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Diagnostic accuracy of biomarker D-dimer in patients after stroke suspected from venous thromboembolism: A diagnostic meta-analysis

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ABSTRACT

D-dimer is a promising biomarker for identification of venous thromboembolism (VTE) in patients with stroke. The purpose of our study is to evaluate the diagnostic value of D-dimer as a promising biomarker for VTE in patients after stroke. We performed an exhaustive search of leading databases including Pubmed, Embase, the Cochrane library, China National Knowledge Infrastructure (CNKI), and China Biology Medicine disc (CBM) from inception to Oct 13, 2017. We included studies written in English and Chinese. We included studies that appraised the diagnostic value of D-dimer with reference standard for VTE diagnosis in patients after stroke. We concurrently constructed a 2 × 2 table with data extracted from included studies. We identified 8 studies that included 1490 patients after stroke from our database searches. The pooled result from limited evidence showed a sensitivity of 0.85 (95% CI 0.76–0.90) and a specificity of 0.77 (95% CI 0.73–0.81). The area under the summary receiver operating characteristic curve was 0.85(95% CI 0.81–0.88). The positive likelihood ratio (LR +) and the negative likelihood ratio (LR-) were 3.8 (95% CI 3.1–4.4) and 0.20(95% CI 0.12–0.31), respectively. In patients after stroke suspected of venous thromboembolism, D-dimer is a beneficial biomarker for diagnosis of VTE. For stroke patients with low probability of VTE, a normal D-dimer test can be used to rule-out VTE. However, we do not recommend using D-dimer as the single definitive test for VTE diagnosis. We recommend diagnosing VTE using multi-branch diagnostic strategy.

1. Introduction

Worldwide, venous thromboembolism (VTE) is a common complication after acute stroke and is a primary cause of mortality after stroke [1]. It is well established that limb paralysis, physical immobility, age especially older patients and atrial fibrillation are important factors that have a positive correlation with the risk of VTE [2–4]. Early diagnosis of VTE is critical in preventing death from pulmonary or respiratory compromise [1]. However, diagnosing patients suspected of venous thromboembolism is a great challenge due to the non-specific signs and symptoms that result in the condition being overlooked by clinicians [5]. In the past, venography was the gold-standard; however it has almost fallen out of favour because it is invasive and expensive. As the cornerstone diagnostic strategy for VTE, venous ultrasound (US) is a safe, noninvasive and reliable alternative for VTE detection [1,6–8]. However, US is limited to only 15%~28% of suspected cases that actually have a thrombosis [9]. Additionally, it is costly to perform and requires a specialist for interpretation [1]. This has led to a search for more efficient strategy.

D-dimer assay is usually applied to raise the cost-effectiveness for VTE diagnosis as a non-invasive and inexpensive screening test. D-dimers is a fibrin degradation product that is generated during fibrinolysis [10]. Currently, plasma D-dimers levels have been identified as a valuable diagnostic test for exclusion of VTE, but they lack adequate clinical sensitivity or specificity for diagnosis of VTE. There are systematic reviews and meta-analyses suggesting that normal D-dimer levels can exclude VTE in patients with a low risk of VTE without the need for additional investigation [11–16].

The meta-analysis mentioned above included various populations was not restricted to patients with stroke. In healthy individuals, plasma D-dimer is rarely elevated. However, in any condition involving the formation and degradation of fibrin including infections, cancer, surgery and stroke, plasma D-dimer may be increased [17,18]. It is unclear that whether the changes in plasma D-dimer concentration over

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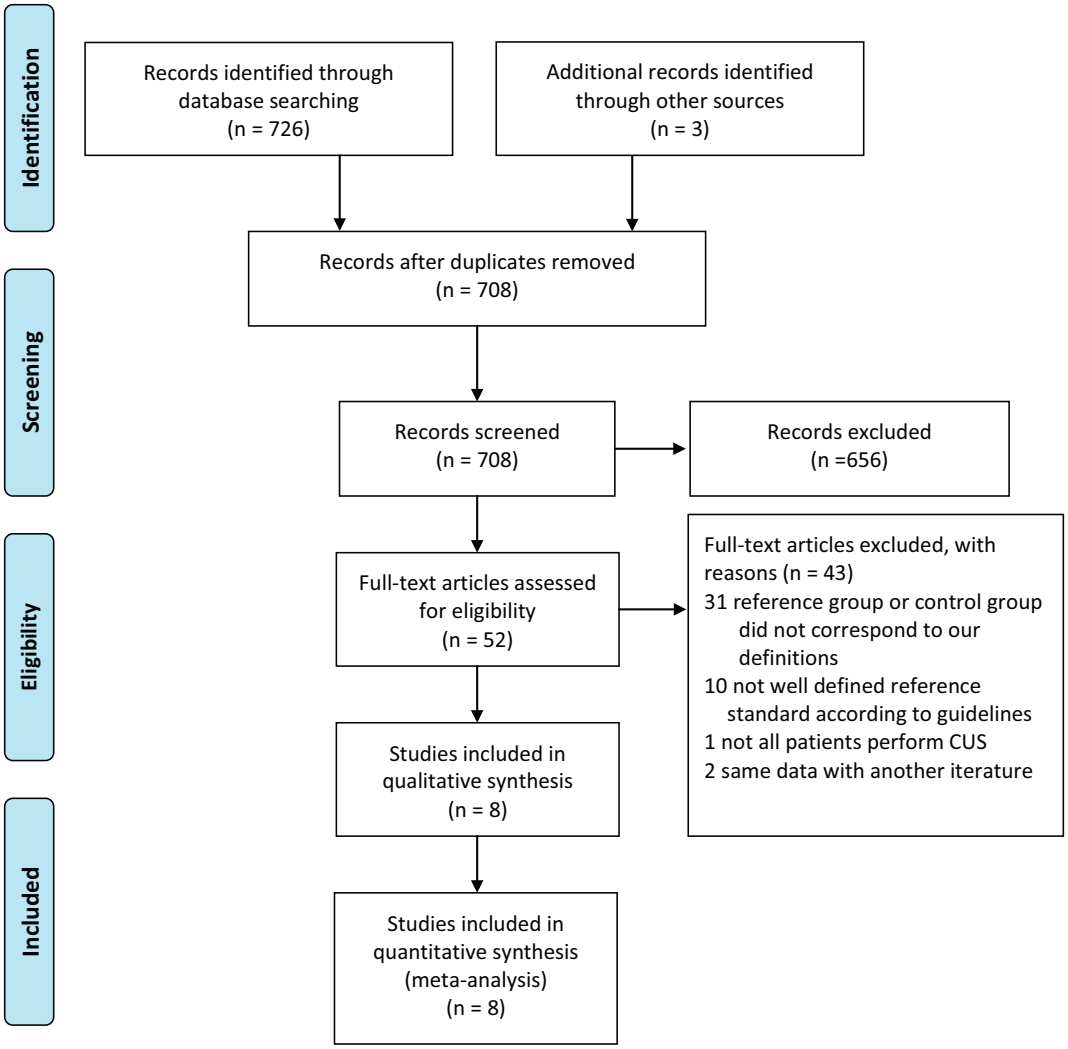

Fig. 1. Flow chart of systematic literature search.

time among patients after stroke are attributable to VTE or stroke. The results from a study conducted by William et al. showed that mean D-dimer levels were slightly elevated during the first week and continued to be increased during the 2 weeks following a stroke [19]. Plasma D-dimer density significantly increased in patients after stroke, leading to a high percentage of these patients whose plasma D-dimers levels are higher than common cut-offs (500 ng/ml) [18].This may lead to more false positive VTE diagnoses (low specificity) using a D-dimer assay in patients after stroke. Whether D-dimer plays the same role in the diagnosis of VTE in patients after stroke was unclear. Recently, results from D-dimer studies have been published, and our understanding of D-dimer continues to develop.

A systematic review can provide evidence for this theme, and a meta-analysis can provide an accurate appraisal of the diagnostic value for D-dimer assays [20]. Therefore, we performed a systematic review and meta-analysis to evaluate the accuracy of D-dimer tests for VTE diagnosis in patients after stroke, with a particular interest in their diagnostic value for excluding DVT(deep venous thrombosis) or PE after stroke.

2. Methods

2.1. Data sources and searches

We performed an exhaustive search of leading databases including Pubmed, Embase, the Cochrane Library, China National Knowledge Infrastructure (CNKI), and China Biology Medicine disc (CBM) for articles assessing the diagnostic value of D-dimer assays for VTE among patients after stroke on 13 October 2017. Our search strategy included ("D-dimer" OR "fibrin fibrinogen degradation products") AND ("venous thrombosis" OR "pulmonary embolism") AND ("Stroke" [Mesh] OR "Cerebrovascular Accident") NOT ("review" OR "letter" OR "meta-analysis" OR "case report"). Duplicate references identified from databases were manually filtered by Endnote X7, version 17.0. We also searched the reference list of included studies and published reviews. We did our analysis according to the guidelines for reporting diagnostic accuracy systematic reviews [21] with a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist. We present a PRISMA flow diagram in Fig. 1 to show the filtering process for included studies [22].

2.2. Study selection

Inclusion criteria and exclusion criteria were prespecified. Studies were included if the study met the following criteria: (1) had a study population of patients after stroke regardless of timing since stroke (2) performed a D-dimer assay in all patients, (3) used compression ultrasonography or venography as a reference standard to detect VTE, and (4) included data on sensitivity, specificity, negative and positive predictive values. Papers that met the following criteria were excluded: (1)

Table 1a
Characteristics of included studies.

Order	Author	Year	Mean age(year)	Proportion Males(%)	Admission category	D-dimer assay	Cutoff (ng/ml)	n	Prevalence (%)	TP	FP	FN	TN	Sensitivity	Specificity	Reference standard
1	Balogun et al. [28]	2016	69	38	AIS & ICH	LPIA	1570	92	20	13	21	5	53	0.71	0.71	CUS
2	Chen et al. [30]	2016	61	62	ICH	IL	1720	60	47	18	5	10	27	0.64	0.83	CUS
3	Cheng et al. [32]	2016	62	48	ICH	IL	1200	210	26	51	45	3	111	0.94	0.71	CUS
4	Guo et al. [33]	2009	67	77	AIS &ICH	IL	246	95	14	10	21	3	61	0.80	0.76	CUS and venography
5	Harvey et al. [1]	1996	63	50	AIS &ICH	ELISA	1591	105	13	13	19	1	72	0.79	0.78	CUS
6	Kong et al. [2]	2016	63	51	AIS	IL	1510	255	22	51	29	5	170	0.91	0.85	CUS
7	Kuwashiro et al. [31]	2012	72	50	AIS& ICH	LPIA	5500	133	46	54	14	7	58	0.89	0.81	CUS
8	Wang et al. [29]	2012	NR	NR	AIS	LPIA	500	540	8	33	122	9	376	0.79	0.76	CUS

Table 1b
Characteristics of included studies.

Order	Author	Average time since stroke	Average time D-dimer test since stroke	Average time CUS since stroke	Other information about included patients	Type of VTE
1	Balogun et al. [28]	48 h	upon enrolment	2 weeks	acute stroke	DVT after stroke
2	Chen et al. [30]	NR	NR	30 days	acute ICH stroke	DVT after stroke
3	Cheng et al. [32]	24 h	7:00–8:00 after admission	15 days	acute ICH stroke	DVT after stroke
4	Guo et al. [33]	NR	1 week	1 week	stroke	DVT after stroke
5	Harvey et al. [1]	3 months	during inpatient rehabilitation	during inpatient rehabilitation	ambulating < 100 ft on rehabilitation admission	DVT after stroke
6	Kong et al. [2]	15 days	NR	NR	ischemic stroke	DVT after stroke
7	Kuwashiro et al. [31]	72 h	on admission	NR	hospitalized acute stroke	DVT after stroke
8	Wang et al. [29]	NR	second day on admission	7–10 day	acute AIS stroke	DVT after stroke

AIS, acute ischemic stroke; CUS, compression ultrasonography;?, not reported; ELISA: enzyme-linked immunosorbent assay; IL, immunoturbidimetric assay; ICH, intracerebral hemorrhage; LPIA: Latex photometric immunoassay; NR, not reported; Prevalence, proportion of VTE; VIDAS is an enzyme-linked fluorescent assay combining the ELISA method with a final detection in fluorescence; TP = true positive, FP = false positive, TN = true negative, FN = false negative; Type of VTE: PE, DVT pre-stroke or DVT after stroke.

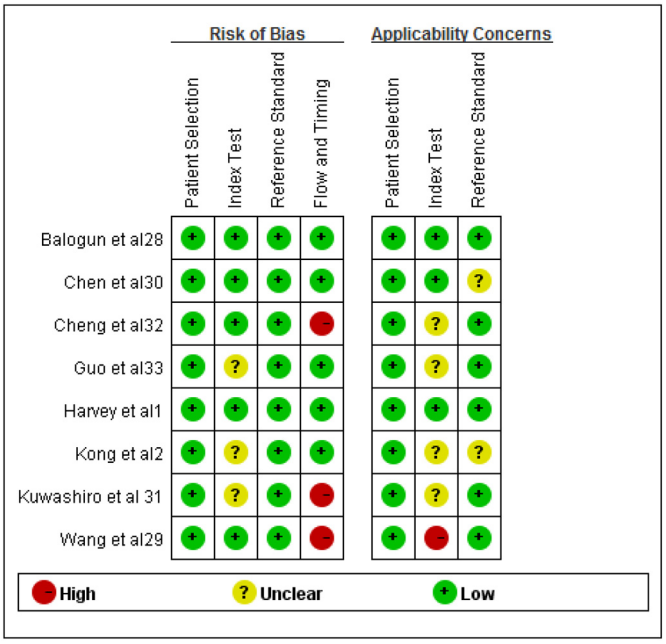

Fig. 2. Risk of bias and applicability concerns Summary.

animal studies, mechanistic studies, case reports, editorials, comments, guidelines or reviews articles; or (2) did not perform D-dimer assays in all patients.

2.3. Data extraction

Two investigators (Fenfen Li and Dongdong Zhang) independently collected data from each study including proportion of males, mean age and prevalence of venous thromboembolism [5].We constructed 2 × 2 tables for patients with the extracted data on true positive(TP), false positive(FP), false negative (FN) and true negative (TN) results according to the reference standard. Discrepancies were settled by consulting a third investigator (Ganqin Du).

2.4. Quality assessment

Two reviewers (Fenfen Li and Dongdong Zhang) independently evaluated the methodological quality of the articles with QUADAS-2 [23]. There are four key domains including patient selection, index test, reference standard, and flow and timing in QUADAS-2, for risk of bias and applicability judgements [24]. Each domain was rated in terms of risk of bias and applicability concern.If there were doubts between reviewers, a third investigator (Du Ganqin) was consulted.

2.5. Data synthesis and analysis

We calculated the overall sensitivity and specificity with 95% CI for D-dimer in random effects bivariate regression models. We constructed a summary receiver operating characteristic (SROC) curves for D-dimer with the primary study using the derived logit estimates. We calculated the area under the curve (AUC) for D-dimer.

Positive likelihood ratio (LR+), negative likelihood ratio (LR-), and diagnostic odds ratio (DOR) are indicators that combine both sensitivity and specificity. We performed calculations of LR+ by dividing sensitivity over (1-specificity) and LR- by dividing (1-sensitivity) over specificity. DOR is defined as the ratio of LR+ over LR-.Although there is no absolute cut-off, an index could be predictive (LR+ > 2, LR- < 0.5, or LR+/LR- ratio > 4), well predictive (LR+ > 5, LR- < 0.2, or LR+/LRratio > 10), or very well predictive (LR+ > 10, LR- < 0.1, or LR+/LR- ratio > 100) [25].

We performed calculations of I^2 to assess heterogeneity. To examine sources of heterogeneity, we did a meta-regression analysis by adding study characteristics to model as covariates. We did a Deek's test of funnel plot asymmetry for publication bias and other sample size effects [26]. Finally, we estimated the predictive value of D-dimer tests including pre-test odds ratio and post-test odds ratio.

We used the MIDAS [27] module of Stata version 14.0 for pooled forest plot, SROC, publication bias, and Fagan's Nomogram. We used Review Manger software, RevMan 5 (Revman 2014) to produce graphs on quality assessment.

3. Result

3.1. Selection, population characteristics and study quality

Our database searches returned 729 records. After screening the titles and abstracts, we excluded 656. After a detailed screen, we excluded an additional 43, eight studies including a total of 1490 patients after stroke were included [1,2,28–33] (Fig. 1). Baseline characteristics are summarized in Table 1. The prevalence of VTE among patients after stroke ranged from 8% to 47%, with most falling between 10% and 30%. The mean age of patients ranged from 61 to 72 (years).

Key information including sensitivity and specificity could be immediately extracted from 9 articles. One of the 8 included didn't report average age of included patients [29]. We searched the reference lists included articles and published reviews [5,9,11,13,34–36] did not alter the result. For inclusion subtype of stroke, two studies included acute Ischaemic patients [2,29], two studies included intracerebral hemorrhage patients [30,32], and four studies included both types of patients [1,28,31,33].

In total, we included different D-dimer assays: 105 tested with patients ELISA, 620 patients tested with IL, 765 patients tested with LPIA, of whom 14/105(13.3%), 151/620 (24.4%), 121/765(15.8%) were diagnosed with VTE, respectively. Average patients' age ranged from 61 to 72 years, and proportion of males ranged from 38%–77%.

Overall methodology quality of the identified studies was moderate (Figs. 3 and 4). All studies included prospectively consecutive patients after stroke suspected of venous thromboembolism. There are concerns about the applicability of the index test because the different D-dimer assays (LPIA, ELISA, IL) may affect the accuracy of the results and

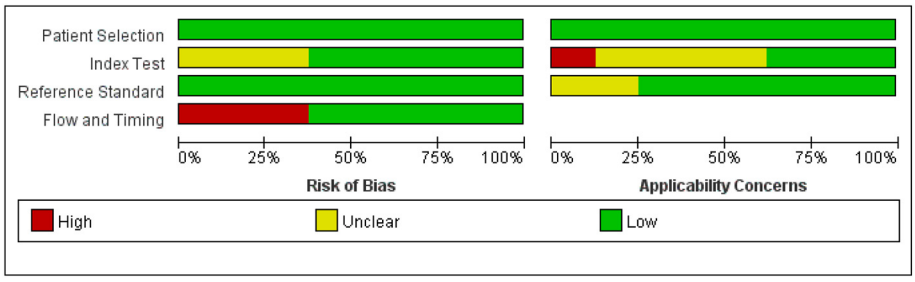

Fig. 3. Risk of bias and applicability concerns Graph.

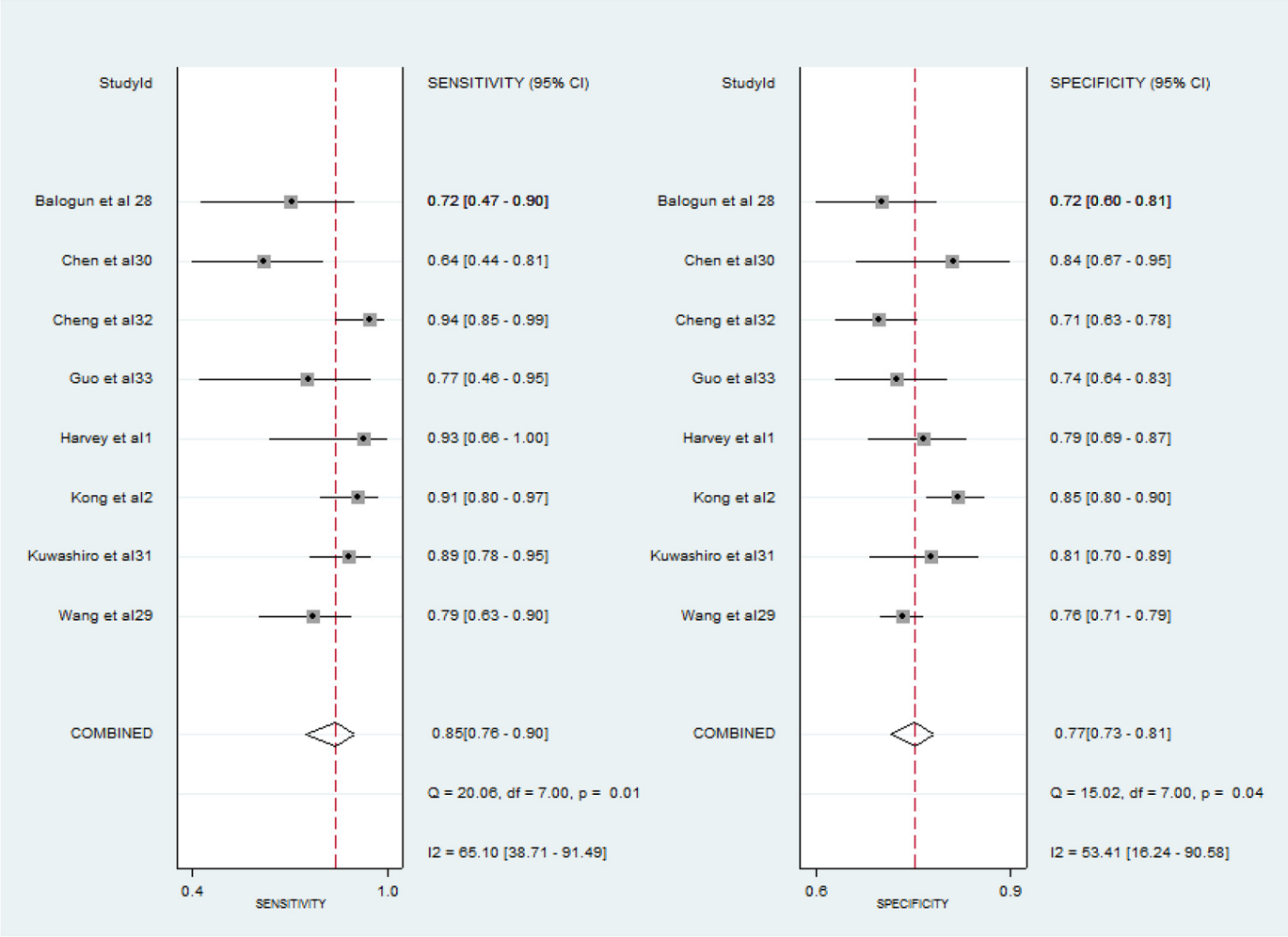

Fig. 4. Forest plot of D-dimer for venous thromboembolism.

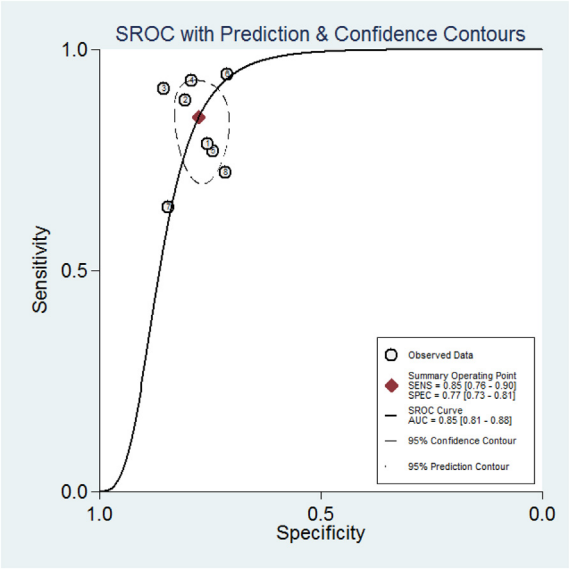

Fig. 5. Summary receiver operating characteristic curve (SROC) for included studies.

introduce bias. In the flow and timing domain, three studies were rated as high-risk bias because not all patients were included in the study or the interval between the D-dimer assay. Regarding applicability concerns, there was approxomately 12% high-risk concern about the index test due to variable results from the different tests. Additionally, D-dimer assays could be affected by many factors Figs. 2 and 8.

3.2. Diagnostic accuracy of D-dimer tests over analysis

The pooled sensitivity and specificity were 0.85 (95% confidence interval 0.76–0.90) and 0.77(0.73–0.81), respectively (Fig. 4). The SROC illustrates the relationship between sensitivity (SEN) and specificity (SPE). It can also determine the presence of a threshold effect. Based on the bivariate approach, which estimates not only the strength but also the shape of the correlation between SEN and SPE, a 95% confidence ellipse and 95% prediction ellipse were drawn (Fig. 5). The area under the summary receiver operating characteristic curve (SROC) was 0.85 (95% confidence interval 0.81–0.88; Fig. 5).

The likelihood ratio for a positive test and negative test were 3.8 (95% confidence interval 3.1–4.6) and 0.20 (95% confidence interval 0.12–0.31), respectively. The pooled diagnostic odds ratio (DOR) was 19 (95% confidence interval 10–35). Analysis of Deeks' regression test demonstrate no significant evidence of bias ($t = -1.41$; $P = .21$, Fig. 6). As anticipated, there was substantial heterogeneity between studies with an I^2 of 65.10% (95% CI 38.70–91.49) for the sensitivity results and 53.41% (95% CI 16.24–90.58) for the specificity results.

To identify potential source of heterogeneity, we did a meta-regression analysis. To compare admission categories of patients after stroke, we divided patients into an AIS group [2,29], ICH group [30,32] and AIS &ICH patients [1,28,31,33].Because some studies include both

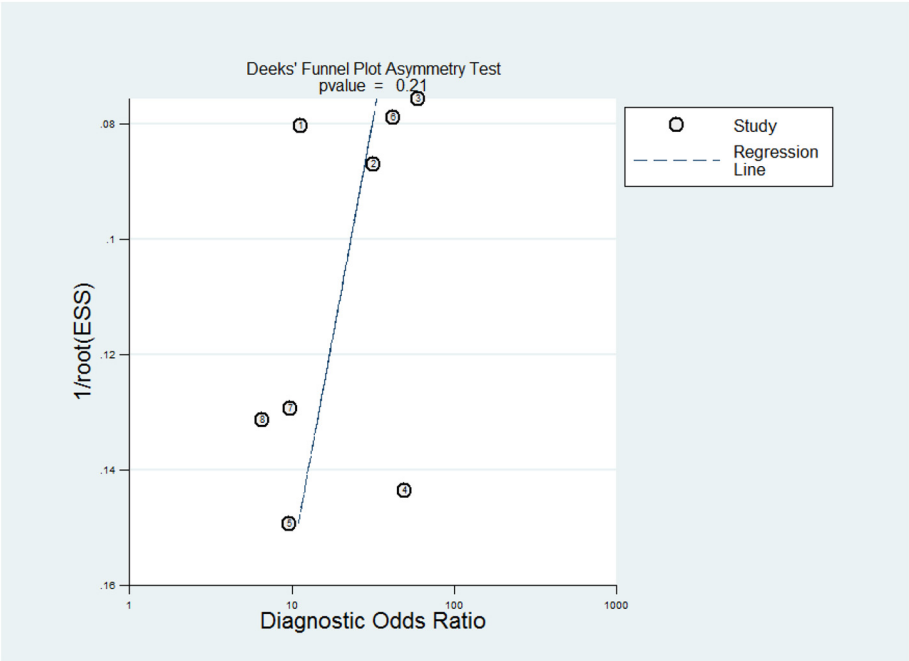

Fig. 6. Deeks' test of funnel plot asymmetry for included studies. Effective sample size ESS, where ESS = $(4n_1{*}n_2)/(n_1 + n_2)$, nondiseased (n1) and diseased (n2) number of sample; number in circle refers to order of study as shown in Tables 1a and 1b.

AIS and ICH patients, we cannot extract data on AIS or ICH alone. We defined no AIS as patients of ICH plus AIS & ICH groups. Similarly, we defined no ICH as patients of AIS and AIS & ICH group. As shown in Fig. 7, sex,presence of ICH and AIS may have been factors that contributed to the heterogeneity of specificity ($P < .05$). The diagnostic value of no ICH group was higher than that of no AIS group (AUC) (0.87 [95% CI 0.84–0.90] versus 0.80 [95% CI 0.76–0.83]; not tested for significance). We also defined baseline data including index (D-dimer assay with IL or not) and sex (proportion of male patients > 50% or not) as covariates for the regression to detect sources of heterogeneity. According to the results of our analysis (Fig. 7.), D-dimer assay with IL or not, male percentages > 50% or not, and AIS patients or not were factors that contributed to heterogeneity for specificity. The proportion of males may be a factor that contributed to heterogeneity of sensitivity.

Setting pre-test probability at 19%, the post-test probability is 47% raising the probability of VTE over 2.47-fold when positive and lowering the probability of VTE to 4% when negative (Fig. 7).

4. Discussion

This is the first diagnostic meta-analysis that attempted to identify current literature regarding the diagnostic accuracy of D-dimer for VTE in patients after stroke. Generally, a normal D-dimer assay that results in combination with a low probability of VTE is widely used to safely rule-out VTE and decrease the number of unnecessary CUS [5]. However, elevated D-dimer concentration in plasma have been reported in association with many factors, including cerebral venous sinus thrombosis, acute pulmonary embolism spontaneous intracerebral hemorrhage, and long-term neurologic outcomes in Childhood-Onset Arterial Ischaemic Stroke [18]. Results from a prospective cohort study by JZ Wen et al. [18] showed that plasma D-dimer levels increased with increased severity of stroke, as defined by NIHSS score and infarct volume. There is dispute on the diagnostic value of D-dimer in patients after stroke and suspected VTE. In particular, older patients and immobile patients would benefit if unnecessary CUS imaging could be safely avoided. This was the purpose of this aggregated meta-analysis.

After an exhaustive search of literature and the application of stringent inclusion-exclusion criteria, and relatively rigorous selection methodology, we included 8 studies involving 1490 patients for our study. Available data from the studies included in this analysis demonstrated that plasma D-dimer assays have a sensitivity for venous thromboembolism of 85% (95% CI 0.76–0.90) and a specificity of 77% (95% CI 0.73–0.81). This means there is a relatively low false negative rate (15%) for diagnostic accuracy of D-dimer but a relatively higher false positive rate (23%). This makes D-dimer assays useful as a rule-out test but means that a positive result will require further investigation with diagnostic imaging. The AUC is 0.85 which indicates a moderate diagnostic performance of 0.85(95% CI 0.81–0.88) [37].

LR and post-probabilities are important reference indicators for doctors. They provide information about the possibility that a patient with a positive or negative test result has VTE. According to the result of our analysis, both the LR and post-test probability are moderate (Fig. 7). LR+ of 4 implied that a patient with VTE is four times more likely to have a positive test than a healthy person. Setting the pre-test probability at 20%, the post-test probability for a positive result is 47% (Fig. 7). Likewise, the negative likelihood ratio is 0.19% for a negative test result. The diagnostic odds ratio for D-dimer is 19 (95% CI 10–35). Although a D-dimer test has the advantage for ruling out VTE, the negative value of the test is not high enough to exclude venous thromboembolism when used alone. However, the certainty of negative diagnosis for VTE or PE can be enhanced if the negative D-dimer result is incorporated into a multi-branch diagnosis pathway including the Wells Clinical Probability Tool and the National Institute of Health Stroke Scale (NHISS) [38]. Because the likelihood was calculated from dichotomized data, the result of a D-dimer test is either positive or negative. This may cause useful information to be lost. Because plasma D-dimer concentration is associated with age and severity of stroke, we recommend calculating likelihood ratios based on multiple cut-offs.

Overall, our analyses increase the database of knowledge for diagnostic accuracy of D-dimer for excluding PE or VTE. As our results show, D-dimer is not a perfect marker for diagnosis of VTE in patients after stroke, but an ideal marker does not exist.

Parameter	category	nstudies	Sensitivity	p1	Specificity	p2
il	Yes	4	0.85 [0.76 - 0.95]	0.20	0.79 [0.73 - 0.84]	0.00
	No	4	0.84 [0.74 - 0.94]	.	0.77 [0.71 - 0.82]	.
sex	Yes	3	0.80 [0.67 - 0.93]	0.03	0.82 [0.77 - 0.87]	0.00
	No	5	0.87 [0.79 - 0.94]	.	0.75 [0.72 - 0.78]	.
ais	Yes	2	0.86 [0.74 - 0.98]	0.34	0.80 [0.75 - 0.85]	0.00
	No	6	0.84 [0.76 - 0.93]	.	0.76 [0.71 - 0.81]	.
ich	Yes	2	0.91 [0.85 - 0.98]	0.67	0.74 [0.67 - 0.82]	0.00
	No	6	0.80 [0.72 - 0.88]	.	0.78 [0.74 - 0.82]	.

Joint Model

Parameter	category	LRTChi2	Pvalue	I2	I2lo	I2hi
il	Yes	0.27	0.87	0	0	100
	No	.	.	.	.	.
sex	Yes	5.18	0.08	61	13	100
	No	.	.	.	.	.
ais	Yes	1.32	0.52	0	0	100
	No	.	.	.	.	.
ich	Yes	5.25	0.07	62	14	100
	No	.	.	.	.	.

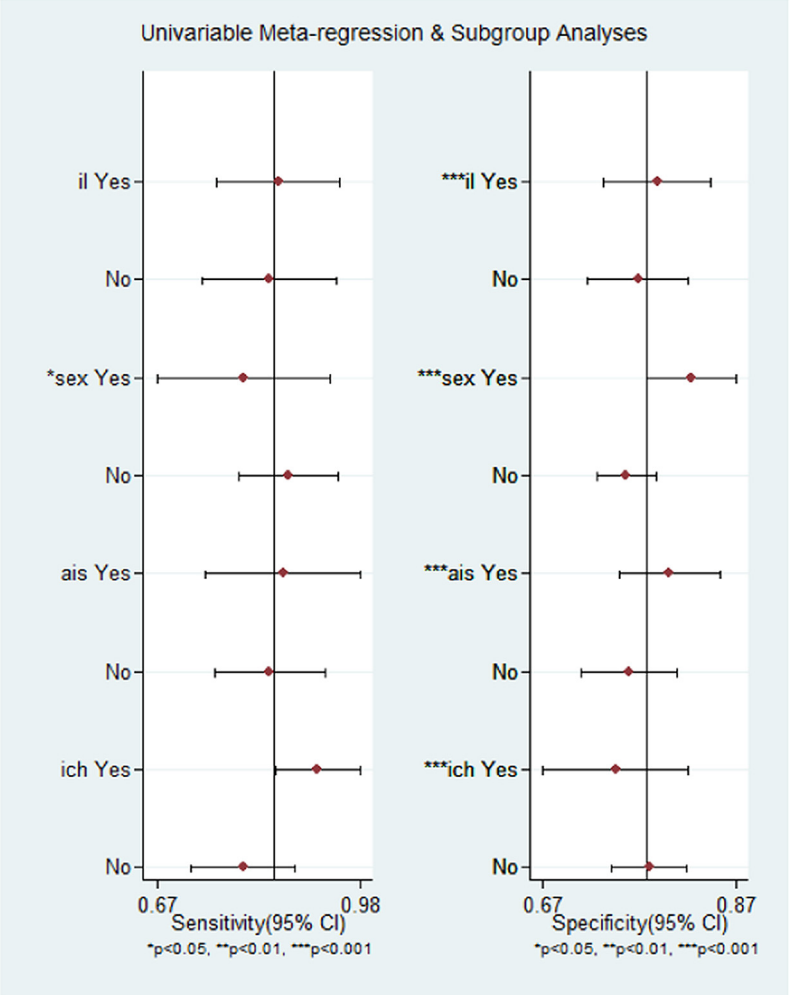

Fig. 7. Meta-regression analysis for D-dimer with following variables D-dimer assay with IL or not, sex males proportion > 50% or not, patients with AIS or not, patients with ICH or not. D-dimer assay with the method of immunoturbidimetric assay or not (Yes = 1, not = 0), percentage of males population > 50% or not (Yes = 1, not = 0), patient with acute ischemic stroke or not (Yes = 1, not = 0), patients with intracerebral hemorrhage or not(Yes = 1, not =0).

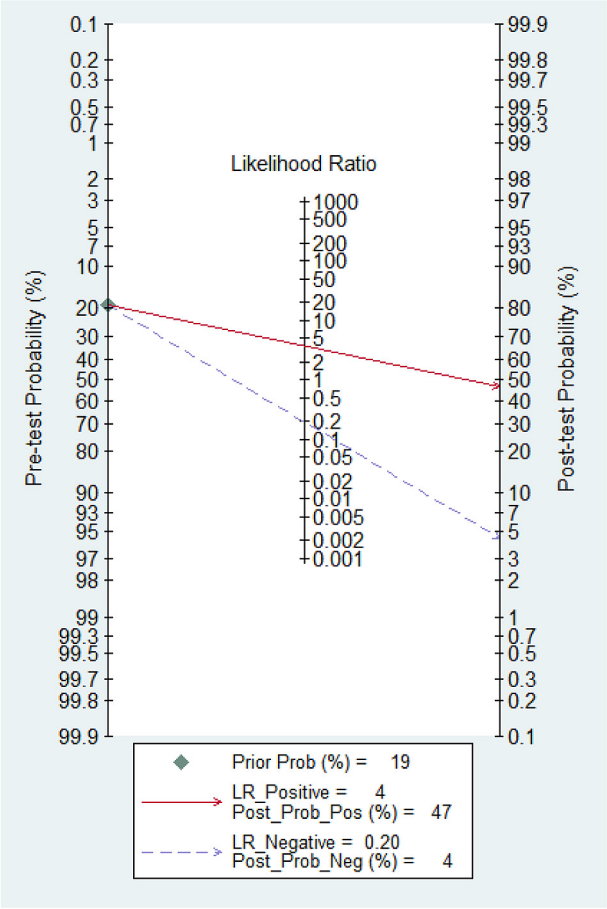

Fig. 8. Fagan's nomogram of the D-dimer test for diagnosis of VTE. LR, likelihood ratio; VTE, venous thromboembolism.

5. Limitations

There are some limitations in our study. First, we did a regression analysis to detect heterogeneity between studies but none of the study characteristics were responsible for heterogeneity. Included studies differ in several respects, including methodological quality, age, admission category and D-dimer assay used. The unrecorded information of studies probably introduces heterogeneity to the result. Because we cannot extract data of AIS and ICH separately, it may introduce heterogeneity for the pooled result.

Second, the included sample of included was small (1490). We restricted the population to patients after stroke and reference standard and D-dimer test performed at the same time in one study. This caused small number of studies to fit for the inclusion criteria. There may be some bias and the results should be carefully interpreted.

Third, for some studies, the quality control of the methodology is not clearly described. Most studies do not declare whether the radiologist is blinded to the D-dimer test. To minimize bias, authors should issue a report or papers according to STARD statement for reporting studies of diagnostic accuracy [39].

Fourth, the D-dimer assays of included studies varied, and the cut-offs were different. Because there were a small number of included studies and limited data from the original studies, we cannot do subgroup analysis based on different cut-offs. The D-dimer assays of included studies varied including IL, LPIA, ELISA. The values for specificity and positive likelihood ratio differed among the assays, but all were within a range considered to be of little clinical value in altering probability of disease. The summary findings of our study are based largely on indirect comparisons of test performance characteristics across studies.

6. Conclusion

In patients after stroke suspected of venous thromboembolism, D-dimer is a beneficial biomarker for diagnosis of VTE. For stroke patients with low probability of VTE, a normal D-dimer test is valuable in ruling out VTE with 15% false negative tests. The 23% false-positive test rates suggests that positive results need to be further confirmed by CUS. Therefore, we do not recommend D-dimer as the single definitive test for VTE diagnosis. We recommend diagnosing VTE in combination with a multi-branch diagnostic strategy.

Further studies for the diagnostic value of D-dimer should contain an analysis in combination with other diagnostic strategy such as Wells score, and be stratified according to the severity of stroke. Further studies should also clearly report details of the manner of index and reference standard interpreted and timing of administration of tests.

Conflicts of interest statement

The authors declare that they have no conflicts of interest.

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