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Original article

Clinical phenotype predicts anti-PLA2R serology in nephrotic range proteinuria

El fenotipo clínico predice la serología anti-PLA2R en la proteinuria en rango nefrótico

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ABSTRACT

Background: The 2021 KDIGO guidelines permit non-invasive diagnosis of membranous nephropathy using anti-PLA2R antibodies in patients with nephrotic syndrome. However, optimal patient selection for anti-PLA2R testing remains undefined, particularly in patients with nephrotic-range proteinuria without nephrotic syndrome.
Methods: We conducted a retrospective analysis of 156 consecutive patients with nephrotic-range proteinuria presenting to a tertiary nephrology center between November 2022 and July 2024. Patients were stratified by clinical phenotype: nephrotic syndrome versus nephrotic-range proteinuria without nephrotic syndrome. Primary outcomes were anti-PLA2R positivity rates and anti-PLA2R-positive membranous nephropathy frequency between groups.
Results: Anti-PLA2R positivity was significantly higher in nephrotic syndrome patients compared to those with nephrotic-range proteinuria without nephrotic syndrome (26.5% vs 9.6%, $p = 0.007$). Membranous nephropathy diagnosis was more frequent in the nephrotic syndrome group (43.3% vs 23.2%, $p = 0.008$). Among patients with confirmed anti-PLA2R-positive membranous nephropathy, anti-PLA2R antibody levels were significantly higher in nephrotic syndrome patients ($p = 0.008$).
Conclusions: Clinical phenotype strongly predicts anti-PLA2R diagnostic yield in nephrotic-range proteinuria. These findings support KDIGO guidelines emphasizing nephrotic syndrome presence for non-invasive anti-PLA2R-positive membranous nephropathy diagnosis and suggest prioritizing anti-PLA2R testing in nephrotic syndrome patients for optimal resource utilization in limited settings.

Palabras clave:
Anticuerpo anti-PLA2R
Nefropatía membranosa
Síndrome nefrótico
Proteinuria en rango nefrótico

RESUMEN

Objetivos: Las guías KDIGO 2021 permiten el diagnóstico no invasivo de la nefropatía membranosa mediante anticuerpos anti-PLA2R en pacientes con síndrome nefrótico. Sin embargo, la selección óptima de pacientes para la prueba anti-PLA2R permanece indefinida, en particular en aquellos con proteinuria en rango nefrótico sin síndrome nefrótico.
Métodos: Se realizó un análisis retrospectivo de 156 pacientes consecutivos con proteinuria en rango nefrótico que acudieron a un centro terciario de nefrología entre noviembre de 2022 y julio de 2024. Los pacientes fueron estratificados según el fenotipo clínico: síndrome nefrótico frente a proteinuria en rango nefrótico sin síndrome nefrótico. Los desenlaces primarios fueron las tasas de positividad de anti-PLA2R y la frecuencia de nefropatía membranosa anti-PLA2R-positiva entre los grupos.

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Resultados: La positividad de anti-PLA2R fue significativamente mayor en los pacientes con síndrome nefrótico en comparación con aquellos con proteinuria en rango nefrótico sin síndrome nefrótico (26,5% frente a 9,6%; p = 0,007). El diagnóstico de nefropatía membranosa fue más frecuente en el grupo con síndrome nefrótico (43,3% frente a 23,2%; p = 0,008). Entre los pacientes con nefropatía membranosa confirmada anti-PLA2R-positiva, los niveles de anticuerpos anti-PLA2R fueron significativamente más altos en los pacientes con síndrome nefrótico (p = 0,008).
Conclusiones: El fenotipo clínico predice de manera sólida el rendimiento diagnóstico de anti-PLA2R en la proteinuria en rango nefrótico. Estos hallazgos respaldan las guías KDIGO que enfatizan la presencia de síndrome nefrótico para el diagnóstico no invasivo de nefropatía membranosa anti-PLA2R-positiva y sugieren priorizar la prueba anti-PLA2R en pacientes con síndrome nefrótico para una utilización óptima de recursos en entornos limitados.

Introduction

Nephrotic-range proteinuria (NRP), defined as urinary protein excretion ≥3.5 g/day, represents a heterogeneous clinical entity with divergent pathophysiological mechanisms and clinical presentations.[1] While classically associated with nephrotic syndrome (NS) – characterized by hypoalbuminemia (< 3.0 g/dL), edema, and hyperlipidemia – a substantial subset of patients maintain normal serum albumin despite massive proteinuria, termed nephrotic-range proteinuria without nephrotic syndrome (NRP without NS).[2,3]

Recent advances suggest that patients with NRP without NS maintain albumin homeostasis through enhanced tubular reabsorption mechanisms, representing distinct pathophysiological processes from full-blown nephrotic syndrome.[4–6]

The diagnostic landscape for membranous nephropathy (MN) has been transformed by the discovery of anti-phospholipase A2 receptor (PLA2R) antibodies, present in 70–80% of primary MN cases.[7] The 2021 KDIGO guidelines represent a paradigm shift, stating that "kidney biopsy is not required to confirm MN diagnosis in patients with nephrotic syndrome and positive anti-PLA2R antibody test".[8] This recommendation, based on studies demonstrating 97–99% specificity and positive likelihood ratios, permits non-invasive diagnosis in 60–70% of MN cases when specific criteria are met.[9,10] Although 80% of patients with primary MN present with NS clinical features, approximately 20% of patients present without nephrotic syndrome.[11]

We aimed to compare anti-PLA2R antibody diagnostic yield between nephrotic syndrome and nephrotic-range proteinuria without nephrotic syndrome phenotypes, to provide evidence for phenotype-based testing algorithms that optimize diagnostic accuracy.

Methods

Study design and setting

This retrospective cohort study included 156 consecutive adult patients (≥18 years) presenting with nephrotic-range proteinuria (≥3.5 g/day) to the Gazi University Nephrology Clinic between November 2022 and July 2024. The study protocol was approved by the Gazi University Ethics Committee (October 22, 2024; Approval No: E-77082166-604.01-1079878) and conducted according to Declaration of Helsinki principles. All data extracted from the medical records were stored de-identified prior to the analysis. Informed consent was not obtained due to the retrospective study design.

Participants

Inclusion criteria were: age ≥18 years; documented nephrotic-range proteinuria (≥3.5 g/day) at presentation; serum anti-PLA2R antibody measurement at initial evaluation; and complete clinical and laboratory data availability. Exclusion criteria were: subnephrotic proteinuria (< 3.5 g/day); incomplete laboratory data; and lost to follow-up before diagnosis establishment. To minimize diagnostic bias, three patients with previously confirmed false-positive anti-PLA2R ELISA results were excluded from the study cohort. The enrollment procedure is outlined in Fig. 1.

Variables and data sources

Comprehensive data were collected from electronic medical records including demographics, body mass index, comorbidities (diabetes, hypertension, heart failure) and laboratory parameters. Estimated glomerular filtration rate was calculated using the CKD-EPI 2021 equation without race adjustment.[12] Laboratory measurements included serum creatinine, albumin, total and low density lipoprotein (LDL) cholesterol, 24-h urinary protein excretion or spot protein/creatinine ratio, and anti-PLA2R antibodies (EUROIMMUN Anti-PLA2R enzyme-linked immunosorbent assays (ELISA), Immunoglobulin G).

Anti-PLA2R antibodies were measured using EUROIMMUN commercial ELISA kit following manufacturer's protocol.[13] Results were interpreted as: negative (< 14 RU/mL), borderline (14–19 RU/mL), and positive (≥20 RU/mL). This threshold aligns with international validation studies demonstrating optimal sensitivity-specificity balance.[14]

Patients were stratified into two groups based on clinical phenotype at presentation. Nephrotic syndrome was defined as: proteinuria ≥3.5 g/day, serum albumin < 3.0 g/dL, clinical edema, and hyperlipidemia (total cholesterol > 200 mg/dL). Nephrotic-range proteinuria without nephrotic syndrome was defined as: proteinuria ≥3.5 g/day, serum albumin ≥3.0 g/dL, and absence of overt clinical edema.

Kidney biopsies were performed according to standard clinical indications. Patients with positive anti-PLA2R results and full NS were generally not biopsied, whereas selected anti-PLA2R negative cases underwent biopsy unless contraindicated (e.g., solitary kidney, anticoagulation, advanced diabetic nephropathy or patient refusal). Specimens were processed for light microscopy and immunofluorescence. Membranous nephropathy diagnosis was made by two experienced nephropathologists.

Statistical analysis

Statistical analyses were performed using SPSS version 22.0. Continuous variables were assessed for normality using Shapiro–Wilk test and presented as mean ± SD or median [IQR] as appropriate. Categorical variables were expressed as frequencies and percentages. Between-group comparisons utilized Student's *t*-test for normally distributed continuous variables, Mann–Whitney *U* test for non-normally distributed variables, and Chi-square or Fisher's exact test for categorical variables. A *p*-values < 0.05 were considered statistically significant.

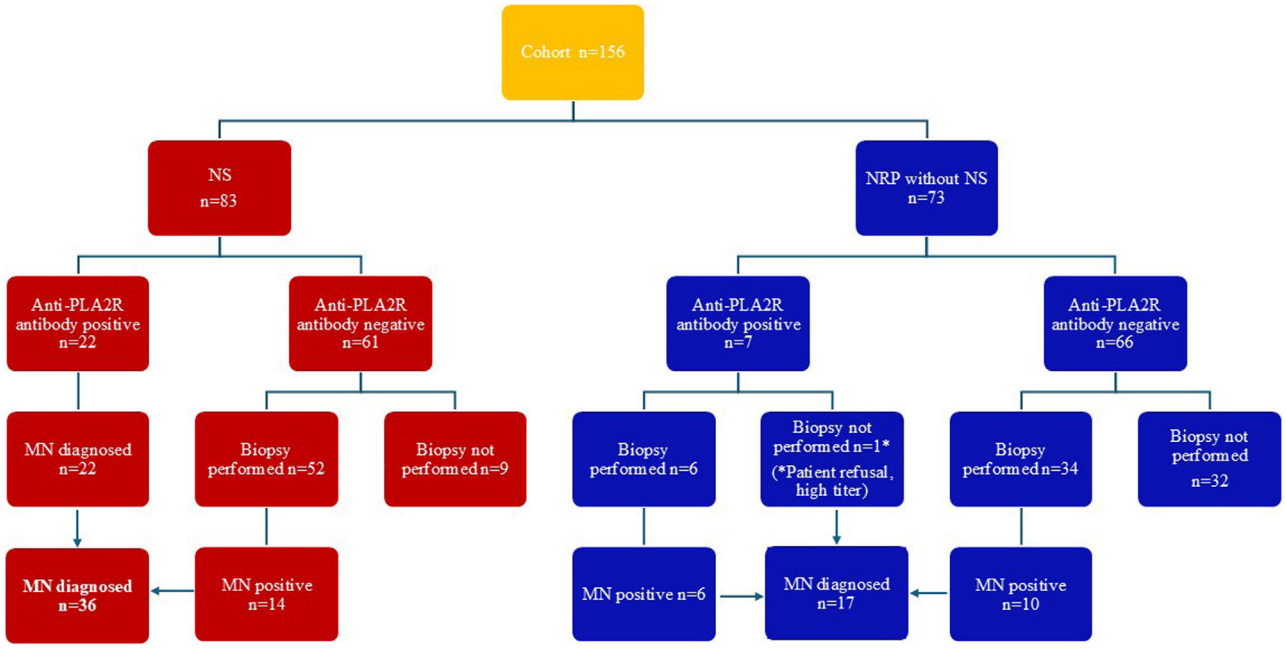

Fig. 1. Characteristics of the cohort. MN: membranous nephropathy, NS: nephrotic syndrome, NRP without NS: nephrotic range proteinuria without nephrotic syndrome, PLA2R: phospholipase A2 receptor.

A multivariate logistic regression analysis was performed to evaluate whether nephrotic syndrome independently predicted anti-PLA2R antibody positivity. Covariates including age, sex, diabetes mellitus, and proteinuria were entered a priori based on established clinical relevance rather than selected through univariate screening, to minimize residual confounding. Odds ratios (ORs), 95% confidence intervals (CIs), and *p*-values were reported for each variable. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test, and explanatory power was quantified with the Nagelkerke R^2 statistic. A two-tailed $p < 0.05$ was considered statistically significant.

Results

A total of 156 patients with nephrotic-range proteinuria were included in the analysis. Seventy-three patients (46.8%) presented with NRP without NS, while 83 patients (53.2%) had NS. The overall cohort had a mean age of 54.3 ± 16.5 years with 45% female representation.

Baseline demographic and clinical characteristics were comparable between the groups. Age, sex distribution, and body mass index showed no differences. Hypertension was the most frequent comorbidity in both groups, without a statistically meaningful variation. Diabetes mellitus was more common in the NRP without NS group, but the difference was not statistically significant (41% vs 27.7%, $p = 0.07$). Serum creatinine and eGFR did not differ significantly between groups.

Anti-PLA2R antibody positivity was significantly higher in patients with NS compared to those with NRP without NS (26.5% vs 9.6%, $p = 0.007$).

Kidney biopsies were performed in 92 patients (58.9% of the total cohort). Combined membranous nephropathy diagnosis (via kidney biopsy or serology) was significantly more frequent in patients with NS compared to those with NRP without NS (43.3% vs 23.2%, $p = 0.008$). The data is presented in Table 1.

Among the 53 patients diagnosed with membranous nephropathy 36 presented with NS and 17 presented with NRP without NS. Both

Table 1
Clinical and laboratory findings of patients.

	NRP without NS $n = 73$ (46.8%)	NS $n = 83$ (53.2%)	*p*-Value
Age (year), mean ± SD	53.9 ± 16	54.7 ± 17	0.76
Sex (female) (*n*/%)	27 (36.9%)	43 (51.8%)	0.06
BMI (kg/m^2), mean ± SD	26.2 ± 1.6	26.5 ± 2	0.37
DM, yes (*n*/%)	30 (41%)	23 (27.7%)	0.07
HT, yes (*n*/%)	47 (64.3%)	53 (63.8%)	0.94
HF, yes (*n*/%)	6 (8.2%)	8 (9.6%)	0.75
Albumin (g/dL), mean ± SD	3.85 ± 0.39	2.72 ± 0.49	**<0.001**
Creatinine (mg/dL), mean ± SD	1.76 ± 1.22	1.53 ± 1.06	0.20
eGFR (CKD-EPI 2021), mean ± SD	61 ± 38	65 ± 36	0.47
Proteinuria (mg/day), median [IQR]	5276 [2876]	8630 [4700]	**<0.001**
Total cholesterol (mg/dL), median [IQR]	206 [56]	270 [122]	**<0.001**
LDL cholesterol (mg/dL), median [IQR]	123 [46.50]	176 [78]	**<0.001**
Anti-PLA2R antibody positive (*n*/%)	7 (9.6%)	22 (26.5%)	**0.007**
MN diagnosis (kidney biopsy + anti PLA2R ELISA positive) (*n*/%)	17 (23.2%)	36 (43.3%)	**0.008**

BMI: body mass index, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, DM: diabetes mellitus, eGFR: glomerular filtration rate, ELISA: enzyme-linked immunosorbent assay, HF: heart failure, HT: hypertension, IQR: interquartile range, LDL: low density lipoprotein, MN: membranous nephropathy, PLA2R: phospholipase A2 receptor, SD: standard deviation.
Bold values indicate statistical significance ($p < 0.05$).

Table 2
Evaluation of patients with membranous nephropathy.

	NRP without NS $n = 17$	NS $n = 36$	p-Value
Age, mean ± SD (year)	50.3 ± 14	57.1 ± 15	0.13
Sex (female) (*n*/%)	9 (53%)	18 (50%)	0.84
DM, yes (*n*/%)	5 (29%)	9 (25%)	0.73
HT, yes (*n*/%)	9 (53%)	21 (58%)	0.71
HF, yes (*n*/%)	0 (0%)	2 (6%)	1
Albumin (g/dL), mean ± SD	3.81 ± 0.41	2.81 ± 0.38	**<0.001**
Creatinine (mg/dL), mean ± SD	0.99 ± 0.56	0.99 ± 0.46	0.94
eGFR (CKD-EPI 2021), mean ± SD	89 ± 33	82 ± 30	0.43
Proteinuria (mg/day), median [IQR]	5852 [3126.50]	8248 [3825.00]	**0.001**
Total cholesterol (mg/dL), median [IQR]	227.00 [59.50]	278.50 [90.75]	**<0.001**
LDL cholesterol (mg/dL), median [IQR]	139 [58]	176 [69]	**0.004**
Anti-PLA2R antibody positive (*n*/%)	7 (41%)	22 (61%)	0.17
Anti-PLA2R antibody level (RU/mL), median [IQR]	27.38 [20.14]	157.64 [341.93]	**0.008**

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, DM: diabetes mellitus, eGFR: glomerular filtration rate, HF: heart failure, HT: hypertension, IQR: interquartile range, LDL: low density lipoprotein, MN: membranous nephropathy, PLA2R: phospholipase A2 receptor, SD: standard deviation.
Bold values indicate statistical significance ($p < 0.05$).

groups had similar eGFR and creatinine values. Anti-PLA2R antibody positivity rates were numerically higher in nephrotic syndrome patients, though this difference did not reach statistical significance (61% vs 41%, $p = 0.17$). Anti-PLA2R antibody levels were significantly higher in nephrotic syndrome patients compared to those with NRP without NS (157.64 [341.93] vs 27.38 [20.14] RU/mL, $p = 0.008$). The data is presented in Table 2.

In the multivariate logistic regression model including age, sex, diabetes mellitus, proteinuria, and clinical phenotype, nephrotic syndrome remained an independent predictor of anti-PLA2R antibody positivity (aOR = 5.00, 95% CI 1.74–14.34, $p = 0.003$). None of the other covariates – including age, sex, diabetes mellitus, or proteinuria – showed a statistically significant association as shown in Table 3.

Discussion

Our study provides the first systematic evaluation of anti-PLA2R antibody diagnostic yield stratified by clinical phenotype, demonstrating a 2.8-fold higher positivity rate in nephrotic syndrome compared to nephrotic-range proteinuria without nephrotic syndrome. As supported by our multivariate analysis, patients with nephrotic syndrome were approximately five times more likely to be anti-PLA2R positive (aOR = 5.00, 95% CI 1.74–14.34, $p = 0.003$), underscoring the strong independent predictive value of clinical phenotype. This finding has important implications for diagnostic algorithms and resource allocation in nephrology practice.

The marked difference in anti-PLA2R positivity between phenotypes likely reflects distinct pathophysiological mechanisms. NRP without NS appears to maintain albumin homeostasis through preserved tubular reabsorption, whereas PLA2R-mediated MN typically causes more extensive glomerular injury, manifesting as full NS. Nonetheless, the identification of MN in 23.2% of NRP without NS patients suggests that a subset may represent early or compensated stages of the same disease spectrum. Consistent with this interpretation, Guerry et al. demonstrated that anti-PLA2R antibodies can be detected before the clinical onset of NS and are associated with a higher likelihood of subsequent progression.[15] Conversely, the low rate of anti-PLA2R positivity in NRP without NS may indicate the presence of alternative target antigens such as thrombospondin type-1 domain-containing 7A (THSD7A) or neural epidermal growth factor-like 1 (NELL-1), or other yet unidentified antigens.[16,17]

Table 3
Multivariate logistic regression analysis for predictors of anti-PLA2R antibody positivity.

	Adjusted OR (95% CI)	p-Value
Nephrotic syndrome (vs NRP without NS)	5.00 (1.74–14.34)	**0.003**
Diabetes mellitus (yes vs no)	1.88 (0.68–5.20)	0.23
Age (per year)	1.02 (0.99–1.05)	0.19
Sex (female vs male)	0.62 (0.26–1.52)	0.30
Proteinuria (per g/day)*	1.00 (1.00–1.00)	0.10

CI: confidence interval, NRP: nephrotic-range proteinuria, NS: nephrotic syndrome, OR: odds ratio.
* Rounded due to scale; no significant association observed.
Bold values indicate statistical significance ($p < 0.05$).

Our findings strongly support the KDIGO 2021 guideline requirement for NS presence in non-invasive MN diagnosis protocols.[8] However, anti-PLA2R–positive MN can also be observed in the NRP without NS group. This may reflect early or subclinical MN in a subset of patients; in our series MN accounted for 23.2% of NRP without NS cases. While previous studies emphasized secondary focal segmental glomerulosclerosis and diabetic nephropathy in this population[2,3] our observation may challenge the traditional view that NRP without NS primarily represents hyperfiltration-mediated disease. If there are no economic constraints, testing for anti-PLA2R antibodies in this group still carries the potential to establish a biopsy-free diagnosis of MN in a subset of patients during initial presentation or follow-up.

Anti-PLA2R antibody titers are well-established markers of disease activity and prognosis in MN.[18–21] In our cohort, MN patients with NS had higher proteinuria, lower albumin, and higher anti-PLA2R titers than those without NS, consistent with prior reports. Nevertheless, the presence of anti-PLA2R positivity – even at lower titers – in NRP without NS suggests early or smoldering MN rather than an inactive state. Such patients require longitudinal follow-up, as some may later develop overt NS.[22]

From a health economics perspective, our findings support phenotype-based testing strategies. Validation studies have demonstrated that anti-PLA2R testing can reliably identify a substantial proportion of membranous nephropathy cases, reducing the need for invasive biopsy and its associated complication risk (0.9–4%), while enabling earlier treatment.[23] However, the cost of testing varies across countries and healthcare systems, which may constitute an economic barrier to widespread use.

Several limitations our work warrant acknowledgment. The retrospective, single-center design restricts generalizability, and these findings require validation across diverse populations and healthcare systems. Regional variations in glomerular disease patterns and healthcare resource availability may affect the applicability of phenotype-based testing algorithms. Another limitation was that anti-PLA2R antibodies were measured using the ELISA method. Given that ELISA has lower sensitivity compared to the immunofluorescence

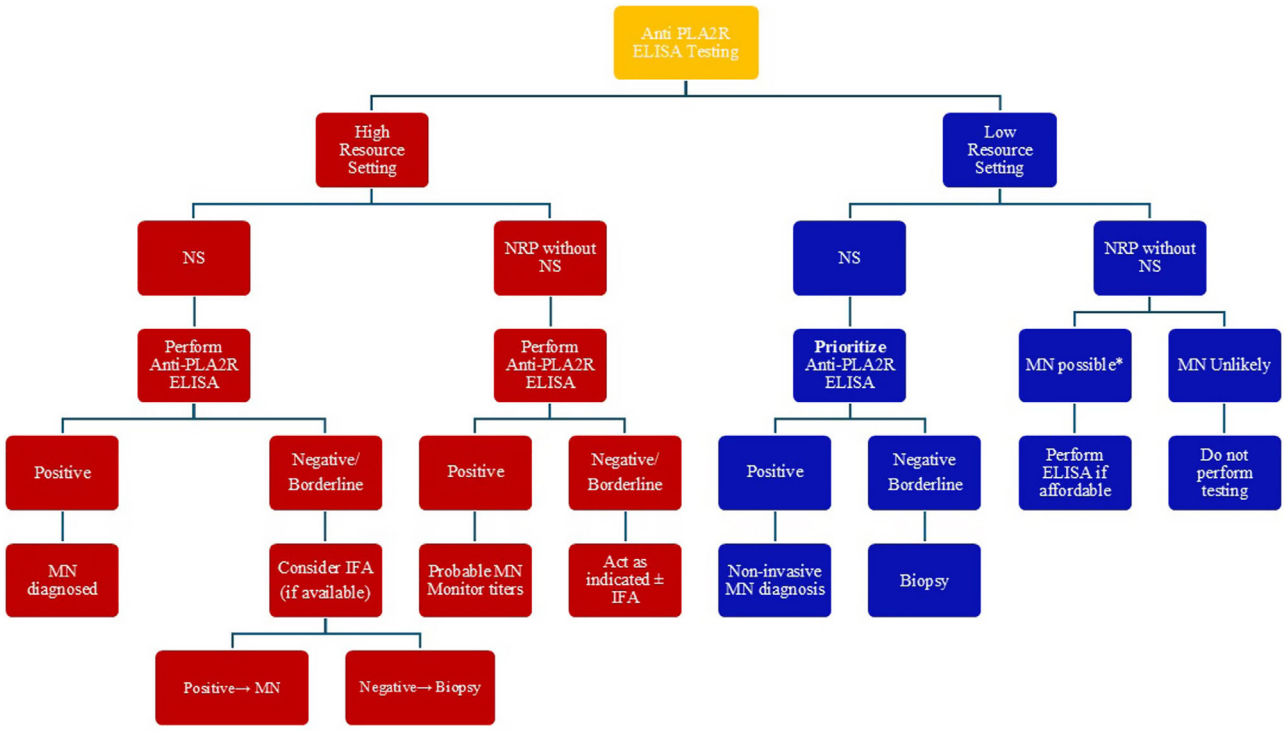

Fig. 2. Proposed algorithm for anti-PLA2R testing in NRP. Negative (<14 RU/mL), borderline (14–19 RU/mL), and positive (≥20 RU/mL). ELISA: enzyme-linked immunosorbent assay, IFA: immunofluorescence assay, MN: membranous nephropathy, NS: nephrotic syndrome, NRP: nephrotic range proteinuria, NRP without NS: nephrotic range proteinuria without nephrotic syndrome, PLA2R: phospholipase A2 receptor, RAAS: renin angiotensin aldosterone system.

assay (IFA) method, our diagnostic sensitivity may have been reduced.[18] In addition, the absence of longitudinal antibody kinetics precluded prognostic assessment. Furthermore, some patients biopsy samples lacked anti-PLA2R staining. Finally, no evaluation of alternative antigens (THSD7A, NELL-1) could be conducted. Although known false-positive anti-PLA2R cases were excluded, not all patients underwent kidney biopsy; therefore, residual false positivity cannot be completely ruled out. This may have slightly affected both diagnostic accuracy and cost estimations.

Based on our findings, we propose a phenotype-oriented diagnostic framework. In NS, routine anti-PLA2R ELISA testing remains both clinically and economically justified, as we recently demonstrated.[24] In contrast, for patients with NRP without NS, the clinical yield and cost-effectiveness of routine ELISA screening remain uncertain. The complementary use of IFA in seronegative or borderline cases may reduce unnecessary biopsies, but this approach requires prospective health-economic validation. Although we are not aware of literature specifically addressing which NRP without NS patients have MN, MN may be clinically suspected in cases with sudden or progressive proteinuria despite renin angiotensin aldosterone system (RAAS) inhibition, absence of diabetes, and mild hypoalbuminemia. The complete proposed diagnostic algorithm incorporating these criteria is illustrated in Fig. 2.

Conclusions

Clinical phenotype independently predicts anti-PLA2R antibody yield in NRP. When anti-PLA2R testing is economically accessible, broad screening of all patients with NRP may be justified; however, in resource-limited settings, restricting testing to those with full NS provides the best balance between diagnostic efficiency and cost-effectiveness.

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Conflicts of interest

The authors declare no conflicts of interest.

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