Meta-Analysis of the Diagnostic Efficiency of THSD7A-AB for the Diagnosis of Idiopathic Membranous Nephropathy

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Thrombospondin type I domain-containing 7A (THSD7A), is a specific autoantigen of adult idiopathic membranous nephropathy (IMN), whose circulating antibody (THSD7A-AB) represents a promising biomarker for diagnosis of IMN. The objective of this meta-analysis is to investigate the diagnostic efficiency of THSD7A-AB for IMN. After rigorous data extraction, quality assessment, and data analysis, 10 articles (4545 patients) are included. For IMN, the summary sensitivity is 4% (2–7%), and the specificity is 99% (98–100%). The summary positive likelihood ratio (PLR) and negative likelihood ratio (NLR) are 5.40 (2.40–11.90) and 0.97 (0.95–0.99), respectively. The diagnostic odds ratio (DOR) is 6.00 (2.00–12.00). The area under the summary receiver operating characteristic curve (AUC) is 0.78 (0.74–0.81). For M-type phospholipase A2 receptor (PLA2R)-negative IMN, the summary sensitivity is 8% (6–10%), specificity is 100% (99–100%). The summary PLR and NLR are 15.80 (5.70–44.00) and 0.93 (0.91–0.95), respectively. The DOR is 17.00 (6.00–48.00). The AUC is 0.99 (0.98–1.00). THSD7A-AB has higher diagnostic value in PLA2R-negative patients than in IMN patients. These results suggest that THSD7A-AB could possibly be applied as an auxiliary non-invasive diagnostic method for PLA2R-negative IMN.

1. Introduction

Membranous nephropathy, which has idiopathic and secondary forms, is one of the leading causes of adult nephrotic syndrome.[1] Except for a few secondary cases due to viral infection, autoimmune diseases, thyroiditis, malignancy, and/or drug abuse, ≈80% of all cases of membranous nephropathy are referred to as idiopathic membranous nephropathy (IMN) because they have unknown etiology.[2] There are significant differences in the treatment of the two forms of diseases; the Kidney Disease: Improving Global Outcomes guidelines recommend corticosteroids combined with calcineurin inhibitors/alkylating agents as the initial therapy for IMN.[3] However, the treatment of secondary membranous nephropathy (SMN) is mainly focused on the etiology. Given the limitations of traditional renal biopsy diagnosis, such as perirenal hematoma, arteriovenous fistulas, infection, and damage to other organs,[4] it is extremely important to find reliable serological biomarkers to differentiate between IMN and SMN.

In 2009, M-type phospholipase A2 receptor (PLA2R) was identified as the first target antigen for IMN,[5] and the circulating antibody against PLA2R (PLA2R-AB) was used for the non-invasive diagnosis of IMN, with 78% sensitivity and 99% specificity.[6] Thrombospondin type I domain-containing 7A (THSD7A), is a specific autoantigen of adult IMN, whose circulating antibody (THSD7A-AB) represents a promising biomarker for the diagnosis of IMN. The objective of this meta-analysis is to investigate the diagnostic efficiency of THSD7A-AB for IMN. After rigorous data extraction, quality assessment, and data analysis, 10 articles (4545 patients) are included. For IMN, the summary sensitivity is 4% (2–7%), and the specificity is 99% (98–100%). The summary positive likelihood ratio (PLR) and negative likelihood ratio (NLR) are 5.40 (2.40–11.90) and 0.97 (0.95–0.99), respectively. The diagnostic odds ratio (DOR) is 6.00 (2.00–12.00). The area under the summary receiver operating characteristic curve (AUC) is 0.78 (0.74–0.81). For M-type phospholipase A2 receptor (PLA2R)-negative IMN, the summary sensitivity is 8% (6–10%), specificity is 100% (99–100%). The summary PLR and NLR are 15.80 (5.70–44.00) and 0.93 (0.91–0.95), respectively. The DOR is 17.00 (6.00–48.00). The AUC is 0.99 (0.98–1.00). THSD7A-AB has higher diagnostic value in PLA2R-negative patients than in IMN patients. These results suggest that THSD7A-AB could possibly be applied as an auxiliary non-invasive diagnostic method for PLA2R-negative IMN.

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DOI: 10.1002/gch2.201900099
the reported diagnostic efficiency of THSD7A-AB has been extremely varied among different studies. For example, the sensitivity of THSD7A-AB tests ranged from 0% to 35%, and the specificity ranged from 90% to 100%. Although THSD7A-AB may be a new biomarker for IMN diagnosis, its efficiency is still controversial. Therefore, we performed the present meta-analysis to comprehensively assess the diagnostic efficiency of THSD7A-AB testing in patients with IMN.

For the sake of clarity, Table 1 presents the full list of abbreviations used in this meta-analysis.

### Table 1. List of abbreviations used in this meta-analysis.

| Abbreviation | Full name                      |
|--------------|--------------------------------|
| THSD7A       | Thrombospondin type I domain-containing 7A |
| IMN          | Idiopathic membranous nephropathy  |
| PLR          | Positive likelihood ratio       |
| NLR          | Negative likelihood ratio       |
| DOR          | Diagnostic odds ratio           |
| AUC          | Area under the summary receiver operating characteristic curve |
| PLA2R        | M-type phospholipase A2 receptor |
| SMN          | Secondary membranous nephropathy  |
| THSD7A-AB    | Antibody against thrombospondin type I domain-containing 7A |
| Wanfang      | Digital Journal of Wanfang Data |
| VIP          | VIP Database for Chinese Technical Periodicals |
| CNKI         | Chinese National Knowledge Infrastructure |
| QUADAS-2     | Quality Assessment of Diagnostic Accuracy Studies-2 |
| SROC         | Summary receiver operating characteristic |
| IFT          | Immunofluorescence test         |

2. Results

2.1. Study Characteristics

As shown in Figure 1, there were 94 papers found in our primary search. Twenty-eight were excluded (16 articles were not relevant to IMN, 12 articles were on the presence of THSD7A in renal tissue). Therefore, there were 66 potentially relevant articles found in our search. Thirty-five articles met the exclusion criteria (27 reviews, 3 letters, and 5 case reports). The remaining 31 articles were retrieved for full-text review. Twenty-one articles were excluded (6 articles did not investigate the test accuracy, 12 articles did not provide sufficient data, 1 article only investigated THSD7A-AB in a pregnant woman and the subjects of 2 articles received immunosuppressive therapy). Finally, 10 articles, including 14 studies, were included in the present meta-analysis. The characteristics of the selected studies are shown in Table 2. The total population of the studies was 4545. THSD7A-AB was detectable by Western blotting in six studies, by ELISA method in five studies and by IFT method in three studies. Studies had an interval between the index test and the renal biopsy, and eight studies did the index test and the renal biopsy simultaneously. Six studies used patients with SMN as controls, 12 studies used patients with other glomerular diseases as controls, and 3 studies used healthy subjects as controls.

2.2. Methodological Quality of the Included Studies

According to the QUADAS-2, the quality assessment of the selected studies is shown in Figure 2. Although the overall quality of the eligible studies was robust, six studies had unclear risk regarding the flow and timing, which was derived from the time interval between index test and reference standard. Meanwhile, nine studies showed unclear risk regarding the index test that was caused by the awareness of the results of the reference standard.

2.3. Meta-Analysis

2.3.1. Diagnostic Efficiency in IMN

In our meta-analysis, Spearman’s correlation coefficient was 0.006 (p = 0.971), which suggested that there was no threshold effect among these eligible studies; then, a random effect model was selected to analyze the accuracy of THSD7A-AB for IMN diagnosis. As shown in Figure 3, the pooled sensitivity was 4% (95% CI: 2–7%), and the pooled specificity was 99% (95% CI: 98–100%). Meanwhile, I² was 90.91% (P < 0.01) for the pooled sensitivity, suggesting high heterogeneity in the sample of studies. The pooled positive likelihood ratio (PLR) was 5.40 (95% CI: 2.40–11.90), the pooled negative likelihood ratio (NLR) was 0.97 (95% CI: 0.95–0.99), and the pooled diagnostic odds ratio (DOR) was 6.00 (95% CI: 2.00–12.00). The summary receiver operating characteristic (SROC) graph with the 95% confidence contour and the 95% prediction contour is shown in Figure 3b, the area under the summary receiver operating characteristic curve (AUC) was 0.78 (95% CI: 0.74–0.81), indicating a relatively acceptable level of summary diagnostic accuracy of THSD7A-AB in IMN patients.

2.3.2. Subgroup and Sensitivity Analysis

A subgroup analysis was then carried out to determine the cause of heterogeneity. As shown in Table 3, the diagnostic accuracy of THSD7A-AB detection was higher when the Western blotting method was used than when the ELISA method was used. Similar findings were also found in the following factors: large sample size, studies with an interval between the index test and the renal biopsy, and studies using patients with other glomerular disease as controls.

Subsequently, we performed a sensitivity analysis to evaluate the effect of individual studies on the pooled diagnostic accuracy of THSD7A-AB testing for IMN. As shown in Table S1 (Supporting Information), the diagnostic accuracy of THSD7A-AB testing for IMN was relatively stable after the removal of each individual study.

2.3.3. Publication Bias Assessment

The publication bias of the selected studies was assessed by the Deeks’ funnel plot asymmetry test. The funnel plot with a superimposed regression line is shown in Figure S1.
(Supporting Information). The result suggested no publication bias among studies ($P = 0.92$).

2.3.4. Diagnostic Efficiency in PLA2R-Negative IMN

A further analysis was performed to evaluate the diagnosis accuracy of THSD7A-AB for the diagnosis of PLA2R-negative IMN cases. The characteristics of the included studies are shown in Table 4. And as shown in Figure 4, the pooled sensitivity and specificity of THSD7A-AB was 8% (95% CI: 6–10%) and 100% (95% CI: 99–100%), respectively. The summary PLR was 15.80 (95% CI: 5.70–44.00), the summary NLR was 0.93 (95% CI: 0.91–0.95), and the summary DOR was 17.00 (95% CI: 6.00–48.00). The SROC graph with the 95% confidence contour and the 95% prediction contour is shown in Figure 4b, the AUC was 0.99 (95% CI: 0.98–1.00), indicating that the summary diagnostic accuracy of THSD7A-AB in PLA2R-negative patients is better than in IMN patients.

3. Discussion

Since THSD7A was discovered as the second antigenic target of autoimmune IMN, a more in-depth understanding of the pathogenesis of this disease has been achieved. In addition to the classic complement activation pathway that leads to sublethal podocyte injury, recent studies\cite{17,18} have indicated that the THSD7A antigen-antibody immune complex in situ might directly interfere with podocyte integrity, leading to glomerular filtration barrier disruption and proteinuria. THSD7A-AB detection shows fairly good application prospects in multiple aspects of IMN, such as diagnosis, disease activity, clinical outcome, and treatment efficacy\cite{12,19}. Despite this, the diagnostic efficiency of THSD7A-AB for IMN is still controversial. Ren et al.'s
systematic review published in 2018 firstly described the prevalence of THSD7A in IMN patients, however, the diagnostic efficiency of THSD7A in IMN was not systematically evaluated. Their results showed that the prevalence of THSD7A was 3% (95% CI: 3–4%) in IMN patients without the exclusion of subjects receiving immunosuppressive therapy and without the identification of antibody detection in the serum or antigen detection in the renal tissue.\(^\text{[20]}\)

Given the actual clinical needs of non-invasive diagnosis, our meta-analysis firstly systematically reviewed the diagnostic efficiency of serum THSD7A-AB testing in patients with IMN with no publication bias, and in view of the effect of immunosuppression on antibody titer, we excluded patients receiving immunosuppressive therapy and found that the summary sensitivity was 4% (95% CI: 2–7%) and the summary specificity was 99% (95% CI: 98–100%). Although it is not sensitive enough, it is very specific for the diagnosis of IMN.

The existence of heterogeneity among the studies may affect the diagnostic efficiency. The results of the subgroup analysis indicated that the heterogeneity may be derived from type of control, sample size, testing method, and time interval. Further analysis revealed that, in addition to the apparent effect of “control type” on the diagnostic efficiency, the test interval between THSD7A-AB detection and renal biopsy was the significant source of heterogeneity. There are several possible explanations for why the testing interval was the significant source of heterogeneity found in our meta-analysis. First, various stages of disease may have been achieved during the testing interval. Second, the effect of immunosuppressive therapy must also be taken into account. Third, the spontaneous remission of disease should also be taken into account. For example, the testing was performed between 0 and 87 months after renal biopsy in

### Table 2. Characteristics of the included eligible studies.

| Year | Study | Region | Method  | Funding | Test interval | Case | Control1 | Control2 | Control3 | TP  | FP1 | FP2 | FP3 | FN  | TN1 | TN2 | TN3 |
|------|-------|--------|---------|---------|---------------|------|----------|----------|----------|-----|-----|-----|-----|-----|-----|-----|-----|
| 2017 | Gao\(^\text{[13]}\) | Asia   | ELISA   | No      | No            | 40   | 10       | 10       | 14       | 2   | 0   | 26  | 8   | 10  |
| 2017 | Hoxha 1\(^\text{[11]}\) | Europe | IFT     | Government | Yes          | 345  | 47       | 8        | 0        | 337 | 47  |
| 2017 | Hoxha 2\(^\text{[11]}\) | Europe | WB      | Government | Yes          | 345  | 47       | 8        | 0        | 337 | 47  |
| 2017 | Hoxha 3\(^\text{[11]}\) | Europe | WB      | Government | Yes          | 192  | 47       | 9        | 0        | 183 | 47  |
| 2017 | Hoxha 4\(^\text{[11]}\) | America | WB | Government | Yes          | 125  | 47       | 5        | 0        | 120 | 47  |
| 2019 | Tian\(^\text{[9]}\) | Asia   | IFT     | Government | No           | 212  | 118      | 84       | 6        | 2   | 0   | 206 | 116 | 84  |
| 2016 | Lin\(^\text{[10]}\) | Asia   | WB      | Government | No           | 99   | 37       | 2        | 1        | 97  | 36  |
| 2014 | Tomas\(^\text{[7]}\) | Europe | WB      | Government | Yes          | 118  | 35       | 76       | 44       | 6   | 1   | 0   | 112 | 34  | 76  | 44  |
| 2017 | Wang\(^\text{[12]}\) | Asia   | IFT     | Government | No           | 578  | 114      | 64       | 20       | 8   | 1   | 0   | 570 | 113 | 64  | 20  |
| 2016 | Wen\(^\text{[8]}\) | Asia   | ELISA   | No       | No           | 86   | 30       | 20       | 0        | 0   | 0   | 86  | 30  | 20  |
| 2017 | Xia 1\(^\text{[14]}\) | Asia   | WB      | Government | No           | 127  | 50       | 9        | 0        | 118 | 50  |
| 2017 | Xia 2\(^\text{[14]}\) | Asia   | ELISA   | Government | No           | 127  | 50       | 10       | 1        | 117 | 49  |
| 2019 | Zaghrini\(^\text{[15]}\) | Europe | ELISA   | Government | Yes          | 1012 | 52       | 28       | 0        | 984 | 52  |
| 2018 | Zhang\(^\text{[16]}\) | Asia   | ELISA   | No       | No           | 114  | 23       | 11       | 0        | 103 | 23  |

1: SMN control, 2: other glomerular disease control, 3: healthy control. Test interval: yes indicates testing after the biopsy; no indicates testing simultaneous with the biopsy. Hoxha 1 indicates the Prospective Hamburg cohort with IFT method in Hoxha’s study. Hoxha 2 indicates the Prospective Hamburg cohort with WB method in Hoxha’s study. Hoxha 3 indicates the Retrospective Hamburg cohort with WB method in Hoxha’s study. Hoxha 4 indicates the Retrospective Boston cohort with IFT method in Hoxha’s study. Xia 1 indicates the WB testing results in Xia’s study. Xia 2 indicates the ELISA testing results in Xia’s study.

Figure 2. The QUADAS-2 results for selected studies.
It is possible that the serum titers of THSD7A-AB decreased in some patients who had entered into an immunologically inactive stage or even have achieved spontaneous remission. Therefore, we suggest that serological testing should be performed at the time of initial diagnosis, rather than a period of time after renal biopsy. This would avoid the possible confusion introduced by therapeutic intervention and prognosis assessment.

To further explore the clinical application value of serum THSD7A-AB detection, we analyzed its value as a diagnostic biomarker in PLA2R-negative IMN patients. Encouragingly, the evaluation indexes for diagnostic efficiency were significantly ameliorated. The summary sensitivity for PLA2R-negative IMN increased by 100% compared to the sensitivity in all IMN patients without significantly changing the specificity. The summary PLR increased from 5.40 to 15.80, which suggested that its capacity for the correct identification of positive subjects was increased nearly 3 times. The summary NLR was reduced from 0.97 to 0.93, which suggested that its capacity for the correct identification of negative subjects was increased by 4%. The summary DOR was increased from 6.00 to 17.00, which suggested that its comprehensive diagnostic capacity was increased.

Table 3. Subgroup analysis for the accuracy of THSD7A-AB for IMN detection.

| Subgroup          | N   | Sensitivity | Specificity | Positive likelihood ratio | Negative likelihood ratio | AUC       |
|-------------------|-----|-------------|-------------|---------------------------|---------------------------|-----------|
| **Method**        |     |             |             |                           |                           |           |
| Western blotting  | 6   | 0.04 (0.03–0.06) | 0.99 (0.98–1.00) | 7.60 (1.70–34.20)           | 0.97 (0.95–0.98)          | 0.72 (0.68–0.76) |
| IFT               | 3   | –           | –           | –                          | –                         | –         |
| ELISA             | 5   | 0.06 (0.02–0.19) | 0.99 (0.91–1.00) | 8.30 (1.00–71.10)            | 0.95 (0.89–1.02)          | 0.68 (0.64–0.72) |
| **Region**        |     |             |             |                           |                           |           |
| Europe            | 5   | 0.03 (0.02–0.04) | 1.00 (0.98–1.00) | 10.20 (1.40–73.40)           | 0.97 (0.96–0.98)          | 0.83 (0.80–0.86) |
| America           | 1   | –           | –           | –                          | –                         | –         |
| Asia              | 8   | 0.04 (0.02–0.11) | 0.99 (0.97–1.00) | 3.60 (1.60–8.50)            | 0.97 (0.93–1.00)          | 0.83 (0.79–0.86) |
| **Sample size**   |     |             |             |                           |                           |           |
| >200              | 7   | 0.03 (0.02–0.03) | 0.99 (0.98–1.00) | 4.90 (1.80–13.40)           | 0.98 (0.97–0.99)          | 0.99 (0.97–0.99) |
| ≤200              | 7   | 0.06 (0.02–0.14) | 0.99 (0.95–1.00) | 5.50 (1.50–21.20)           | 0.95 (0.91–1.00)          | 0.76 (0.72–0.79) |
| **Interval**      |     |             |             |                           |                           |           |
| No                | 8   | 0.04 (0.02–0.11) | 0.99 (0.97–1.00) | 3.60 (1.60–8.50)            | 0.97 (0.93–1.00)          | 0.83 (0.79–0.86) |
| After biopsy test | 6   | 0.03 (0.02–0.04) | 1.00 (0.98–1.00) | 11.80 (1.60–83.00)          | 0.97 (0.96–0.98)          | 0.85 (0.81–0.87) |
| **Control**       |     |             |             |                           |                           |           |
| SMN               | 6   | 0.03 (0.01–0.10) | 0.98 (0.93–0.99) | 1.50 (0.60–3.80)            | 0.99 (0.96–1.02)          | 0.65 (0.61–0.69) |
| Other glomerular disease | 12 | 0.04 (0.02–0.08) | 1.00 (0.98–1.00) | 30.4 (2.70–339.20)          | 0.96 (0.94–0.98)          | 0.86 (0.83–0.89) |
| Health            | 3   | –           | –           | –                          | –                         | –         |
nearly 3 times. Collectively, the results suggested THSD7A-AB has higher diagnostic value for PLA2R-negative patients than for IMN patients, so we suggest that serum THSD7A-AB detection should be combined with PLA2R-AB to applied for the non-invasive diagnosis of IMN. After the discovery of THSD7A, neural epidermal growth factor-like 1 protein [21] and Semaphorin 3B[22] have also been recognized as the target antigens of IMN, their potential value as the diagnostic markers for IMN needs further systematic evaluation. We believe that with the discovery of more and more specific antigen-antibody targets for IMN, the era of complete non-invasive diagnosis of IMN will surely come.

A comprehensive literature search is the strength of our meta-analysis, but there were still several limitations within this study that must be acknowledged. First, THSD7A-AB is a newly discovered biomarker, therefore, more well-designed studies are needed to verify our conclusions. Second, not all included articles were of high quality. For example, the majority of studies did not report whether the antibody examination was performed while the investigator was blind to the renal biopsy results. Such methodological limitations might have biased our final conclusions.

In conclusion, this is the first study that systematically assessed the diagnostic efficiency of THSD7A-AB testing in patients with IMN. In addition, we found that THSD7A-AB has a higher diagnostic value for PLA2R-negative patients than for IMN patients. It could be applied as an auxiliary non-invasive diagnostic method for PLA2R-negative IMN. Considering our limitations and the heterogeneity among our chosen studies, well-designed multicenter prospective studies with large sample sizes are needed to further validate the results of this meta-analysis.

Table 4. Characteristics of the included eligible studies about PLA2R-AB-negative IMN cases.

| Year | Study | Region | Method | Funding | Test interval | Case | Control1 | Control2 | Control3 | TP | FP1 | FP2 | FP3 | FN | TN1 | TN2 | TN3 |
|------|-------|--------|--------|---------|--------------|------|----------|----------|----------|----|-----|-----|-----|----|-----|-----|-----|
| 2017 | Hoxha 1[11] | Europe | IFT | Government | Yes | 86 | 47 | 8 | 0 | 78 | 47 |
| 2017 | Hoxha 2[11] | Europe | WB | Government | Yes | 86 | 47 | 8 | 0 | 78 | 47 |
| 2017 | Hoxha 3[11] | America | WB | Government | Yes | 141 | 47 | 9 | 0 | 132 | 47 |
| 2017 | Hoxha 4[11] | Europe | WB | Government | Yes | 43 | 47 | 5 | 0 | 38 | 47 |
| 2019 | Tian[12] | Asia | IFT | Government | No | 59 | 107 | 84 | 5 | 2 | 0 | 54 | 105 | 84 |
| 2014 | Tomas[13] | Europe | WB | Government | Yes | 44 | 35 | 76 | 44 | 6 | 1 | 0 | 38 | 34 | 76 | 44 |
| 2017 | Wang[14] | Asia | IFT | Government | No | 184 | 85 | 64 | 20 | 6 | 1 | 0 | 178 | 84 | 64 | 20 |
| 2016 | Wen[15] | Asia | ELISA | No | No | 15 | 26 | 20 | 0 | 0 | 0 | 15 | 26 | 20 |
| 2019 | Zaghrini[16] | Europe | ELISA | Government | Yes | 325 | 52 | 25 | 0 | 300 | 52 |
| 2018 | Zhang[17] | Asia | ELISA | No | No | 49 | 23 | 6 | 0 | 43 | 23 |

1: SMN control, 2: other glomerular disease control, 3: healthy control. Test interval: yes indicates testing after the biopsy; no indicates testing simultaneous with the biopsy. Hoxha 1 indicates the Prospective Hamburg cohort with IFT method in Hoxha’s study. Hoxha 2 indicates the Prospective Hamburg cohort with WB method in Hoxha’s study. Hoxha 3 indicates the Retrospective Hamburg cohort with WB method in Hoxha’s study. Hoxha 4 indicates the Retrospective Boston cohort with IFT method in Hoxha’s study.

Figure 4. Forest plots (a) and summary receiver operating characteristic curve (b) of the diagnostic efficiency of THSD7A-AB for PLA2R-negative IMN patients.
4. Experimental Section

Data Sources and Search Strategy: PubMed, Embase, ClinicalTrials, SinoMed, Digital Journal of Wanfang Data (Wanfang), VIP Database for Chinese Technical Periodicals (VIP), and Chinese National Knowledge Infrastructure (CNKI) were searched to identify eligible studies published prior to Nov. 1st, 2019. The search terms used were “thrombospondin type I domain-containing 7A,” “THSD7A protein,” and “THSD7A.” Studies were also identified by manually searching the references cited in selected articles. No language restriction was imposed in the meta-analysis. Two authors (Yipeng Liu and Xiaoli Zheng) independently determined the eligibility of the studies, and disagreements were resolved by discussion and consensus.

Study Selection: Studies included in the current meta-analysis met the following criteria: (1) evaluated the accuracy of THSD7A-AB testing for IMN diagnosis; (2) estimated the sensitivity and specificity of the THSD7A-AB test; and (3) used renal biopsy results as the diagnostic gold standard. The exclusion criteria included: (1) case report, review, letter, editorial, or comment; (2) did not report test accuracy; (3) study subjects received immunosuppressive therapy; or (4) did not provide sufficient data. If studies had overlapping subjects, only the largest study was included.

Data Extraction and Quality Assessment: Two investigators (Yipeng Liu and Ying Lian) independently extracted the following data from all included articles: first author, year of publication, region, test method, funding source, the time interval between biopsy and THSD7A-AB testing, sample size and evaluation indexes (true positive, false positive, true negative, and false negative). The extracted data were confirmed by the third investigator (Chaoqun Ma).

The methodological quality of studies was evaluated independently by two researchers (Shanshan Zheng and Ying Lian) with the 4-component Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2).[23] The four components were as follows: (1) patient selection, (2) index test, (3) reference standard, and (4) flow and timing. Each item of the component was assessed as “yes,” “no,” or “unclear.” When discrepancies in assessment existed, a consensus was reached.

Data Analysis: The Spearman’s correlation coefficient was calculated to assess the threshold effect. A random effect model was used in the meta-analysis to calculate the summary sensitivity, specificity, PLR, NLR, and DOR across studies. A SROC curve was then used to plot the consistency of results among all studies as well as the accuracy of the test, and the AUC was calculated. The heterogeneity among studies was evaluated with I² and chi-square tests. The I² < 25% was considered as low heterogeneity, and I² > 75% as high heterogeneity. Subgroup analyses were carried out to identify the sources of heterogeneity. Such sources included the following: region (e.g., Europe, America, Asia), type of control (e.g., patients with SMN, patients with other glomerular diseases, healthy controls), sample size (>200 vs ≤200), testing method (e.g., Western blotting, immunofluorescence test (IFT), ELISA), and time interval (e.g., testing simultaneously with the biopsy versus testing after the biopsy). Sensitivity analysis was performed by omitting one study at a time to further evaluate the stability of the findings.

Deeks’ funnel plot asymmetry test was used to explore potential publication biases. All analyses were performed in mdias module in Stata 12.0 (College Station, TX, USA). A two-sided P < 0.05 was defined as statistically significant, except for heterogeneity testing, which had a boundary level of 0.10.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.
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