

Diagnostic Accuracy of Dual-energy CT for Bone Marrow Edema in Patients with Acute Knee Injuries: A Systematic Review and Meta-analysis

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Abstract

Background: The prevalence of knee injury is high and early diagnosis is significant to guide clinical treatment. MRI is recognized as the gold standard for detecting bone marrow edema (BME) in patients with acute knee injury, but limitations still exist. Dual-energy CT (DECT) is investigated as a promising alternative.

Methods: We systematically retrieved studies from EMBASE, Scopus, PUBMED, and the Cochrane Library and collected gray literatures. According to PRISMA-DTA guidelines, a systematic review was performed from inception to July 31, 2021, assessing the diagnostic accuracy of DECT for detecting BME in at least 10 adult patients with acute knee injuries and with an MRI reference standard. Study details were independently extracted by two reviewers. Meta-analysis was performed using a bivariate mixed-effects regression model with subgroup analysis performed to evaluate for sources of variability.

Results: Nine studies evaluating 290 patients between the ages of 23–53 with acute knee injuries undergoing DECT and MRI were included in analysis. Summary sensitivity, specificity, and AUC values for BME were 85% (95% confidence interval (CI) 77–90%), 96% (95% CI 93–97%), and 0.97 (95% CI 0.95–0.98), respectively. There were no statistically significant differences in specificity and sensitivity amongst comparative subgroups to account for presumed variability amongst studies.

Conclusion: DECT is accurate for detecting BME in patients with acute knee injuries and can be used as an alternative to MRI, particularly when MRI is contraindicated or unavailable.

Introduction

The prevalence of knee injury is high and early diagnosis is significant to guide clinical treatment. Early diagnosis and early treatment can prevent the further development of injury, especially for traumatic bone marrow injury without obvious fracture line [1]. Bone marrow edema (BME) is a universally acknowledged biomarker of subtle bone injury such as microfracture and hemorrhage concentrated in the trabecular bone and can be detected by MRI accurately [2]. MRI, therefore, is recognized as the gold standard for detecting occult fractures in patients with acute knee injury [1]. However, MRI requires a long examination time and is limited by certain medical devices such as pacemakers. Furthermore, the patient must remain still during the procedure, and this is occasionally impossible for elderly or trauma patients [2, 3].

Dual-energy CT (DECT) is investigated as a promising alternative to MRI with advanced three-material decomposition technique which can remove the materials with relevant photoelectric effects to BME such as calcium and iodine [4–6]. The clinical value of DECT in assessing BME in adult patients with acute knee injuries is still under debate and exploration. The accuracy of DECT needs to be proven systematically prior to implementation as a substitute to MRI. Therefore, the aim of this systematic review and meta-analysis was to synthesize and evaluate published data on the accuracy of DECT for detecting BME in adult patients with acute knee injuries and to determine whether MRI is still indispensable for these patients.

Methods

This systematic review and meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis - Diagnostic Test Accuracy (PRISMA-DTA) guidelines [7]. The approaches to evidence searching and data processing described in this article were based on the Cochrane Collaboration's diagnostic test accuracy method [8]. No ethical approval or informed consent was required for this article because all data were obtained from published literatures. Searching for studies, identifying eligibility, extracting data, and assessing quality were performed by two investigators independently. Any disagreement was resolved through discussion until they reach a consensus.

Search strategy

Four electronic databases, PubMed, EMBASE, Scopus and Cochrane Library, were searched for entries recorded from the time of database inception to July 31, 2021. Vocabulary and syntax were specifically adapted according to the database. The initial search included variations of title/abstract/keywords and medical subject heading terms including “dual energy” AND (“computed tomography” OR “CT”) AND “bone” AND “edema” and were modified as needed by individual database. No language restrictions were applied [9]. To find any additional possible records, a gray literature search was performed by one author with evaluation of recent annual meeting for the American Roentgen Ray Society (ARRS), as well as recent years of conference proceedings from the Radiological Society of North America (RSNA) and the European Congress of Radiology (ECR). Conference abstracts that met the inclusion criteria and were not yet available in full text were included in analysis.

Literatures from each database and other sources were combined into a list from which duplicates were removed and were then screened initially with title and abstract for relevance. Subsequently, full-text review of the potentially relevant studies was conducted.

Inclusion criteria

The following criteria needed to be met for the studies included in this systematic review: (1) BME was evaluated around knee joints, (2) BME was the target finding and DECT was the index test, (3) MRI was used as the reference standard, (4) at least 10 patients were included, (5) sufficient data could

be extracted to construct a 2 × 2 contingency table. Non-original researches (including case reports, commentaries, consensus statements, guidelines, and narrative reviews) were excluded. If more than one study provided overlapping data, only the most comprehensive or latest study was included.

Data extraction

Requisite data extracted and recorded in the standardized Excel files (version 16.54, Microsoft). Study characteristics including surname of the first author, year and country of publication, prospective versus retrospective study design, time between DECT and MRI, number of readers, presence of consensus reading, and reader experience were recorded. Patient characteristics including total number and inclusion interval of patients, mean age (Range), number of male and female, and number of knees (regions) with BME after acute knee injury were recorded. Additionally, specific site of pathology, true positive (TP), false positive (FP), false negative (FN), true negative (TN), and threshold value was recorded for each assessment.

Risk of bias assessment

The methodological quality of the included studies was appraised according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool, which based on four separate domains: (1) patient selection, (2) index test(s), (3) reference standard, and (4) flow and timing [10]. Risk of bias (ROB) was assessed in each domain, and concerns about applicability were assessed in the first three domains with signaling questions. These questions were answered with “yes” for a low risk of bias/concern, “no” for a high risk of bias/concern, or “unclear” when relevant information was not clearly provided. Studies considered high risk for any single signaling question within a domain were considered to have a high ROB for that respective domain.

Statistical analyses

Generally, a 2 × 2 contingency table was developed for each included study. If both qualitative and quantitative analysis were reported in a study, two separate contingency tables were created. Pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were calculated using the bivariate meta-analysis framework (bivariate mixed effects regression model). In addition, summarized receiver operating characteristic (sROC) curves were constructed, with the area under the curve (AUC) depicting the accuracy of the tests.

To examine potential sources of variability, extensive subgroup analysis was performed on the studies. And univariate analysis was performed when bivariate regression model did not converge due to limited number of studies (< 4) and zero values in the 2 × 2 contingency table. A two-sided p value < 0.05 was considered statistically significant in all statistical tests. Simultaneously, statistical evaluation for publication bias was performed. Stata version 16 (StataCorp, College Station, TX) was used to analyze data from the included studies, and Review Manager Software version 5.4 (Cochrane Collaboration, Oxford, UK) was used to assess the methodological quality of the included studies.

Results

Literature search

The PRISMA flow diagram for the literature search is depicted in Figure 1. A total of 237 articles were identified by searching databases and removing duplicates. After initial screening of titles and abstracts, 64 articles were further assessed by scrutinizing the full texts against the predesigned criteria, and 9 articles [11-19] were eventually included in analysis.

Study characteristics

The main characteristics of the included studies are summarized in Table 1. Nine studies involved a total of 290 patients with mean age ranging between 23 and 53 years and evaluated 2809 bone regions around the knee for BME. Four studies were performed in European institutions, four studies were performed in Asian institutions and one study was performed in a North American institution. Seven study was prospective, two studies were retrospective. Time interval between DECT and MRI was variable by study, but generally performed within 1 week. All studies involved at least two readers with five studies undergoing consensus review.

Diagnostic performance

Integrated data for individual studies by site of pathology is summarized in Table 2. Region-based characterization is used for all studies to ensure the consistency of data. As shown in Figure 2, the pooled sensitivity and specificity for DECT detecting BME in patients with acute knee injuries are 85% (95% confidence interval (CI) 77–90%) and 96% (95% CI 93–97%), respectively. As shown in Figure 3 and 4, the pooled PLR, NLR, and DOR were 18.89 (95% CI 11.24–31.73), 0.16 (95% CI 0.10–0.25), and 116.79 (95% CI 52.33–260.64), respectively. The AUC values for DECT detecting BME in patients with acute knee injuries is 0.97 (95% CI 0.95–0.98) in Figure 5. The I^2 statistics for sensitivity and specificity values are 90.87% (95% CI 86.76–94.97%, $p = 0.00$) and 89.06% (95% CI 83.89–94.24%, $p = 0.00$), respectively, indicating substantial heterogeneity in the included studies.

Subgroup analysis is demonstrated in Table 3. All studies were divided into two groups according to each of six significant factors. Studies with a retrospective study design were assessed with univariate analysis due to limited number of studies (< 4) in subgroup. Studies using a qualitative assessment method had a trend toward lower sensitivity compared with quantitative studies (80% (68–88%) versus 91% (85–95%), NS), but no

difference in specificity. Studies from North American and European institutions had a trend toward lower specificity compared with Asian institutions (93% (88–95%) versus 98% (95–99%), NS), but no difference in sensitivity. No other significant differences were found between the comparison subgroups to account for presumed variability amongst studies.

Risk of bias assessment

Results for the QUADAS-2 tool for evaluating individual studies for risk of bias and applicability is included in Figure 6. Studies were predominantly low risk for both risk of bias and applicability. One study was rated high risk of bias for flow and timing domain for inappropriate time interval (more than 2 weeks) between DECT and MRI [11]. Two study assessed both quantitative and qualitative evaluation and only the quantitative evaluation was deemed high risk as the threshold is identified in advance [13, 15]. One additional study was considered high risk of bias for index test for applying a retrospective threshold as well [18].

Publication bias

As shown in Figure 7, Deek's funnel plot asymmetry test indicated the existence of publication bias ($p = 0.13$).

Discussion

Knee injury is a common health problem at all ages and early diagnosis and early treatment can prevent the further development of injury. Bone marrow edema, as a universally acknowledged biomarker of subtle bone injury, can be detected by MRI accurately. However, a long examination time, a stationary state, incompatibility of certain medical devices such as pacemakers suggest that limitations still exist. At present, DECT is investigated as a promising alternative to MRI with advanced three-material decomposition technique which can remove the materials with relevant photoelectric effects to BME such as calcium and iodine. The clinical value of DECT in assessing BME in adult patients with acute knee injuries is still under debate and the accuracy of DECT needs to be proven. Therefore, the aim of this systematic review and meta-analysis was to synthesize and evaluate published data on the accuracy of DECT for detecting BME in patients with acute knee injuries and to determine whether MRI is still indispensable for these patients.

This meta-analysis demonstrates that DECT is highly specific and accurate for detecting BME in patients with acute knee injuries when using MRI as the reference standard, with excellent pooled specificity (96% (95% CI 93–97%)) and AUC (0.97 (95% CI 0.95–0.98)). These results indicate that DECT can be used as alternative to MRI in patients with occult but suspected bone fracture after acute knee injury, particularly when MRI is contraindicated or unavailable. A slightly lower sensitivity of DECT for detecting BME when using an MRI reference standard (85% (95% CI 77–90%)) suggests that patients with negative results on DECT but persistent clinical manifestations may still require an MRI to detect more concealed bone injuries.

An extensive subgroup analysis to examine for potential sources of presumed variability and increase the confidence of the generalizability of these results was a highlight. There were no statistically significant differences in specificity and sensitivity between these comparative subgroups. Notably, studies using a qualitative assessment method had a trend toward lower sensitivity compared with quantitative studies and studies from North American and European institutions had a trend toward lower specificity compared with Asian institutions. This study provides several opportunities for future research to further evaluate particular subgroups, including DECT protocols not yet involved and determine the optimized applicability and interpretation of DECT dependent on patient and imaging specific details in patients with acute knee injuries. Further, although most studies were low risk for bias and applicability, a few studies used retrospective thresholds and one study used prolonged intervals between DECT and MRI which increase the risk of bias in both index test and flow and timing domains, respectively.

In addition, some intrinsic limitations of DECT maintain MRI as the preferred imaging modality at present, including (1) the non-specificity of BME for fracture (e.g., bone infarction can result in BME); (2) accompanied bone injuries when soft tissues such as meniscal and ligament are frequently injured; (3) increased radiation dose; (4) risk for non-diagnostic virtual non-contrast reconstructions; (5) and limited field of view in virtual non-contrast reconstructions [13, 14, 18]. Be that as it may, this systematic review and meta-analysis reveals that DECT can be applied as an alternative to MRI for patients with acute knee injuries under appropriate circumstances. Patients with a negative DECT but high suspicion for bone injuries may still require an MRI to evaluate for occult fractures.

Conclusions

Based on the results of this meta-analysis, it could be concluded that DECT is accurate for detecting BME in patients with acute knee injuries with high with high sensitivity and specificity, indicating it can be used as an alternative to MRI, particularly when MRI is contraindicated or unavailable.

Declarations

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Competing interests. The authors declare that they have no competing interests, and all authors should confirm its accuracy.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

SW and GFQ contributed to the conception of the study;

CXL, LZZ, FH, XYX and LCX contributed significantly to literature search, data extraction, quality assessment, data analyses and manuscript preparation;

SLJ, FXY, XX helped perform the analysis with constructive discussions;

SW revised the manuscript and approved the final version.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1

Patient and study characteristics of included studies

Author, Published year	Country	No. patients (Inclusion interval)	Mean age (Range)	Male/Female	No. knees with edema (No. regions)	Study design	Time interval between DECT and MRI	No. readers	Consensus reading	Reader experience (Years)
Ai, 2014	USA	14 (2009.03-2011.07)	24.6 (18-48)	11/3	NR (36/56 regions)	Retrospective	< 99 days	2	Yes	MSK radiologists (11 + 19)
Bjorkman, 2019	Sweden	48 (2017.10-2018.03)	23 (15-37)	26/22	52 (85/192 regions)	Prospective	< 7 days	2	Yes	Resident (3) + Radiologist (> 7)
Booz, 2020	Germany	57 (2017.01-2018.05)	50 (20-82)	27/30	36 (197/684 regions)	Retrospective	< 7 days	6	No	Qualitative: 4 residents (3-4) + 2 radiologists (7-10) Quantitative: medical students (2)
Cao, 2015	China	32 (2012.04-2012.08)	39.9 (20-60)	24/8	32 (127/384 regions)	Prospective	≤ 6 days	2	Yes	Radiologists (vastly experienced)
Foti, 2021	Italy	33 (2019.01-2019.06)	52.2 (31-76)	20/13	25 (85/396 regions)	Prospective	< 6 days	2	Yes	Radiologists (20 + 16)
Juhng, 2013	South Korea	23 (NR)	47.4 (14-72)	11/12	NR (84/378 regions)	Prospective	NR	2	No	Radiologists (5 + 25)
Liang, 2020	China	23 (2018.07-2019.06)	47 (21-73)	10/13	24 (121/288 regions)	Prospective	NR	5	No	MSK radiologists (8 + 10 + 4 + 5 + 20)
Pache, 2010	Germany	21 (2009.01-2009.05)	35.9 (19-60)	16/5	NR (59/236 regions)	Prospective	≤ 5 days	2	No	MSK radiologists (5 + 7)
Wang, 2019	China	39 (2018.03-2018.11)	36.3 (13-89)	22/17	NR (43/195 regions)	Prospective	≤ 5 days	3	Yes	Radiologists (>5)
No., number; DECT, dual-energy computed tomography; MRI, Magnetic resonance imaging; NR, not reported.										

Table 2

Integrated data for individual studies by site of pathology

Author	Published year	Site of pathology	No. total regions	No. marrow edema	TP	FP	FN	TN	Threshold value*
Ai	2014	Knee	56	36	22	0	14	20	qualitative
Bjorkman	2019	Knee-Femur	95	43	26	11	17	41	qualitative
		Knee-Tibia	96	41	26	14	15	41	qualitative
Booz	2020	Knee-Femur	342	91	85	11	6	240	qualitative
		Knee-Tibia	342	106	100	11	6	225	qualitative
		Knee-Femur	342	91	86	12	5	239	-42 HU
		Knee-Tibia	342	106	102	7	4	229	-51 HU
Cao	2015	Knee-Femur	192	49	36	2	13	141	qualitative
		Knee-Tibia	192	67	61	0	6	125	qualitative
Foti	2021	Knee	396	85	77	20	8	291	qualitative
		Knee	396	85	72	20	13	291	-15 HU
Juhng	2013	Knee-Femur	162	29	17	7	12	126	qualitative
		Knee-Tibia	162	44	33	3	11	116	qualitative
		Knee-Femur + Tibia + Patella	378	84	54	9	30	285	
Liang	2020	Knee	288	121	99	9	22	158	qualitative
Pache	2010	Knee-Femur	114	19	15	2	4	93	-33 HU
		Knee-Tibia	122	40	38	7	2	75	-60 HU
Wang	2019	Knee	195	43	38	3	5	149	-67 HU
No., number; TP, true positive; FP, false positive; FN, false negative; TN, true negative; HU, Hounsfield unit.									
*Threshold value for quantitative studies determined as a region of interest measuring a circumference of at least 3 mm and placed at least 1 mm from the cortical margin.									

Table 3

Subgroup analysis of included studies evaluating for causes of presumed variability amongst studies

	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95% CI)
All	85% (77-90%)	96% (93-97%)	0.97 (0.95-0.98)
Qualitative only	80% (68-88%)	96% (90-98%)	0.95 (0.93-0.97)
Quantitative only	91% (85-95%)	95% (94-97%)	0.98 (0.96-0.99)
Femur only	81% (66-91%)	95% (91-98%)	0.96 (0.94-0.98)
Tibia only	89% (79-95%)	96% (89-98%)	0.97 (0.96-0.99)
North America/Europe	87% (77-93%)	93% (88-95%)	0.96 (0.94-0.97)
Asia	80% (71-87%)	98% (95-99%)	0.97 (0.95-0.98)
Prospective	82% (74-88%)	95% (91-98%)	0.95 (0.92-0.96)
Retrospective*	89% (62-97%)	96% (94-97%)	
Consensus	81% (70-88%)	96% (89-98%)	0.94 (0.91-0.91)
No consensus	88% (77-94%)	96% (95-97%)	0.96 (0.94-0.98)
Mean Age 20-39	79% (67-88%)	96% (88-99%)	0.93 (0.91-0.95)
Mean Age 40-59	88% (79-93%)	95% (94-96%)	0.96 (0.94-0.97)

*Univariate analysis performed when bivariate regression model did not converge due to limited number of studies (< 4) and zero values in the 2 × 2 contingency table.

Figures

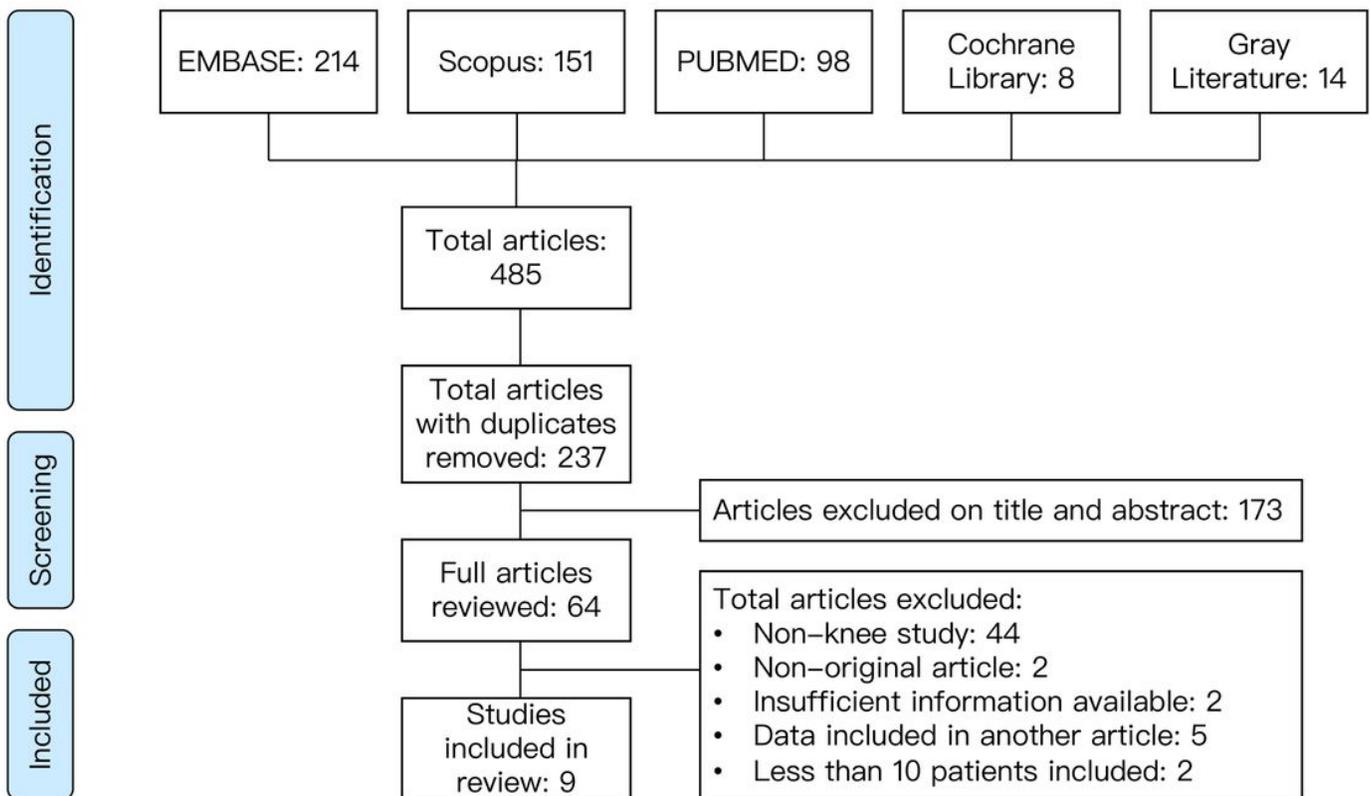


Figure 1

PRISMA flow diagram showing screening and selection of studies included in the analysis.

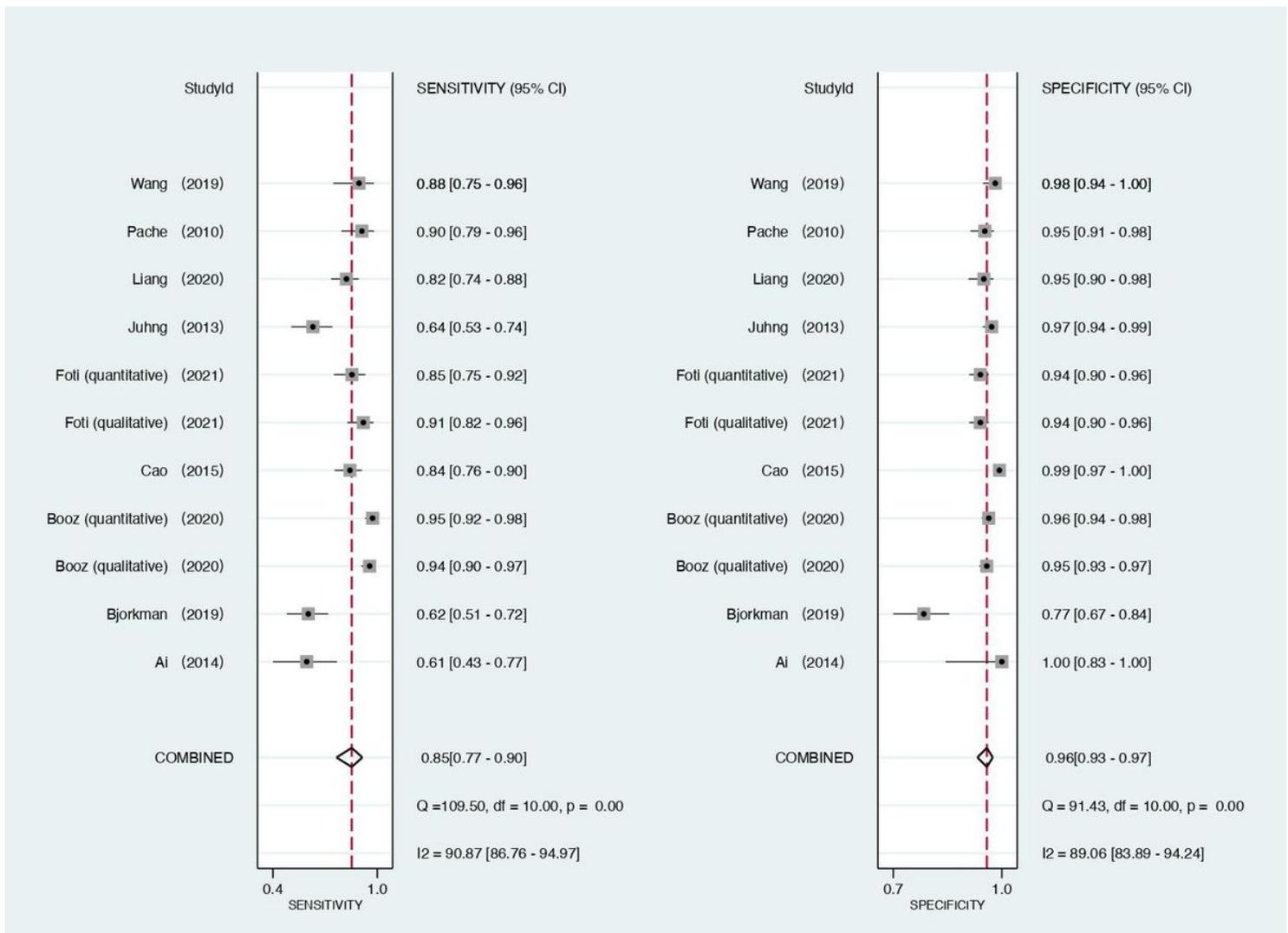


Figure 2
 Forest plots of the sensitivity (left) and specificity (right) of dual-energy CT for detecting bone marrow edema in patients with acute knee injuries.

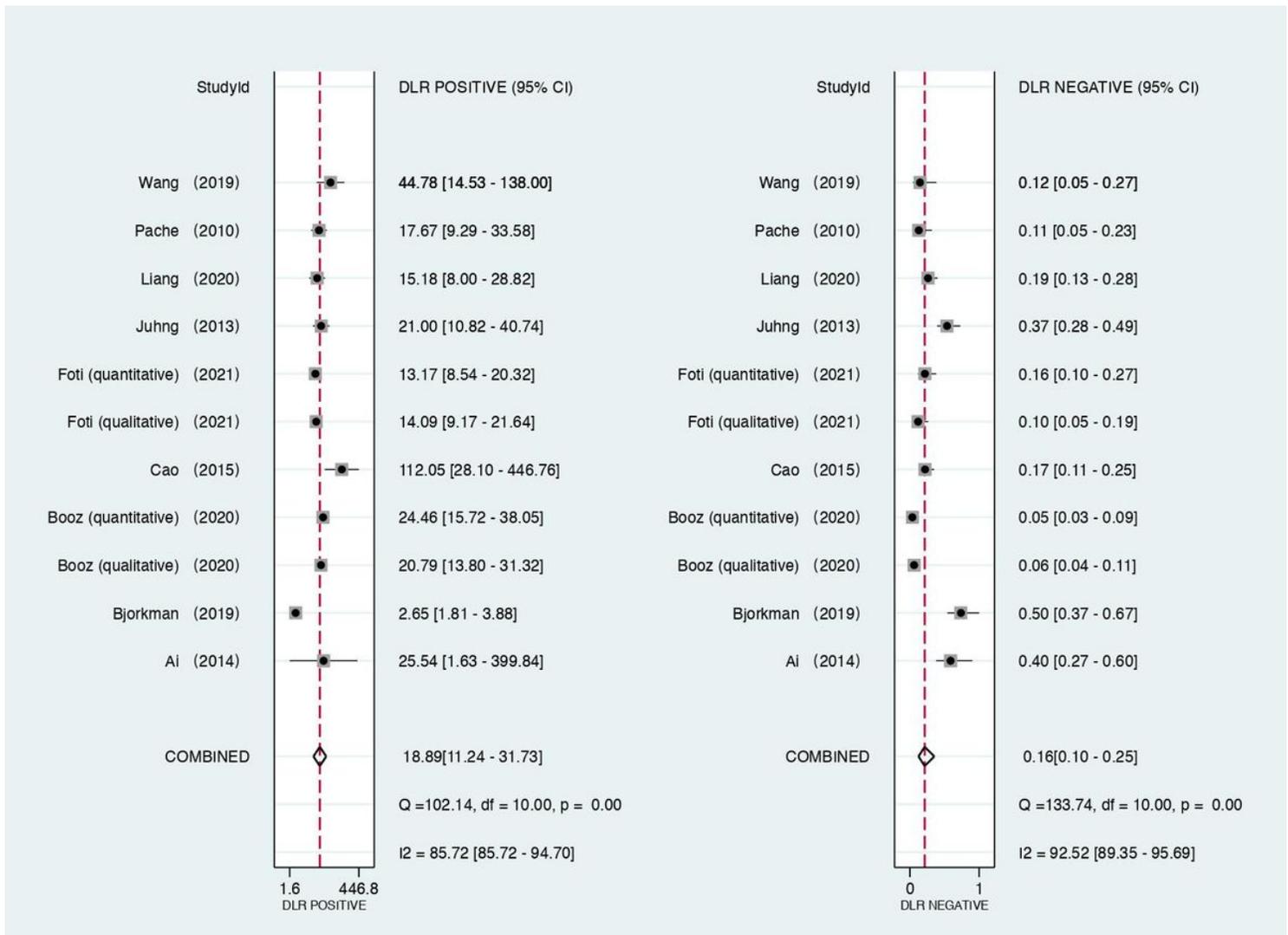


Figure 3

Forest plots of the PLR and NLR of dual-energy CT for detecting bone marrow edema in patients with acute knee injuries.

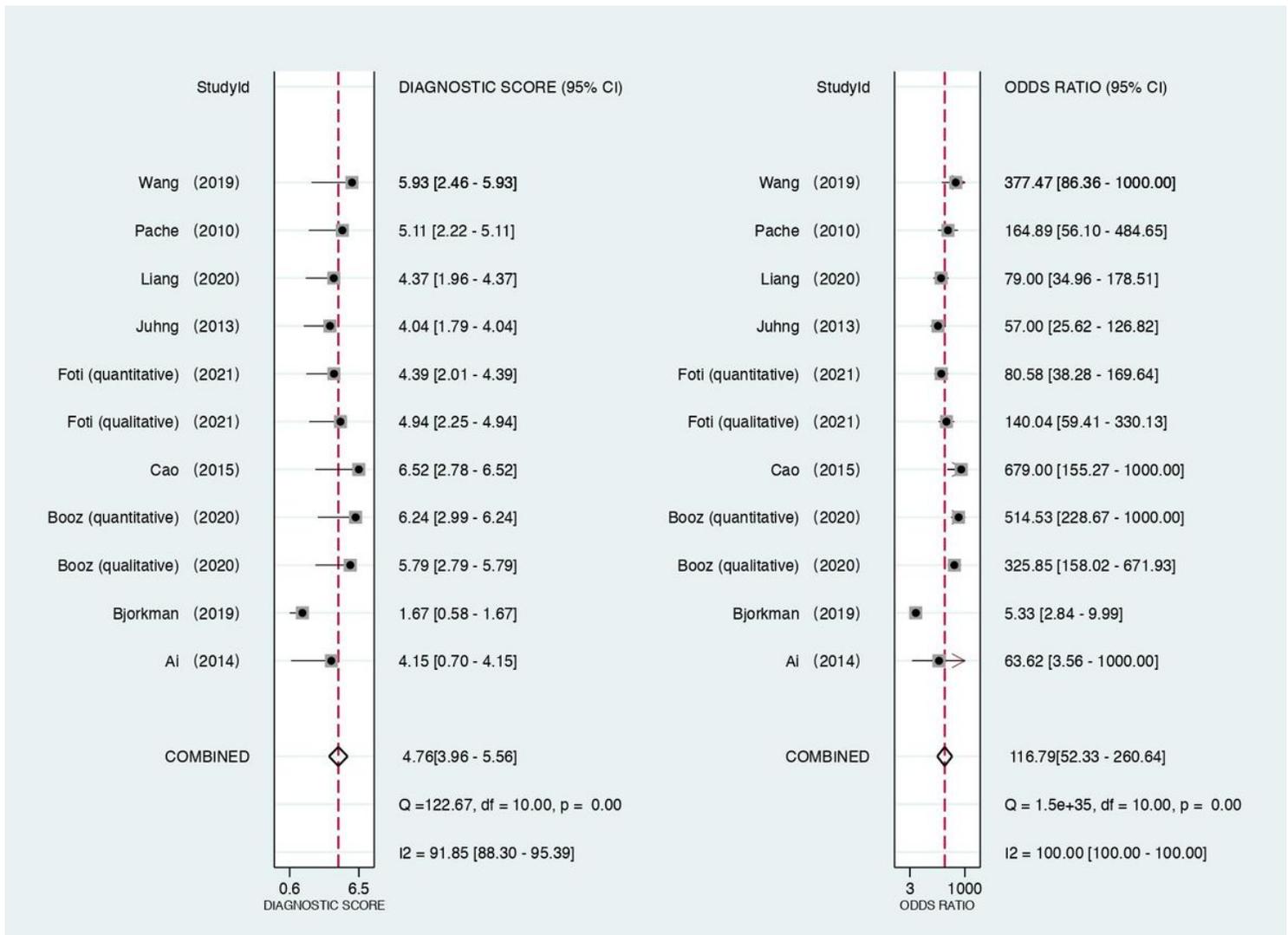


Figure 4

Forest plots of the diagnostic score and DOR of dual-energy CT for detecting bone marrow edema in patients with acute knee injuries.

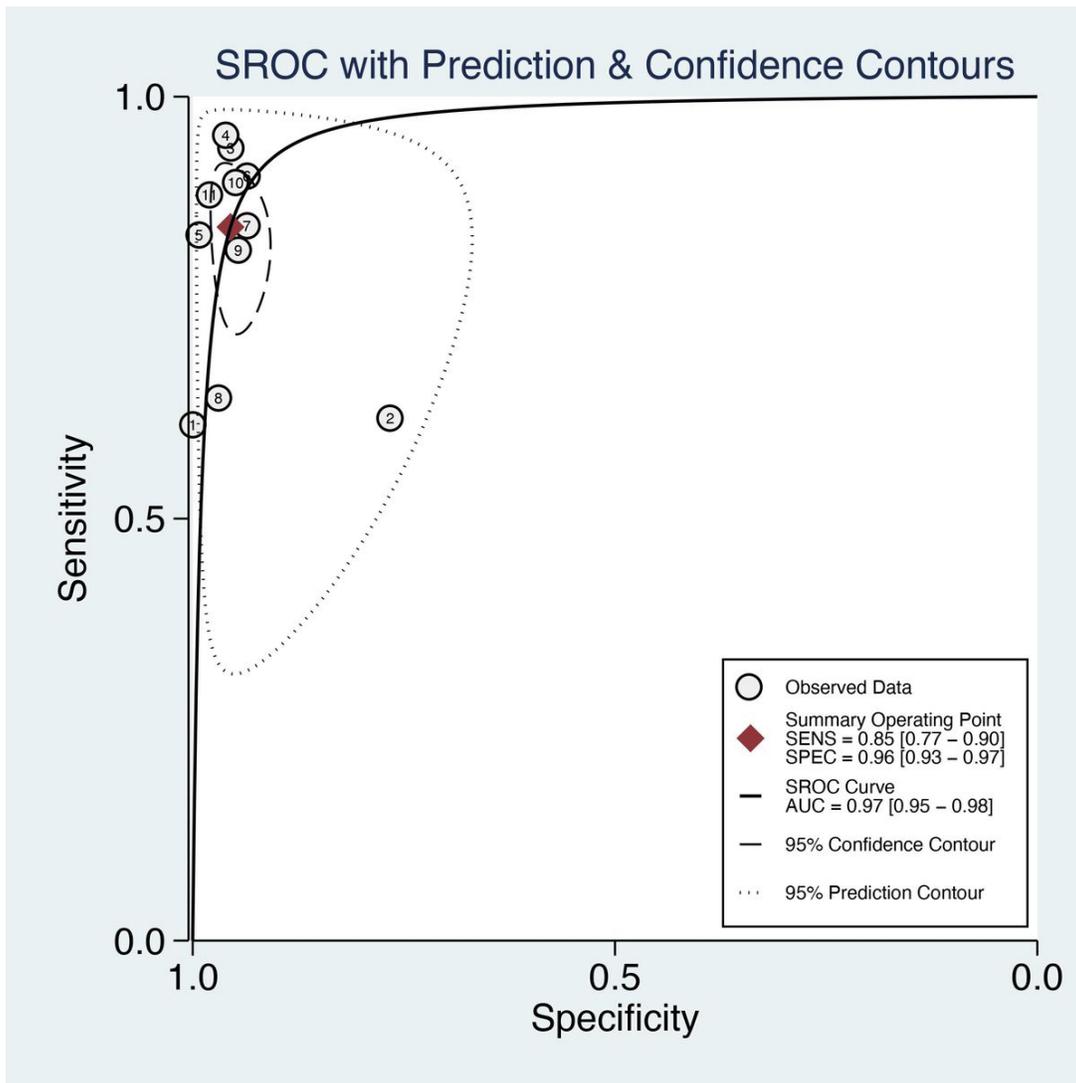


Figure 5

Summarized receiver operating characteristic curve (sROC) of dual-energy CT for detecting bone marrow edema in patients with acute knee injuries.

	<u>Risk of Bias</u>				<u>Applicability Concerns</u>		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Ai 2014	+	+	+	-	+	+	+
Bjorkman 2019	+	+	+	+	+	+	+
Booz 2020 (qualitative)	+	+	+	+	+	+	+
Booz 2020 (quantitative)	+	-	+	+	+	+	+
Cao 2015	+	+	+	+	+	+	+
Foti 2021 (qualitative)	+	+	+	+	?	?	+
Foti 2021 (quantitative)	+	-	+	+	?	?	+
Juhng 2013	?	+	+	?	+	+	+
Liang 2020	+	+	+	?	+	+	+
Pache 2010	+	-	+	+	+	+	+
Wang 2019	+	+	+	+	+	+	+

 High	 Unclear	 Low
------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------

Figure 6

Results of QUADAS-2 tool evaluation of individual studies for risk of bias and applicability. Red in figure indicates high risk, yellow represents unclear risk and green means low risk.

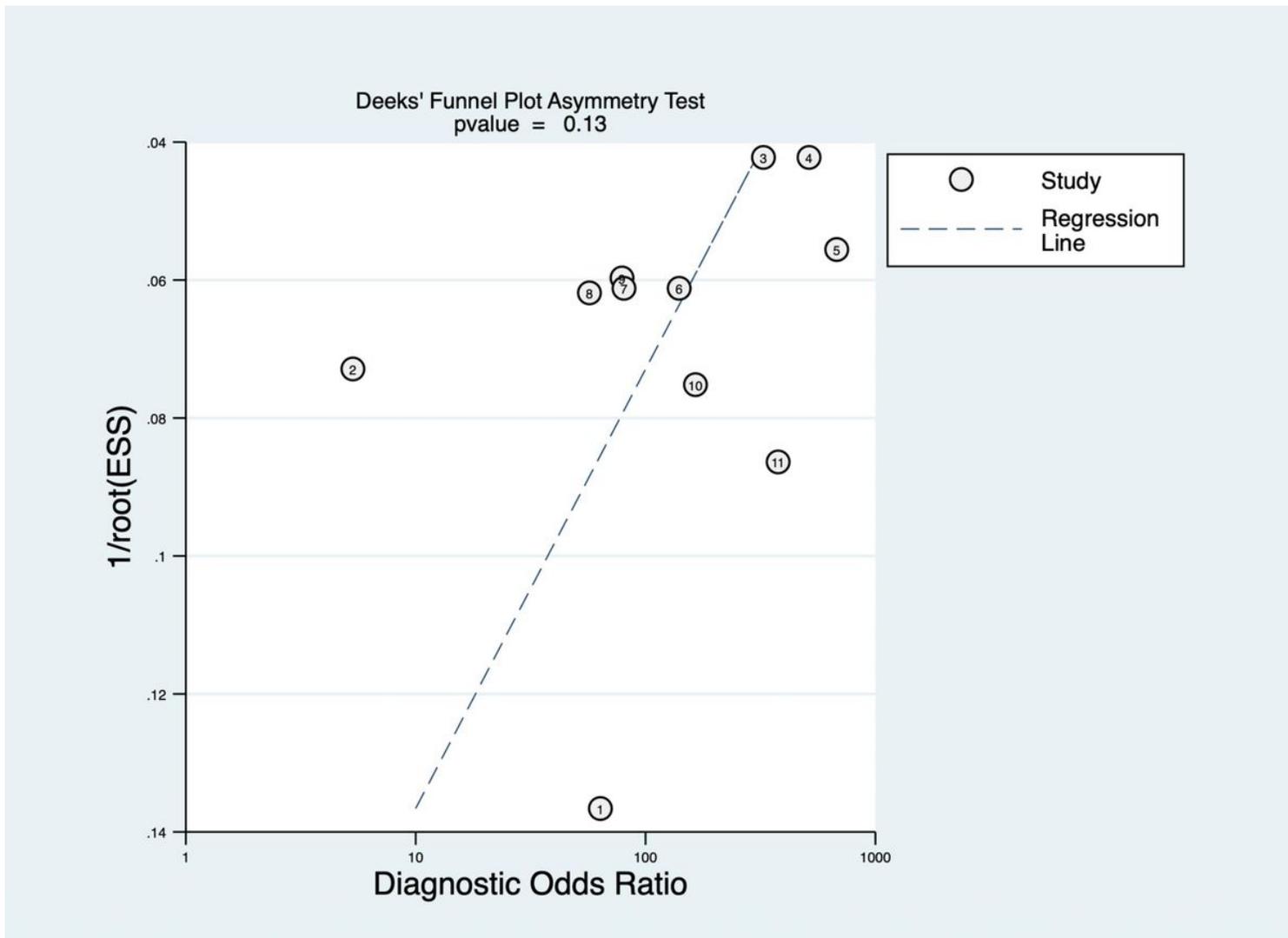


Figure 7

Deek's funnel plot asymmetry test indicated the existence of publication bias.

Supplementary Files

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