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 antibody against phospholipase A2 receptor (PLA2R-AB), antibody against thrombospondin type I domain-containing 7A (THSD7A-AB), lysosome membrane protein-2 (LIMP-2) and circular RNAs. The diagnostic efficiency of PLA2R-AB for IMN had a combined sensitivity of 60% and a combined specificity of 100%. The diagnostic efficiency of THSD7A-AB 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-AB and THSD7A-AB 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.

Keywords Idiopathic membranous nephropathy · Phospholipase A2 receptor · Thrombospondin type I domain-containing 7A · Lysosome membrane protein-2

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 nephropathy (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, PLA2R, THSD7A 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. PL\(A_2\)R and THSD7A are a kind of macro-molecular transmembrane glycoproteins, which are mainly expressed on the surface of podocytes and participate in inducing the humoral immune response dominated by IgG4. PL\(A_2\)R and THSD7A are major autoantigens in IMN, but we can measure circulating autoantibodies to them. PL\(A_2\)R-AB 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 PL\(A_2\)R 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 would include the original observational studies that reported the biomarkers of IMN and contained disease and healthy control groups. The disease control groups included SMN, other glomerular disease or other non-renal related diseases 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, because they were review articles, or irrelevant to the current analysis and 207 articles remained. 114 articles were excluded because of insufficient data. 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 Fig. 1.

The characteristics of the included studies are shown in Table 1. The total population of the studies was 7562. The studies included 20 serum samples and 4 urine samples. Biomarkers included PL\(A_2\)R-AB, THSD7A-AB, LIMP-2 and circular RNA in exosomes. PL\(A_2\)R-AB 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-AB 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 Fig. 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 PLA2R-AB in IMN

As shown in Fig. 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 PLA2R-AB in IMN is relatively acceptable.

Diagnostic value of THSD7A-AB in IMN

As shown in Fig. 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 Fig. 4b. The AUC was 0.52 (95% CI 0.48–0.57), indicating that THSD7A-AB 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%). As shown in Fig. 5. 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%). As shown in Fig. 6.

Predicted posterior probability of PLA2R-AB and THSD7A-AB in IMN

As shown in Fig. 7, the pre-test probability of PLA2R-AB was 20%, and the post-test probability of PLA2R-AB was 97%. The pre-test probability of THSD7A-AB was 20%, and the post-test probability of THSD7A-AB was 50%.
### 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 | FP3 | FP4 | FN | TN1 | TN2 | TN3 | TN4 |
|------|-------|---------|--------|-------------|------------|------------|---------------|---------------|---------------|---------------|----|-----|-----|-----|-----|----|-----|-----|-----|-----|
| 2009 | Beck  | USA     | Serum  | PLA₂R-AB   | WB         | 37         | 8             | 15            | 30            | 7             | 26 | 0   | 0   | 0   | 11 | 8  | 15 | 30 | 7   |
| 2011 | Hoxha | Germany | Serum  | PLA₂R-AB   | IFT        | 100        | 17            | 90            | 153           | 52            | 0  | 0   | 0   | 48  | 17 | 90 | 153|
| 2012 | Murtas | Italy   | Serum  | PLA₂R-AB   | WB         | 186        | 92            | 96            | 96            | 111           | 0  | 0   | 0   | 75  | 92 | 96 |
| 2013 | Behnert| Germany | Serum  | PLA₂R-AB   | IIF-CBA    | 165        | 50            | 50            | 85            | 80            | 0  | 0   | 0   | 50  | 50 | 50 |
| 2014 | Tomas | France  | Serum  | THSD7A-AB  | WB         | 118        | 35            | 76            | 44            | 6             | 1  | 0   | 0   | 112 | 34 | 76 | 44 |
| 2015 | Kim   | Korea   | Serum  | PLA₂R-AB   | ELISA      | 93         | 14            | 41            | 12            | 41            | 0  | 0   | 0   | 52  | 14 | 41 | 12 |
| 2015 | Rood  | The Neth | Serum  | LIMP-2     | Proteomics | 5          | 5             | 3             | 5             | 0             | 0  | 0   | 0   | 5   | 3  | 5  |
| 2015 | Yang  | China   | Serum  | PLA₂R-AB   | IIF        | 20         | 10            | 5             | 12            | 2             | 0  | 8   | 8   | 5   |    |     |
| 2015 | Li1   | China   | Serum  | PLA₂R-AB   | ELISA      | 82         | 22            | 40            | 20            | 51            | 7  | 0   | 0   | 31  | 15 | 40 | 20 |
| 2015 | Li2   | China   | Serum  | PLA₂R-AB   | IIF-CBA    | 82         | 22            | 40            | 20            | 53            | 8  | 0   | 0   | 29  | 14 | 40 | 20 |
| 2017 | Wang1 | China   | Serum  | PLA₂R-AB   | WB         | 578        | 114           | 64            | 20            | 394           | 29 | 0   | 0   | 184 | 85 | 64 | 20 |
| 2017 | Wang2 | China   | Serum  | THSD7A-AB  | WB         | 578        | 114           | 64            | 20            | 8            | 1  | 0   | 0   | 570 | 113| 64 | 20 |
| 2017 | Zhang | China   | Serum  | PLA₂R-AB   | TRFIA      | 69         | 9             | 94            | 286           | 49            | 0  | 0   | 0   | 20  | 9  | 94 | 286|
| 2017 | Radice| Italy   | Serum  | PLA₂R-AB   | IIF        | 252        | 32            | 80            | 43            | 72            | 178| 1  | 0   | 74  | 23 | 79 | 43 | 72 |
| 2019 | Cheng | China   | Serum  | PLA₂R-AB   | ELISA      | 146        | 51            | 62            | 102           | 100           | 0  | 0   | 0   | 44  | 51 | 62 |
| 2019 | Ma1   | China   | Serum  | circRNAs in exosomes | RT-PCR | 10 | 10 | 10 | 0 | 0 | 10 |
| 2019 | Ma2   | China   | Urine  | circRNAs in exosomes | RT-PCR | 10 | 10 | 10 | 0 | 0 | 10 |
| 2019 | Zaghiri1 | France | Serum  | PLA₂R-AB   | ELISA      | 1012       | 52            | 687           | 0             | 325           | 0  | 32  | 187 | 52  |    |     |
| 2019 | Zaghiri2 | France | Serum  | THSD7A-AB  | ELISA      | 1012       | 52            | 28            | 0             | 984           | 52 |
| 2020 | Huang | China   | Serum  | PLA₂R-AB   | ELISA      | 142        | 22            | 187           | 40            | 110           | 0  | 0   | 0   | 32  | 187| 40 |
| 2020 | Maifata1 | Malaysia | Serum  | PLA₂R-AB   | ELISA      | 47         | 22            | 24            | 13            | 1             | 0  | 34  | 21 | 24  |
| 2020 | Maifata2 | Malaysia | Urine  | PLA₂R-AB   | ELISA      | 47         | 22            | 24            | 13            | 1             | 0  | 34  | 21 | 24  |
| 2020 | Maifata3 | Malaysia | Serum  | THSD7A-AB  | ELISA      | 47         | 22            | 24            | 4             | 2             | 0  | 43  | 20 | 24  |
| 2020 | Maifata4 | Malaysia | Urine  | THSD7A-AB  | ELISA      | 47         | 22            | 24            | 0             | 0             | 0  | 47  | 22 | 24  |
This means that PLA2R-AB and THSD7A-AB can improve the diagnosis of IMN.

Subgroup and sensitivity analysis of PLA2R-AB

The causes of heterogeneity were analyzed by subgroup analysis. As shown in Table 2, the diagnostic accuracy rate of PLA2R-AB testing in Asia was higher than that in Europe. There were also other factors, such as method, sample, controls, and sample size.
Fig. 3  Forest map (a) and AUC (b) of the diagnostic accuracy of PLA2R-AB in IMN

Fig. 4  Forest map (a) and AUC (b) of THSD7A-AB in diagnosing IMN

Fig. 5  Forest map of LIMP-2 in diagnosing IMN

Fig. 6  Forest map of circRNAs in diagnosing IMN
Fig. 7 Predicted posterior probability of PLA2R-AB (a) and THSD7A-AB (b) in IMN

Table 2 Subgroup analysis of PLA2R-AB 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 (0.8e- 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 (5.00–91,324.20) | 0.31 (0.28–0.35) | 0.74 (0.70–0.77) |
Table 3 Subgroup analysis of THSD7A-AB 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 | –            | –            | –    | –    | –    |

Fig. 8 The publication bias of PLA2R-AB (a) and THSD7A-AB (b)

Subgroup and sensitivity analysis of THSD7A-AB

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

Publication bias evaluation

The publication bias of the included studies was evaluated by Deeks’ funnel plot asymmetry test. As shown in Fig. 8, the results showed that the PLA2R-AB (P = 0.80) and THSD7A-AB (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 PLA2R-AB and THSD7A-AB 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 (PLA2R-AB, THSD7A-AB, LIMP-2 and circRNAs) that met the inclusion criteria of the study.

In 2009, Beck [15] found that PLA2R is specific to the antigen of adult MN, and its specific PLA2R antibody was a serum biomarker for detecting IMN, with high sensitivity and specificity. We included 16 studies about the diagnostic value of PLA2R-AB 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 PLA2R-AB testing is an important clinical diagnostic value of IMN. That is consistent with the research of Hu [30].

Therefore, there was a high level of heterogeneity in the sensitivity of our meta-analysis (I² = 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 [31].
THSD7A is structurally similar to PLA2R, which has been determined to be the second autoantigen of IMN in adults [19]. We included 5 studies about the diagnostic value of THSD7A-AB 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 [7]. Although not sensitive enough, the diagnosis of IMN is very specific. The prevalence of THSD7A-AB in PLA2R-AB negative patients was higher than that in IMN patients [32]. THSD7A-AB testing is important for the clinical diagnostic value of IMN. In this meta-analysis, the small number of studies on THSD7A-AB explored the source of heterogeneity. We need more research on the diagnostic value of THSD7A-AB 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-AB and THSD7A-AB 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 PLA2R-AB and THSD7A-AB are of important diagnostic value for IMN. Future studies are needed to uncover the diagnostic value of LIMP-2 and circular RNAs for IMN.

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Data availability All relevant data are within the paper.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose. The authors have no competing interests to declare that are relevant to the content of this article. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript. The authors have no financial or proprietary interests in any material discussed in this article.

Ethical approval For this type of study, ethical approval is not required.

Informed consent For this type of study, formal consent is not required.

References

1. Bobkova IN, Kamysheva ES (2020) Modern view on treatment of membranous nephropathy. Ter Arkh 92:99–104. https://doi.org/10.26442/00403660.2020.06.000676
2. Sim JJ, Bhandari SK, Batech M et al (2018) End-stage renal disease and mortality outcomes across different glomerulonephropathies in a large diverse US population. Mayo Clin Proc 93:167–178. https://doi.org/10.1016/j.mayocp.2017.10.021
3. Rozenberg I, Kotliroff A, Zahavi T et al (2018) Outcome of idiopathic membranous nephropathy: a retrospective study. Isr Med Assoc J 20:186–189
4. Lai WL, Yeh TH, Chen PM et al (2015) Membranous nephropathy: a review on the pathogenesis, diagnosis, and treatment. J Formos Med Assoc 114:102–11. https://doi.org/10.1016/j.jfma.2014.11.002
5. Xu X, Wang G, Chen N et al (2016) Long-term exposure to air pollution and increased risk of membranous nephropathy in China. J Am Soc Nephrol 27:3739–3746. https://doi.org/10.1681/ASN.2016101093
6. Tang L, Yao J, Kong X et al (2017) Increasing prevalence of membranous nephropathy in patients with primary glomerular diseases: a cross sectional study in China. Nephrology (Carlton) 22:168–173. https://doi.org/10.1111/nep.12739
7. Liu Y, Zheng S, Ma C et al (2020) Meta-analysis of the diagnostic efficiency of THSD7A-AB for the diagnosis of idiopathic membranous nephropathy. Glob Chall 4:1900099. https://doi.org/10.1002/gch2.201900099
8. Wu X, Wen S, Zhu X et al (2017) Diagnostic value of renal phospholipase A2 receptor and IgG4 in patients with membranous nephropathy. Zhong nan da xue xue bao Yi xue ban 42:395–399. https://doi.org/10.11817/j.issn.1672-7347.2017.04.005
9. Liu L, Chang B, Wu X et al (2018) Expression of phospholipase A2 receptor in patients with membranous nephropathy. Vasc Health Risk Manag 14:103–108. https://doi.org/10.2147/VHRM.S160883
10. Rood IM, Merchant ML, Wilkey DW et al (2015) Increased expression of lysosome membrane protein 2 in glomeruli of patients with idiopathic membranous nephropathy. Proteomics 15:3722–3730. https://doi.org/10.1002/pmc.201500127
11. Ma H, Xu Y, Zhang R et al (2019) Differential expression study of circular RNAs in exosomes from serum and urine in patients with idiopathic membranous nephropathy. Arch Med Sci 15:738–753. https://doi.org/10.5114/ams.2019.84690
12. Whiting PF, Rutjes AW, Westwood ME et al (2011) QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 155:529–536. https://doi.org/10.7326/0003-4819-155-8-20110180-00009
13. Xu M, Rui D, Yan Y et al (2017) Oxidative damage induced by arsenic in mice or rats: a systematic review and meta-analysis. Biol Trace Elem Res 176:154–175. https://doi.org/10.1007/s12011-016-0810-4
14. Crippa A, Orsini N (2016) Dose-response meta-analysis of differences in means. BMC Med Res Methodol 16:91. https://doi.org/10.1186/s12874-016-0189-0
15. Beck LH Jr, Bonegio RG, Lambeau G et al (2009) M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med 361:11–21. https://doi.org/10.1056/NEJMoa0810457
16. Hoxha E, Harendza S, Zahner G et al (2011) An immuno-fluorescence test for phospholipase-A2-receptor antibodies and its clinical usefulness in patients with membranous

International Urology and Nephrology (2023) 55:2517–2526
glomerulonephritis. Nephrol Dial Transplant 26:2526–2532. https://doi.org/10.1093/ndt/grf247
17. Murtas C, Bruschi M, Candiano G et al (2012) Coexistence of different circulating anti-podocyte antibodies in membranous nephropathy. Clin J Am Soc Nephrol 7:1394–1400. https://doi.org/10.2215/CJN.02170312
18. Behnert A, Fritzler MJ, Teng B et al (2013) An anti-phospholipase A2 receptor quantitative immunoassay and epitope analysis in membranous nephropathy reveals different antigenic domains of the receptor. PLoS One 8:e61669. https://doi.org/10.1371/journal.pone.0061669
19. Tomas NM, Beck LH Jr, Meyer-Schwesinger C et al (2014) Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. N Engl J Med 371:2277–2287. https://doi.org/10.1056/NEJMoa1409354
20. Kim YG, Choi YW, Kim SY et al (2015) Anti-phospholipase A2 receptor antibody as prognostic indicator in idiopathic membranous nephropathy. Am J Nephrol 42:250–257. https://doi.org/10.1159/000440983
21. Yang X, Pan Y, Ding G (2015) Correlation of secreted phospholipase A2-I-B, anti-phospholipase A2 receptor antibody with idiopathic membranous nephropathy among adult patients. Chinese General Practice 18:1018–1022, 1028. https://doi.org/10.3969/j.issn.1007-9572.2015.09.009
22. Li X, Wei D, Zhou Z et al (2016) Anti-PLA2R antibodies in Chinese patients with membranous nephropathy. Med Sci Monit 22:1630–6. https://doi.org/10.12659/msm.896900
23. Wang J, Cui Z, Lu J et al (2017) Circulating antibodies against thrombospondin domain-containing 7A in Chinese patients with idiopathic membranous nephropathy. Clin J Am Soc Nephrol 12:1642–1651. https://doi.org/10.2215/CJN.01460217
24. Zhang Q, Huang B, Liu X et al (2017) Ultrasensitive quantitation of anti-phospholipase A2 receptor antibody as a diagnostic and prognostic indicator of idiopathic membranous nephropathy. Sci Rep 7:12049. https://doi.org/10.1038/s41598-017-12014-1
25. Radice A, Pieruzzi F, Trezzi B et al (2018) Diagnostic specificity of autoantibodies to M-type phospholipase A2 receptor (PLA2R) in differentiating idiopathic membranous nephropathy (IMN) from secondary forms and other glomerular diseases. J Nephrol 31:271–278. https://doi.org/10.1080/0886022X.2018.1456457
26. Cheng G, Liu J, Gilbert A et al (2019) Serum phosphorylase A2 receptor antibodies and immunoglobulin G subtypes in adult idiopathic membranous nephropathy: clinical value assessment. Clin Chim Acta 490:135–141. https://doi.org/10.1016/j.cca.2018.12.027
27. Zaghrini C, Seitz-Poliski B, Justino J et al (2019) Novel ELISA for thrombospondin type 1 domain-containing 7A autoantibodies in membranous nephropathy. Kidney Int 95:666–679. https://doi.org/10.1016/j.kint.2018.10.024
28. Zhenzhen H, Yuan F, Wei C (2020) Effects of the expression of serum PLA2R antibody on the diagnosis and immunological therapy of idiopathic membranous nephropathy. Int J Clin Exp Med 13:5959–5966
29. Maifata SM, Hod R, Zakaria F et al (2020) Role of serum and urine biomarkers (PLA2R and THSD7A) in diagnosis, monitoring and prognostication of primary membranous glomerulonephritis. Biomolecules 10:319. https://doi.org/10.3390/biom10020319
30. Hu SL, Wang D, Gou WJ et al (2014) Diagnostic value of phospholipase A2 receptor in idiopathic membranous nephropathy: a systematic review and meta-analysis. J Nephrol 27:111–116. https://doi.org/10.1007/s40062-014-0042-7
31. Burbelo PD, Joshi M, Chaturvedi A et al (2020) Detection of PLA2R autoantibodies before the diagnosis of membranous nephropathy. J Am Soc Nephrol 31:208–217. https://doi.org/10.1681/ASN.2019050538
32. Ren S, Wu C, Zhang Y et al (2018) An update on clinical significance of use of THSD7A in diagnosing idiopathic membranous nephropathy: a systematic review and meta-analysis of THSD7A in IMN. Ren Fail 40:306–313. https://doi.org/10.1080/0886022X.2018.1456457

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