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Prognostic value of phospholipase A2 receptor in primary membranous nephropathy: a systematic review and meta-analysis

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Abstract

Purpose We aimed to evaluate the prognostic value of serum anti-PLA2R and glomerular PLA2R deposit (gPLA2R) in predicting remission of proteinuria in Primary Membranous Nephropathy (PMN) patients.

Methods PUBMED, EMBASE, WEB OF SCIENCE, COCHRANE LIBRARY and CNKI were searched from 2008 January to December 2018. Heterogeneity was assessed by Cochran Q test and I^2. Source of heterogeneity was explored by subgroup analysis and sensitivity analysis.

Results Totally 2345 patients from 29 cohort studies were eligible for inclusion. The results suggested that PMN patients with negative anti-PLA2R at the time of biopsy had a 1.31 times (95% CI 1.12–1.46, $p < 0.05$) higher possibility in achieving remission than those with positive anti-PLA2R. The clearance of anti-PLA2R at the end of immunosuppressive therapy showed an even greater chance of achieving remission (RR = 2.86, 95% CI 1.75–4.69, $p < 0.05$). The relative ratios for complete remission and spontaneous remission with negative anti-PLA2R were 1.65 (95% CI 1.46–1.87, $p < 0.05$) and 1.93, respectively (95% CI 1.53–2.45, $p < 0.05$), and heterogeneity percentages were $I^2 = 18\%$ and 46%, respectively. The possibility for remission was significantly greater among PMN patients with negative gPLA2R (RR = 1.30, 95% CI 1.13–1.50, $p < 0.05$). Subgroup analyses revealed that retrospective design of study might be the potential source of heterogeneity.

Conclusions Negative anti-PLA2R or gPLA2R might predict higher possibility of remission, and the presence of anti-PLA2R or gPLA2R might serve as a useful biomarker for clinical outcome and predicting response to immunosuppressive therapy in PMN.

Keywords Receptor, Phospholipase A2 · Anti-PLA2R · gPLA2R · Membranous nephropathy · Prognosis · Meta-analysis

Introduction

Membranous nephropathy (MN) is a common cause of massive proteinuria in adults, accounting for about 30% of cases of nephrotic syndrome in Caucasian [1] and 23.4% of renal biopsies in China, as reported by a cross-sectional study with 71,151 native biopsies collected and analyzed from 938 hospitals in China [2]. The clinical outcome of MN is known to be highly variable among individuals, varying from spontaneous remission to persistent proteinuria and to end-stage renal disease (ESRD). The response to immunosuppressive agents in patients with MN is difficult to predict, which leads to the controversy and debate about the optimal modality, timing and duration of treatment in MN because of a lack of reliable biomarker. An individualized and rationalized therapy, guided by biomarker and based on new insights towards the exact pathogenesis, is warranted in MN. Primary membranous nephropathy (PMN), the most common type of MN [1], is characterized by diffuse thickening of glomerular basement membrane (GBM) in the absence of significant hyper-cellularity and with sub-epithelial or intramembranous deposits of immunoglobulin G (IgG) and complement 3. Therefore, it is also known as a kidney-specific autoimmune disease. The autoimmune nature of PMN was delineated in a ground-breaking finding reported by Beck et al. in

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2009 with the identification of the M-type phospholipase A2 receptor (PLA2R) as a major autogenic target on glomerular podocytes [3]. In this pioneering study, anti-PLA2R autoantibody was identified in 70% of patients with PMN but not with secondary membranous nephropathy (SMN). In the past 10 years, substantial advances have been made in the understanding of the immunopathogenesis of PMN, which built the foundation for the progress and opportunities for serological diagnosis and therapeutic interventions in the future [4]. Recently, a meta-analysis showed that anti-PLA2R demonstrated a good diagnostic accuracy in differentiating PMN from non-PMN with a pooled sensitivity of 65% and pooled specificity of 97%, which indicated that anti-PLA2R antibody could be a useful marker in non-invasive serology-based diagnosis [5]. However, the prognostic value of anti-PLA2R and gPLA2R in predicting nephrotic outcome has shown conflicting results and has not been fully explored or illustrated before. We aimed to quantify the association between status of PLA2R and clinical outcome of patients with PMN.

Methods

Eligibility criteria

Eligibility criteria included the following: (1) the study was designed to investigate the prognostic role of anti-PLA2R or gPLA2R in predicting the proteinuric outcome in PMN patients; (2) test method for measuring anti-PLA2R or gPLA2R was reported; (3) the remission/complete remission or spontaneous remission of proteinuria was chosen as study outcome and their definitions were clearly elucidated; (4) renal biopsy was used as the gold standard to diagnose PMN; (5) absolute number of events and totals were reported or could be derived, or sufficient information was provided for the calculation of relative risk (RR). Exclusion criteria were the following: (1) duplicate studies (studies originating from the same subjects by the same investigators but published in different journals); (2) articles providing insufficient data to calculate RR; (3) poor article quality, defined by scoring less than 6 in Newcastle–Ottawa quality assessment scale. Meta-analysis was executed and reported according to Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement 2000 [6] (Online Resource 1).

Search strategy and studies selection

A comprehensive literature search was conducted in PUBMED, EMBASE, WEB OF SCIENCE, COCHRANE LIBRARY, CNKI (China national knowledge infrastructure) from 2008 January to December 2018. Search terms included: "Receptor, Phospholipase A2", "PLA (2) Receptor", "Phospholipase A2 Receptor", "anti-PLA2R", "aPLA2R","PLA2R" AND "Glomerulonephritis, Membranous", "membranous nephropathy", "Heymann Nephritis". In addition, manual searches were performed through the reference lists of published articles and review papers to identify any additional relevant studies. Gray literature, including conference abstracts and unpublished studies, was strictly scrutinized and could be included in this analysis if they met the eligibility standards. Attempt was made to contact authors when it was necessary. There was no language restriction for search and selection. When multiple articles for a single study had been published, the latest publication was selected and supplemented with data from the earlier publication if necessary. Two reviewers (M. D. and M. D.) reviewed potential studies and determined eligibility independently. Disagreements were resolved by discussion and common consensus. Reviewers initially screened the titles and abstracts to detect the potential relevant papers, and then the shortlisted studies were screened again to evaluate their adherence to the eligibility criteria.

Data extraction

Data from all studies were collected by two reviewers independently (M. D. and M. D.) and combined to develop a definitive data collection sheet. Discrepancies during data extraction and assessment of study quality were resolved by discussion. The extracted information included name of the authors, date of publication, sample size, demographic characteristics of the population, study design, test method for measuring anti-PLA2R or gPLA2R, cutoff value, mean albumin, mean serum creatine, mean 24 h proteinuria, percentage of patients received immunosuppressive therapy (IST), duration of follow-up, relative risks and their 95% corresponding confidence interval. Studies were sorted alphabetically by names of the first author.

Study quality assessment

The study quality assessment was performed according to the Newcastle–Ottawa quality assessment scale (NOS). This assessment scale allowed us to examine the quality of studies by evaluating the representativeness of cohorts, how well the studies were adjusted for confounding variable and whether the outcomes were measured in a standard, valid and reliable way. The maximum possible score is nine points, and studies scoring ≥ 6 points were regarded as high-quality studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

Statistical analysis

The statistical analysis was performed using Review Manager (RevMan, version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Relative risks (RR) with 95% confidence intervals for proteinuric outcome with different status of anti-PLA2R or gPLA2R at the time of biopsy (baseline) or at the end of immunosuppressive therapy were pooled, respectively. The overall effects were computed using the DerSimonian and Laird's method (Random Effects Model) when I^2 was above 50% or $p < 0.1$, otherwise Mantel–Haenszel method (Fixed Effects Model) was chosen to compute the overall effect. Heterogeneity was evaluated by Cochran Q test and I^2 statistics. Source of heterogeneity was explored by subgroup analysis and sensitivity analysis. Subgroup analysis was conducted to investigate the potential heterogeneity brought by ethnicity, study design and method type for measuring anti-PLA2R. Sensitivity analyses were performed by sequential omission of each individual study to validate the stability of overall effect and explore the potential source of heterogeneity. Publication bias was explored by funnel plot. Asymmetry of funnel plot was considered to be significant in publication bias. $p < 0.05$ was considered to be statistically significant.

Results

Search results

Overall, 177 articles were identified through database searching, 12 additional records were identified from reference lists of the included articles. Then 147 records remained after duplicate removal, and were screened by titles and abstracts. Next, 62 records were retrieved for full-text assessment. The following thirty-four records were excluded: 23 were excluded due to lack of sufficient data, 5 were excluded on account of using kidney function as study outcome, one was excluded because of inadequate antibody test, one was excluded due to repeated publication, and 4 were excluded due to low quality. Finally, 29 articles were eligible for quantitative synthesis. Twenty-three studies reported the correlation between serum anti-PLA2R and proteinuric outcome in PMN patients and six studies reported the predictive value of gPLA2R deposit at baseline in reaching remission. The flow diagram of the literature search is presented in Fig. 1.

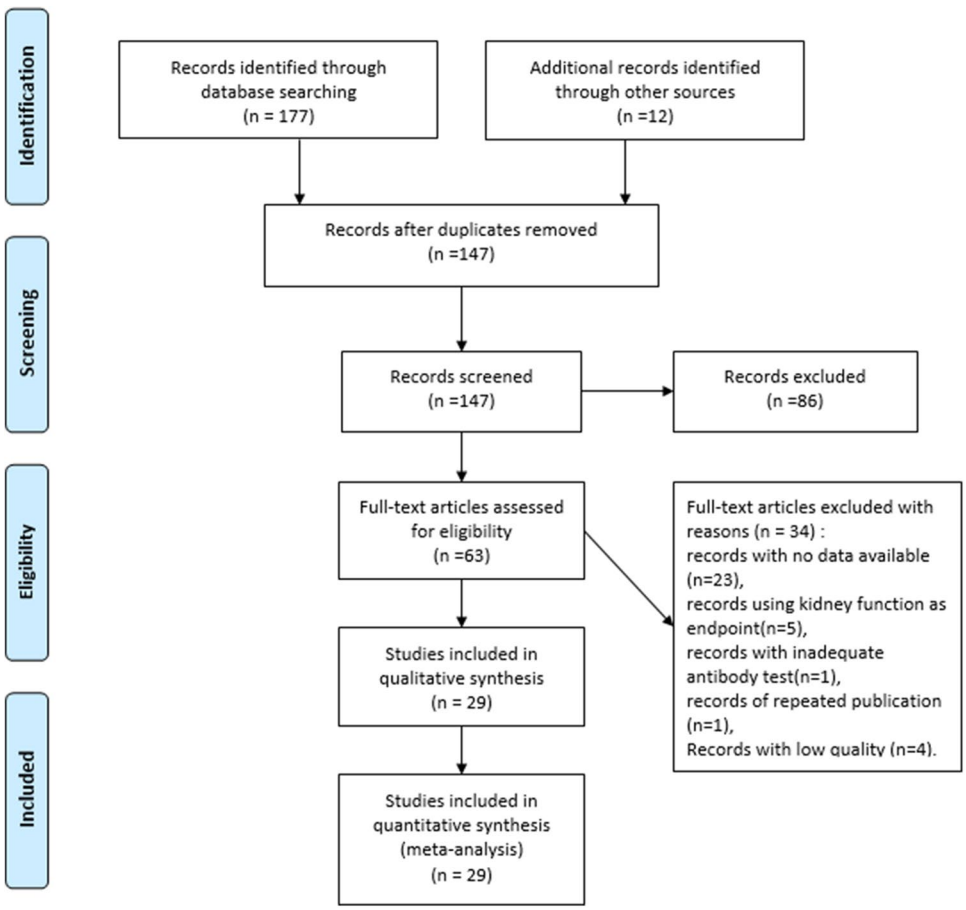

Fig. 1 Flow diagram for the literature search

Table 1 Baseline characteristics for studies reporting the prognostic value of serum anti-PLA2R and gPLA2R

Author/year	Country	Gender	Age	Sample size	Study design	Method	Cutoff value	Serum albumin[e]	Proteinuria (g/24 h)	Serum creatine (μmol/L)	eGFR(ml/min per 1.73m2)	Treatment	follow up[f]
Baseline characteristics for studies reporting the prognostic value of serum anti-PLA2R													
Bech/2014 [11]	Netherland	37:11	55 (34–75)	48	Prospective	ELISA	> 40 U/ml	2.6 (1.5–3.9)	10.10 (3.2–25.2)[a]	1.60 (0.98–3.37)[b]	47 (21–96)	IST:100%	52 (0–60)
Beck/2011 [15]	the USA	28:7	48.2 ± 11.1	35	Prospective	WB	>1000 U	NR	12.36 ± 5.19	1.47 ± 0.49[b]	87 ± 34	RTX:100%	24
Song/2018 [18]	Korea	29:19	56.6 ± 12.7	48	Retrospective	ELISA	> 20 U/ml	2.5 ± 0.6/3.3 ± 0.7	7.92 ± 3.98/4.32 ± 3.30	0.78 ± 0.33		IST:47.9%	65 (3–133)
Hofstra/2012 [14]	Europe	91:26	51 ± 16	117	Prospective	ELISA	>40 U/ml	2.25 ± 0.63	10.2 (3.6–37.9)	95 (51–320)	73 ± 27	IST:62%	54 (2–277)
Hoxha/2014 [19]	German	20:13	50.1 ± 19.2	33	Prospective	ELISA	> 20 U/ml	NR	2.03 ± 0.88	1.0 ± 0.5[b]	NR	IST:45%	25.3 ± 8.8
Hoxha/2015 [20]	German	140:54	54.4 ± 15.5/57.6 ± 15.9[c]	194	Prospective	ELISA	>20 U/ml	NR	9.3 ± 4.8/7.9 ± 5.0[c]	1.3 ± 0.7/1.1 ± 0.5[b]	NR	IST:59.3%	33.8 ± 9.6
Huazhang/2016 [21]	China	327:187	46 (30–57)/42 (30–52)	514	NR	ELISA	> 20 U/ml	27.8 (24.4–31.6)/32.4 (29.3–35.3)	4.0 (2.4–6.2)/2.4 (1.6–3.9)	NR	105 (88–118)/110 (100–122)	IST:90.7%	24
Jatem/2015 [22]	Spain	61:24	49 ± 16.4/57.8 ± 15.7	85	Retrospective	ELISA	> 20 U/ml	2.39 ± 0.56/2.54 ± 0.68[c]	10.6 ± 4.6/8.6 ± 4.2[c]	1.03 ± 0.3/1.48 ± 1.08[b]	81.8 ± 23.65/69.11 ± 27.28[c]	IST:76.5%	12
Kim/2015 [23]	Korea	53:40	58.20 ± 1.86/55.19 ± 2.13	93	NR	ELISA	>14 U/ml	2.60 ± 0.09/3.06 ± 0.10[c]	7.44 ± 0.82/5.32 ± 0.57[a]	0.99 ± 0.08/0.84 ± 0.55[b]	85.74 ± 4.59/96.73 ± 4.30[c]	IST:69.9%	≥ 12
Oh/2013 [24]	Korea	40:37	55 ± 13.9	77	NR	WB	1:100[d]	2.5 ± 0.6	6.80 (4.80–9.98)[a]	0.92 ± 0.35	89 ± 29	IST:67.5%	30
Pourcine/2017 [25]	France	53:32	54.0 (40.5; 65.1)	85	Retrospective	ELISA	> 14 U/ml	2.0 (1.6–2.6)	7.1 (3.5–10.8)	NR	74.0 (58.0–99.0)	IST:76.5%	30.4 (17.7–56.7)
Ruggenenti/2015 [13]	Italy	100:32	55.7 ± 15.4	132	Prospective	ELISA	14 RU/ml	2.21 ± 0.59	9.1 (5.8–12.7)	1.21 (1.00–1.73)[b]	NR	RTX:77.3%	30.8 (6.0–145.4)
Timmermans/2014 [26]	Netherland	69:40	53.7 ± 15.7	109	Retrospective	ELISA	> 20 U/ml	NR	6.1 (0.2–22.5)	87 (53–614)	95 ± 35	IST:37.0%	NR
Wang/2016 [27]	China	31:25	41.1 ± 11.9	56	Retrospective	ELISA	> 20 U/ml	2.49 ± 0.81	4.9 ± 2.7	67.0 ± 20.3	132.0 ± 68.8	IST:37.4%	14 (12–25)
Yang/2016 [28]	China	353:85	41.2 ± 16.2/40.1 ± 13.0[c]	438	Retrospective	ELISA	> 20 U/ml	23.0 ± 3.9/23.9 ± 3.5[c]	7.3 ± 1.8/7.6 ± 2.0[c]	NR	96.8 ± 39.9/95.4 ± 30.5[c]	IST:73.3%	18
Kanigicherla/2013 [16]	UK	64:26	54 (41–62)	90	Retrospective	ELISA	> 40 U/ml	NR	8.3 (6.2–11.8)	94 (76–115)	NR	IST:37.8%	90 (46–147)
Wei/2016 [29]	China	72:41	48.22 ± 12.74	113	NR	ELISA	> 20 U/ml	2.52 ± 0.67	10.78 ± 6.81	NR	105.66 ± 32.33	IST:78.8%	≤20
Mahmoud/2017 [30]	Egypt	17:13	32.3 ± 12.2/33.2 ± 11.7[c]	30	Prospective	IIFT	1:10[d]	2.65 ± 0.60/2.75 ± 0.95[c]	4.10 ± 2.25/4.60 ± 3.35[c]	0.90 ± 0.35/1.70 ± 1.20	NR	IST:100%	9
Ramachandran/2016 [31]	India	67:47	41.39 ± 13.32	114	Prospective	ELISA	> 20 U/ml	2.29 ± 0.64	5.86 ± 3.14	0.91 ± 0.27[b]	NR	IST:100%	> 12

Table 1 (continued)

Author/year	Country	Gender	Age	Sample size	Study design	Method	Cutoff value	Serum albumin[e]	Proteinuria (g/24 h)	Serum creatine (μmol/L)	eGFR(ml/min per 1.73m2)	Treatment	follow up[f]
Wang/2016 [32]	China	30:26	51 ± 15/53 ± 12[c]	56	Prospective	IIFT	1:50	2.26 ± 0.50/2.37 ± 0.77[c]	7.0 ± 4.1/6.7 ± 3.2[c]	76 ± 16/81 ± 39[c]	93 ± 18/89 ± 27[c]	CTX:100%	12
Zhang/2017 [33]	China	24:12	51.0 ± 20.6	36	Prospective	ELISA	> 20 U/ml	2.26 ± 0.34/2.73 ± 0.21[c]	6.90 ± 1.30/4.80 ± 0.83[c]	78.30 ± 28.10/84.70 ± 30.16[c]	NR	CsA:100%	6
Zhou/2016 [34]	China	21:15	49.8 ± 10.6/50.3 ± 11.2[c]	61	Retrospective	ELISA	> 2.1	1.74 ± 0.53/1.81 ± 0.72[c]	7.65 ± 2.19/7.49 ± 2.20[c]	77.9 ± 19.0/75.3 ± 24.9[c]	90.8 ± 27.7/91.9 ± 20.5[c]	IST:100%	6
Xu/2017 [35]	China	33:17	53.5 ± 13.0	50	Retrospective	IIFT	1:10	2.40 ± 0.36/2.41 ± 0.26[c]	7.6 ± 3.8/6.9 ± 3.0[c]	81.0 ± 49.6[c]/77.0 ± 46.5	NR	CsA:100%	6
Lin/2016 [36]	China	79:57	39.8 (15–83)	136	Prospective	ELISA	> 20 U/ml	2.1 (1.0–3.9)	5.43 (0.59–21.02)	68 (23–262)	108 (22–151)	IST:0%	17 (3–39)
Baseline characteristics for studies reporting prognostic value of gPLA2R													
Liu/2016 [37]	China	20:11	50. 6 ± 14. 6	31	Retrospective	IIFT	1:100	2.48 ± 0.61/2.71 ± 0.30[c]	5.9 ± 3.8/4.3 ± 2.0[c]	73.5 ± 28.9/81.1 ± 14.6[c]	91.5 ± 30.4/86.4 ± 16.0[c]	IST:62.3%	> 12
Huazhang/2016 [21]	China	327:187	46 (30–57)/42 (30–52)	514	NR	ELISA	> 20 U/ml	27.8 (24.4–31.6)/32.4 (29.3–35.3)	4.0 (2.4–6.2)/2.4 (1.6–3.9)	NR	105 (88–118)/110 (100–122)	IST:90.7%	24
Wang/2017 [38]	China	57:34	53.8 ± 14.6/53.5 ± 17.5	91	Retrospective	IIFT	1:500	1.95 ± 0.51/2.16 ± 0.91[c]	5.5 (4.0, 7.7)/5.2 (2.3, 12.5)[c]	78 (61.7, 93.8)/68.6 (60, 132.5)[c]	NR	IST:100%	15
Xu/2017 [39]	China	110:76	54 (44–62)	186	Retrospective	IIFT	1:500	2.33 ± 0.69	4.24 (2.56–5.89)	73 (57–91)	NR	IST:61.1%	6
Ding/2015 [40]	China	18:12	49.73 ± 11.22	30	Prospective	IHC	1:30	2.52 ± 0.63	3.93 ± 1.65	81.27 ± 31.22	NR	NR	12
Ling/2017 [41]	China	52:30	52.1 ± 13.4	82	Prospective	IIFT	> 2.1	NR	NR	NR	NR	CTX:100%	12

WB Western Blot, *NR* not reported, *IST* immunosuppressive therapy, *RTX* rituximab, *IIFT* indirect immunofluorescent test, *IHC* immunohistochemistry, *CTX* cyclophosphamide, *CsA* cyclosporin A

[a]The value of proteinuria creatine ratio (PCR) was reported, unit: g/g

[b]Serum creatine (Scr) was reported by mg/dL

[c]Baseline data was reported and grouped by anti-PLA2R positivity

[d]Serum dilution titer was reported in western blot and IIFT

[e]The unit for serum albumin was synchronized to g/dL

[f]The unit for follow-up duration was months

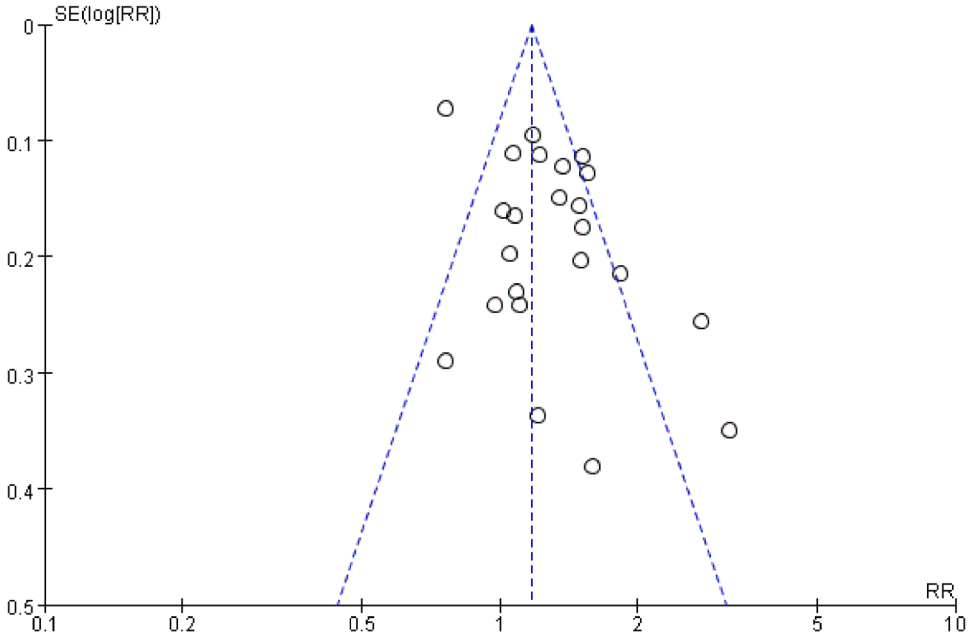

Fig. 2 Funnel plot. Twenty-three studies analyzing the association between the status of anti-PLA2R and proteinuric outcome were included for exploration of publication bias

Study characteristics

Totally 29 records and 2345 subjects were enrolled in this analysis. Renal biopsy was used as gold standard for diagnosing PMN in all included studies. The definition of proteinuric outcome was clearly elucidated in all studies with a good homogeneity among studies. Included studies covered a wide spectrum of country including the USA, The Netherlands, the UK, Germany, Spain, France, Italy, India, Korea, Egypt and China. In the analysis of demographic characteristics, the gender ratio of PMN patients in all included studies featured significant male preponderance. Median age of onset in the majority of studies was in the fifth decade except for two reports: one by Mahmoud et al. from Egypt and another one by Lin et al. from China, with median age of 32.3 and 39.8 years old, respectively. A prospective study design was used in 44.8% of included studies. The test methods for measuring anti-PLA2R antibody vary from enzyme-linked immunosorbent assay (ELISA), Indirect Immunofluorescence Test (IIFT) and western blot. ELISA was chosen as the test method in 79.2% of studies. The test method for measuring gPLA2R was mostly IIFT and immunohistochemistry (IHC). All the studies reported cutoff value. The percentage of patients who received immunosuppressive therapy varies between studies and the strategies for IST were quite different. The clinical end points were defined according to Kidney Disease, Improving Global Outcomes (KIDIGO) guideline in the majority of studies. Specifically, complete remission (CR) was defined as proteinuria < 0.3 g/day, partial remission (PR) was defined as proteinuria ≤ 3.5 g/day and > 50% reduction from baseline proteinuria. Remission was a combined end point of complete remission and partial remission. Spontaneous remission (SR) was defined as achieving remission without immunosuppressive therapy. Most of the studies included in this meta-analysis had adjusted for age, sex, baseline proteinuria, albumin, kidney function and history of immunosuppressive therapy before enrollment. The baseline characteristics of included studies are presented in Table 1. Funnel plot showed the absence of dots on the left lower corner of the plot, implying the potential of publication bias (Fig. 2).

Quality assessment

All the studies that scored less than 6 on the Newcastle–Ottawa quality assessment scale were excluded in quantitative synthesis. Nevertheless, 34.5% of included studies scored relatively low in the assessment of the representativeness of cohort. This group of studies enrolled a specific high-risk cohort of patients, mostly or all treated with immunosuppressive therapy, which might lead to potential bias in patient selection. In almost all included studies, determination of the status of anti-PLA2R antibody and gPLA2R was conducted by objective measurement method, therefore, the scoring in ascertainment of exposure was relatively high. Potential confounding factors such as age, gender, baseline proteinuria, IST ratio at baseline and baseline kidney function were compared and analyzed between two cohorts in 77.4% of studies. In the analysis of quality of outcome, almost all included studies provide a clear definition about study end points. The median follow-up period was longer than 12 months in 79.3% of the studies, but 34.5% of studies had a relatively high lost-to-follow-up ratio. The study quality assessment are summarized in Table 2.

Table 2 Studies quality assessment by Newcastle–Ottawa quality assessment scale

Study	Selection				Comparability	Outcome			Total score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Bech/2014 [11]	0	1	1	1	2	1	1	0	7
Beck/2011 [15]	0	1	1	1	0	1	1	1	6
Song/2018 [18]	1	1	1	0	1	1	1	0	6
Hofstra/2012 [14]	1	1	1	1	2	1	1	1	9
Hoxha/2014 [19]	1	1	1	1	1	1	1	1	8
Hoxha/2015 [20]	0	0	1	1	2	1	1	0	6
Huazhang/2016 [21]	0	0	1	1	2	1	1	1	7
Jatem/2015 [22]	1	1	1	0	1	1	0	1	6
Kim/2015 [23]	1	1	1	0	2	1	1	1	8
Oh/2013 [24]	1	1	1	0	2	1	1	0	7
Pourcine/2017 [25]	1	1	1	0	1	1	1	0	6
Ruggenenti/2015 [13]	0	0	1	1	1	1	1	1	6
Timmermans/2014 [26]	1	1	1	0	1	1	0	1	6
Wang/2016 [27]	1	1	1	0	0	1	1	1	6
Yang/2016 [28]	1	1	1	0	1	1	1	1	7
Kanigicherla/2013 [16]	1	1	1	0	2	1	1	1	8
Wei/2016 [29]	1	1	1	0	2	1	0	1	7
Mahmoud/2017 [30]	0	0	1	1	2	1	0	1	6
Ramachandra/2016 [31]	0	0	1	1	2	1	1	1	7
Lin/2016 [36]	0	0	1	1	2	1	1	0	6
Wang/2016 [32]	1	1	1	1	0	1	1	1	7
Zhang/2017 [33]	1	1	1	1	1	1	0	1	7
Zhou/2016 [34]	1	1	1	0	1	1	0	1	6
Xu/2017 [35]	1	1	1	0	2	1	0	0	6
Liu/2016 [37]	1	1	1	0	1	1	1	0	6
Wang/2017 [38]	0	0	1	0	2	1	1	1	6
Xu/2017 [39]	1	1	1	0	2	1	0	0	6
Ding/2015 [40]	0	0	1	1	2	1	1	0	6
Ling/2017 [41]	1	1	1	1	1	1	1	1	8

Quantitative synthesis

Meta-analysis of 23 cohort studies indicated that PMN patients with negative baseline anti-PLA2R had a 1.31 times (RR = 1.31, 95% CI 1.12–1.46, $p < 0.05$) higher chance of achieving remission than those with positive anti-PLA2R (Fig. 3). The heterogeneity analysis indicated that $Chi^2 = 83.4$, $df = 22$ ($p < 0.05$), and I^2 was 74%. The prognostic value of negative baseline anti-PLA2R in predicting complete remission and spontaneous remission was

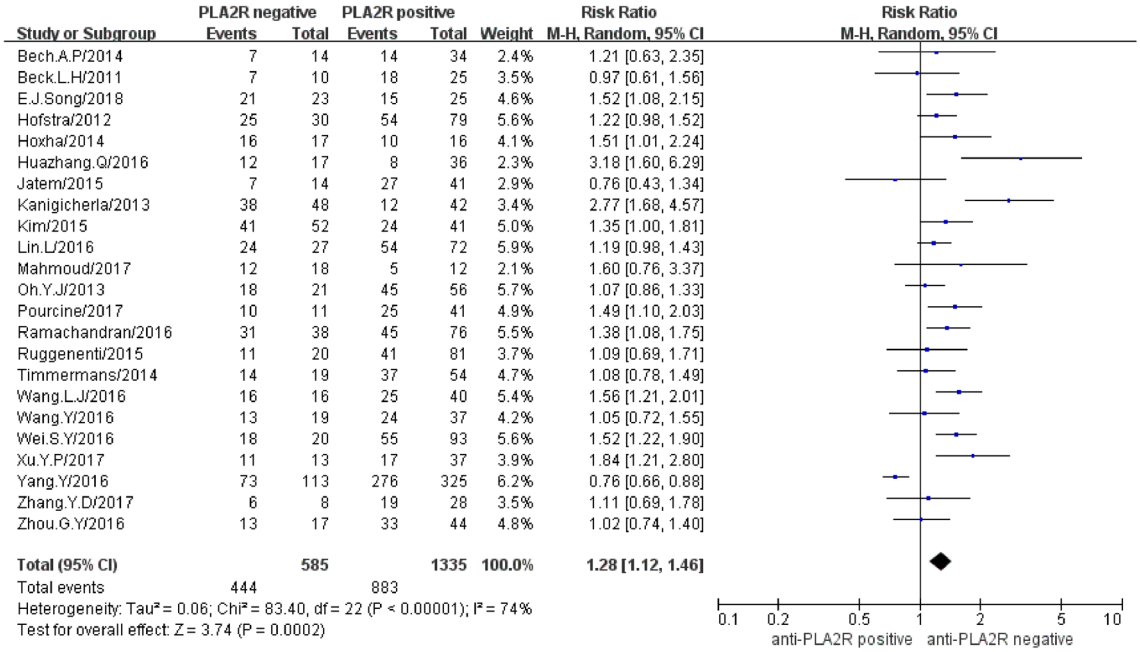

Fig. 3 Forest plot for relative ratios for remission with no detectable anti-PLA2R at baseline. Random-effects model was used for computing relative risk. Relative ratio for complete remission was 1.31 (95% CI 1.12–1.46, $p < 0.0001$) with negative test result of anti-PLA2R at baseline

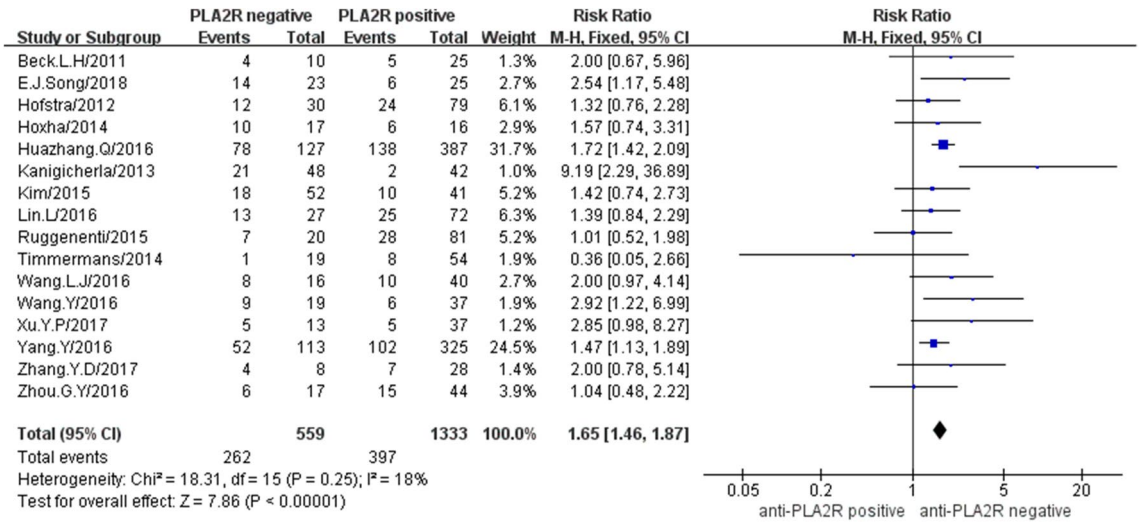

Fig. 4 Forest plot for relative ratios of achieving complete remission with no detectable anti-PLA2R at baseline. Mantel–Haenszel method was used for statistical analysis. Fixed-effects model was used for computing relative risk. Relative ratio for complete remission was 1.65 (95% CI 1.46–1.87, $p < 0.00001$) with negative test result of anti-PLA2R at baseline

also analyzed, and it was observed that there was 1.65 times (RR = 1.65, 95% CI 1.46–1.87, $p < 0.05$) increased chance of achieving complete remission and 1.93 times (95% CI 1.53–2.45, $p < 0.05$) increased chance of achieving spontaneous remission (Figs. 4, 5). The heterogeneity analyses showed that $\text{Chi}^2 = 18.31$, $df = 15$ ($p = 0.25$), and I^2 was 18% for complete remission and $\text{Chi}^2 = 12.89$, $df = 7$ ($p = 0.07$), and I^2 was 46% for spontaneous remission. Regarding the relative chance for achieving remission with negative result of anti-PLA2R post-IST, it revealed a 2.86 times (RR = 2.86, 95% CI 1.75–4.69, $p < 0.0001$) greater chance comparing patients with positive anti-PLA2R after receiving immunosuppressive treatment (Fig. 6). No heterogeneity was detected: $\text{Chi}^2 = 2.43$, $df = 3$ ($p = 0.49$), and I^2 was 0%. The status of gPLA2R at baseline could also predict remission at

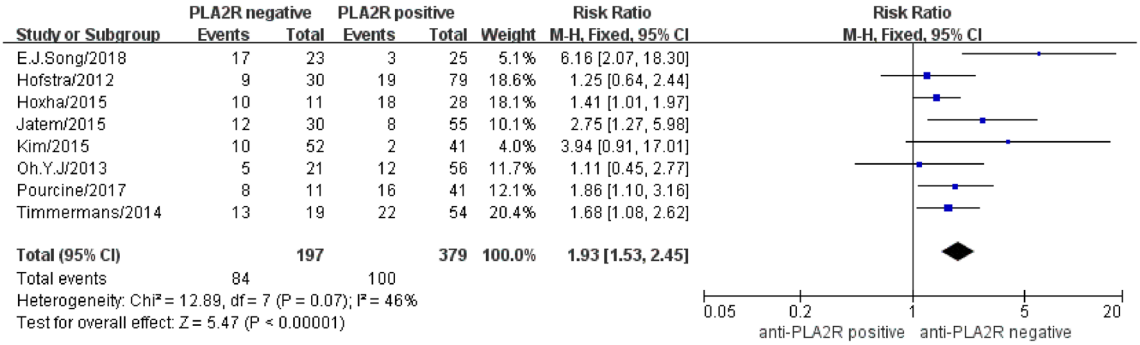

Fig. 5 Forest plot for relative ratios for spontaneous remission with no detectable anti-PLA2R at baseline. Mantel–Haenszel method was used for statistical analysis. Fixed-effect model was used for computing relative risk. Relative ratio for spontaneous remission was 1.93 (95% CI 1.53–2.45, $p < 0.00001$) with negative test result of anti-PLA2R at baseline

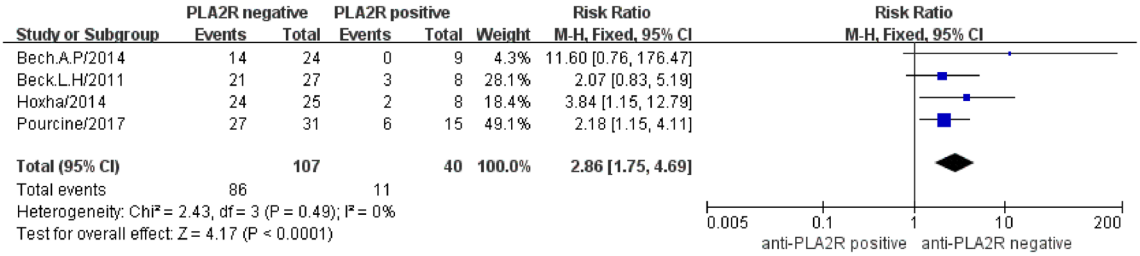

Fig. 6 Forest plot for relative ratio for remission with no detectable anti-PLA2R at the end of immunosuppressive therapy. Mantel–Haenszel method was used for statistical analysis. Fixed-effect model was used for computing relative risk. Relative ratio for remission was 2.86 (95% CI 1.75–4.69, $p < 0.00001$) with negative test result of anti-PLA2R post-IST

the end of follow-up in patients with PMN (RR = 1.30, 95% CI 1.13–1.50, $p = 0.002$) (Fig. 7).

Subgroup analysis

First, studies were stratified according to the ethnicity. The result indicated that the relative ratios for remission in Asian and Caucasian were 1.11 (95% CI 1.03–1.20, $p < 0.05$) and 1.37 (95% CI 1.20–1.58, $p < 0.05$) respectively. The predictive value of anti-PLA2R was slightly higher among Caucasian. Heterogeneity increased after the stratification of variable with an I^2 of 81% ($p = 0.005$) and I^2 of 52% ($p < 0.05$) for each subgroup. Low consistency was detected between two subgroups ($I^2 = 75\%$, $p < 0.05$) (Fig. 8). In the stratified analysis by study design, the result showed that in the subgroup with

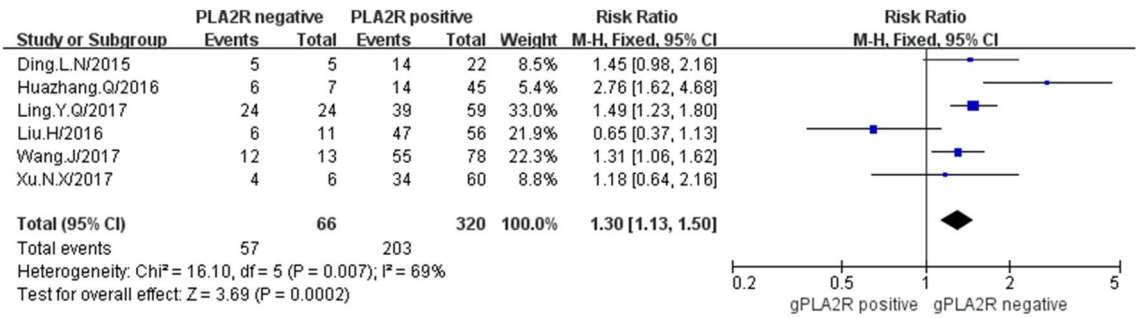

Fig. 7 Forest plot for relative ratios for remission with no detectable gPLA2R at baseline. Mantel–Haenszel method was used for statistical analysis. Fixed-effect model was used for computing relative risk. Relative risk for remission was 1.30 (95% CI 1.13–1.50, $p < 0.00001$) with negative gPLA2R

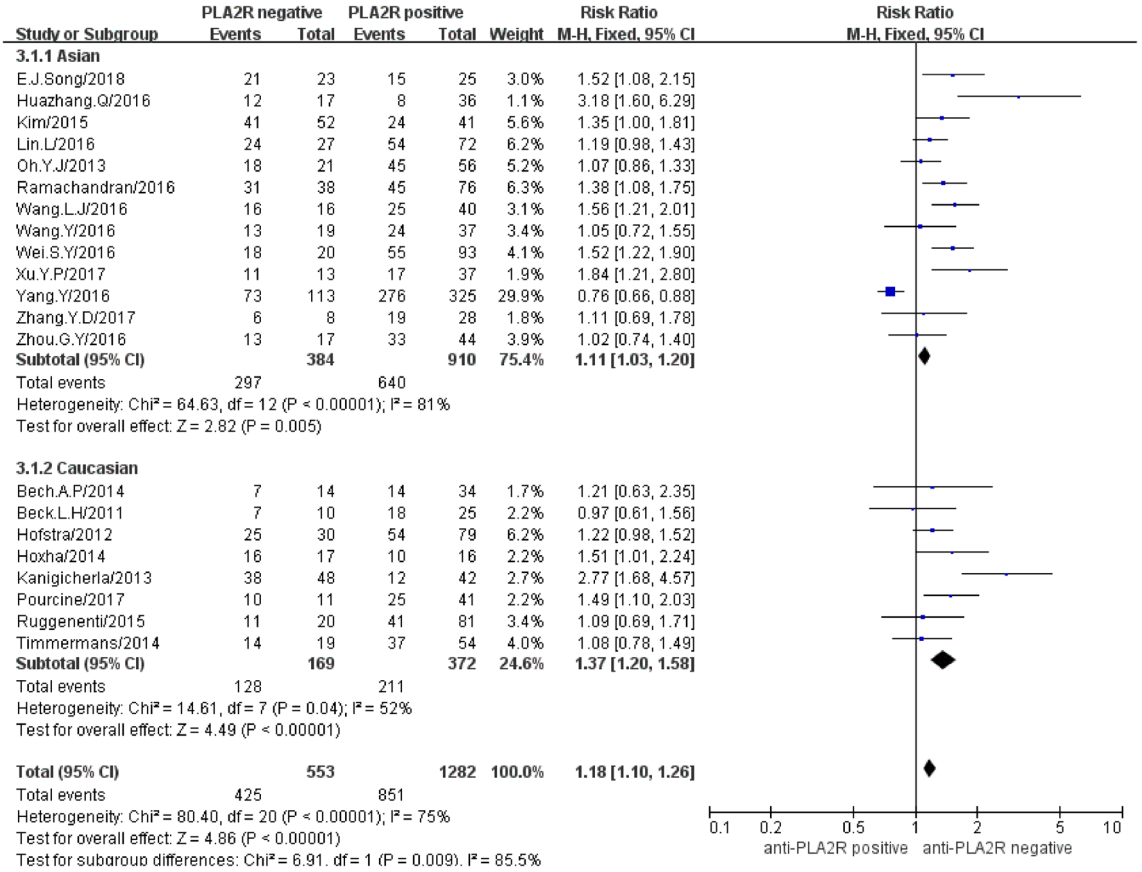

Fig. 8 Subgroup analysis. Studies were stratified according to the ethnicity. The relative ratios for remission in Asian and Caucasian were 1.11 (95% CI 1.03–1.20, $p < 0.05$) and 1.37 (95% CI 1.20–1.58, $p < 0.05$) respectively

prospective design, the pooled relative risk was 1.27 (95% CI 1.14–1.41, $p < 0.05$). In comparison, a pooled relative risk in the subgroup with retrospective design was 1.12 (95% CI 1.03–1.22, $p = 0.007$). The overall relative risk was statistically significant and higher in the subgroup with prospective design. Moreover, the heterogeneity analysis showed that studies with prospective design demonstrated a significantly lower heterogeneity than those with retrospective design ($I^2 = 0\%$, $p = 0.66$ vs $I^2 = 74\%$, $p < 0.05$), which indicated a higher quality and good consistency in the subgroup of studies with prospective design (Fig. 9). In addition, subgroup by method type of measurement revealed that heterogeneity remained high in the subgroup with studies using only ELISA as test method ($I^2 = 76\%$, $p < 0.05$) (Fig. 10). In summary, subgroup analyses illustrated that study design might be the potential sources of heterogeneity, but it was less likely that method type for measurement contributed to the heterogeneity (Tables 3, 4, 5).

Sensitivity analysis

Finally, a leave-one-out sensitivity analysis was performed by sequentially removing one study at a time, to assess the effect of each study on the pooled RR and heterogeneity. After omitting studies one-by-one, it was observed that the heterogeneity decreased dramatically after excluding the study by Yang et al. ($I^2 = 48\%$, $p = 0.007$) while the results did not show significant changes when any other records were omitted (Online Resource 2). Yang et al. reported higher remission rate in PMN patients with positive anti-PLA2R antibody at baseline, while a lower complete remission rate with no detectable anti-PLA2R antibody. We reviewed this study carefully to investigate the possible explanation for the discrepancy. The study had a retrospective design and there was significant difference on baseline characteristics such as gender ratio and strategy of immunosuppressive therapy between two groups with or without detectable anti-PLA2R. Since immunosuppressive modality plays a significant role on the outcome of the disease, a biased conclusion might be drawn without adjustment for this important variable.

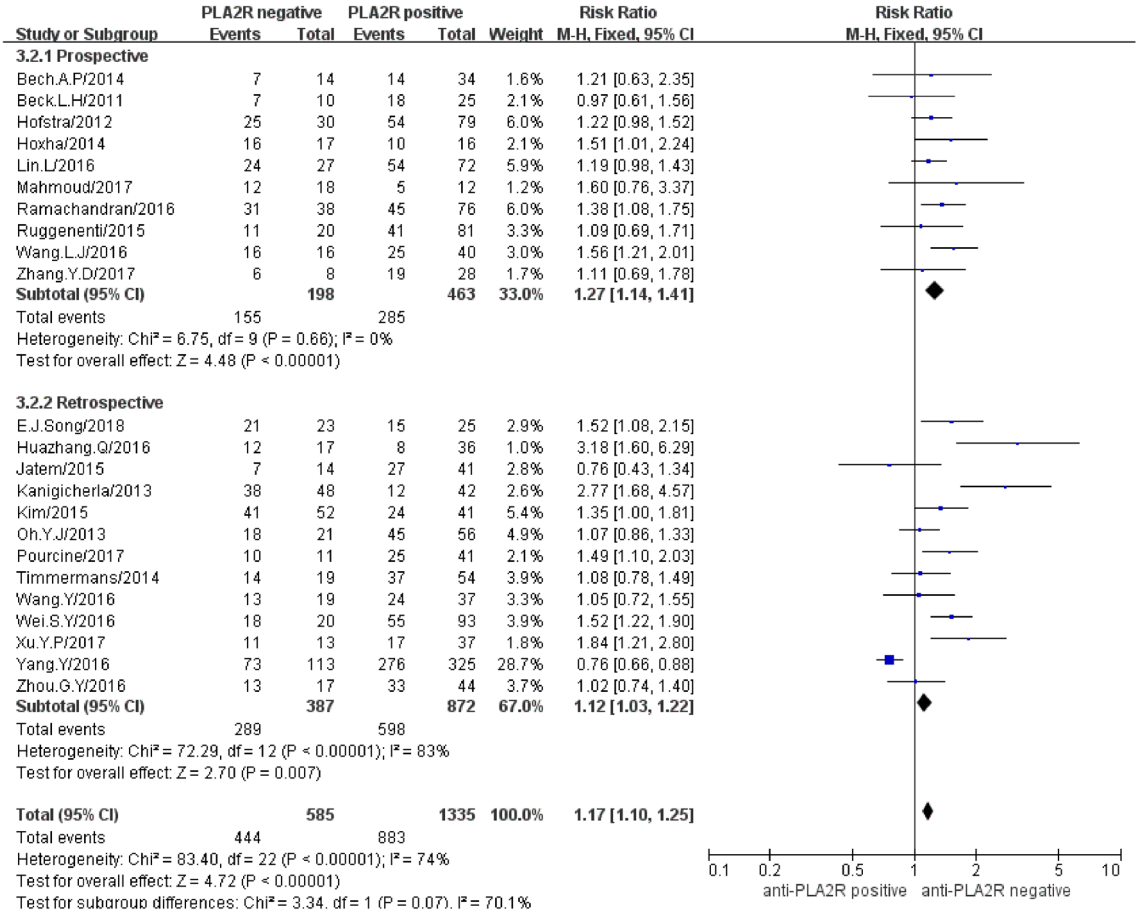

Fig. 9 Subgroup analysis. Studies were stratified according to the study design. Heterogeneity in subgroup of studies with prospective design dropped significantly to $I^2=0\%$, however, subgroup of studies with retrospective design showed a persistent high heterogeneity ($I^2=74\%$, $p<0.05$)

Discussion

The discovery of PLA2R antigen, a 185-kD transmembrane receptor on glomerular podocytes, has inspired robust research on its role in the pathogenesis of PMN. A substantial body of evidence suggests that anti-PLA2R autoantibody might play a causal role in the occurrence of PMN. Beck et al. found that circulating autoantibody could only be eluted from the kidney biopsy of patients with PMN but not with SMN or controls [3]. The titer of anti-PLA2R autoantibody was significantly correlated with the clinical status and immunological activity of the disease [7, 8]. Furthermore, high level of anti-PLA2R autoantibody before transplantation was associated with a higher chance of clinically significant recurrence of membranous nephropathy post-kidney transplantation [9, 10]. A plausible speculation is that the recognition and binding of anti-PLA2R autoantibody and PLA2R antigen on podocytes triggers autoimmune reaction with subsequent formation of sub-epithelial deposit. Nevertheless, direct evidence from animal model by transfer experiments has not yet been made available, which was hampered by an apparent lack of expression of PLA2R in rodent glomeruli.

Our study demonstrated that PMN patients with negative baseline anti-PLA2R at the time of biopsy showed a higher rate of reaching remission, and this association to more favorable outcomes was even stronger in patients with negative post-IST anti-PLA2R. It is known that titer of anti-PLA2R autoantibody is changing along with the progression or recovery of disease. The positive result for anti-PLA2R at baseline might turn negative after receiving immunosuppressive therapy, and vice versa, a negative result for anti-PLA2R autoantibody at the time of biopsy might found to be positive as the disease develops and progresses. Some studies reported that the presence of anti-PLA2R at baseline was not associated with remission, but status of anti-PLA2R post-IST predicted long-term outcome [11]. Therefore, it seems that antibody status at the end of immunosuppressive

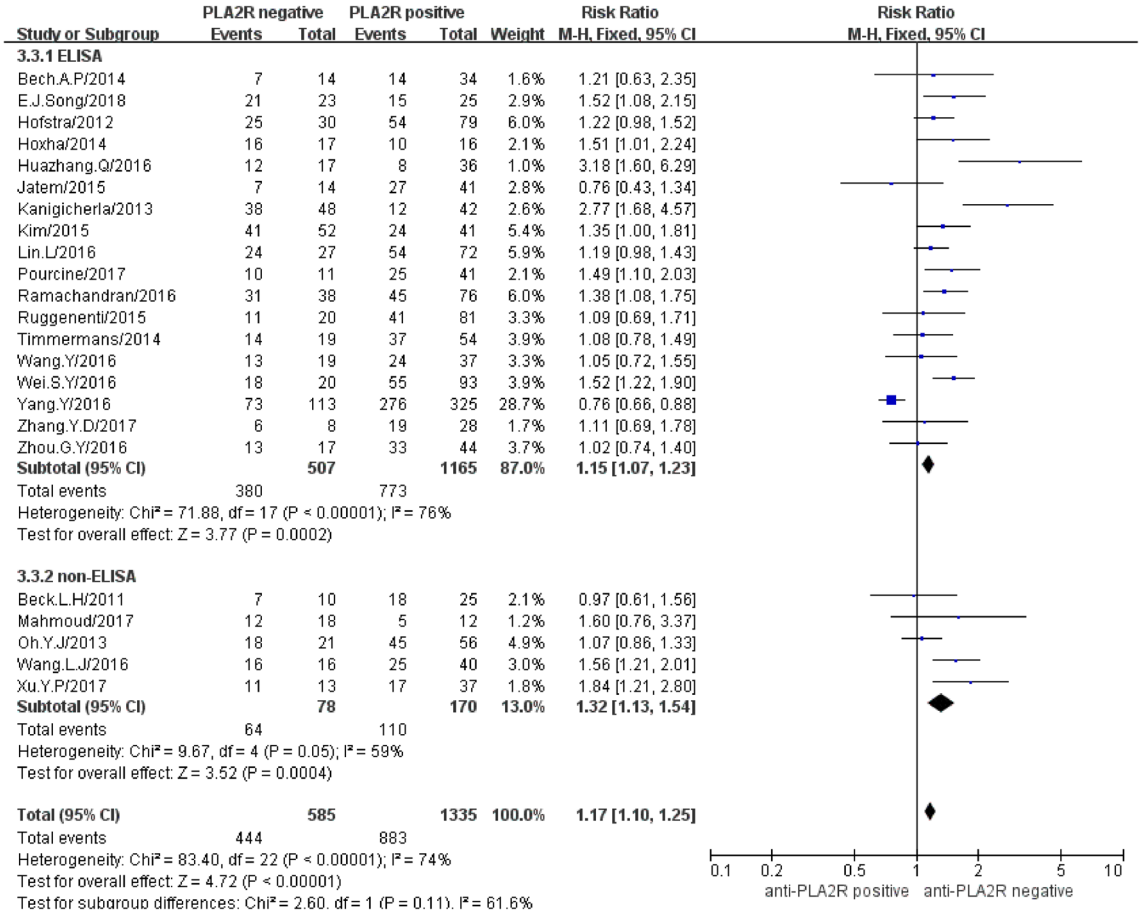

Fig. 10 Subgroup analysis. Studies were stratified according to the method type for measuring anti-PLA2R. In the subgroup with studies using ELISA as method for measuring anti-PLA2R, heterogeneity remained to be high ($I^2 = 76\%$, $p < 0.001$)

therapy has a higher prognostic value than the seropositivity of anti-PLA2R at baseline. But studies on the predictive value of antibody level post-IST were limited; more studies evaluating the correlation between anti-PLA2R positivity at end of immunosuppressive therapy and long-term remission would provide us with more insights, which might suggest a favorable response towards therapy. But it is still worth noting that serial monitoring of anti-PLA2R autoantibody should be emphasized.

More research tried to answer the question about the association between antibody titer and proteinuric outcome. Ruggenenti et al. [12] reported that outcomes of patients with or without detectable anti-PLA2R autoantibody at baseline were similar, although it might be caused by a biased selection of PMN patients with more progressive diseases. In contrast, lower anti-PLA2R antibody titer at baseline and full antibody depletion 6 months post-IST strongly predicted remission with hazard ratio of 7.9 [13]. Similar results were found in another study, which suggested that highest level of antibody titer at presentation was less likely to develop spontaneous remission [14], and a decline of anti-PLA2R was associated with a better

Table 3 Relative ratio for remission with negative serum anti-PLA2R at baseline

Author/year	P:N	Remission ratio in negative	Remission ratio in positive	Relative risk
Bech/2014 [11]	34:14	7/14	14/34	1.21 [0.63, 2.35]
Beck/2011 [15]	25:10	7/10	18/25	0.97 [0.61, 1.56]
Song/2018 [18]	25:23	21/23	15/25	1.52 [1.08, 2.15]
Hofstra/2012 [14]	79:30	25/30	54/79	1.22 [0.98, 1.52]
Hoxha/2014 [19]	16:17	16/17	10/16	1.51 [1.01, 2.24]
Huazhang/2016 [21]	36:17	12/17	8/36	3.18 [1.60, 6.29]
Jatem/2015 [22]	41:14	7/14	27/41	0.76 [0.43, 1.34]
Kanigicherla/2013 [16]	42:48	38/48	12/42	2.77 [1.68, 4.57]
Kim/2015 [23]	41:52	41/52	24/41	1.35 [1.00, 1.81]
Lin/2016 [36]	72:27	24/27	54/72	1.19 [0.98, 1.43]
Mahmoud/2017 [30]	12:18	12/18	5/12	1.60 [0.76, 3.37]
Oh/2013 [24]	56:21	18/21	45/56	1.07 [0.86, 1.33]
Pourcine/2017 [25]	41:11	10/11	25/41	1.49 [1.10, 2.03]
Ramachandran/2016 [31]	76:38	31/38	45/76	1.38 [1.08, 1.75]
Ruggenenti/2015 [13]	81:20	11/20	41/81	1.09 [0.69, 1.71]
Timmermans/2014 [26]	54:19	14/19	37/54	1.08 [0.78, 1.49]
Wang. L.J/2016 [32]	40:16	16/16	25/40	1.56 [1.21, 2.01]
Wang. Y/2016 [27]	37:19	13/19	24/37	1.05 [0.72, 1.55]
Wei/2016 [29]	93:20	18/20	55/93	1.52 [1.22, 1.90]
Xu/2017 [35]	37:13	11/13	17/37	1.84 [1.21, 2.80]
Yang/2016 [28]	325:113	73/113	276/325	0.76 [0.66, 0.88]
Zhang/2017 [33]	28:8	6/8	19/28	1.11 [0.69, 1.78]
Zhou/2016 [34]	44:17	13/17	33/44	1.02 [0.74, 1.40]

clinical outcome [13, 15]. Hofstra et al. also showed that spontaneous remissions occurred significantly less frequently among patients with high antibody titers [14]. Accumulating evidence suggests that a higher titer of anti-PLA2R is not only significantly correlated with persistent proteinuria and even survival of kidney function [16, 17], but also was associated with clinical response to treatment, which shows a more rapid response to treatment than traditional clinical parameters such as proteinuria. Research data suggested that anti-PLA2R titer reduction preceded equivalent proteinuria reduction by 10 months, which implies that immunologic response measured by anti-PLA2R precedes and may modulate the clinical response. On the other hand, re-emergence of circulating antibody predicted disease relapse [13]. In summary, anti-PLA2R antibody exhibits the potential to be a good biomarker of early response to treatment and clinical outcome, and measuring anti-PLA2R levels by immunoassay may be a method to monitor and predict response to treatment in patients with PMN [15]. But the thresholds for defining high and low titer of anti-PLA2R autoantibody were very different among studies, therefore, consensus

Table 4 Relative ratio for complete remission and spontaneous remission with negative serum anti-PLA2R at baseline and relative ratio for remission with negative serum anti-PLA2R tested at end of immunosuppressive therapy

Author/year	P:N	CR ratio in Negative	CR ratio in Positive	relative risk
Relative ratio for achieving complete remission with negative serum anti-PLA2R at baseline				
Beck/2011 [15]	25:10	4/10	5/25	2.00 [0.67, 5.96]
Song/2018 [18]	25:23	14/23	6/25	2.54 [1.17, 5.48]
Hofstra/2012 [14]	79:30	12/30	24/79	1.32 [0.76, 2.28]
Hoxha/2014 [19]	16:17	10/17	6/16	1.57 [0.74, 3.31]
Huazhang/2016 [21]	387:127	78/127	138/387	1.72 [1.42, 2.09]
Kanigicherla/2013 [16]	42:48	21/48	2/42	9.19 [2.29, 36.89]
Kim/2015 [23]	41:52	18/52	10/41	1.42 [0.74, 2.73]
Lin/2016 [36]	72:27	24/27	54/72	1.39 [0.84, 2.29]
Ruggenenti/2015 [13]	81:20	7/20	28/81	1.01 [0.52, 1.98]
Timmermans/2014 [26]	54:19	1/19	8/54	0.36 [0.05, 2.66]
Wang. L.J/2016 [32]	40:16	8/16	10/40	2.00 [0.97, 4.14]
Wang. Y/2016 [27]	37:19	9/19	6/37	2.92 [1.22, 6.99]
Xu/2017 [35]	37:13	5/13	5/37	2.85 [0.98, 8.27]
Yang/2016 [28]	325:113	52/113	102/325	1.47 [1.13, 1.89]
Zhang/2017 [33]	28:8	4/8	7/28	2.00 [0.78, 5.14]
Zhou/2016 [34]	44:17	6/17	15/44	1.04 [0.48, 2.22]
Relative ratio for achieving spontaneous remission with negative serum anti-PLA2R at baseline				
Song/2018 [18]	25:23	17/23	3/25	6.16 [2.07,18.30]
Hofstra/2012 [14]	79:30	9/30	19/79	1.25 [0.64, 2.44]
Hoxha/2015 [20]	28:11	10/11	18/28	1.41 [1.01, 1.97]
Jatem/2015 [22]	55:30	12/30	8/55	2.75 [1.27, 5.98]
Kim/2015 [23]	41:52	10/52	2/41	3.94 [0.91, 17.01]
Oh/2013 [24]	56:21	5/21	12/56	1.11 [0.45, 2.77]
Pourcine/2017 [25]	41:11	8/11	16/41	1.86 [1.10, 3.16]
Timmermans/2014 [26]	54:19	13/19	22/54	1.68 [1.08, 2.62]
Relative ratio for achieving remission with negative serum anti-PLA2R at the end of therapy				
Bech/2014 [11]	9:24	14/24	0/9	11.60 [0.76, 176.47]
Beck/2011 [15]	17:8	21/27	3/8	2.07 [0.83, 5.19]
Hoxha/2014 [19]	8:25	24/25	2/8	3.84 [1.15, 12.79]
Pourcine/2017 [25]	15:31	27/31	6/15	2.18 [1.15, 4.11]

M–H model, fixed model, 95% confidential range

and agreement must be reached in demarcating high or low titer of anti-PLA2R to pave the way to the future clinical application of monitoring anti-PLA2R titer.

Our analysis also suggested that negative glomerular PLA2R deposit at baseline predicts a higher possibility of reaching remission. In the aspect of diagnostic value of gPLA2R, it was found that gPLA2R has a higher sensitivity in diagnosing PMN than serum anti-PLA2R autoantibody. The predictive value of gPLA2R in PMN was explored in some other studies. Debiec et al. observed the discordant findings of anti-PLA2R by western blot immunoassay and gPLA2R by IIFT. Of the eighteen patients with no detectable PLA2R autoantibody in serum, ten had PLA2R in glomerular deposits. This disparity might be explained by the shorter half-life and rapid clearance of circulating anti-PLA2R or to the late referral of patients when proteinuria persisted because of irreversible ultrastructural changes [9]. In comparison, a good consistency between ELISA and IIFT was observed in some other studies [8]. The availability of standardized method for measuring anti-PLA2R autoantibody and gPLA2R might contribute to a better understanding towards the concordance of test result of anti-PLA2R autoantibody and gPLA2R. In addition, it was suggested that combined assessment of both circulating PLA2R antibody and PLA2R deposit in biopsy samples may better categorize patients into PLA2R-related and PLA2R non-related

Table 5 Relative ratio for remission with negative gPLA2R at baseline

Author/year	P:N	Remission ratio in negative	Remission ratio in positive	Relative risk
Ding/2015 [40]	22:5	5/5	14/22	1.45 [0.98, 2.16]
Huazhang/2016 [21]	45:7	6/7	14/45	2.76 [1.62, 4.68]
Ling/2017 [41]	59:24	24/24	39/59	1.49 [1.23, 1.80]
Liu/2016 [37]	56:11	6/11	47/56	0.65 [0.37, 1.13]
Wang/2017 [38]	78:13	12/13	55/78	1.31 [1.06, 1.62]
Xu/2017 [39]	60:6	4/6	34/60	1.18 [0.64, 2.16]

groups which might exhibits more accurate prognostic and therapeutic implications.

The limitation of our study was the observation of relatively high heterogeneity in the analysis of correlation between the status of anti-PLA2R autoantibody at baseline and remission, although one specific study was found to contribute a big part of heterogeneity in sensitivity analysis. Besides that, asymmetry was observed in the funnel plot with more studies appearing toward the right (indicating higher odds ratio) in the bottom of the graph, which indicated the possibility that some studies might be missing on the left. More efforts in searching for gray literature might be helpful in filling the missing spots in the left bottom of the graph. However, a higher proportion of gray literature might also lower the overall quality of the synthesis.

Conclusion

The baseline status of anti-PLA2R or gPLA2R might have a reliable predictive value on remission of proteinuria in PMN patients, and negative anti-PLA2R tested at the end of immunosuppressive therapy was highly correlated with a more favorable outcome. Both anti-PLA2R and gPLA2R might be promising biomarkers for prognosis in patients with PMN. Serial monitoring of circulating anti-PLA2R might be useful in predicting response to therapy and long-term proteinuric outcome; therefore, its monitoring should be highlighted.

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Author contributions WL took the major role in conceptualization, literature search and review, data collection, data analysis, article drafting and writing. YZ contributed by data collection, editing and reviewing. PF contributed by general supervision, reviewing and validation.

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Compliance with ethical standards

Conflict of interest There is no conflict of interest.

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