Establishment and validation of a novel risk stratification scale in adult IgA vasculitis nephritis: a cohort study based on a systematic review and meta-analysis

Y. Shi[1,2], Z. Hong[1,2], B. Lou[1,2], C. Zhu[1,2]

[1]Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University, Hangzhou; [2]Department of Nephrology (Key Laboratory of Kidney Disease Prevention and Control Technology), Hangzhou Hospital of Traditional Chinese Medicine, Hangzhou, China.

Abstract

Objective

This study aimed to develop and validate a risk stratification scale for unfavourable outcomes in adult patients with IgA vasculitis nephritis (IgAVN).

Methods

The derivation cohort in this study was constructed using the existing prognosis data from adult IgAVN cohorts. We extracted the risk factors and their hazard ratios. Only statistically significant risk factors were included in our final risk stratification scale. Then this study validated the risk stratification scale in an external cohort of Chinese patients. The performance of the risk stratification scale was evaluated by the receiver operating characteristic (ROC), calibration, decision, and Kaplan-Meier curves.

Results

Ten cohorts involving 1,814 adult patients with IgAVN were included in this meta-analysis. Serum albumin (ALB), estimated glomerular filtration rate (eGFR), endocapillary hypercellularity (E1), and tubular atrophy/interstitial fibrosis (T1/2) were included in the risk stratification and scored according to their weightings (maximum score: 6.5). An external cohort comprising 133 patients was used to validate the risk stratification scale. The area under the curve (AUC) value of the scoring scale was 0.88 (95%CI: 0.78–0.99), with a sensitivity of 0.79 (95%CI: 0.49–0.95) and specificity of 0.89 (95%CI: 0.82–0.94), at a cut-off value of 3. The calibration, decision, and Kaplan-Meier curves further confirmed the robust performance of the risk stratification scale.

Conclusion

In this study, we established a simple and practical tool to identify adult IgAVN patients at high risk of unfavourable outcomes. Reasonable use of the risk stratification scale can help make early clinical decisions and facilitate the development of precision medicine.

Key words

IgA vasculitis, meta-analysis, cohort studies, nephritis

Yueyi Shi, MD
Zhuoning Hong, MD
Bojian Lou, MD
Caifeng Zhu, MD

Please address correspondence:
Caifeng Zhu
Department of Nephrology
(Key Laboratory of Kidney Disease Prevention and Control Technology),
Hangzhou Hospital of Traditional Chinese Medicine,
310007 Hangzhou, China.
E-mail: zhcaifeng@126.com

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Introduction

IgA vasculitis (IgAV), previously called Henoch-Schönlein purpura, is a type of immune-mediated small-vessel vasculitis (1-3). It is characterised by the deposition of galactose-deficient IgA1 (Gd-IgA1) dominant immune complexes in small vessels, resulting in multi-system damage, including the skin, gastrointestinal tract, kidneys, and joints (4). IgA vasculitis nephritis (IgAVN) is the most severe complication of IgAV and is typically observed within 4–6 weeks following the onset, but may be delayed for months even after symptoms have resolved (5). The incidence of IgAVN is 20–60% in children with IgAV and 45–85% in adults (6-8). Adult patients with IgAVN typically exhibit more severe symptoms and have a poorer prognosis (9, 10). It is reported that approximately 30% of adult patients with IgAVN progressively develop end-stage kidney disease (ESKD) (11, 12).

Although renal biopsy is the gold standard for diagnosing IgAVN, the correlation between pathological findings and clinical prognosis remains unclear. Decreased renal function and crescents present in more than 50% of the glomeruli have generally been reported as predictors of unfavourable outcomes in IgAVN (10, 13, 14). However, some studies dispute their predictive value in the prognosis of IgAVN (15-17). Most existing prediction models for unfavourable outcomes in IgAVN are developed based on paediatric populations. The course and prognosis of IgAVN in adults remain much less understood (18). Moreover, the performance of existing prediction models of IgAVN requires further validation and improvement. Therefore, there is a need for an in-depth investigation into the risk factors associated with poor prognosis in IgAVN to facilitate early diagnosis, prevention, and treatment.

This study aimed to comprehensively assess various potential risk factors and develop a novel risk stratification scale for the early identification of high-risk patients. Early identification and hierarchical management of severe nephritis may halt disease progression and improve long-term renal outcomes in adult IgAVN patients.

Methods

Systematic review registration

This meta-analysis was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration no. CRD42025649898).

Study population

- Derivation cohort

The derivation cohort was obtained through a systematic review and meta-analysis of 10 cohort studies (19-28), including 4 prospective and 6 retrospective studies. We searched PubMed, Excerpta Medica Database, Web of Science and the Cochrane Library from the time of their inception to January 2025 using the following medical subject heading (MeSH) terms or keywords: "nephritis", "IgA vasculitis", "prognosis", "renal insufficiency", and "kidney failure". To minimise potential publication bias, we searched for grey literature in the Data Archiving and Networked Services (DANS) and ProQuest Dissertations & Theses Global (PQDT Global).

The final derivation cohort included 1,814 adult patients with IgAVN from the UK, China, South Korea, and Japan. All included cohort studies reported hazard ratios (HRs) and corresponding 95% confidence intervals (95% CIs) of risk factors, and were assessed using the Newcastle-Ottawa Scale (NOS). A flowchart illustrating the study selection methodology is presented in Figure 1a, while the search strategy, data extraction process, and quality assessment are elaborated in the Supplementary Data.

- Validation cohort

This study included IgAVN patients initially hospitalised in the Nephrology Department of Hangzhou Hospital of Traditional Chinese Medicine and who underwent renal biopsy from December 31, 2012, to December 31, 2023. The pathological images of the renal biopsy are independently evaluated by at least two renal pathologists.

The inclusion criteria were as follows: 1) age >18 years; 2) patients were hospitalised in the Nephrology Department for the first time and diagnosed as IgAVN by renal biopsy; and 3) patients

with a follow-up duration of at least 12 months. Meanwhile, the exclusion criteria were as follows: 1) age≤18 years; 2) previous diseases causing renal injury (including diabetic kidney disease, chronic glomerulonephritis, hypertensive nephrosclerosis, tubulointerstitial nephritis, obstructive nephropathy, or other structural renal abnormalities); 3) those with severe heart, liver, brain, or other debilitating diseases; 4) end-stage kidney disease (ESKD) (eGFR <15 mL/min/1.73 m^2 or requiring continuous renal replacement therapy); 5) inadequate medical record information; and 6) the follow-up period was less than 12 months. Ultimately, 133 patients with IgAVN were included in the validation cohort. Figure 1b presents a flowchart illustrating the involved patients' selection process.

Outcome

The unfavourable outcome of IgAVN was defined as a composite endpoint comprising a ≥30% reduction in eGFR from baseline and/or an increase in Scr of ≥50% and/or progression to end-stage kidney disease (ESKD) (eGFR <15 mL/min/1.73 m^2 or requiring continuous renal replacement therapy), or death.

Ethics statement

This study was conducted in accordance with the Helsinki Declaration. It received approval from the Institutional Review Board of Hangzhou Hospital of Traditional Chinese Medicine (approval no. 2024KLL209), and the ethics committee waived the requirement for informed consent given the retrospective nature of the study.

Statistical analysis

- Risk stratification scale establishment

The HRs and their corresponding 95% CIs for the risk factors included in each study's multivariate Cox regression models were extracted. The heterogeneity among studies was evaluated using the Cochrane Q test and measured by I^2. The I^2 value greater than 50% or the P value of the Cochrane Q test less than 0.05 indicated statistically significant heterogeneity. When significant heterogeneity was present, we employed the random effects model to pool the HRs and their 95% CIs. Otherwise, the fixed effects model was chosen. If there were significant heterogeneity, subgroup or sensitivity analysis would be performed. Then we used the pooled HRs and 95% CIs to calculate the β-coefficients. The score for each risk factor was calculated using the β-coefficients and rounded to one decimal place (with the final digit being either 0 or 5). All risk factors in the risk stratification scale were classified based on both meta-analysis results and clinical practice relevance. The total score was calculated by summing the scores of all risk factors. A higher total score was associated with an increased risk of unfavourable outcomes in IgAVN. There was a statistically significant difference when the *p*-value was <0.05.

- Risk stratification scale validation

The generalisability of the risk stratification scale was verified by using external data from the above cohort. The total scores were calculated using the risk stratification scale and subsequently used to construct the Receiver Operating Characteristic (ROC) curve. The true positives (TP), false positives (FP), true negatives (TN), false negatives (FN), Youden index, sensitivity, and specificity were calculated for different cut-off scores. The optimal cut-off score was determined using the maximum Youden index. Based on the optimal cut-off score, the patients were divided into low-risk and high-risk groups. Decision curve analysis was used in clinical practice to assess the clinical utility of the risk stratification scale and determine its effectiveness in real-world scenarios. The calibration degree of the risk stratification scale was evaluated using the calibration curve. To verify the risk stratification scale's predictive ability, the incidence rate of unfavourable outcomes in adult patients with IgAVN was calculated, and Kaplan-Meier curves were generated in each risk group.

- Other statistical methods

Continuous data were tested for normality using the Shapiro-Wilk test and histograms, with *p*>0.05 indicating normally distributed data. Normally distributed continuous data were analysed using a t-test and expressed as mean ± standard deviation (SD). Continuous data were compared between groups using the Mann-Whitney U-test and presented as median (interquartile range (IQR): Q1, Q3). Categorical data were analysed using the chi-square or Fisher's exact test, depending on the sample size, and described as the number (percentage) of patients. A *p*-value <0.05 was considered statistically significant. All statistical analyses were conducted using R (v. 4.4.2).

Results

Derivation cohort

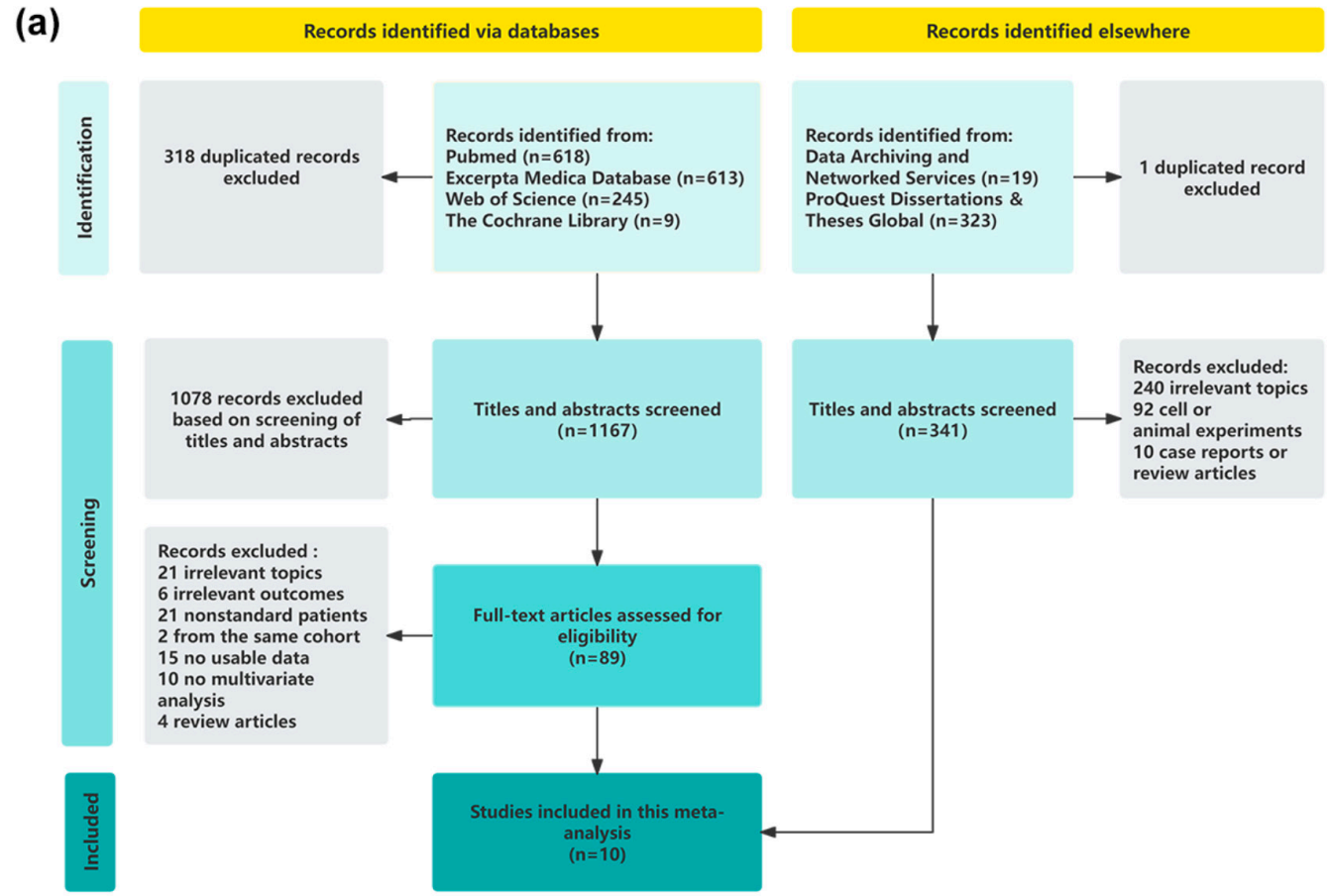
We identified 1,814 adult patients with IgAVN from 10 cohort studies published between 2014 and 2024. During a medium follow-up of 2–8.5 years (3,628–15,419 person-years), unfavourable outcomes of IgAVN were observed in 180 patients (9.92%). Approximately 52.65% of the enrolled patients were male. The baseline characteristics of the derivation cohort are presented in Supplementary Table S1.

Data were included in the meta-analysis if at least three studies independently reported the same risk factor's HRs (95% CIs). These cohort studies reported 10 potential risk factors, including age, sex, hypertension (HTN), urinary protein (UP), eGFR, serum creatinine (Scr), albumin (ALB), endocapillary hypercellularity (E1), tubular atrophy/interstitial fibrosis (T1/2), and crescents (C1/2) (known as the Oxford Classification MEST-C score system) (29). Supplementary Table S2 provides detailed information on risk factors, sample size, and HR (95% CI). The results of the overall response and subgroup/sensitivity analysis of the 10 risk factors are shown in Supplementary Table S3.

All included studies were of high quality according to the Newcastle-Ottawa Scale (NOS), with scores ranging from 6 to 9 (mean score: 8.1). Supplementary Table IV provides detailed information regarding the quality assessment.

Validation cohort

The validation cohort included 133 adult patients diagnosed with IgAVN,



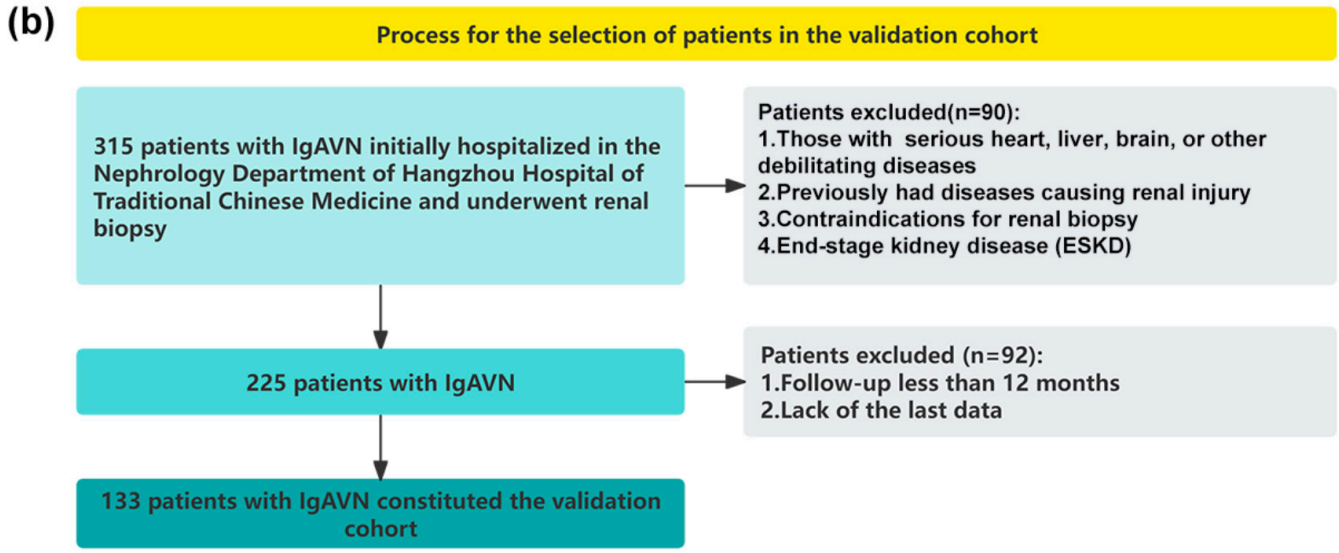


Fig. 1. **(a)** Flowchart of the literature search and study selection process for risk factors associated with unfavourable outcomes in adult patients with IgAVN. **(b)** The process for identifying and selecting adult patients with IgAVN in the validation cohort.

among whom 36% were male, with a median age of 36 (IQR: 27, 55) years. The median follow-up time was 33.91 months (IQR: 19.98, 49.30). The patients with IgAVN were divided into two groups based on their outcomes: 14 patients with unfavourable outcomes and 119 patients without unfavourable outcomes. Patients with unfavourable outcomes were significantly older, had higher eGFR levels, and were more likely to have T1/2 than those with favourable outcomes ($p<0.001$). Additionally, ALB levels were significantly lower in the unfavourable outcome group ($p<0.001$). The baseline characteristics of the patients in the validation cohort are shown in Supplementary Table S5.

Table I. Risk stratification scale for unfavourable outcomes in adult patients with IgAVN.

Risk factors	Category	Score
ALB	>35 g/L	0
	30-35 g/L	0.5
	25-30 g/L	1
	<25 g/L	2
eGFR	≥60 mL/min/1.73 m^2	0
	<60 mL/min/1.73 m^2	2
E	E0	0
	E1	1
T	T0	0
	T1/2	1.5

ALB: albumin; eGFR: estimated glomerular filtration rate; E1: endocapillary hypercellularity; T1/2: tubular atrophy/interstitial fibrosis.

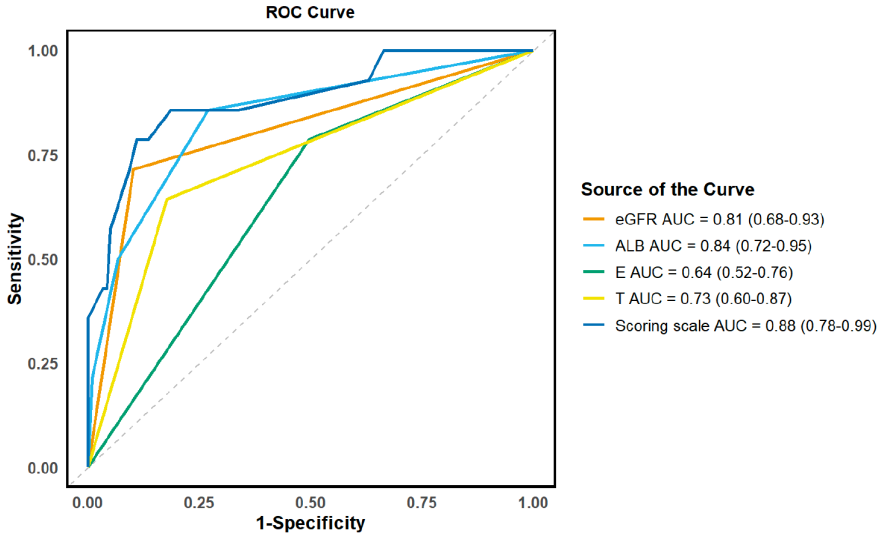


Fig. 2. ROC curve of the unfavourable outcomes scoring scale and each predictor in the validation cohort.

Risk stratification scale establishment

Out of the 10 risk factors identified in the meta-analysis, five risk factors were linked to the unfavourable outcomes in IgAVN: ALB (HR=0.90; 95%CI: 0.84–0.96; p=0.0028), 1 μmol/L increase in Scr (HR=1.01; 95%CI: 1.01–1.02; p=0.0004), E1 (*vs*. E0) (HR=3.33; 95%CI: 1.29–8.60; p=0.01) and T1/2 (*vs*. T0) (HR=4.91; 95%CI: 1.99-12.11; p=0.0005), eGFR (HR=0.16; 95%CI: 0.08–0.32; p<0.0001). Supplementary Fig. S1-S5 show the forest plots of these risk factors. We selected eGFR over Scr for the risk stratification scale because it provides a more accurate and standardised estimate of kidney function, accounting for age, sex, and race. And the combined sample size across studies reporting eGFR was substantially larger than that of studies reporting Scr.Pooled HR (95% CI), sample size, and β-coefficients of risk factors included in the risk stratification scale are listed in Supplementary Table S6. Finally, the simple risk stratification scale for unfavourable outcomes in adult IgAVN achieved following results: ALB (g/L; ≥35=0, 30–35=0.5, 25-30=1, <25=2), eGFR (mL/min/1.73 m^2; ≥60=0, <60=2), E (E0=0, E1=1) and T (T0=0, T1/2=1.5). Table I presents the risk stratification scale. This risk stratification scale achieves a maximum score of 6.5 and is recommended for initial risk assessment in biopsy-proven adult IgAVN.

Risk stratification scale validation

Figure 2 shows the ROC curve of the scoring scale and each predictor in the validation cohort. The scoring scale had a high AUC value of 0.88 (95% CI: 0.78–0.99). The AUC value of each predictor alone was lower than the AUC value of the scoring scale: eGFR (AUC=0.81; 95%CI:0.68–0.93), ALB (AUC=0.84; 95%CI:0.72–0.95), E (AUC=0.64; 95%CI:0.52–0.76), and T (AUC=0.73; 95%CI:0.60–0.87).

Supplementary Table S7 shows the confusion matrix, Youden index, sensitivity, and specificity of different cut-off scores. We determined the optimal cut-off score to be 3.0 based on the highest Youden index, and the corresponding sensitivity and specificity were 0.79 (95%CI: 0.49–0.95) and 0.89 (95%CI: 0.82–0.94).

The calibration curve presented in Figure 3a was generated using bootstrap validation with 2,000 repetitions. The nearly diagonal calibration curve demonstrates excellent concordance between predicted and observed probabilities.

Figure 3b shows the decision curve analysis of the risk stratification scale. When the threshold probability ranged from 0.03 to 0.86, utilising this risk stratification scale to predict the risk of unfavourable outcomes provided greater net benefit than treating all patients or treating none.

Based on the optimal cut-off score, 133 adult patients with IgAVN were categorised into two risk-level groups: a low-risk group (n=109) with risk scores <3 and a high-risk group (n=24) with risk scores of 3–6.5. Among the patients, 3 (2.8%) in the low-risk group and 11 (45.8%) in the high-risk group developed unfavourable outcomes by the end of the follow-up period (Fig. 3 c).

The Kaplan-Meier analysis demonstrated that the median survival time in the high-risk group was significantly shorter compared to the low-risk group (49.7 months *vs*. not reached) (Fig.3 d). The Log-rank test confirmed a statistically significant difference between the two groups (p<0.001). The low-risk group was associated with a 94.4% risk reduction for unfavourable outcomes (HR=0.056, 95% CI: 0.02–0.20) compared to high-risk group.

Discussion

IgAVN is a prevalent form of secondary glomerulonephritis that can occur in individuals of any age. IgAVN in adults is more complex and tends to be associated with more severe outcomes compared to children (30). Clinicians face challenges in managing adult patients with IgAVN due to the controversy surrounding the relationship between initial clinical manifestations and long-term prognosis (31). Therefore, exploring the risk factors associated with unfavourable outcomes in adult patients with IgAVN is crucial for effective clinical management. In this study, a novel risk stratification scale

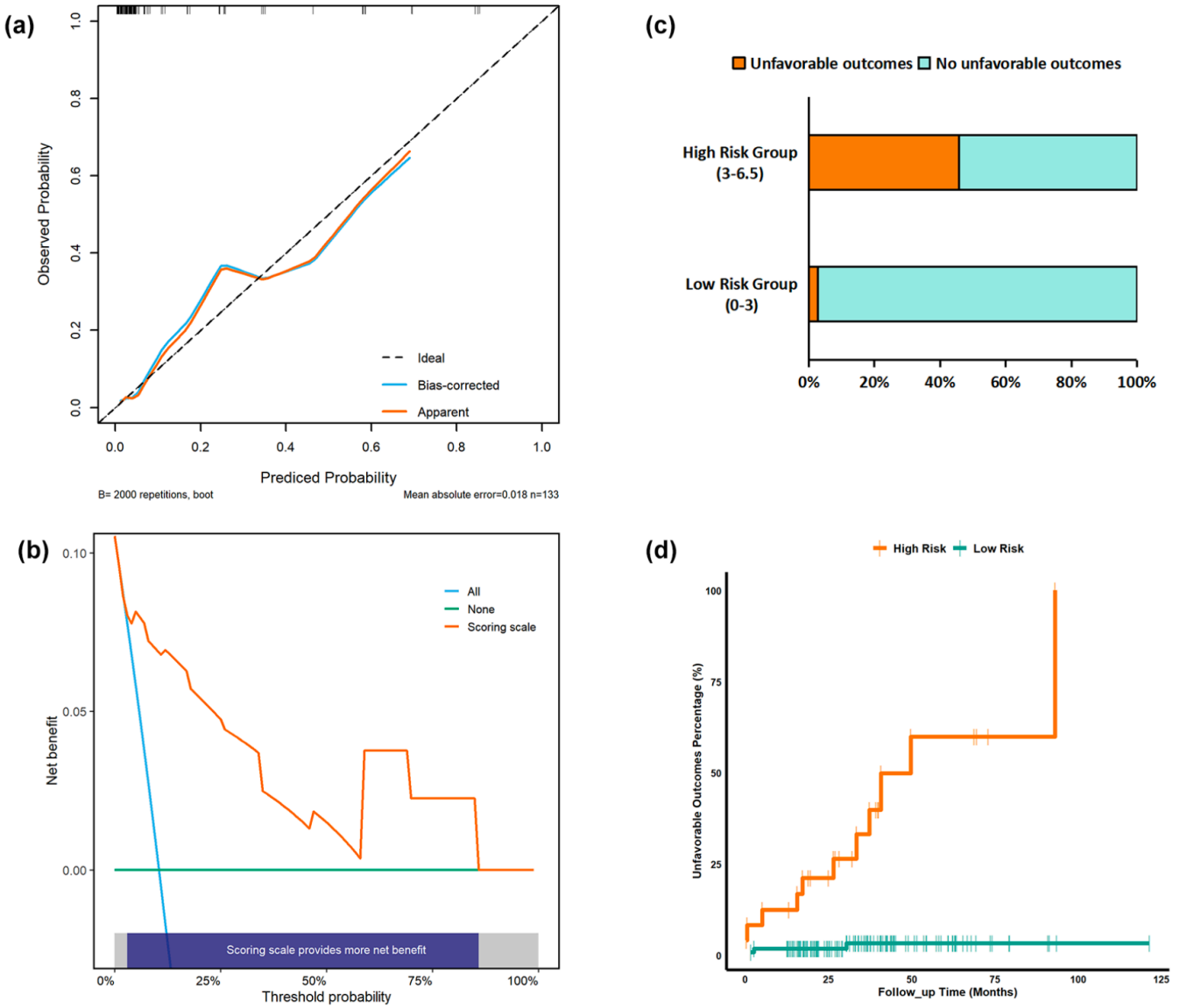


Fig. 3. **(a)** Calibration curve of risk stratification scale in the validation cohort. **(b)** Decision curve of risk stratification scale for validation cohort. **(c)** Prevalence of unfavourable outcomes in the low-risk group and the high-risk group. **(d)** Kaplan-Meier's curve of unfavourable outcomes for the low-risk and high-risk groups.

in adult IgAVN was developed through systematic reviews and meta-analyses. ALB, eGFR, T lesions, and E lesions were included in the risk stratification scale.

Estimated glomerular filtration rate (eGFR) is a central standard for renal assessment. It adjusts serum creatinine levels for age, sex, and race to provide a standardised assessment of renal filtration capacity (32, 33). The long-term prognosis of IgAVN depends on the severity of renal damage (34). Therefore, eGFR serves as both a marker of disease progression and a predictor of prognosis in IgAVN.

Several studies have demonstrated that a reduction in serum ALB levels is correlated with an unfavourable prognosis in patients with kidney disease (35-37). The association between ALB levels and the prognosis of IgAVN can primarily be attributed to inflammatory processes (38). The sustained and irreversible renal damage in IgAVN is caused by the inflammatory cascade and feedback loop triggered by Gd-IgA1 immune complex deposition in the glomerular mesangium and small vessels (39, 40). The increased protein leakage due to the disruption of the glomerular filtration barrier may explain the reduction in serum ALB levels (41). Under inflammatory conditions, the proliferation of monocytes leads to increased by-products that inhibit albumin synthesis (42). Therefore, as a biomarker of inflammatory state, ALB reflects the severity of renal damage in IgAVN and demonstrates a close association with the long-term prognosis (43). Furthermore, lower serum albumin levels are associated with cardiovascular events and may increase cardiovascular mortality in patients with IgAVN (44) (45).

The International Study of Diseases of Children (ISKDC) classification is the most widely used histologic system for IgAVN. However, it was developed in paediatric populations, and its applicability to adults remains unclear. This

system primarily assesses crescent formation but does not account for chronic changes such as tubulointerstitial fibrosis and glomerulosclerosis (46). Due to the similarities in the pathogenesis and clinical manifestations between IgAVN and IgA nephropathy, the Oxford classification of IgA nephropathy has been widely applied to predict the prognosis of IgAVN (47-50). Zhao *et al*. demonstrated that while both ISKDC classification and MEST-C scores showed clinical correlations in IgAVN patients, only the MEST-C scoring system exhibited significant prognostic value for long-term renal outcomes (27). In this study, T and E lesions were strong determinants of unfavourable outcomes in IgAVN. The T lesions represent the feature of kidney fibrosis and serve as a critical indicator of the progression in chronic kidney disease. Its pathogenesis involves glomerular infiltration of inflammatory cells, activation of mesangial cells into myofibroblasts, and epithelial-mesenchymal transition (EMT) of the podocytes (51, 52). The deposition of Gd-IgA1 immune complexes on the endothelium, along with the neutrophil abnormal activation mediated by the IgA Fc receptor FcαRI (CD89), contributes to E lesions in IgAVN (53-55). This process impairs the structural integrity and filtration function of the glomerulus.

The risk stratification scale exhibited remarkable performance in an external validation cohort recruited from Hangzhou Hospital of Traditional Chinese Medicine. The risk stratification scale can identify adult patients with IgAVN who are at high risk of progressing to unfavourable outcomes. For low-risk patients, the interval between follow-up visits can be appropriately extended. For patients at high risk, more aggressive therapeutic interventions should be implemented as early as feasible. Risk stratification enables clinicians to develop more personalised treatment strategies for adult patients with IgAVN, while alleviating the economic burden on patients and society. This will be the first risk stratification scale established based on meta-analysis for predicting unfavourable outcomes and risk stratification of adult IgAVN.

This study has several limitations. Firstly, due to the scarcity of studies on adult IgAVN, our meta-analysis encompassed 10 cohort studies with 1,814 adult patients with IgAVN. We expect future research to involve additional prospective, large-scale cohort studies, allowing us to enhance and refine our meta-analysis. Secondly, patients in the derivation cohort were from several countries, but the risk stratification scale was validated exclusively using retrospective cohorts of Chinese patients with IgAVN. We plan to conduct multicentre prospective validation studies with matched designs in diverse populations to assess the generalisability of the scale. Thirdly, while we implemented rigorous review procedures, interobserver variability in histological interpretation remains an inherent limitation that may influence our results. Lastly, the progression to an unfavourable outcome in IgAVN is a lengthy process that may last several decades. The median follow-up time of 33.91 months in the validation cohort might be insufficient. Future studies should incorporate more extended follow-up periods better to evaluate the progression and prognosis of patients with IgAVN.

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