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Association between different proportions of crescents and the progression of IgA nephropathy (IgAN): a systematic review and meta-analysis

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Abstract

Background Immunoglobulin A nephropathy (IgAN) is a complex renal disease with a highly variable clinical course. Identifying reliable prognostic markers is crucial for risk stratification and treatment decisions. This study aimed to understand the influence of different proportions of crescents (Cs) on the progression of IgAN.

Methods Four databases (PubMed, Web of Science, Embase, and Cochrane Library) were searched until September 25, 2023. The study encompassed IgAN patients, focusing on kidney outcomes and end-stage kidney disease (ESKD). Statistical analysis included calculating hazard ratios (HR) for binary outcomes and examining publication bias.

Results The meta-analysis involved thirteen studies comprising 11,849 patients. For kidney outcomes, crescent formation may be linked to an elevated risk (HR = 2.01, 95%CI 1.40–2.87, $P < 0.001$). Furthermore, significantly increased risks of kidney outcomes were observed with a crescent proportion > 10 (HR = 1.8, 95%CI 1.32–2.45, $P < 0.001$) and > 25%(HR = 2.11, 95% CI 1.47–3.02, $P < 0.001$). Regarding ESKD, a proportion > 25% also displayed an elevated risk (HR = 1.70, 95% CI 1.18–2.44, $P = 0.004$). However, a proportion > 10% (including > 25%) did not show a significant association with ESKD (HR = 1.12, 95% CI 0.36–3.47, $P = 0.842$) versus less.

Conclusions This systematic review and meta-analysis established a strong association between crescent proportions and the progression of IgAN. Higher proportions, notably exceeding 25%, were reliable prognostic markers, indicating a greater risk of adverse kidney outcomes and ESKD. These findings have significant clinical implications, offering the potential for more precise risk stratification in IgAN patients.

Keywords Immunoglobulin a nephropathy, Systematic review, Crescent, End stage kidney disease

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Background

Immunoglobulin A nephropathy (IgAN) is a diverse condition, and the likelihood of its progression to end-stage kidney disease (ESKD) within a decade varies considerably, ranging from less than 10% to as high as 60% [1]. Hence, accurately identifying individual patients facing an elevated risk of disease progression poses a considerable challenge. Therefore, developing techniques for the precise risk assessment of patients with IgAN is crucial. Since it may enable us to provide patients with prognosis information, balance the benefits of immunosuppression with the expected risks [2, 3], and enhance the design of clinical trials in IgAN by enabling the targeted inclusion of more clinically consistent patient cohorts.

The clinical and pathological diversity inherent to IgAN leads to considerable inter-individual variation in disease prognosis and progression. Hence, Uncovering the risk factors that impact the advancement and prognosis of IgAN is crucial. Crescent formations (Cs) represent a frequently observed pathological feature in IgAN, appearing in about 18.8–66.4% of renal biopsy samples. The development of glomerular crescents initiates with cellular crescents, progressing to a stage of cellular/fibrous crescents, ultimately leading to irreversible fibrous crescents. This process ultimately culminates in glomerulosclerosis, resulting in irreversible renal injury and, in severe cases, ESKD [4, 5]. The presence of crescents is closely intertwined with several clinicopathological characteristics; it demonstrates a positive association with proteinuria and serum creatinine (Scr) [6]. Moreover, it is linked to segmental glomerulosclerosis, global sclerosis, renal tubulointerstitial abnormalities, and endocapillary proliferation. Consequently, while the issue remains debated, the presence of crescents is acknowledged as an essential prognostic indicator for IgAN. A 2016 study by Haas and his team [7] examined 3,096 patients diagnosed with IgAN. It established that crescents' presence independently contributes to a heightened risk, correlating with a poor prognosis among individuals with IgAN. Individuals with Cs present in 25% or more of their glomeruli face a significantly greater risk of renal progression than those with less than 25% of their glomeruli affected by crescents. The revised Oxford classification (2017) acknowledges the independent prognostic significance of Cs. It has included them in its system, classifying them as C0 (no crescents), C1 (crescents in less than 25% of glomeruli), and C2 (crescents in 25% or more of glomeruli) [7]. However, the association between distinct proportions of crescents and the progression of IgAN remains a subject of ongoing debate within the medical community. This systematic review and meta-analysis aim to compile a comprehensive synthesis of the current evidence regarding the association between various crescent proportions and the progression of IgAN. By collating and analyzing data from a wide range of studies, we aim to offer valuable insights into crescents' prognostic significance and to assist in refining risk stratification for IgAN patients.

Methods

Search strategy

The search encompassed electronic databases like PubMed, Cochrane Library, Embase, and Web of Science, extending up to September 25, 2023, and included citations written in English. The search incorporated key terms such as crescent, nephropathy, and Immunoglobulin A. Supplementary Table 1 provides a comprehensive breakdown of the detailed search strategy.

Inclusion and exclusion criteria

Inclusion criteria were: (1) patients diagnosed with IgAN from native kidney biopsy. (2) primary IgAN is classified as crescent proportion > 10% and crescent proportion > 25%, and crescents here can be acute (cellular), subacute (fibrocellular), or chronic (fibrous) [8]. (3) study endpoints included kidney outcome and ESKD. (4) Prospective or retrospective cohort study in English. We excluded case reports, editorials, reviews, conference abstracts, and comments if indicators were unavailable for inclusion in the study.

Data extraction and quality assessment

Two reviewers carried out the independent extraction of data from each study, and any disparities in the collected data were resolved following consultations with a third reviewer. All studies underwent quality assessment using the Newcastle–Ottawa Scale (NOS) [9, 10]. *High-quality articles* were defined as studies with a score of seven or higher.

Statistical analysis

Stata V.14 software was employed to perform the statistical analyses. The effect sizes for binary outcomes were evaluated through hazard ratios (HR) and calculating their 95% confidence intervals (CI). The heterogeneity assessment involved using Q and I^2 test statistics, where I^2 values surpassing 50% denoted considerable heterogeneity. The choice between a fixed or random-effects model was contingent on the obtained results. A significance level for effect size disparities was also set at $P<0.05$ [11]. A sensitivity analysis involving meta-influence was implemented [12]. We intended to assess publication bias through Egger's and Begg's tests [13], and Trim and Fill analysis would be applied in the presence of bias. Significant disparities are denoted by a P-value less than 0.05.

Results

Selection of the relevant studies

After implementing the search strategy, 3,821 publications were discovered (PubMed: 878, Embase: 1,969, Cochrane: 33, Web of Science: 941). Once 1,573 duplicate papers were removed, 2,248 documents were screened, and exclusion was applied to 2,234 as they did not meet the eligibility criteria. After the remaining 24 studies underwent a thorough full-text review, thirteen studies [14–26] were chosen for analysis. Figure 1 contains

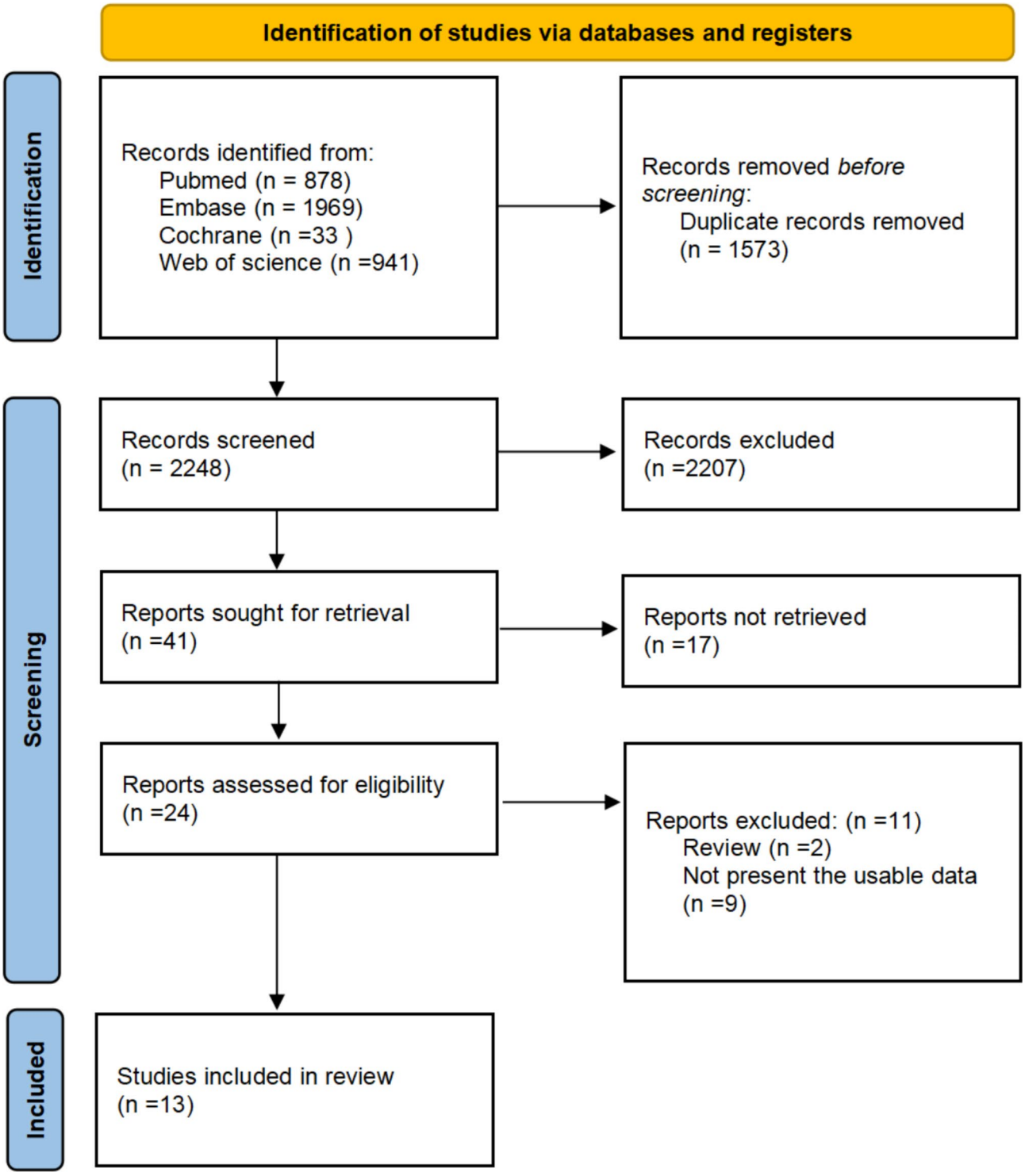

Fig. 1 PRISMA flowchart of included studies

the PRISMA flow diagram. Thirteen studies contributed data for the analysis, involving 11,849 patients. The systematic review and meta-analysis encompassed 13 studies published from 2013 to 2023. Of the thirteen studies, ten were executed in China, and the remaining three took place in the USA, Korea, and Iran. No overlap in the included cohorts was discovered. Table 1 provides a summary of the characteristics of all 13 included studies. These studies achieved a high-quality rating based on the Newcastle–Ottawa Scale score (Table 2).

Kidney outcome in crescent formation

Thirteen studies with 11,849 patients reported kidney outcomes in crescent formation. The meta-analysis showed that crescent formation was associated with an increased risk of kidney outcome (HR = 2.01, 95%CI 1.40–2.87, $P<0.001$) (Fig. 2A). The results of subgroup analysis based on sample size are entirely consistent with the overall results (Fig. 2B).

Kidney outcome in crescent proportion

Nine studies with 10,745 patients reported kidney outcomes in crescent proportion. The meta-analysis showed that a crescent proportion > 10% (HR = 1.8, 95%CI 1.32–2.45, $P<0.001$) and >25% (HR = 2.11, 95%CI 1.47–3.02, $P<0.001$) were associated with an increased risk of kidney outcome (Fig. 3A and B). The results of subgroup analysis based on sample size are shown in Figures S1A and S1B.

ESKD in crescent proportion

Four studies with 5,242 patients reported ESKD in crescent proportion. The meta-analysis showed that a crescent proportion > 25% (HR = 1.70, 95%CI 1.18–2.44, $P=0.004$) was associated with an increased risk of ESKD (Fig. 4A). However, a crescent proportion > 10% (HR = 1.12, 95%CI 0.36–3.47, $P=0.842$) was not associated with an increased risk of ESKD (Fig. 4B). The results of subgroup analysis based on sample size are shown in Figure S2.

Sensitivity analysis

Individual study exclusions in the sensitivity analysis showed no notable impact on the overall effect size (Fig. 5).

Publication bias

The *P*-value of Egger's and Begg's tests showed no publication bias for kidney outcome at crescent proportion > 25% (Egger's test $P=0.848$; Begg's test $P=1.000$) (Fig. 6A), ESKD at crescent proportion > 10% (Begg's test $P=1.000$) (Fig. 6B) and crescent proportion > 25%(Egger's test $P=0.951$; Begg's test $P=1.000$) (Fig. 6C). However, the P-value of Egger's or Begg's test confirmed the existence of publication bias for kidney outcome at crescent proportion > 10% (Egger's test P = 0.04; Begg's test P = 0.089) (Figure S3A). and kidney outcome at crescent formation (Egger's test P = 0.001; Begg's test P = 0.2) (Figure S3B). The trim and fill analysis for kidney outcome at crescent proportion > 10% indicated an estimated missing study, with the corresponding pooled estimate being 0.541 (95% CI: 0.238, 0.844) (Figure S3C). Four missing studies were estimated for the trim and fill' analysis concerning kidney outcome at crescent formation, yielding a pooled odds ratio estimate of 0.509 (95% CI: 0.202, 0.815) (Figure S3D).

Discussion

IgAN represents a clinical conundrum due to its diverse presentation and unpredictable progression. This systematic review and meta-analysis have taken a significant step toward unravelling one of the enigmas in IgAN - the role of crescents in disease progression. This study, including ten high-quality studies, revealed that IgAN patients with higher proportions of Cs, particularly > 25%, faced an increased risk of kidney outcomes and ESKD. The implications are significant, as these findings enable more personalized risk stratification for IgAN patients, which can inform treatment decisions and enhance clinical trial designs.

Despite employing similar entry criteria, including the exclusion of patients whose eGFR falls below 30 ml/min per 1.73 m^2 during biopsy or those experiencing rapid progression to ESKD, crescents were not established as an independent predictor of adverse renal outcomes in patients with IgAN, according to the initial Oxford study [27] and several subsequent validation investigations [28–31]. On the contrary, several studies with more lenient entry criteria [32–35] did establish a significant link between crescents and a composite endpoint that involved either ESKD or a doubling of SCR ≥ 50% reduction in eGFR. Haas and colleagues [14] conducted a study investigating crescents observed in kidney tissue from individuals diagnosed with IgAN and assessed their impact on the progression of renal function. In a multicenter retrospective cohort comprising 3,096 patients with IgAN, Haas and colleagues discovered that the presence of crescents in one-fourth or more of glomeruli (C2) retained its predictive value for the combined event, irrespective of whether patients underwent immunosuppression. However, in less than one-fourth of glomeruli (C1), crescents lost their predictive significance after patients received immunosuppression. Afterwards, multiple validation studies demonstrated a strong connection between C2 and the adverse prognosis in IgAN, with the ongoing debate about how C1 affects the renal outcome of the disease. In a retrospective analysis of 1,328 patients suffering from IgAN, Peng and colleagues [17]

Table 1 Characteristics of the studies included in this meta-analysis

Author	Country	Age	Male (%)	MAP	Proteinuria	patients	Immunosuppression (%)	Follow up (Y, M)	Outcomes assessed	Interstitial fibrosis/ tubular atrophy
Lv, 2013 [23]	China	36.3 ± 15.1	58.5	118.1 ± 19.7	4.44 ± 2.63	113	71.7	23.7 M	ESRD	1–50%: 43 > 50%: 66
Haas, 2017 [7]	USA	35 ± 14	58	97 ± 15	1.2(0.7–2.3)	3096	37	4.7Y	≥ 50% decline in eGFR or ESRD (combined event)	/
Zhang, 2017 [24]	China	32 ± 10	43.7	NA	0.8(0.4–1.5)	538	NA	51 M	renal outcome comprising doubling of baseline serum creatinine (SCr) and ESRD (maintenance hemodialysis, maintenance peritoneal dialysis, or renal transplantation).	Interstitial fibrosis: Mild = 206; Moderate = 113; Severe = 14; Tubular atrophy: Mild = 277; Moderate = 148; Severe = 36
Zhang, 2018 [14]	China	35.4 ± 12	49.1	95.8 ± 13.5	1.42(0.72–2.62)	1152	52.5	45 M	eGFR decline equal to or greater than 50% or to ESRD	Oxford classifcation: M1 = 469; E1 = 459; S1 = 839; T1 + T2 = 364
Park, 2019 [15]	Korea	36(24–47)	50.2	93(83–101)	1.06(0.49–2.1)	3380	NA	8.74Y	Merge of progression to ESRD and halving of eGFR from baseline	Interstitial fibrosis: Mild = 1776; Moderate = 228; Severe = 93; Tubular atrophy: Mild = 1395; Moderate = 439; Severe = 192
Peng, 2019 [16]	China	34.2 ± 11.2	45.6	NA	2.8 ± 3.0	1328	60.5	46.1 M	eGFR decline equal to or greater than 10% or to ESRD	Oxford classifcation: M1 = 1043; E1 = 64; S1 = 675; T1 + T2 = 328
Ma, 2020 [25]	China	32.1 ± 11.1	59.8	97.5 ± 15.5	2.1 ± 2.5	338	73.4	49.9 M	a ≥ 50% reduction in eGFR or ESRD.	Oxford classifcation: M1 = 115; E1 = 61; S1 = 78; T1 + T2 = 142
Lin, 2021 [17]	China	30(26–39)	44.9	92(83.5–100)	0.8(0.43–1.58)	305	36.1	34.8 M	≥ 15% decline in the eGFR after 1 year or ≥ 30% decline in the eGFR after 2 years	Oxford classifcation: M1 = 245; E1 = 34; S1 = 158; T1 = 37
Chen, 2022 [18]	China	35.99 ± 11.99	46.25	99.76 ± 13.31	1.61 ± 2.14	144	NA	16 M	ESRD or eGFR decreasing by 50%	/
Du, 2022 [19]	China	34.97 ± 12.58	43.5	94.88 ± 12.64	1.59(1.00-3.10)	595	62.5	43 M	ESKD or ≥ 50% decline in eGFR	Interstitial fibrosis: Mild = 141; Moderate = 14; Severe = 7;
Ossareh, 2022 [20]	Iran	37 ± 13	76	NA	3.4 ± 2.5	115	NA	43 M	ESKD or death due to kidney disease	Oxford classifcation: M1 = 20; E1 = 19; S1 = 56; T1 = 50; C1 = 40

Table 1 (continued)

Author	Country	Age	Male (%)	MAP	Proteinuria	patients	Immunosuppression (%)	Follow up (Y, M)	Outcomes assessed	Interstitial fibrosis/ tubular atrophy
Ruan, 2022 [21]	China	34 ± 10.2	43.5	94.7 ± 14.1	0.8 ± 0.9	458	18.8	48 M	ESKD or ≥ 50% decline in eGFR	Oxford classifcation: T0 = 193; T1 = 58; T2 = 4;
Di,2023 [22]	China	37 ± 13.1	51.9	100 ± 14	NA	287	55.7	57 M	Kidney survival	/

MAP: Mean arterial pressure; Y: year; M: month; ESKD: end stage renal disease; NA: Not available

determined that C2 predicted unfavourable renal survival (HR = 2.366, 95% CI 1.434–3.904), whereas C1 did not have predictive value for the renal outcome. In their study, Zhao and colleagues [36] explored the connection between the Oxford classification and the renal prognosis in cases of IgAN. Their findings revealed that the Kaplan-Meier (K-M) survival curve illustrated a more unfavourable prognosis for the C2 group than the C0 and C1 groups, with kidney survival times comparable between the C1 and C0 groups. The presence of heterogeneity in crescents among C1 patients, including factors like crescent volume, is suggested to be a significant element influencing the prognosis of IgAN. Within the scope of this study, a notable link was observed between crescent proportions and the progression of IgAN. Higher proportions, notably exceeding 25%, were reliable prognostic markers, indicating a greater risk of adverse kidney outcomes and ESKD. Our meta-analysis demonstrates the independent prognostic value of the presence of crescents, but there is currently insufficient data to suggest what is the optimal treatment of IgAN patients with a high crescent proportion [37–39]. At the same time, the impact of new treatment methods on the prognosis of crescents is still unknown. Treatment with glucocorticoids, such as budesonide, can achieve complete disappearance of crescents in repeat biopsies and remission of proteinuria, but improvement in renal prognosis remains uncertain [2, 3]. Immunosuppressive therapy, such as BAFF/APRIL inhibitors and complement inhibitors, may respond to crescents, but treatment may reduce their prognostic value [40, 41].

While our study sheds light on the prognostic value of crescent proportions in IgAN, it is essential to acknowledge its limitations. First, the studies included in our meta-analysis exhibited heterogeneity. This heterogeneity may introduce potential sources of bias and impede the broader applicability of our findings. Larger, more diverse patient populations should be the focus of future research to validate our findings. Second, our analysis primarily relies on retrospective and prospective cohort studies, which may introduce selection and publication biases. Further high-quality evidence from randomized controlled trials may be necessary for research in this field. Finally, The relationship between crescent proportions and disease progression in IgAN requires additional exploration to uncover the underlying mechanisms. Enhanced insights into the molecular and immunological processes could facilitate the development of targeted therapies.

Conclusions

In conclusion, our systematic review and meta-analysis provide compelling evidence of the prognostic significance of crescent proportions in IgAN. Higher crescent proportions, especially when they exceed 25% of glomeruli, are associated with an increased risk of kidney outcomes and ESKD. These findings have direct clinical implications, allowing for improved risk stratification, personalized treatment decisions, and enhanced clinical trial designs. However, it is essential to acknowledge that IgAN is a multifactorial disease, and crescents are just one part of the intricate puzzle. Future research should explore other contributors, such as genetic factors and the gut-kidney axis, to develop tailored interventions.

Table 2 Methodological quality of the studies included in the meta-analysis[1]

First author	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor	Outcome assessment	Was Follow-Up Long Enough for Outcomes to Occur	Adequacy of Follow Up of Cohorts	Total quality scores
Lv [23]	☆	☆	☆	☆	☆	☆	☆	☆	8
Haas [7]	☆	☆	☆	☆	☆	☆	☆	—	7
Zhang17 [24]	☆	☆	☆	☆	☆	☆	☆	☆	8
Zhang [14]	☆	☆	☆	☆	☆	☆	☆	☆	8
Park [15]	☆	☆	☆	☆	☆	☆	☆	☆	8
Peng [16]	☆	☆	☆	☆	☆	☆	☆	☆	8
Ma [25]	☆	☆	☆	☆	☆	☆	☆	☆	8
Lin [17]	☆	☆	☆	☆	☆	☆	☆	—	7
Chen [18]	☆	☆	☆	☆	☆	☆	—	☆	7
Du [19]	☆	☆	☆	☆	☆	☆	☆	☆	8
Ossareh [20]	☆	☆	☆	☆	☆	☆	☆	☆	8
Ruan [21]	☆	☆	☆	☆	☆	☆	☆	☆	8
Di [22]	☆	☆	☆	☆	☆	☆	☆	—	7

[1] A study could be awarded a maximum of one star for each item except for the item Control for important factor or additional factor

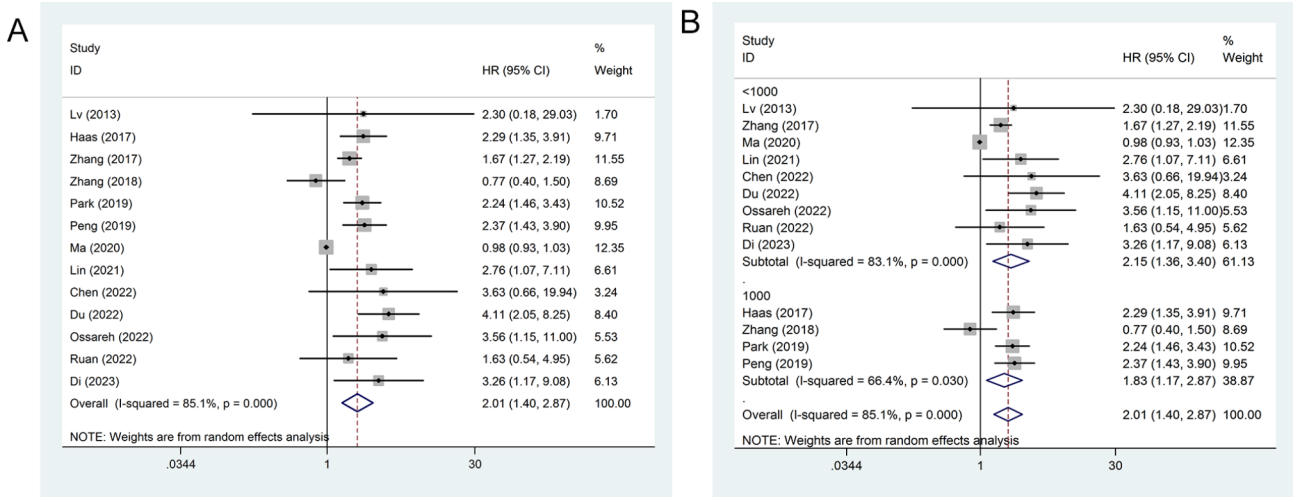

Fig. 2 Forest plots of crescent formation and kidney outcomes. (**A**) pooling results; (**B**) subgroup analysis

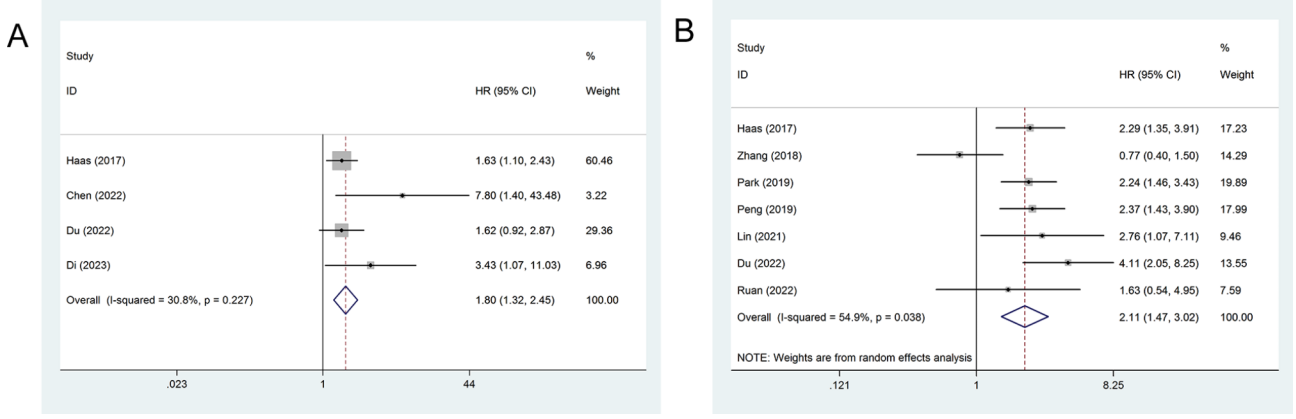

Fig. 3 Forest plots of various proportions of crescents and kidney outcomes. (**A**) crescent proportions > 10%; (**B**) crescent proportions > 25%

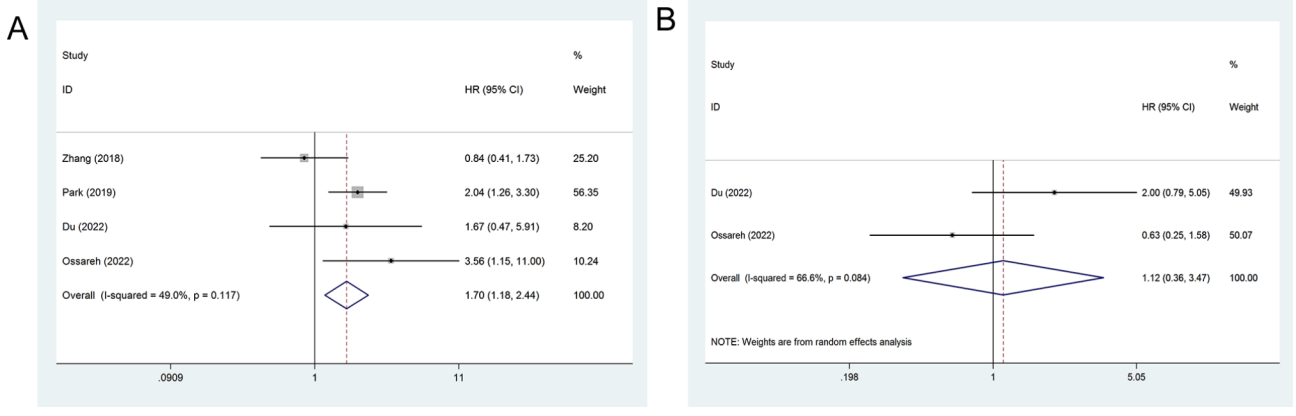

Fig. 4 Forest plots of various proportions of crescents and ESKD. (**A**) crescent proportions > 25%; (**B**) crescent proportions > 10%

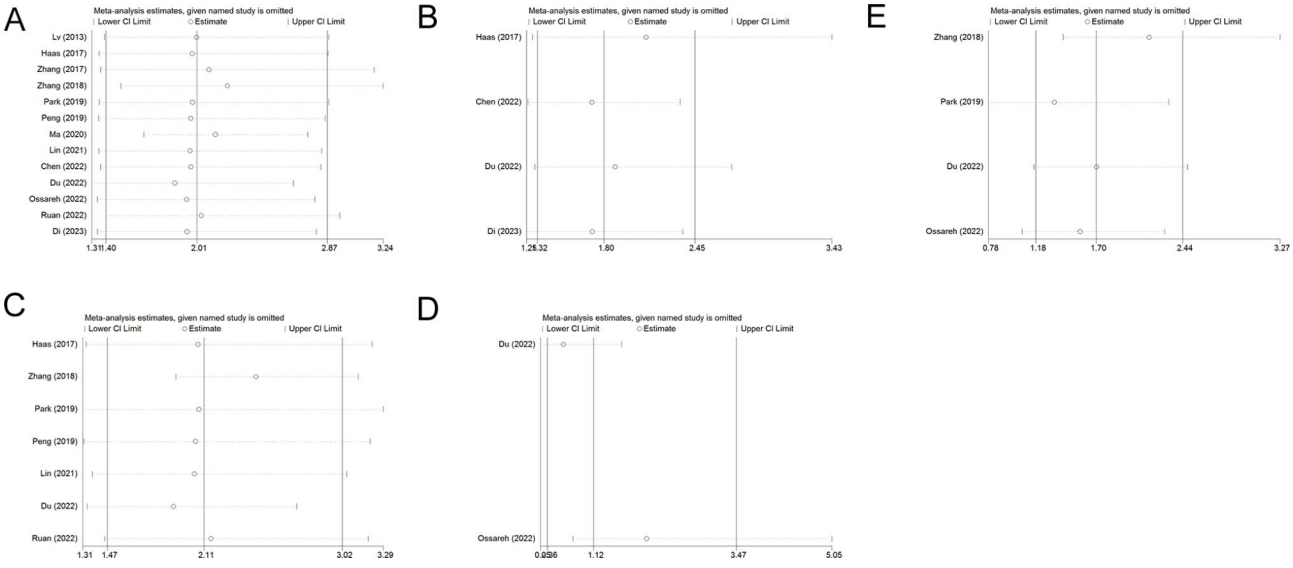

Fig. 5 Sensitivity analysis examining the influence of individual studies on pooled results. (**A**) crescent formation; (**B**) kidney outcomes in crescent proportions > 10%; (**C**) kidney outcomes in crescent proportions > 25%; (**D**) ESKD in crescent proportions > 10%; (**E**) ESKD in crescent proportions > 25%

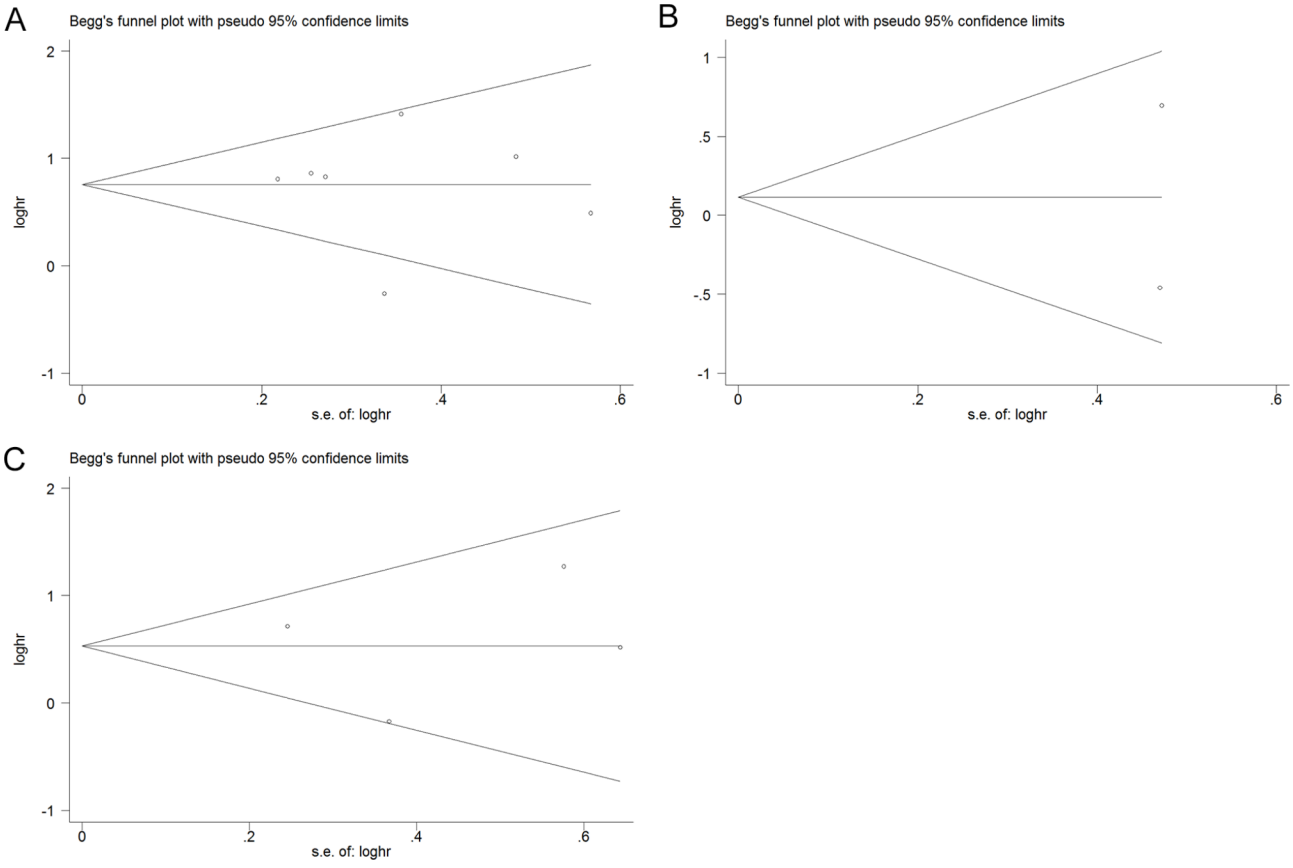

Fig. 6 Funnel plot for publication bias. (**A**) kidney outcomes in crescent proportions > 25%; (**B**) ESKD in crescent proportions > 10%; (**C**) ESKD in crescent proportions > 25%

Abbreviations

IgAN	Immunoglobulin A nephropathy.
Cs	Crescents.
ESKD	End stage kidney disease.
HR	Hazard ratios.
Scr	Serum creatinine.
NOS	Newcastle–Ottawa Scale.
CI	Confidence intervals.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Not applicable.

Author contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Li Yu, Hao Zhang, Yunfeng Wu. The first draft of the manuscript was written by Li Yu and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
All data generated or analysed during this study are included in this published article and its supplementary information file.

Declarations

Ethics approval and consent to participate
Not applicable, as this study is a systematic review and meta-analysis.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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