	7
SEN (95 % CI)	0.84(0.77, 0.90)	0.83(0.75, 0.89)
SPE (95 % CI)	0.68(0.54, 0.80)	0.62(0.52, 0.72)
PLR (95 % CI)	2.7(1.8, 4.1)	2.2(1.8, 2.8)
NLR (95 % CI)	0.23(0.15, 0.35)	0.27(0.20, 0.37)
DOR (95 % CI)	12(5, 23)	8(6, 12)
AUC	0.85(0.82, 0.88)	0.80(0.77, 0.84)
CI: confidence interval, SEN: sensitivity, SPE: specificity, PLR: positive likelihood ratio, NLR: negative likelihood ratio, DOR: diagnostic odds ratio, AUC: area under the curve		

Sepsis was defined as life-threatening organ dysfunction resulting from a dysregulated host response to infection, and septic shock was a serious subset of sepsis[19]. Despite great progress in anti-infection and care, sepsis is still one of the main causes of death or disability in critically ill patients with the in-hospital mortality high at 25-30%[20, 21]. For each hour of delay in completion of the sepsis bundle, the relative risk of death increases by 4%[22]. Therefore, early diagnosis is the key to complete timely treatment and antibiotic use.

Both Sepsis2.0 and Sepsis3.0 are built based on the infection[19, 23]. However, positive culture or molecular biological identification techniques are slow and cumbersome, and cannot be used for the early identification of sepsis[24]. In addition, culture-negative sepsis, viral and fungal sepsis can affect the initial diagnosis[25, 26]. To facilitate simple recognition in the prehospital, ward, and emergency department, the Sepsis-3 Task Force recommended a quick sepsis-related organ dysfunction assessment scoring prompt called "qSOFA"[19]. Whereas, qSOFA also has limitations. Relying only on qSOFA screening tools in the emergency department may delay the diagnosis of sepsis[27]. Therefore, the use of biomarkers may have the intended effect in the diagnosis of sepsis.

CRP has been used for many years, while PCT was considered to be a more specific and better prognostic marker than CRP[28]. Nonetheless, both of these have more than one limitation[29, 30]. Monocytes were the first to respond to pathogenic signals produced by microorganisms[31]. The shape or size of the cell changes in response to the pathogen-associated molecular patterns and is proportional to the intensity of exposure to the bacterial, fungal, or viral pathogen[6, 32].MDW is a parameter that reflects the volume changes of circulating monocytes caused by pro-inflammatory signals of infected organisms[33]. In addition, MDW is easy to obtain and

can be reported as part of a routine complete blood count (CBC), which makes it a practical tool to support the diagnosis of sepsis[34]. Recently, increasing evidence showed that MDW can be used as an effective biomarker for the early diagnosis of sepsis[6–13].

Several studies demonstrated MDW to be used as an early screening tool for sepsis with the following advantages: 1) MDW is easily available as part of the CBC and is faster and cheaper[35], 2) MDW has good performance in sepsis caused by a variety of pathogens[11],3) compared with CRP and PCT, MDW has better diagnostic performance with higher specificity and sensitivity[10, 11, 13].

However, conclusions about its diagnostic performance have shown inconsistencies in different studies. For example, a study by Agnello, L et al. revealed that MDW can be used for the diagnosis of sepsis with high sensitivity and specificity of 92.0% and 92.9 %[10], respectively, but another study from Chihhuang Li et al. showed a low specificity of only 37.1 % in sepsis detection[12]. The conflict in the results could be explained by differences in the source of patients (ED vs. others), the type of anticoagulant (K3-EDTA vs. K2-EDTA), and the criteria of sepsis (Sepsis2.0 vs. Sepsis3.0), which makes interpretation difficult. For purpose of evaluating the diagnostic accuracy of MDW as a biomarker for early diagnosis of sepsis, we conducted this meta-analysis to provide a comprehensive analysis. This meta-analysis included eight studies from seven articles. As the results show, the pooled parameter for sepsis diagnoses of MDW, including sensitivity, specificity, PLR, NLR, AUC, and DOR are as follows: 0.84, 0.68, 2.7, 0.23, 12, and 0.85, respectively. Combined with Fagan's nomogram, MDW has a moderate ability to distinguish healthy controls (Figure 7). PLR>10 and NLR<0.1 are recognized to be greater accuracy[36]. In addition, the AUC of the SORC curve generated by MDW is 0.85, which represents the high accuracy of MDW as a biomarker for the early diagnosis of sepsis.

This meta-analysis also implemented meta-regression to explore the potential sources of heterogeneity. We found that the type of anticoagulant used (K2-EDTA or K3-EDTA) and the MDW cut-off value used have a significant impact on the inter-study heterogeneity. As Luisa Agnello et al. found, using K2-EDTA MDW cut-off and K3-EDTA samples may lead to higher false positives, and vice versa, it will increase the possibility of false negatives. However, we failed to perform subgroup analysis by reason of the small sample size. In addition, we found no significant difference in the diagnostic value of MDW in Sepsis 2.0 or Sepsis 3.0 (**Supplement** Figure 1-2).

The advantages of our meta-analysis are as follows: (1) We strictly select studies that meet our baseline requirements, which strengthens our credibility in evaluating the diagnostic value of MDW. (2) We conducted a meta-regression analysis to find the source of suspicious heterogeneity. The robustness of the test was evaluated through impact analysis and outlier detection. (3) The absence of publication bias confirms the reliability and robustness of our analysis results.

However, this meta-analysis also has its limitations. First of all, the number of articles we have included is limited, and it is not ruled out that some available studies may still be missed during the screening process. Secondly, we have not been able to comprehensively evaluate the diagnostic efficacy of MDW combined with other biomarkers for sepsis. Crouser ED et al. previously reported the potential benefits of the combined use of MDW and WBC counts[6, 7], while A la Woo et al. found that the combined use did not improve AUC[12]. Thirdly, the impact of immune function status on the diagnostic value of MDW is also worthy of evaluation. Despite the above limitations, our study is the first meta-analysis to fully demonstrate the value of MDW in the early diagnosis of sepsis.

In conclusion, the results of this meta-analysis show that MDW, as a marker for early diagnosis of sepsis, has high accuracy in distinguishing patients with sepsis from healthy controls. However, due to the small number of included studies, more and larger prospective studies and further improvements are urgently needed to confirm our findings and their utilization for routine clinical diagnosis in the future. MDW combined with other biomarkers for collaborative diagnosis also has promising prospects.

Abbreviations

MDW
Monocyte distribution width
ED
Emergency department
WBC
White blood cell count
CRP
C-reactive protein
PCT
Procalcitonin
QUADAS-2
Quality Assessment of Diagnostic Accuracy Studies-2
CIs
Confidence intervals
PLR
Positive likelihood ratio
NLR
Negative likelihood ratio
DOR
Diagnostic odds ratio
SROC
Summary receiver operator characteristic
AUC
Area under curve
qSOFA
Quick sequential organ failure assessment
CBC
Complete blood count

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Jiahao Chen: conceived and designed study, screened studies, assessed risk of bias, extracted data, analysed and interpreted data, prepared figures and drafted manuscript.

Qiang Guo: supervised design of study, assisted with screening of studies, supervised data analysis and interpretation.

Acknowledgements

Everyone who has contributed to the work has been listed.

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Figures

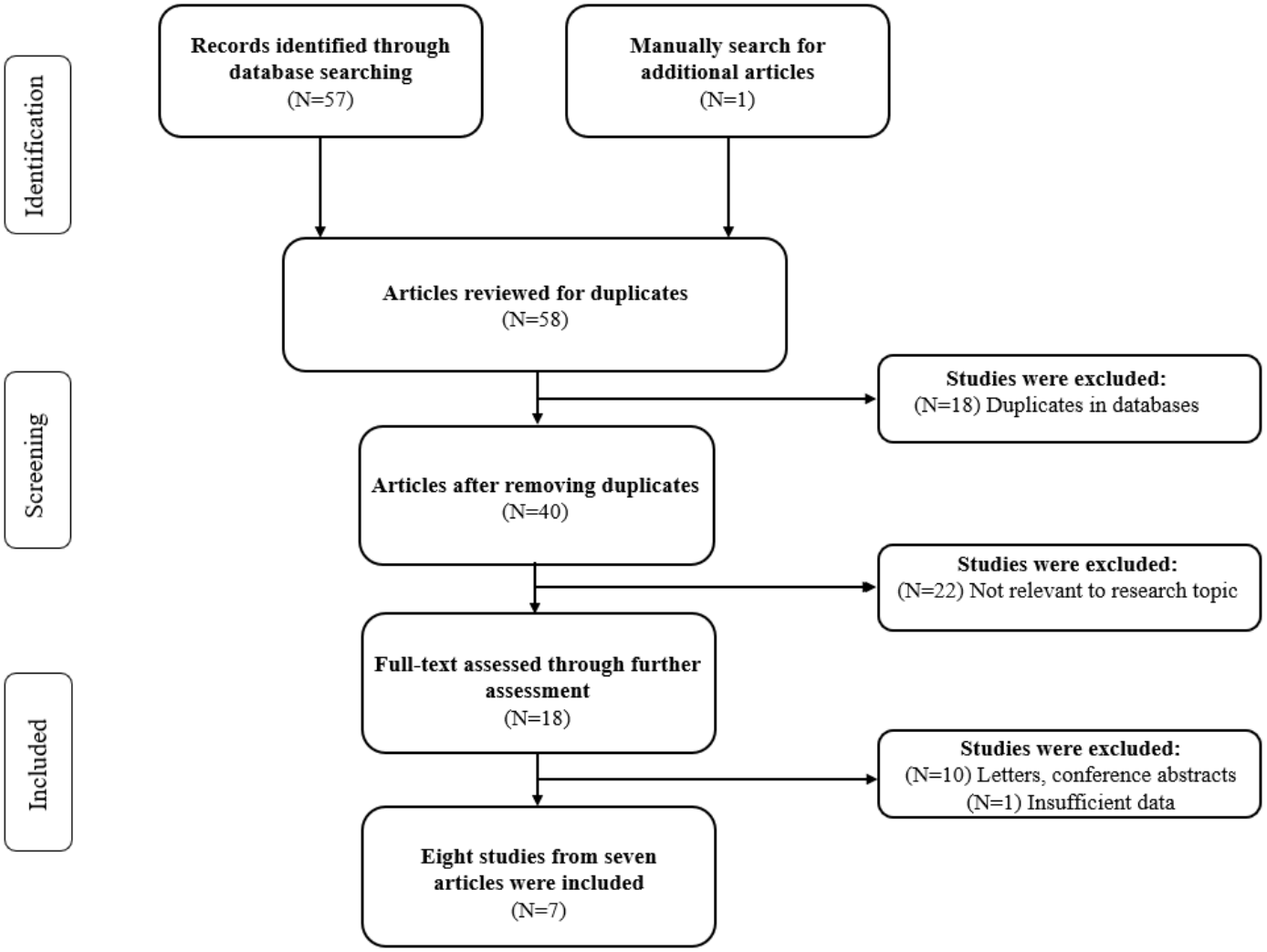

Figure 1

Flowchart of the study selection process.

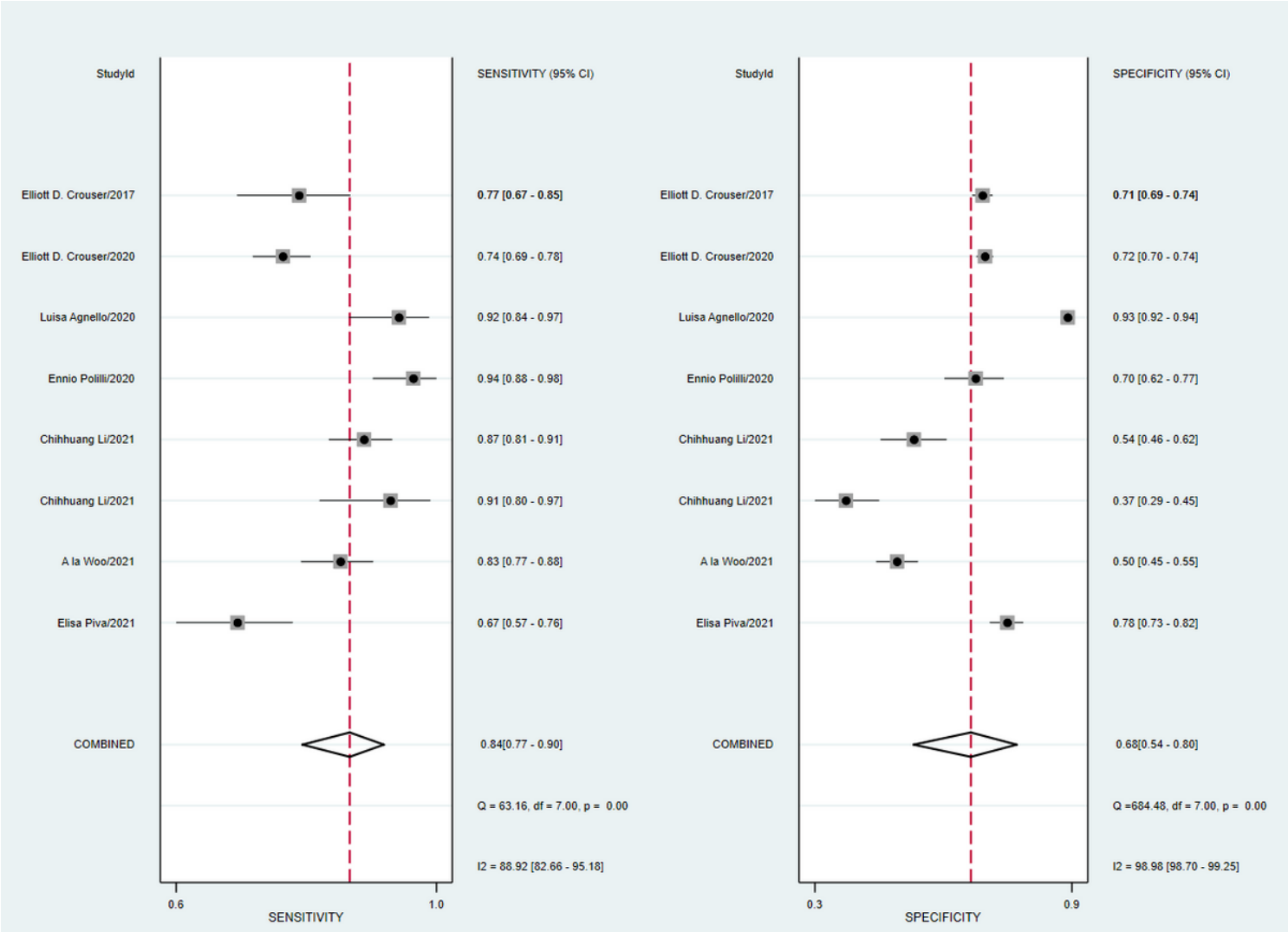

Figure 2

Forest plots of sensitivity and specificity analyses for the overall studies.

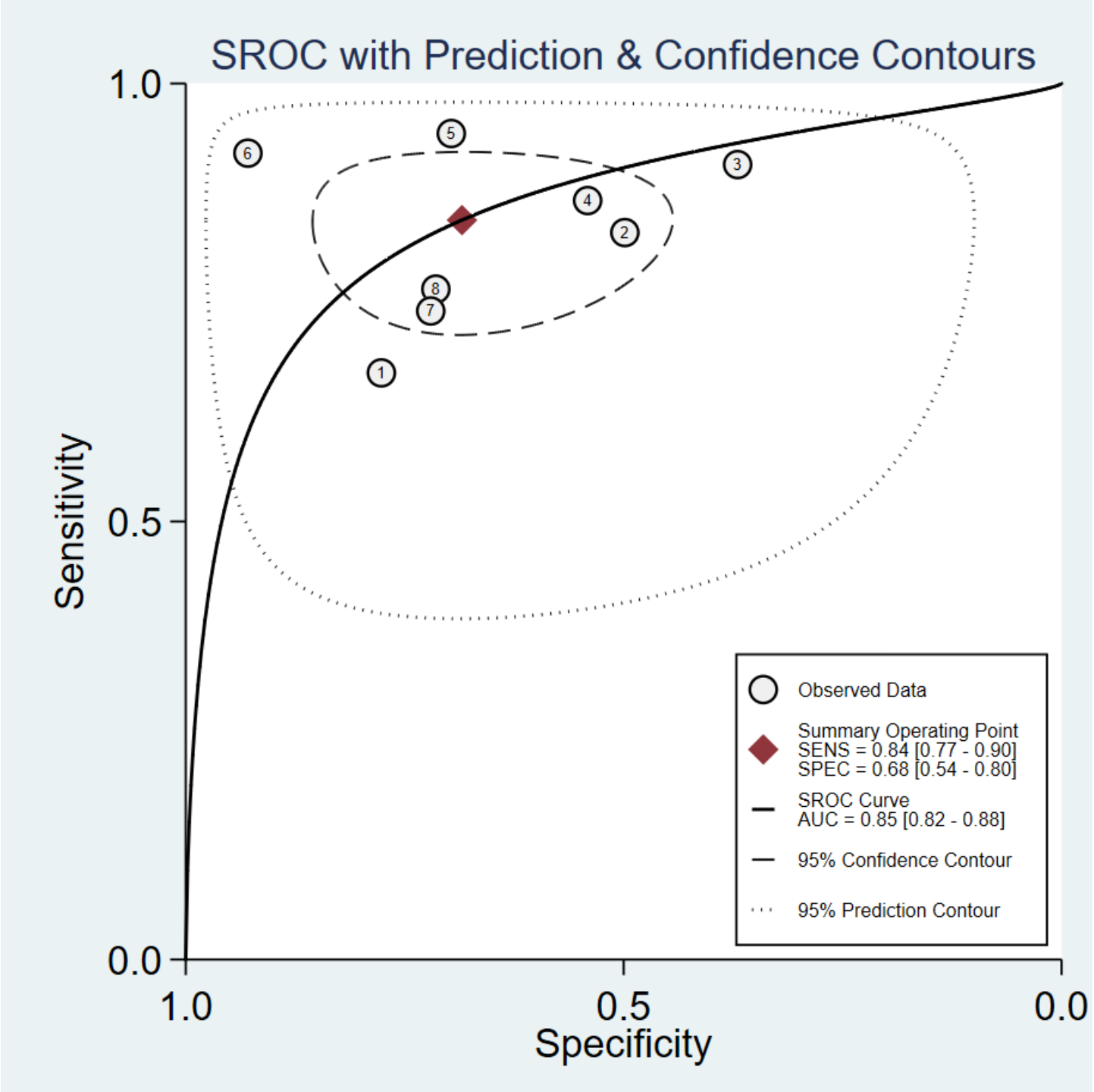

Figure 3

SROC curve with pooled estimates of sensitivity, specificity, and AUC.

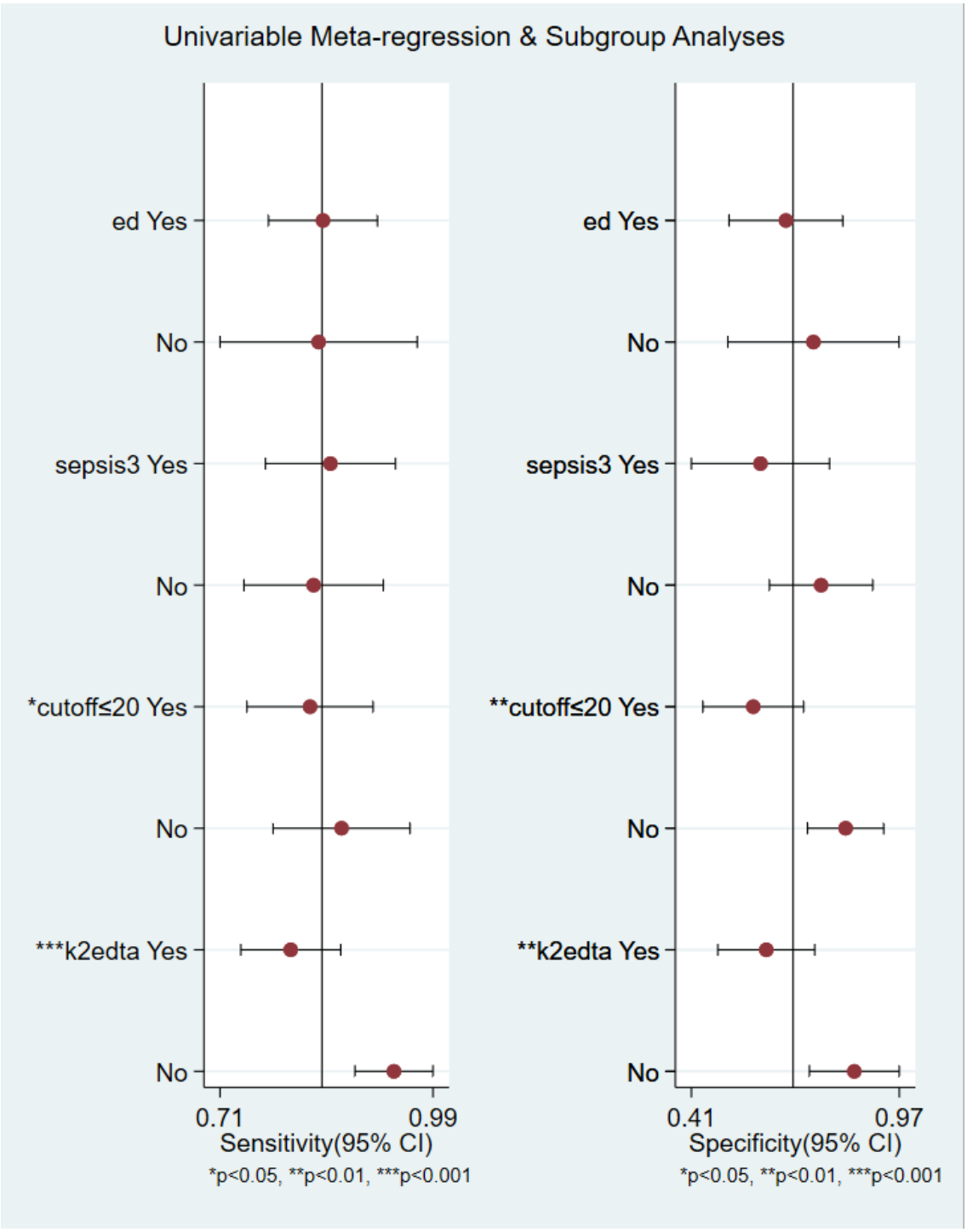

Figure 4

Univariate meta-regression for sensitivity and specificity.

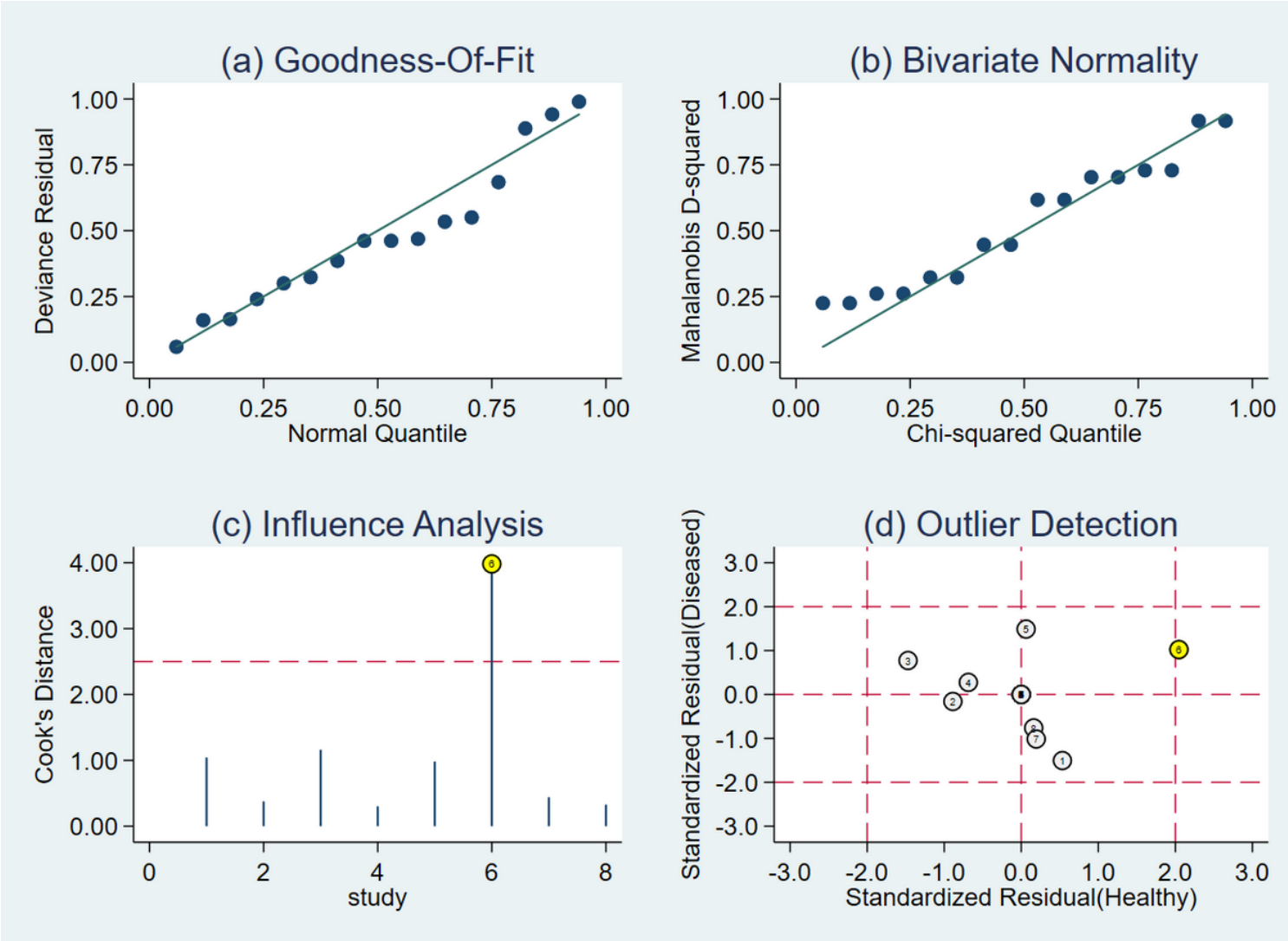

Figure 5

Graphs for sensitivity analyses: a goodness of fit, b bivariate normality, c influence analysis, and d outlier detection.

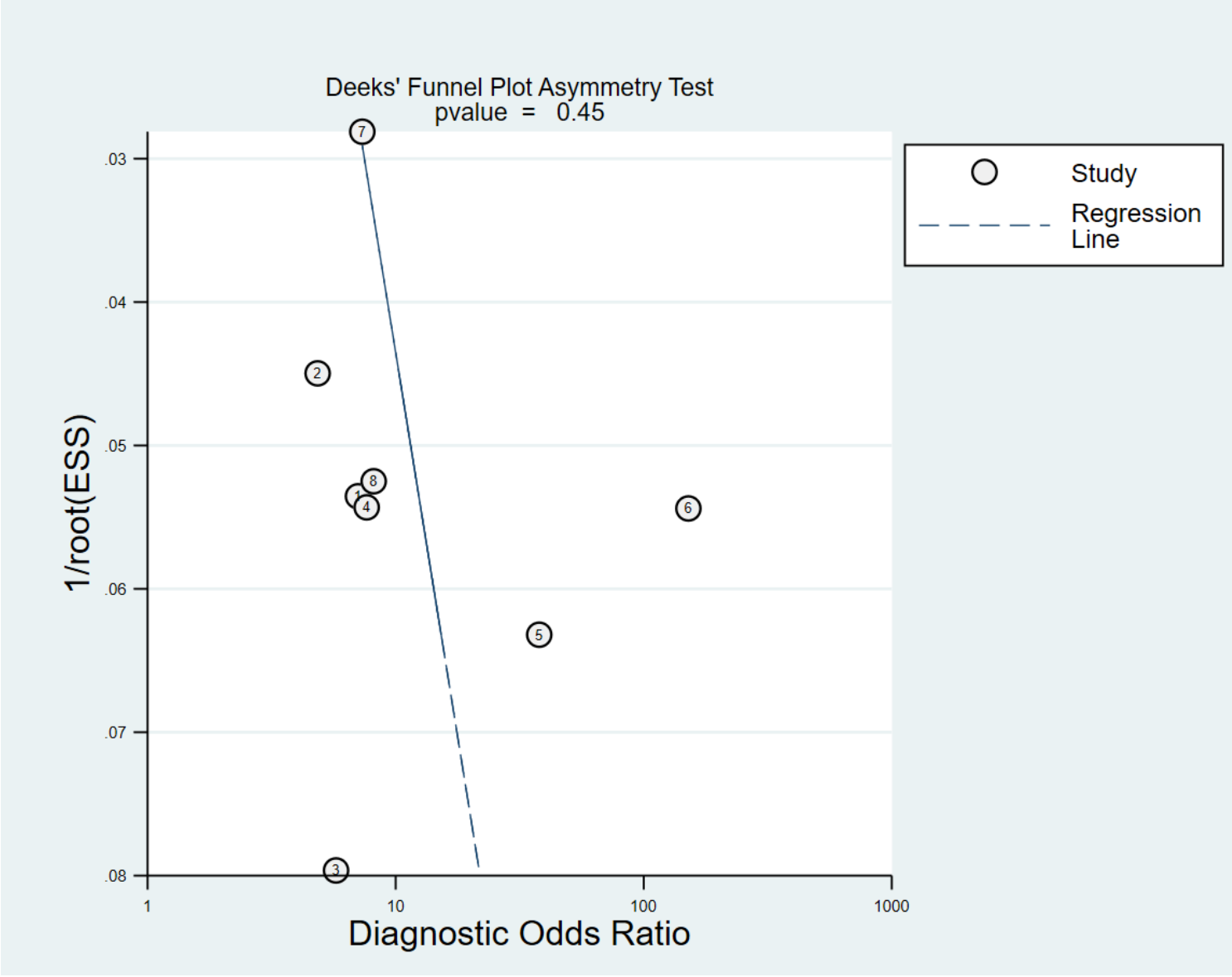

Figure 6

Graph of Deeks' funnel plot asymmetry test.

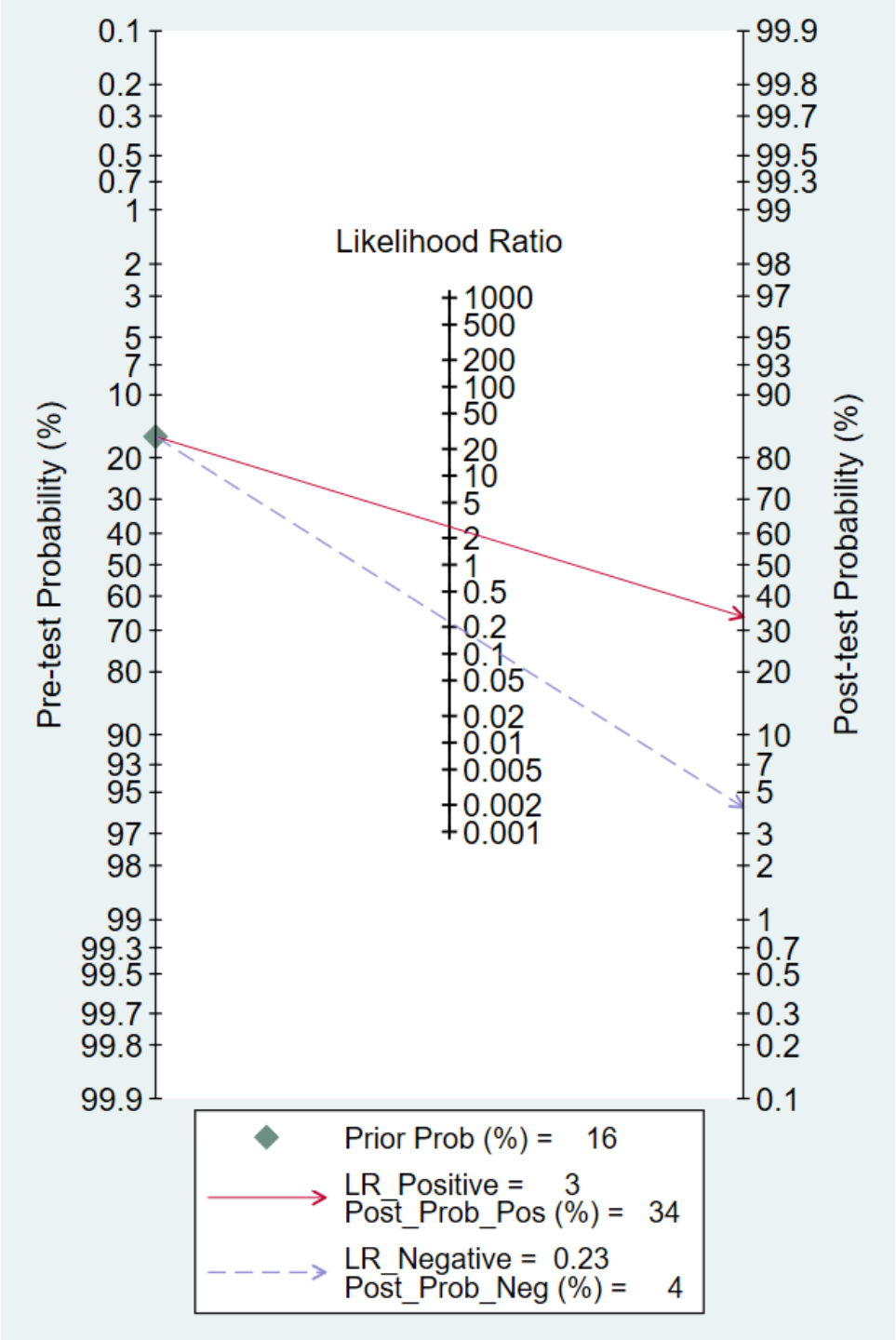

Figure 7

Fagan's nomogram for assessing the post-test probabilities.

Supplementary Files

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