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ORIGINAL ARTICLE

Diagnostic Accuracy of Intestinal Fatty Acid Binding Protein for Acute Intestinal Ischemia: a Systematic Review and Meta-Analysis

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SUMMARY

Background: **Some studies have investigated the diagnostic value of intestinal fatty acid binding protein (I-FABP) for acute intestinal ischemia (II), but the results were not always consistent. Therefore, we performed a systematic review and meta-analysis to determine the diagnostic accuracy of I-FABP for II.**
Methods: **Publications included in the PubMed and EMBASE before April 7, 2019 were retrieved to identify studies investigating the diagnostic accuracy of I-FABP for II. The Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) was used to assess the quality of eligible studies. Diagnostic accuracy of I-FABP in all eligible studies was pooled by a bivariate model. Summary receiver operating characteristic (ROC) curves (AUC) were constructed to calculate the overall diagnostic accuracy of I-FABP.**
Results: **A total of 10 studies with 1,265 (219 IIs and 1,046 controls) subjects were included in this systematic review and meta-analysis. The major design weaknesses of included studies were patient selection bias. The overall diagnostic sensitivity, specificity, and AUC of I-FABP were 0.75 (95% CI: 0.68 - 0.82), 0.85 (95% CI: 0.74 - 0.92), and 0.82 (95% CI: 0.79 - 0.86), respectively. In patients with acute abdominal pain, the sensitivity, specificity, and AUC of I-FABP were 0.71 (95% CI: 0.59 - 0.81), 0.89 (95% CI: 0.69 - 0.97) and 0.80 (95% CI: 0.76 - 0.83), respectively.**
Conclusions: **I-FABP has moderate diagnostic accuracy for II. Due the patient selection bias of available studies, further studies with rigorous design are needed to evaluate the diagnostic accuracy of I-FABP for II.**
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KEY WORDS

intestinal fatty acid binding protein, intestinal ischemia, diagnostic accuracy, systematic review, meta-analysis

INTRODUCTION

Intestinal ischemia (II) is fatal among emergency cases, with extremely high mortality and morbidity [1]. Timely and accurate diagnosis is crucial for improving the prognosis of II [2]. However, because the clinical presentation of II is non-specific, it is really a challenge for clinicians to identify II patients among suspected II patients, especially at the early phase. The gold standard for II diagnosis is surgery with pathological findings [1, 2]. However, the clinical use of surgery is often limited because it is an invasive approach. Computed tomography (CT) is widely used as an alternative approach for

II diagnosis, but the diagnostic accuracy of CT is greatly affected by the experience of clinicians and radiologists [3]. In addition, long-term hazards related to radiation exposure and high cost are not to be ignored. Therefore, it is of great value to develop serum or plasma markers for II diagnosis. Obviously, the major advantages of blood markers are low cost, noninvasiveness, and their diagnostic accuracy are less affected by the experience of clinicians [4,5].

Intestinal fatty acid binding protein (I-FABP) is a cytosolic protein responsible for the uptake and intracellular transport of fatty acids [6]. It is expressed in the enterocytes at the tips of the intestinal mucosal villi. In the condition of mucosal tissue injury, I-FABP entered into the bloodstream. Therefore, circulating I-FABP can be used as an adjunctive diagnostic test of II [5]. During past years, several studies have investigated the diagnostic accuracy of I-FABP for II, but the results were not always consistent. Here, we performed a systematic review and meta-analysis to pool the results of published studies.

MATERIALS AND METHODS

Literature search strategy

This systematic review and meta-analysis was performed and reported in accordance with the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) [7]. We searched PubMed and EMBASE to identify relevant studies up to April 7, 2019. The search algorithm in PubMed included: ("fatty acid-binding protein" or "I-FABP" or "FABP") and ("intestine*" or "gut" or "mesentery*" or bowel) and (ischemia* or infarction or obstruction). Similar search strategy was used in EMBASE. Manual search was performed with the references listed at the end of eligible studies or relevant reviews. All potential studies were imported into Endnote, a literature management software, to remove duplicate records.

Study selection

Two investigators independently screened abstract and title of the searched studies to verify their eligibility. Disagreement was resolved by consensus or full text review. The inclusion criteria of this systematic review and meta-analysis were: (i) studies investigating the diagnostic accuracy of I-FABP for intestinal ischemia; (ii) studies have sufficient details to construct a two-by-two table. Exclusion criteria were: (i) animal studies; (ii) review, editorial or conference abstract; (iii) studies in which the subjects are postoperative; (iv) sample size less than 10; (v) case report or series.

Quality assessment and data extraction

Two investigators independently assessed the quality of eligible studies with the Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) [8]. Study data extracted from eligible studies included the first author, publication year, country, sample size, studies population characteristics, area under receiver operating curve (AUC), sensitivity and specificity, diagnostic threshold, type of data collection (prospective or retrospective), subject enrollment, and gold criteria for II. Any disagreements in quality assessment and data extraction were resolved by consensus or a third investigator.

Data analysis

Using sensitivity, specificity, and sample size, a two-by-two table was constructed for each eligible study. The bivariate random-effects model and hierarchical summary receiver operating characteristic (HSROC) curves were used to pool data [9]. Funnel plots and Deeks' test were used to determine the degree of publication bias [10]. We performed all analyses with Stata 13.0 (Stata Corp LP, College Station, TX, USA) and the midandi command.

RESULTS

Characteristics of included studies

Figure 1 is a flowchart of study selection. Finally, 10 studies were included in this systematic review and meta-analysis [11-20]. The characteristics of the included studies were summarized in Table 1. Five studies were performed in Japan [11,13,15,17,20], the remaining six studies were performed in the USA [12], Turkey [16], China [18], Canada [19], and Netherlands [14]. The sample sizes of included studies range from 18 to 371, with the total sample size of 1,265 (219 IIs and 1,046 controls). The studied population in included studies were various, including patients with acute abdominal pain visiting emergency department [11,13,14,16,18], with suspected AMI [16,19], and small bowel obstruction [12,17]. The prevalence of II ranged from 5% to 72%. Eight of included studies were prospective designs and the remaining 2 were retrospective [17,20]. Subjects were consecutively enrolled in only 4 studies [14,15,19,20], but the remaining 6 studies were not consecutively enrolled or not reported. The reference methods used to define II included surgery, imaging, and clinical details.

The quality of included studies was presented in Figure 2. The major design weaknesses of included studies were: (i) Patient selection bias because of retrospective design or non-consecutive subject enrollment; (ii): Thresholds of I-FABP in included studies were not prespecified; (iii) The time of blood collection was not reported and not all subjects were included into final analysis.

Diagnostic accuracy of I-FABP

Table 2 summarizes the diagnostic accuracy of I-FABP in each of the included studies. The pooled sensitivity, specificity, PLR, NLR, and DOR of I-FABP were 0.75

Table 1. Summary of eligible studies.

Author	Year	Country	Disease/ Control	Studied population	Target disease	Data collection	Consecutive enrollment	Reference			
								SGR	IMG	CLN	NR
Kanda [11]	1996	Japan	13/48	AAP	II	Prospective	Unknown				●
Cronk [12]	2006	USA	3/18	Mechanical SBO	II	Prospective	Unknown			●	
Kanda [13]	2011	Japan	52/309	AAP	II	Prospective	No	●		●	
Thuijls [14]	2011	Netherlands	22/24	AAP	II	Prospective	Yes	●			
Matasumoto [15]	2014	Japan	24/184	Suspected II	Vascular II	Prospective	Yes	●	●		
Uzun [16]	2014	Turkey	7/132	AAP	AMI	Prospective	No		●	●	
Kittaka [17]	2014	Japan	21/16	SBO	Strangulated SBO	Retrospective	Unknown	●		●	
Shi [18]	2015	China	39/233	AAP	II	Prospective	Unknown	●	●		
Salim [19]	2016	Canada	13/5	Suspected AMI	AMI	Prospective	Yes	●			
Matasumoto [20]	2019	Japan	25/71	Suspected AMI	NOMI	Retrospective	Yes	●		●	

Note: AMI - acute mesenteric ischemia, NOMI - nonocclusive mesenteric ischemia, AAP - acute abdominal pain, II - intestinal ischemia, SBO, small bowel obstruction, NR - not reported, SGR - surgery, IMG - Imaging, CLN - clinical.

Table 2. Diagnostic accuracy of HE4 in the eligible studies.

Author	AUC (95% CI)	Cutoff	Sensitivity	Specificity	TP	FP	FN	TN
Cronk [12]	0.89	100.0 pg/mL	1.00	0.78	3	4	0	14
Kanda [13]	0.79	3.1 ng/mL	0.79	0.74	41	81	11	228
Uzun [16]	0.76	144.9 pg/mL	0.71	0.95	5	7	2	125
Kanda [11]	NR	100.0 ng/mL	0.54	1.00	7	0	6	54
Thuijls [14]	0.70	268.0 pg/mL	0.68	0.71	15	7	7	17
Shi [18]	0.85	82.4 ng/mL	0.76	0.75	30	59	9	174
Salim [19]	0.66	0.7 ng/mL	0.92	0.40	12	3	1	2
Matasumoto [20]	0.81	8.3 ng/mL	0.76	0.80	19	14	6	57
Matasumoto [15]	0.88	9.1 ng/mL	0.83	0.89	20	20	4	164
Kittaka [17]	0.85	6.5 ng/mL	0.71	0.94	15	1	6	15

Note: AUC - area under ROC curve, TP - true positive, FP - false positive, TN - true negative, FN - false negative, NR - not reported.

(95% CI: 0.68 - 0.82), 0.85 (95% CI: 0.74 - 0.92), 5.1 (95% CI: 2.9 - 9.1), 0.29 (95% CI: 0.23 - 0.37), and 18 (95% CI: 9 - 33), respectively. Figure 2 is a SROC for I-FABP with an AUC of 0.82 (95% CI: 0.79 - 0.86). The heterogeneity across all studies was 0.90 (95% CI: 0.80 - 1.00), and all heterogeneity was likely due to threshold effect.

The target population in some studies is patients with acute abdominal pain, and it is of great value to estimate the diagnostic accuracy of I-FABP in these patients. Therefore, we performed a subgroup analysis in these studies. The pooled sensitivity, specificity, PLR, NLR, and DOR of I-FABP were 0.71 (95% CI: 0.59 - 0.81), 0.89 (95% CI: 0.69 - 0.97), 6.3 (95% CI: 2.2 - 17.9), 0.33 (95% CI: 0.24 - 0.46), and 19 (95% CI: 6 - 56), respectively. The area under SROC was 0.80 (95% CI: 0.76 - 0.83).

Sensitivity and specificity are not straightforward met-

Table 3. Predictive values of I-FABP under different thresholds.

Prevalence of II (%)	PPV (%)	NPV (%)
0.01	< 0.01	98.90
0.03	< 0.01	74.86
0.5	< 0.01	64.08
1	0.01	47.02
3	0.02	22.47
5	0.04	14.55
8	0.06	9.34
10	0.08	7.47
15	0.13	4.83
20	0.18	3.46

PPV - positive predictive value, NPV - negative predictive value.

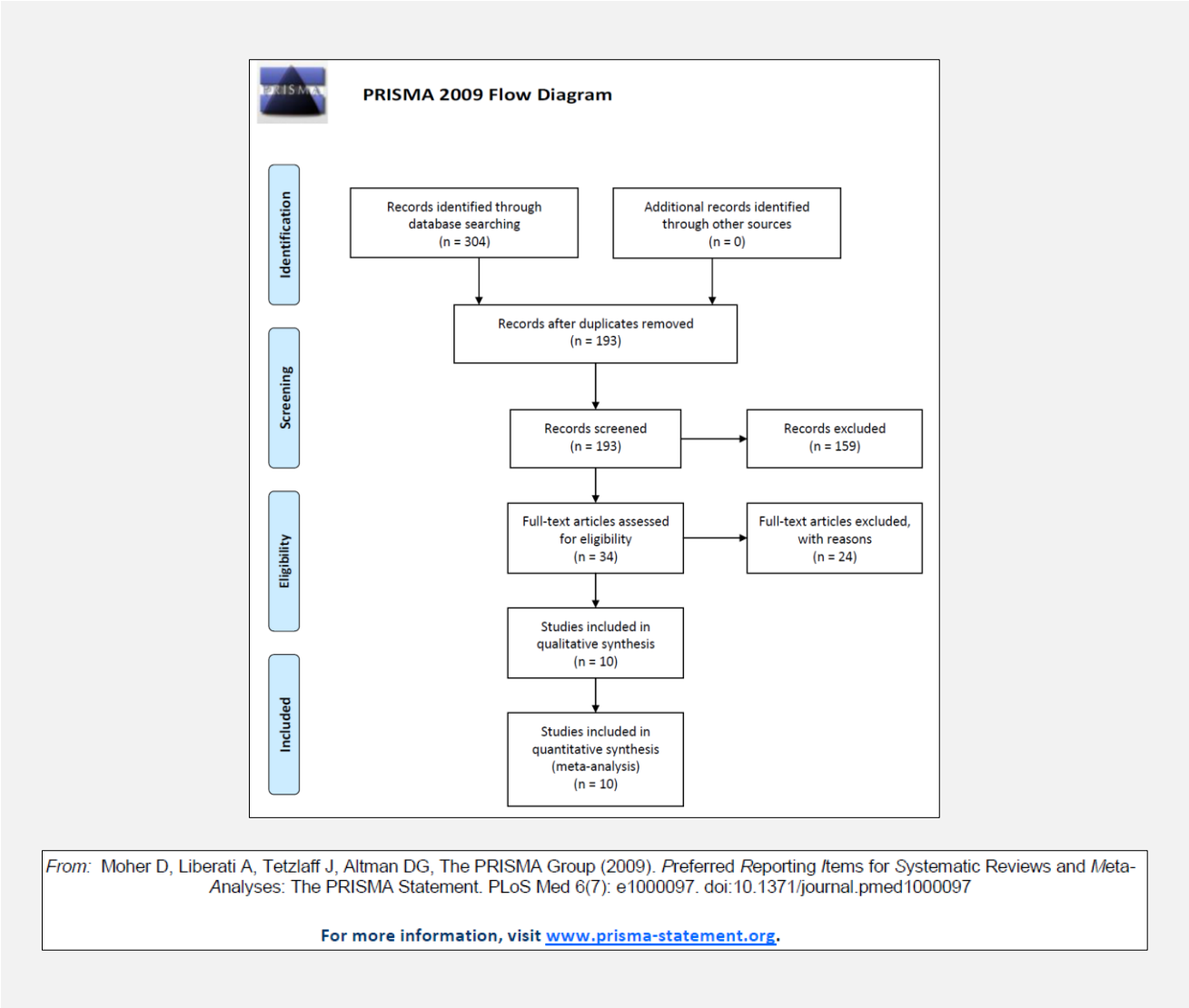

Figure 1. Flowchart of study selection.

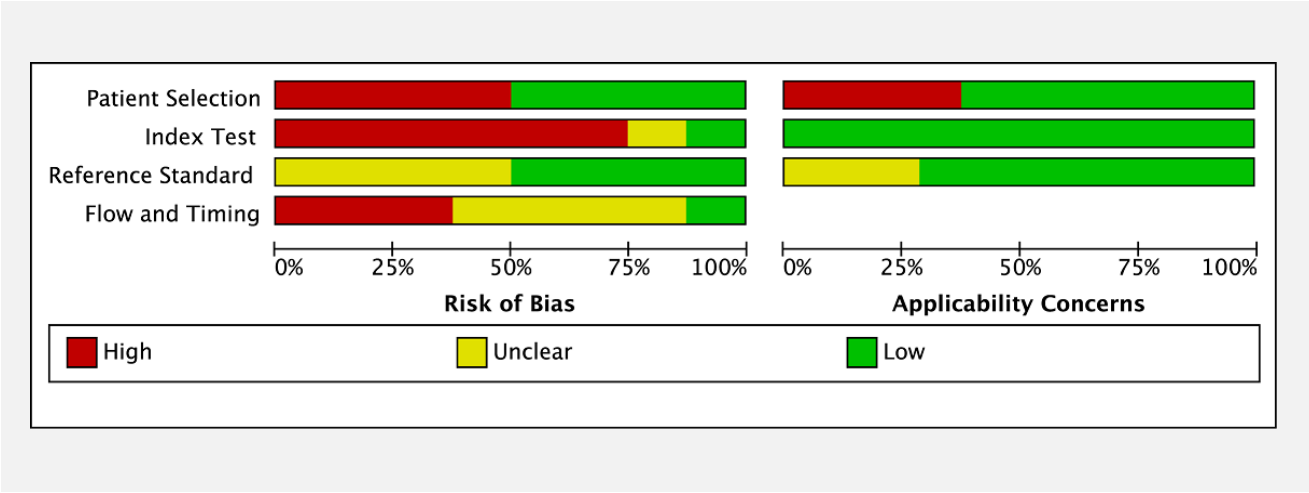

Figure 2. Summary of Quality Assessment tool for Diagnostic Accuracy tests (QUADAS-2).

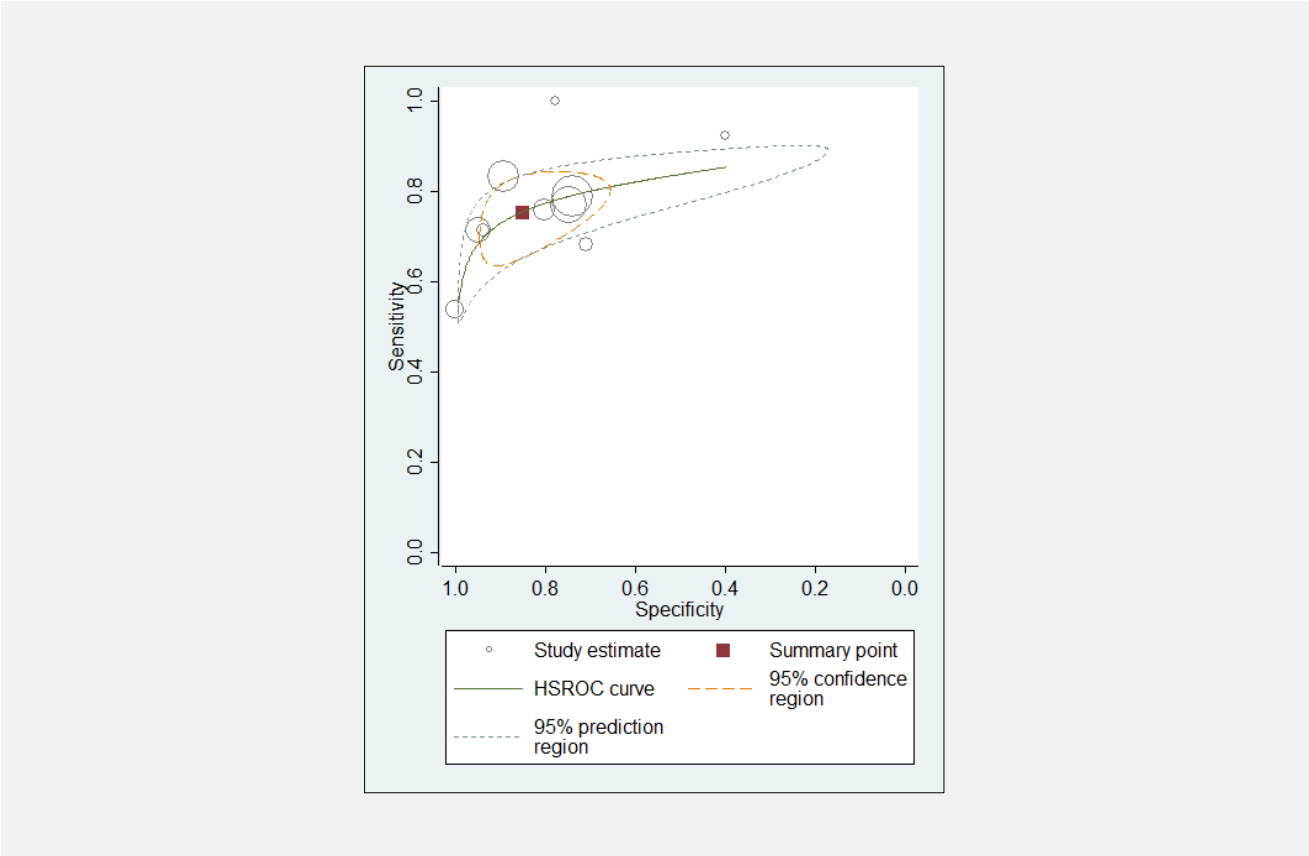

Figure 3. Summary receiver operating characteristic curve for iFABP.

rics to measure the diagnostic accuracy of an index test. By contrast, positive and negative predictive values (PPV and NPV) are more clinically meaningful. However, both PPV and NPV are greatly affected by prevalence of target disease [21]. Therefore, we calculated the PPV and NPV of I-FABP under different prevalence and the results are summarized in Table 3.

Publication bias

No publication bias was observed (p = 0.32), as shown in Figure 4.

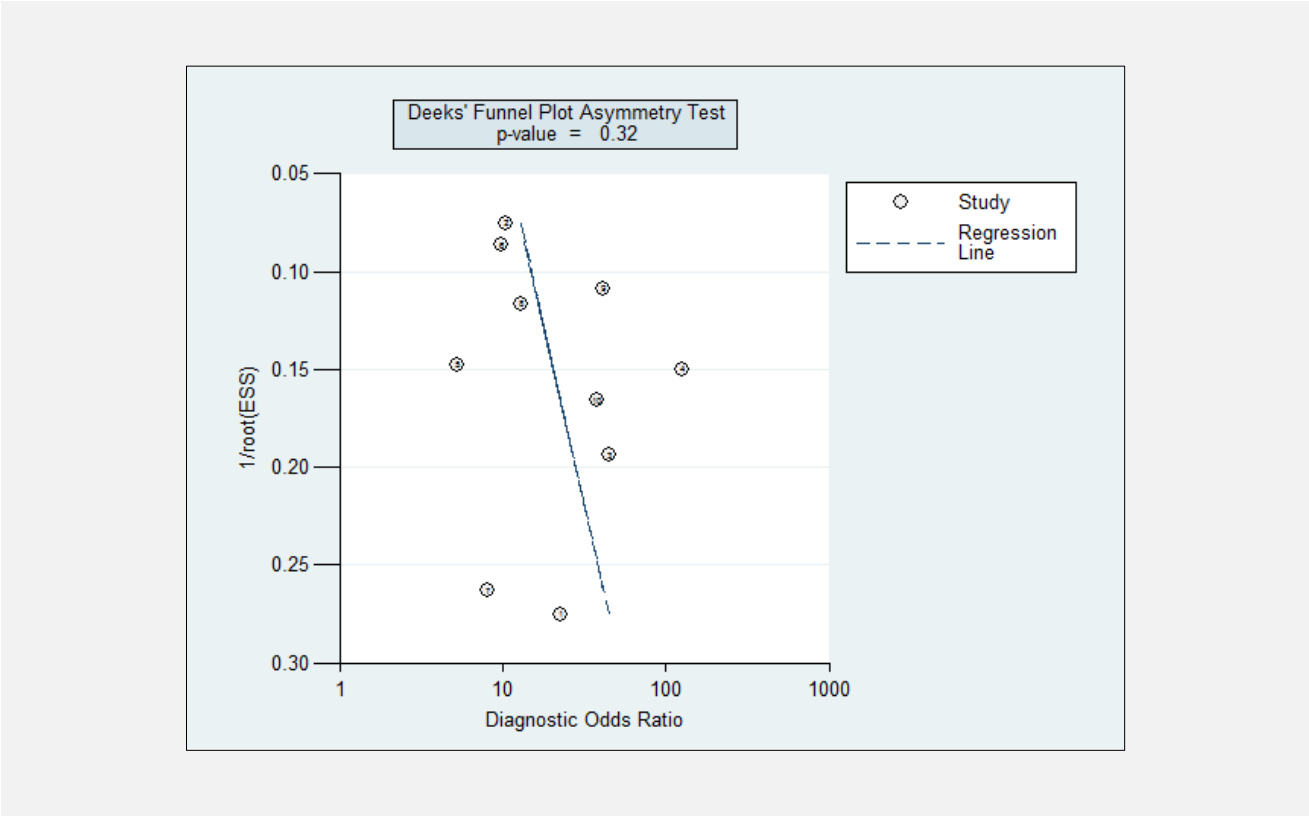

Figure 4. The Deek's funnel plot for the assessment of potential publication bias.

DISCUSSION

The major findings of this systematic review and meta-analysis were: (i) A total of 10 studies investigated the diagnostic accuracy of I-FABP for II; (ii) The overall diagnostic accuracy of I-FABP for II was moderate, with a sensitivity of 0.75 and a specificity of 0.85; (iii) In patients with acute abdominal pain, the diagnostic sensitivity and specificity of I-FABP were 0.71 and 0.89; (iv) The quality of available studies is fair and more studies with rigorous design are needed in future; (v) There was no publication bias.

Compared with a previous meta-analysis investigating the diagnostic accuracy of I-FABP for II [22], our study has its strengths. First, we updated the previous study as the last literature search time in our work is April 2019. Second, we calculated the diagnostic sensitivity and specificity of I-FABP in patients with acute abdominal pain. Furthermore, the PPV and NPV of I-FABP under different prevalence were also calculated.

The clinical interpretation of PPV and NPV is more straightforward than sensitivity and specificity, because the probability of the presence or absence was clearly indicated [23]. However, unlike sensitivity and specificity, both NPV and PPV are affected by the prevalence of the target disease in study cohort. To ensure the representativeness of the study cohort, subjects should be enrolled consecutively under uniform inclusion and exclusion criteria [24]. We noted that in some of the eligible studies, subjects were not consecutively enrolled. Therefore, these studies may have patient selection bias and their results may be unreliable. We noted that the prevalence of II in eligible studies varied, ranging from 5% to 72%. It seems that the prevalence of II in acute abdominal pain is much higher than some well-designed studies [25]. This may be due to the fact that the majority of the subjects in eligible studies have received surgery and thus represent patients with a high likelihood ratio of II. Actually, the prevalence of II in patients with acute abdominal pain is very high. In studies that consecutively enroll patients with acute abdominal pain, the prevalence of II in patients with acute abdominal pain is only 1% [25,26]. We found that at a prevalence of 1%, the PPV of I-FABP was only 0.01%, indicating that the probability of II is extremely low when I-FABP is positive. The NPV under such conditions was 47.02%, indicating that in patients with negative I-FABP, the probability of non-II is only 47.02%. Therefore, the diagnostic accuracy of I-FABP in clinical settings (e.g., patients with acute abdominal pain visiting emergency department) with low prevalence of II seems limited, and its clinical significance should be interpreted within the clinical content.

We noted that the quality of eligible studies was fair. In

addition to the patient selection bias mentioned above, nearly all eligible studies did not prespecify the I-FABP threshold before calculating sensitivity and specificity. It is widely accepted that data-driven selection of optimal thresholds may overestimate the diagnostic accuracy of an index test [27]. Another weakness of eligible studies was that all of them did not report the study results in accordance with the Standards for Reporting of Diagnostic Accuracy (STARD) guideline [28,29]. Therefore, it is difficult to assess the bias of eligible studies. Last but not the least, all of the eligible studies only reported the sensitivity, specificity, and AUC. Although these metrics have been widely used in diagnostic trials, they only reflect the diagnostic accuracy of an index test and do not incorporate information on consequences. Therefore, we suggest further studies using some advanced statistical methods, such as decision curve analysis [30], to calculate the net benefit of I-FABP test in patients with acute abdominal pain.

CONCLUSION

Taken together, our systematic review and meta-analysis suggest that I-FABP has shown some diagnostic accuracy for II and its diagnostic value should be interpreted within clinical content. Due the weaknesses in study design and reporting, further studies with rigorous design are needed to evaluate the diagnostic accuracy of I-FABP for II.

Declaration of Interest:
The authors have no conflicts of interest to declare.

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