Diagnostic Utility of Serum and Urine Biomarkers in Idiopathic Membranous Nephropathy: a Systematic Review and Meta-analysis

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Abstract

Background

Membranous nephropathy is an autoimmune nephropathy that is one of the most common pathological types of nephrotic syndrome. It is important to find and apply specific biomarkers for the noninvasive diagnosis of idiopathic membranous nephropathy (IMN). However, there are limited data about their diagnostic value. Therefore, an overall meta-analysis helps to identify effective biomarkers for the clinical diagnosis of IMN.

Methods

A systematic literature search was carried out in PubMed, Embase, Cochrane and Web of Science from inception until December 31, 2020. Two researchers searched for studies that met the inclusion criteria. The results of the joint study were expressed in terms of sensitivity and specificity.

Results

The meta-analysis included 24 studies with biomarkers for the clinical diagnosis of IMN, including phospholipase A2 receptor (PLA2R), thrombospondin type I domain-containing 7A (THSD7A), lysosome membrane protein-2 (LIMP-2) and circular RNAs. The diagnostic efficiency of PLA2R for IMN had a combined sensitivity of 60% and a combined specificity of 100%. The diagnostic efficiency of THSD7A for IMN had a combined sensitivity of 3% and a combined specificity of 99%. The diagnostic efficiency of urinary LIMP-2 for IMN was 100%, and the specificity was 100%. The diagnostic efficiency of exosomal circRNAs for IMN was 100%, and the specificity was 100%.

Conclusions

This meta-analysis shows that PLA2R and THSD7A are of important diagnostic value for IMN. More studies are needed in the future to reveal the diagnostic value of LIMP-2 and circRNAs for IMN. At the same time, other new diagnostic biomarkers in IMN need to be found in the future.

Introduction

Membranous nephropathy (MN) is the most common cause of adult nephrotic syndrome [1]. Approximately 20% of MN patients will progress to end-stage renal disease, and approximately 10% of them will die within 5 to 10 years [2, 3]. MN can be divided into idiopathic membranous nephropathy (IMN) and secondary membranous nephropathy (SMN). Approximately 75% of MN patients have idiopathic membranous nephopathy (IMN), while 20% - 25% of patients are secondary to different diseases, such as autoimmune diseases, infection, drugs, and malignancy [4].

In the past 10 years, the incidence of IMN has increased significantly, and it has been the main pathological type of primary glomerular disease [5, 6]. At present, the diagnosis of IMN mainly depends on kidney biopsy. Although kidney biopsy is the gold standard for diagnosing IMN, there are many potential complications in this method, such as perirenal hematoma, infection and other organ damage. Second, some patients cannot undergo renal biopsy, including isolated kidneys, abnormal coagulation function, hypertension dissatisfied with drug control and mental illness. Therefore, we have been committed to finding reliable biomarkers to guide clinical diagnosis through simple and noninvasive technology.

In recent years, several biomarkers in serum, THSD7A, PLA_2R, and IgG4 antibodies, have been assessed for their clinical significance in diagnosing idiopathic membranous nephropathy [7–9]. However, the current research still has some limitations. PLA_2R is the most commonly used method for the diagnosis of IMN, and the clinical value of other serum biomarkers still needs to be further explored. There are few studies on urine biomarkers, such as lysosome membrane protein-2 (LIMP-2) and circular RNAs [10, 11], but they have broad prospects and need to be confirmed by large, multicenter studies.

In this article, we performed the first systematic review and meta-analysis of serum and urine biomarkers in IMN patients, with the hope of promoting clinical diagnosis through noninvasive techniques.

Methods

Data sources and search strategy

Two researchers, Gao and Zhao, conducted a systematic review of qualified articles on PubMed, Embase, Cochrane and Web of Science from the beginning until December 31, 2020. The search terms were “idiopathic membranous nephropathy and (phospholipase A2 receptor or PLA2R or the thrombospondin type I domain-containing 7A or THSD7A or IgG4 or lysosome membrane protein-2 or LIMP-2 or circular RNAs)”. The literature search was limited to human studies and was published in English.

Study selection

We will include reports of original observational studies of IMN biomarkers and healthy control groups. These were exclusion criteria: (1) IMN biomarkers measured in animal models; (2) cadaver specimens; (3) in vitro data; (4) no healthy controls; (5) complications with other serious diseases or complications.

Data extraction and quality assessment

Two researchers (D.G. and Z.Z.) extracted data independently from all eligible initial documents. Disagreements were discussed and resolved by a third person's point of view (L.L.). The extracted information included the year of article publication, author, country, sample type, type of markers, experimental method, numbers of case groups, control groups, true positive (TP), false positive (FP), false negative (FN), and true negative (TN) results in each included study. Two authors (Gao and Lu) assessed the quality of the included studies using the updated Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [12].

Statistical analysis

All of the data were analyzed using Review Manager 5.3 and Stata MP 16.0 (Multiprocessor computers) software. TP, FP, FN and TN were used to describe various indicators in the studies. According to the Cochrane Handbook, I^2 is divided into 0.25, 0.50 and 0.75, representing mild, moderate and high heterogeneity, respectively [13]. When P<0.05 and I^2 >50%, we used the random effect model. When P>0.05 and I^2 <50%, we used the fixed effect model [14]. The results of the combination of the studies were expressed by sensitivity, specificity, PLR, NLR and DOR. Forest maps were used to describe the 95% CI (95% confidence interval) sensitivity and specificity in the study. Deeks' Funnel Plot Asymmetry Test was used to reflect literature publication bias.

Results

Search results and study characteristics

We obtained 1003 records from the PubMed database and 872 records from the Web of Science, Embase and Cochrane databases. Excluding duplicated articles, 1103 articles remained. We browsed the titles and abstracts of the articles, and 207 articles remained. 93 of the full-text articles were assessed for eligibility, but 76 articles were excluded for reasons (49 were mainly about IMN therapy, 8 did not provide enough data, 6 did not meet the accuracy of the test, 13 were without healthy controls). Finally, the meta-analysis included 17 articles, including 24 studies. Article selection flow chart is shown in Figure 1.

Table 1
Informations of the qualified studies.

Year	Study	Country	Sample	Biomarker	Method	Test group	Control group1	Control group2	Control group3	Control group4	TP	FP1	FP2	FP
2009	Beck [15]	USA	Serum	PLA_2R	WB	37	8	15	30	7	26	0	0	0
2011	Hoxha [16]	Germany	Serum	PLA_2R	IFT	100	17	90	153		52	0	0	0
2012	Murtas [17]	Italy	Serum	PLA_2R	WB	186		92	96		111		0	0
2013	Behnert [18]	Germany	Serum	PLA_2R	IIF-CBA	165			50	50	85			0
2014	Tomas [19]	France	Serum	THSD7A	WB	118	35	76	44		6	1	0	0
2015	Kim [20]	Korea	Serum	PLA_2R	ELISA	93	14	41	12		41	0	0	0
2015	Rood [21]	The Netherlands	Urine	LIMP-2	Proteomics	5		5	3		5		0	0
2015	Yang [22]	China	Serum	PLA_2R	IIF	20	10		5		12	2		0
2016	Li1 [23]	China	Serum	PLA_2R	ELISA	82	22	40	20		51	7	0	0
2016	Li2 [23]	China	Serum	PLA_2R	IIF-CBA	82	22	40	20		53	8	0	0
2017	Wang1 [24]	China	Serum	PLA_2R	WB	578	114	64	20		394	29	0	0
2017	Wang2 [24]	China	Serum	THSD7A	WB	578	114	64	20		8	1	0	0
2017	Zhang [25]	China	Serum	PLA_2R	TRFIA	69	9	94	286		49	0	0	0
2018	Radice [26]	Italy	Serum	PLA_2R	IIF	252	32	80	43	72	178	9	1	0
2019	Cheng [27]	China	Serum	PLA_2R	ELISA	146		51	62		102		0	0
2019	Ma1 [28]	China	Serum	circRNAs in exosomes	RT-PCR qPCR	10			10		10			0
2019	Ma2 [28]	China	Urine	circRNAs in exosomes	RT-PCR qPCR	10			10		10			0
2019	Zaghrini1[29]	France	Serum	PLA_2R	ELISA	1012			52		687			0
2019	Zaghrini2[29]	France	Serum	THSD7A	ELISA	1012			52		28			0
2020	Huang [30]	China	Serum	PLA_2R	ELISA	142		187	40		110		0	0
2020	Maifata1 [31]	Malaysia	Serum	PLA_2R	ELISA	47	22		24		13	1		0
2020	Maifata2 [31]	Malaysia	Urine	PLA_2R	ELISA	47	22		24		13	1		0
2020	Maifata3 [31]	Malaysia	Serum	THSD7A	ELISA	47	22		24		4	2		0
2020	Maifata4 [31]	Malaysia	Urine	THSD7A	ELISA	47	22		24		0	0		0

1: SMN control group, 2: other glomerular disease control group, 3: healthy control group, 4: other immune disease control group. Li1 indicates the study with CBA method. Wang1 indicates the study of biomarker PLA_2R. Wang2 indicates the study of biomarker THSD7A. Ma1 indicates the study of circRNAs in exos circRNAs in exosomes from urine. Zaghrini1 indicates the study of biomarker PLA_2R. Zaghrini2 indicates the study of biomarker THSD7A. Maifata1 indicates indicates the study of PLA_2R from urine. Maifata3 indicates the study of THSD7A from serum. Maifata4 indicates the study of THSD7A from urine.

The characteristics of the included studies are shown in Table 1. The studies included 20 serum samples and 4 urine samples. Biomarkers included PLA_2R, THSD7A, LIMP-2 and circular RNA in exosomes. PLA_2R was detected by Western blotting (WB) in three studies, by enzyme-linked immunosorbent assay (ELISA) in seven studies, by immunofluorescence test (IFT) in one study, by indirect immunofluorescence cell-based assay (IIF-CBA) in two studies, by indirect immunofluorescence (IIF) in two studies and by time-resolved fluoroimmunoassay (TRFIA) in one study. THSD7A was detected by WB in two studies and by ELISA in three studies. LIMP-2 was detected by Proteomics. Circular RNAs in exosomes were detected by reverse transcription polymerase chain reaction (RT–PCR) followed by quantitative PCR (qPCR) in two studies. 15 studies used SMN patients as controls, and 14 studies used other glomerular disease patients as controls.

Quality evaluation

The quality evaluation of the selected studies was based on the QUADAS-2, which is shown in Figure 2. Overall, the quality evaluation of the included studies was reliable, but 11 studies had unclear risks in terms of flow and timing, and 2 studies had higher risks in terms of flow and timing. At the same time, 6 studies were unclear on the risks of the index test.

Diagnostic value of PLA_2R in IMN

As shown in Figure 3a, in our meta-analysis, the random-effect model was chosen because I^2 was 88.47% (P<0.01), implying a high degree of heterogeneity in the study sample. The combined sensitivity was 60% (95% CI: 53%-67%), and the combined specificity was 100% (95% CI: 97%-100%). The combined PLR was 153.30 (95% CI: 21.80-1076.30), the combined NLR was 0.40 (95% CI: 0.34-0.48), and the combined DOR was 382.00 (95% CI: 53.00-2777.00). Figure 3b shows a summary of the receiver operating characteristics (SROC) of the 95% confidence profile and the 95% predicted profile, with an AUC of 0.81 (95% CI: 0.77-0.84), indicating that the diagnostic accuracy of PLA_2R in IMN is relatively acceptable.

Diagnostic value of THSD7A in IMN

As shown in Figure 4a, in our meta-analysis, the random-effect model was chosen because I^2 had a combined sensitivity of 72.08% (P<0.05), which implies a high degree of heterogeneity in the study sample. The combined sensitivity was 3% (95% CI: 1%-5%), and the combined specificity was 99% (95% CI: 97%-100%). The combined PLR was 4.00 (95% CI: 1.20-13.90), the combined NLR was 0.98 (95% CI: 0.96-1.00), and the combined DOR was 4.00 (95% CI: 1.00-14.00). The SROC summary chart with 95% confidence contour and 95% prediction contour is shown in Figure 4b. The AUC was 0.52 (95% CI: 0.48-0.57), indicating that THSD7A has a relatively low level of influence on the diagnostic accuracy of IMN.

Diagnostic value of other biomarkers in IMN

There was one study testing LIMP-2 in urine with proteomics. The sensitivity was 100% (95% CI: 48%-100%), and the specificity was 100% (95% CI: 63%-100%). There were two studies testing circRNAs in exosomes in serum and urine. The sensitivity was 100% (95% CI: 69%-100%), and the specificity was 100% (95% CI: 69%-100%).

Predicted posterior probability of PLA_2R and THSD7A in IMN

As shown in Figure 5, the pre-test probability of PLA_2R was 20%, and the post-test probability of PLA_2R was 97%. The pre-test probability of THSD7A was 20%, and the post-test probability of THSD7A was 50%. This means that PLA_2R and THSD7A can improve the diagnosis of IMN.

Subgroup and sensitivity analysis of PLA_2R

The causes of heterogeneity were analyzed by subgroup analysis. As shown in Table 2, the diagnostic accuracy rate of PLA_2R testing in Asia was higher than that in Europe. There were also other factors, such as method, sample, controls and sample size.

Table 2
Subgroup analysis of PLA_2R in the diagnosis of IMN

Subgroup	N	Sensitivity	Specificity	PLR	NLR	AUC
Region						
America	1	-	-	-	-	-
Europe	5	0.61(0.54-0.68)	1.00(0.57-1.00)	1853.5(0.8- 4.1e+0.6)	0.39(0.32-0.47)	0.76(0.72-0.80)
Asia	10	0.58(0.47-0.69)	0.99(0.93-1.00)	51.1(8.20-317.10)	0.42(0.32-0.55)	0.82(0.79-0.85)
Method						
WB	3	-	-	-	-	-
IFT	1	-	-	-	-	-
IIF-CBA	2	-	-	-	-	-
TRFIA	1	-	-	-	-	-
IIF	2	-	-	-	-	-
ELISA	7	0.55(0.40-0.69)	1.00(0.97-1.00)	151.60(9.00-2559.30)	0.45(0.32-0.63)	0.88(0.85-0.91)
Sample						
serum	15	0.62(0.56-0.68)	1.00(0.97-1.00)	206.90(22.20-1930.60)	0.38(0.32-0.45)	0.79(0.76-0.83)
urine	1	-	-	-	-	-
Control						
SMN	11	0.57(0.47-0.66)	0.98(0.94-1.00)	36.50(9.30-143.80)	0.44(0.35-0.54)	0.81(0.77-0.84)
SMN+other glomerular disease	8	0.63(0.57-0.68)	1.00(0.82-1.00)	131.00(3.20-5442.00)	0.38(0.32-0.44)	0.73(0.69-0.76)
Other immune disease	3	-	-	-	-	-
Sample size						
≤300	10	0.53(0.44-0.62)	0.99(0.95-1.00)	69.80(10.80-451.60)	0.47(0.38-0.58)	0.79(0.75-0.82)
>300	6	0.69(0.65-0.72)	1.00(0.88-1.00)	678.40(5.00-91324.20)	0.31(0.28-0.35)	0.74(0.70-0.77)

Subgroup and sensitivity analysis of THSD7A

Table 3 shows that the diagnostic accuracy rate of THSD7A in serum is higher than that in urine.

Table 3
Subgroup analysis of THSD7A in the IMN diagnosis

Subgroup	N	Sensitivity	Specificity	PLR	NLR	AUC
serum	4	0.03(0.02-0.06)	0.99(0.97-1.00)	3.7(1.2-11.7)	0.98(0.96-1.00)	0.55(0.5-0.59)
urine	1	-	-	-	-	-

Publication bias evaluation

The publication bias of the included studies was evaluated by Deeks' funnel plot asymmetry test. As shown in Figure 6, the results showed that the PLA_2R (P=0.80) and THSD7A (P=0.61) studies had no publication bias. P<0.05 indicates publication bias.

Discussion

This systematic review and meta-analysis focused on the diagnostic value of serum and urine biomarkers in IMN. At the same time, this is the first meta-analysis for the diagnostic value of different biomarkers of IMN. There was a meta-analysis of the diagnostic value of PLA_2R and THSD7A separately. In this meta-analysis, the study group included healthy controls, and the criteria for inclusion in the literature were different from those of previous meta-analyses. The specimen type was obtained from serum and urine. There were several biomarkers (PLA_2R, THSD7A, LIMP-2 and circRNAs) that met the inclusion criteria of the study.

In 2009, Beck [15] found that PLA_2R is specific to the antigen of adult MN, and its specific PLA_2R antibody was a serum biomarker for detecting IMN, with high sensitivity and specificity. We included 16 studies about the diagnostic value of PLA_2R that met the inclusion criteria. The sensitivity was 60% (95% CI: 53%-67%), and the specificity was 100% (95% CI: 97%-100%). The AUC was 0.81 (95%CI: 0.77-0.84). Serum PLA_2R antibody testing is an important clinical diagnostic value of IMN. That is consistent with the research of Hu [32].

Therefore, there was a high level of heterogeneity in the sensitivity of our meta-analysis (I^2 =88.47%), probably due to the region of studies, test method, specimen type, control group classification and sample size. Then, subgroup analysis further explored the source of heterogeneity. In our meta-analysis, studies were mainly distributed in Asia, followed by Europe and only America. More studies that meet the inclusion criteria are needed in the future. Then, detection methods and the grouping of studies can lead to sources of heterogeneity. Regarding the control group of the studies, we were included in the IMN and contained healthy controls, which was different from the control group of other studies. Studies in other meta-analyses may not have a healthy control group. However, we think it is necessary to include a healthy control group in the study and play the role of disease screening [33].

THSD7A is structurally similar to PLA_2R, which has been determined to be the second autoantigen of IMN in adults [19]. We included 5 studies about the diagnostic value of THSD7A that met the inclusion criteria. The sensitivity was 3% (95% CI: 1%-5%), and the specificity was 99% (95% CI: 97%-100%). The results are consistent with the research of Liu [34]. Although not sensitive enough, the diagnosis of IMN is very specific. The prevalence of THSD7A in PLA_2R-negative patients was higher than that in IMN patients [35]. THSD7A testing is important for the clinical diagnostic value of IMN. In this meta-analysis, the small number of studies on THSD7A explored the source of heterogeneity. We need more research on the diagnostic value of THSD7A in IMN.

Noninvasive diagnosis of IMN was performed according to the actual clinical needs of patients, we first conducted a systematic meta-analysis, and reviewed the diagnostic efficiency of PLA2R and THSD7A for IMN patients without publication bias.

In our meta-analysis, LIMP-2 in urine and circular RNAs in exosomes had important clinical value in the diagnosis of IMN, although there were few articles included. They were highly specific and sensitive by proteomics.

In conclusion, this meta-analysis shows that PLA_2R and THSD7A are of important diagnostic value for IMN. Future studies are needed to uncover the diagnostic value of LIMP-2 and circular RNAs for IMN. At the same time, other new diagnostic biomarkers in IMN need to be found and applied as noninvasive diagnostic methods for IMN in the future.

Declarations

Author contrubutions

Designed the experiments: Z.Zhao. Screened literature: (D. Gao and Z.Zhao). Extracted data: (D. Gao, Z. Zhao and L.Lu). Assessed the quality of the included studies: (D. Gao and L.Lu). Contributed to statistical analysis: (D. Gao and Z.Zhao). Wrote the manuscript: D.Gao.

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Competing interests

On behalf of all authors, the corresponding author states that there are no competing interests.

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Figures

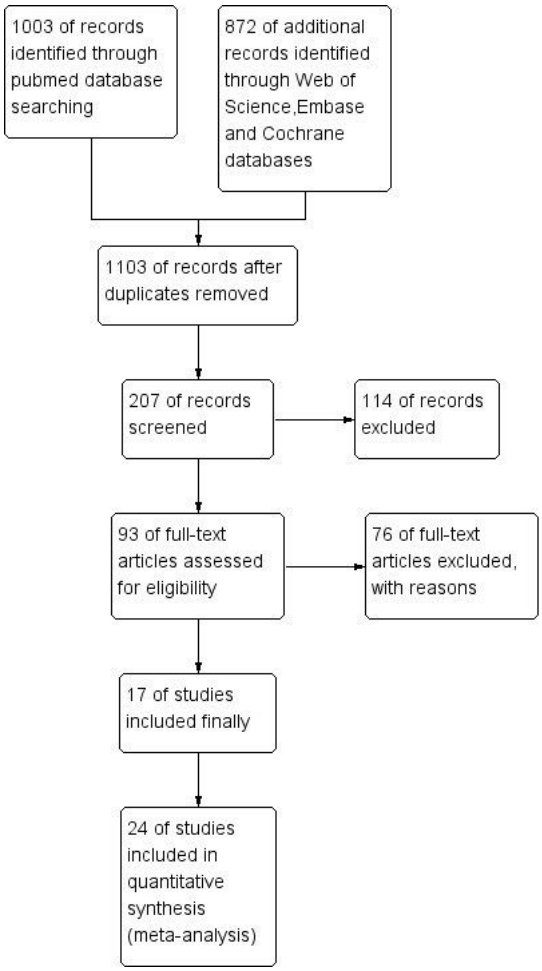

Figure 1

Article selection flowchart

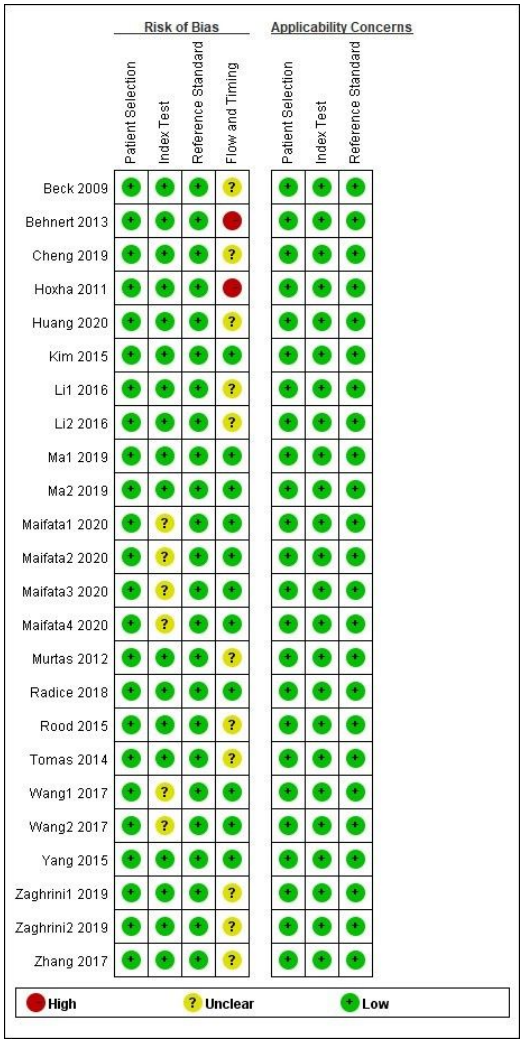

Figure 2

The quality evaluation results of included studies

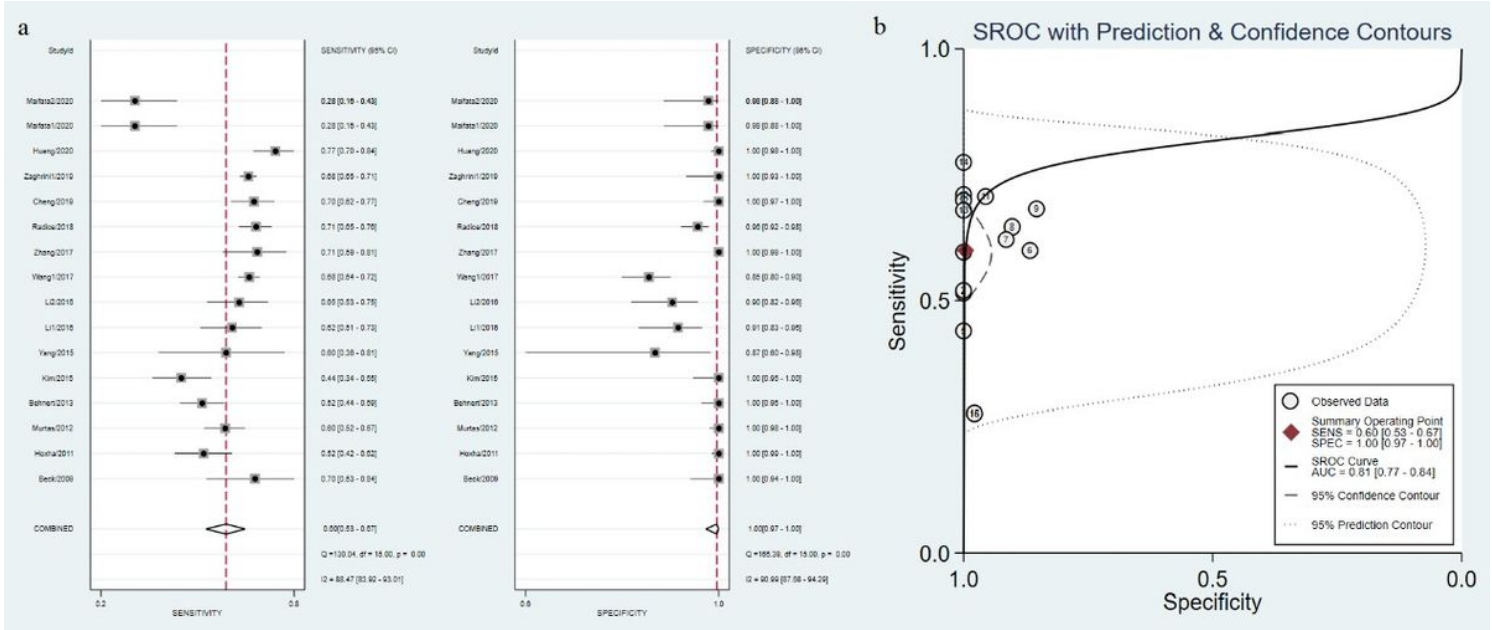

Figure 3

Forest map (a) and AUC (b) of the diagnostic accuracy of PLA2R in IMN

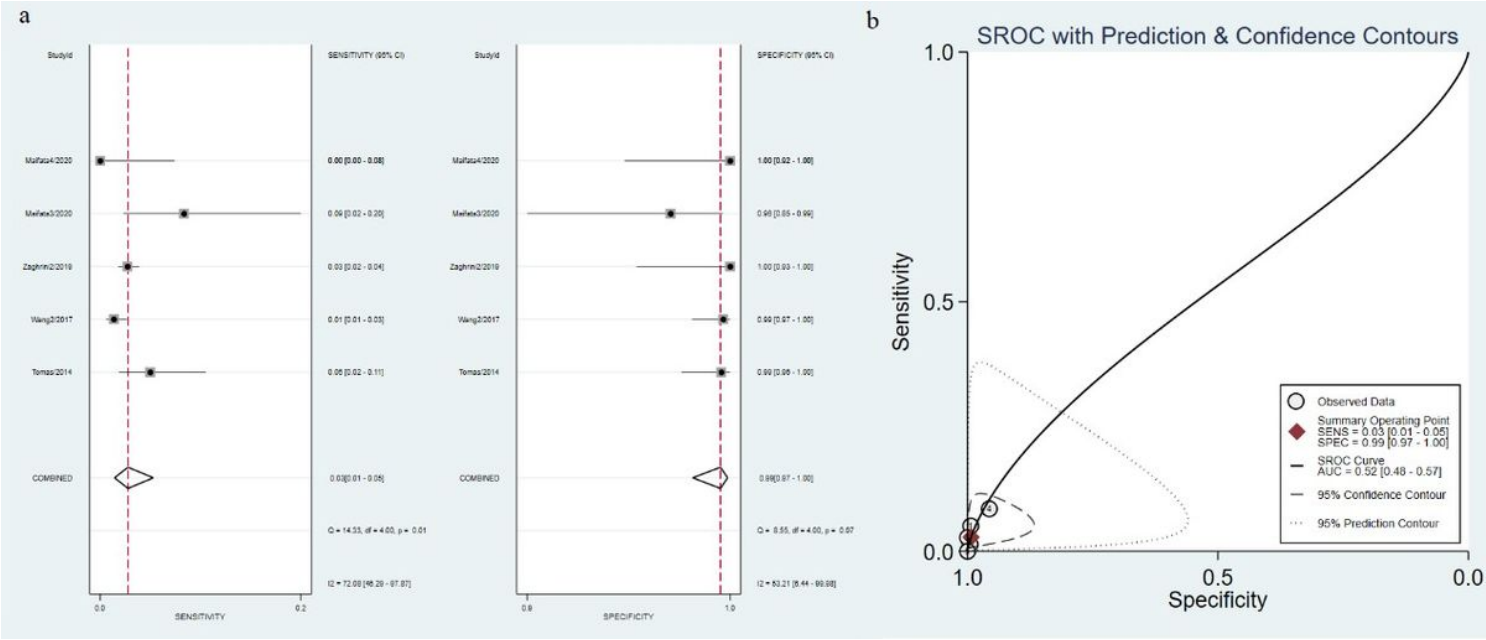

Figure 4

Forest map (a) and AUC (b) of THSD7A in diagnosing IMN

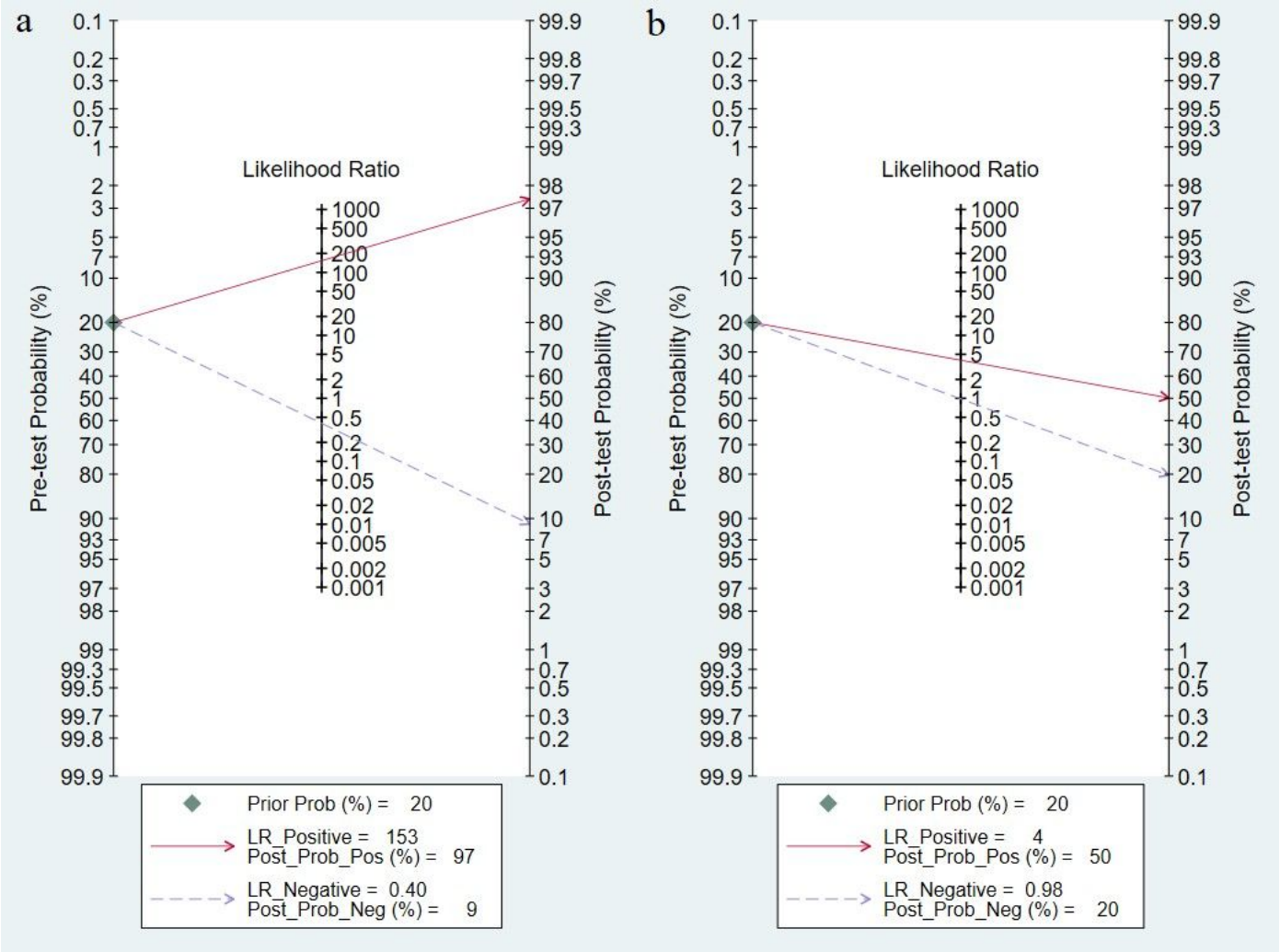

Figure 5

Predicted posterior probability of PLA2R(a) and THSD7A(b) in IMN

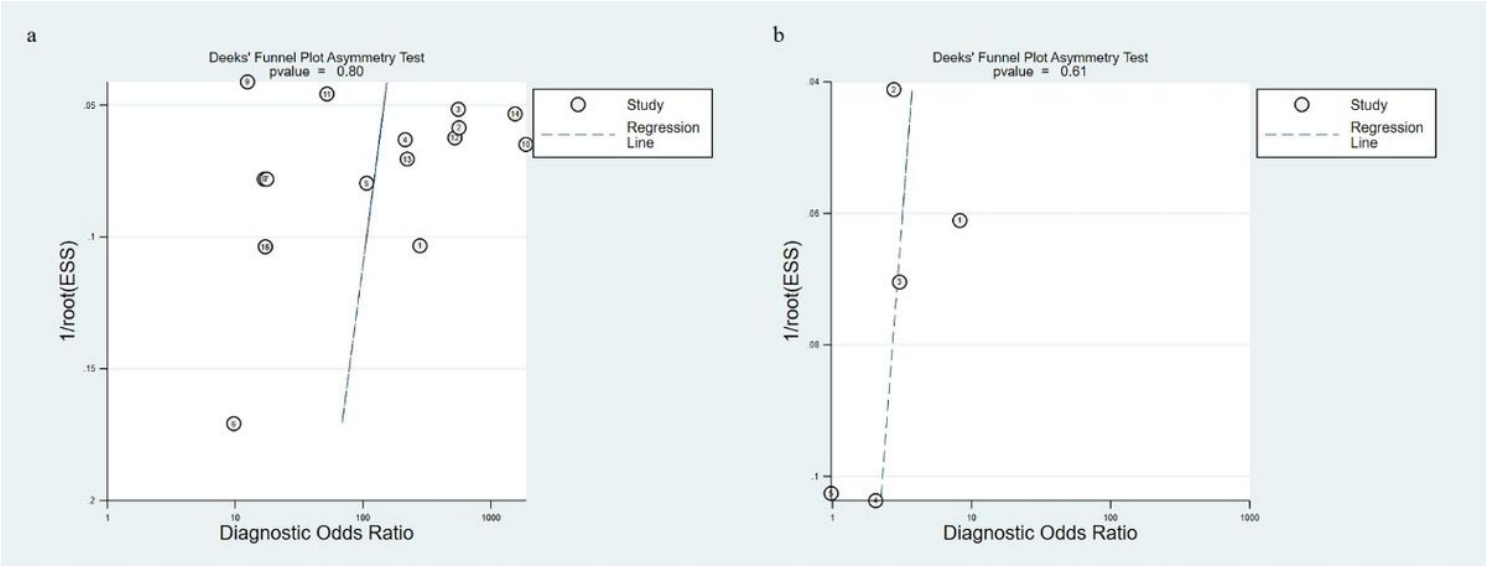

Figure 6

The publication bias of PLA2R(a) and THSD7A(b)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMAchecklist.docx
- PRISMAflowchart.jpg