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Enhancing prognostic guidance in renal light-chain amyloidosis: a new staging system incorporating pathological characters

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Abstract

Background Advancements in treatment regimens have led to improved outcomes in renal Immunoglobulin light-chain amyloidosis. Nevertheless, a subset of patients may still experience renal adverse events despite achieving hematologic very good partial response or better. This discrepancy may be attributed to the deposition pattern of amyloid in renal tissue. To enhance prognostic assessment, a staging system that incorporates both pathological characteristics and clinical indicators should be developed.

Methods Patients newly diagnosed through renal biopsy between January 1, 2017, and December 31, 2022, were included. The renal pathology of patients was evaluated according to amyloid score (AS). Risk factors for end-stage renal disease or renal progression were identified by the competing risk model, then to develop a renal staging system. The Concordance index (C-index), internal cross-validation and Decision Curve Analysis (DCA) were used to evaluate the performance of the new staging system.

Results 74 patients were included, and 16 (21.6%) patients had end-stage renal disease or renal progression within 24.7 (11.9, 50.7) months. AS and estimated glomerular filtration rate (eGFR) were identified as independent risk factors and the staging system based on them, which the C-index was 0.81 (95%CI, 0.73–0.89), had greater improvement than previous staging systems. The internal cross-validation and DCA also confirmed its great clinical benefits.

Conclusion The AS demonstrated its prognostic significance in Chinese patients, and the novel renal staging system based on AS and eGFR may provide great prognostic guidance for these patients.

Keywords Immunoglobulin light-chain amyloidosis · Prognosis · Renal pathology · Risk factor · Staging system

Introduction

Immunoglobulin light-chain (AL) amyloidosis is a plasma cell dyscrasia that is characterized by the production of monoclonal free light chains (FLCs) and misfolded amyloidogenic proteins [1]. The estimated incidence rate was 10 cases per million population with an increase in disease prevalence of 12% per year [2, 3]. All organs except for the central nervous system may be affected and up to 57%–70% of AL amyloidosis patients had renal involvement [4, 5]. Nephrotic range proteinuria is the major clinical presentation of renal AL amyloidosis patients, which may lead to end-stage renal disease (ESRD) eventually. According to previous studies, the mortality of AL amyloidosis patients with advanced cardiac involvement remained high (around 40%) in 3 months from treatment [6]. But the decreased estimated glomerular filtration rate (eGFR) only appeared in the stage of irreversible damage of amyloid protein to the kidney. Therefore, patients often face a great risk of death in the early stages of AL amyloidosis, leading to insufficient understanding of renal adverse outcomes. With the progress of treatment regimens, the outcome of AL amyloidosis has improved. However, there are still some patients who experience renal adverse outcomes despite achieving hematologic very good partial response (VGPR) or better [7, 8]. The

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reason for this phenomenon may be related to the deposition status of amyloid in renal tissue [9]. Nonetheless, the renal pathological features of AL amyloidosis patients were often overlooked.

In 2017, a novel scoring tool that quantifies the degree of amyloid deposition in the kidney was proposed by Rubinstein et al. and the amyloid score (AS) was found to be associated with progression to ESRD by a 12-month landmark analysis in a case–control study of 39 patients [10], and the correlation between AS and adverse renal outcomes was validated in another independent cohort [11]. Nevertheless, the definitive effects of AS when taking into other clinical factors and its suitability needed to be tested. In addition, the current staging systems for renal outcome in renal AL amyloidosis patients were developed without including renal pathological features [12, 13], which may ignore the value of renal pathology for guiding treatment and offering prognostic information.

Therefore, the objective of this study was to elucidate the precise significance of that pathological scoring tool in conjunction with other clinical factors and further explore a new renal prognostic staging system including pathological indicators for renal AL amyloidosis patients, thereby providing references for avoiding bad outcomes.

Methods

Patients

This study included AL amyloidosis patients with renal involvement who were newly diagnosed by renal biopsy at Xijing Hospital from January 1, 2017, to December 31, 2022. The involvement of organs was assessed according to the 10th International Symposium on Amyloid and Amyloidosis, and renal involvement was defined as 24-h urine total protein (24UTP) excretion more than 500 mg/day [14]. Patients were recruited if they had (1) symptoms of renal involvement; (2) evidence of monoclonal protein; (3) Congo red-positive fibril deposition on renal biopsy or confirmed as AL amyloidosis by mass spectrometry; (4) not been treated with anti-plasma regimens. Exclusion criteria were as follows: (1) secondary to multiple myeloma according to the criteria by the International Myeloma Working Group [15], (2) lack of renal pathological information or evidence of renal pathology indicating the presence of alternative forms of nephropathy, (3) eGFR < 15 ml/min/1.73m^2 at the confirmation of AL amyloidosis, (4) follow-up time less than 3 months unless they met the endpoint. This study was authorized by Xijing Hospital's ethics committees and review board, and informed consent was not required because of the nature of the retrospective study.

Data collection

Patients' clinical characteristics, renal pathological features, and treatment responses were extracted from the amyloidosis-specialized database. Clinical characteristics, such as demographic and laboratory examination data, were based on the results at the time of renal biopsy. All patients were regularly followed up in the amyloidosis specialist outpatient clinic at Xijing Hospital. Two experienced pathologists independently reviewed and evaluated the original renal biopsy slides of patients. Discrepancies in assessment results were resolved by discussion. If they cannot reach a unified conclusion on the pathological results, we will seek another senior pathologist to make a final judgment. To assess the effect of early treatment on the prognosis of patients, we also collected the change of the difference between involved and uninvolved free light chain (dFLC) and 24UTP at the time of two cycles of treatment.

Definition

The endpoint of this study was the occurrence of kidney events, which were ESRD or renal progression. eGFR less than 15 ml/min/1.73m^2, requiring long-term dialysis, or kidney transplantation were defined as ESRD. Progression in renal function is defined as eGFR decreased by more than 25% [16]. Time to kidney events was defined from the date of renal biopsy until ESRD or renal progression, whichever occurred first. Patients were censored if they died without kidney events at the date of death or the last follow-up until May 31, 2023. The renal pathological characters of AL amyloidosis patients was evaluated according to the AS proposed by Rubinstein et al. AS is the sum of AL amyloid deposition scores at mesangial, capillary, interstitial and vascular, which was scored on a semiquantitative scale of 0 to 3 (0 = absent, 1 ≤ 25%, 2 = 25–50% and 3 ≥ 50% of glomerular tuft) [10]. Hematologic and organ response was evaluated according to the criteria of 2023 National Comprehensive Cancer Network guidelines [16], in which the renal response (RR) is 24UTP drop more than 30% or below 0.5 g/24 h without renal progression. Patients who had kidney events within 3 months were classified as no RR. The hematologic response was defined as no response if the patient died within 3 months.

Statistical analysis

The continuous variables were presented by mean (standard deviation) or median (interquartile range), and the categorical variables were expressed as number (frequencies). The *t* test or the Mann–Whitney *U* test was performed to compare

continuous variables, and the $\chi 2$ test or the Fisher exact test was applied for categorical variables. Death due to all-causes was set as competing events for adverse kidney events. The variables had statistically significant in univariate and multivariate competing risk models (Fine-Gray subdistribution hazard model) were identified as the independent risk factors. The optimal cut-point of variables was generated according to maximally selected rank statistics (MSRS). MSRS can be used for survival analysis where the sample data does not follow a normal distribution. It also has strong robustness in studies with a small sample size. The cumulative hazard curve was made to observe the probability of kidney events in renal AL amyloidosis patients over time, and the Log-rank test was utilized to assess the differences across groups. The Concordance index (C-index) and five-fold internal cross-validation were calculated to evaluate the model's performance. Besides, the Decision Curve Analysis (DCA) was also performed to confirm the clinical benefits of different models. All statistical analyses were finished by R version 4.3.0 (R Project for Statistical Computing) and SPSS software package version 25.0 (IBM, Armonk, New York). Two-sided *P* values less than 0.05 were considered statistically significant. Specific R packages used were "cmprsk 2.2–11", "survminer 0.4.9", and "rms 6.7–0".

Results

Baseline characteristics

A total of 74 patients were included in this study among 131 AL amyloidosis patients (Fig. 1). The baseline characteristics of enrolled patients are presented in Table 1. The mean age was 57.9 ± 9.7 years. 43 (58.1%) patients were male. 58 (78.4%) patients had lambda amyloidogenic light chains. All patients had renal involvement and 47 (63.5%) patients had cardiac involvement. At diagnosis, the median eGFR and 24UTP were 87 (66.9, 101) mL/min/1.73m^2 and 3030 (1448, 4784) mg/24 h, respectively. According to Mayo 2012 staging system, 27 (36.5%), 20 (27.0%), 18 (24.3%) and 9 (12.2%) patients were in the I, II, III and IV stage. By comparison, patients who experienced kidney events had worse eGFR with higher cystatin c (CysC), n-terminal pro-brain natriuretic peptide (NT-proBNP), 24UTP and the ratio of 24UTP to eGFR. Meanwhile, they also had a greater proportion of cardiac involvement.

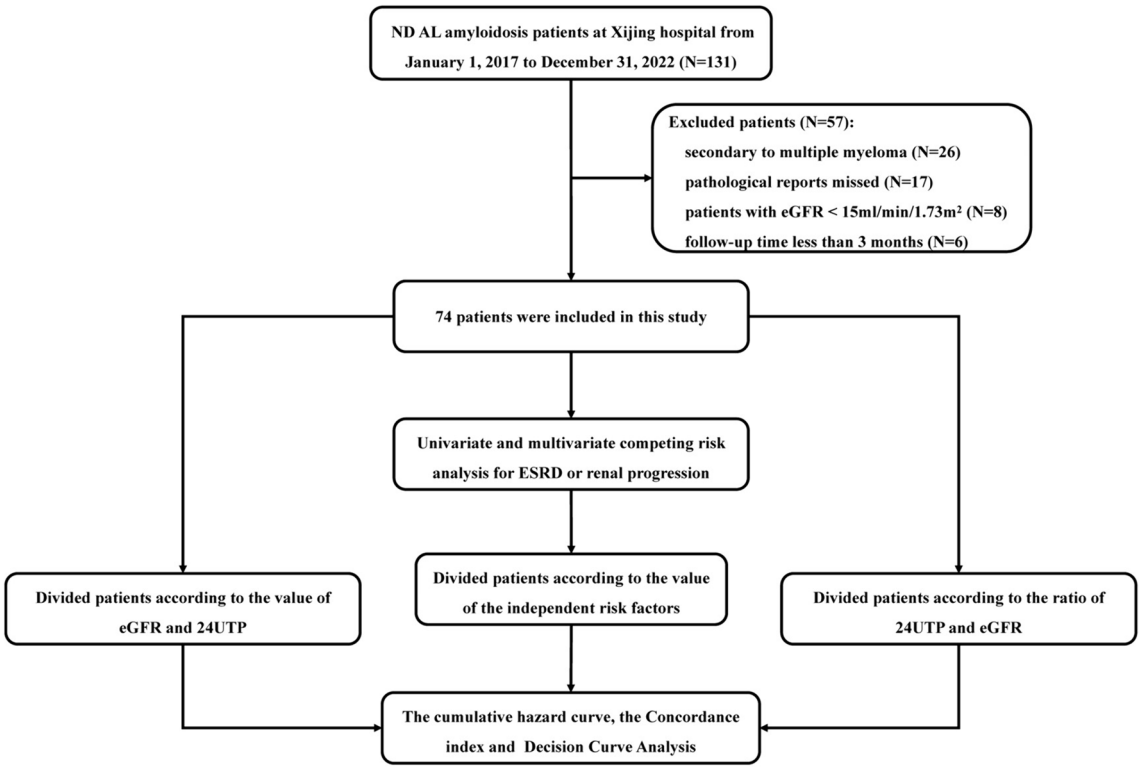

Fig. 1 Flowchart of this research. *ND AL amyloidosis* newly diagnosed immunoglobulin light-chain amyloidosis; *eGFR* estimated glomerular filtration rate; *24UTP* 24-h urine total protein; *ESRD* end-stage renal disease

Table 1 Baseline characteristics of enrolled patients

Characteristic	All patients ($N=74$)	No kidney events ($N=58$)	Kidney events ($N=16$)	P value
Age, years	57.9 (9.7)	58.0 (8.8)	57.4 (12.8)	0.878
Male, *n* (%)	43 (58.1)	36 (62.1)	7 (43.8)	0.304
Hb, g/L	129 (118, 144)	128 (119, 146)	130 (94, 140)	0.577
TBIL, μmol/L	9.4 (6.7, 13.0)	9.8 (7.4, 13.9)	8.7 (5.3, 10.7)	0.099
ALB, g/L	25.9 (20.3, 33.4)	26.1 (20.6, 34.0)	22.9 (19.3, 30.0)	0.259
ALP, IU/L	72.5 (59.2, 98.2)	72.5 (59.2, 95.2)	75.0 (58.5, 129)	0.753
CHO, mmol/L	6.09 (4.74, 7.96)	6.09 (4.73, 7.96)	5.85 (4.95, 7.87)	0.813
HDL, mmol/L	1.36 (1.08, 1.77)	1.22 (1.07, 1.77)	1.52 (1.40, 1.77)	0.200
LDL, mmol/L	3.81 (2.73, 5.11)	3.87 (2.85, 5.07)	3.54 (2.66, 5.31)	0.932
CysC, mg/L	1.27 (1.09, 1.50)	1.19 (1.07, 1.43)	1.65 (1.33, 2.11)	< 0.01
eGFR, mL/min/1.73m^2	87.0 (66.9, 101)	93.5 (74.2, 102)	59.8 (53.9, 75.5)	< 0.01
eGFR < 50, mL/min/1.73m^2	5 (6.8)	2 (3.4)	3 (18.8)	0.110
UA, μmol/L	328 (265, 402)	326 (265, 402)	336 (272, 386)	0.859
24UTP, mg/24 h	3030 (1448, 4784)	2252 (1270, 4388)	4257 (3687, 6185)	0.017
24UTP > 5000, mg/24 h	17 (23.0)	12 (20.7)	5 (31.3)	0.580
24UTP/eGFR, mg/mL/min/1.73m^2	32.6 (16.6, 66.9)	24.5 (14.5, 53.9)	61.7 (46.0, 121.9)	< 0.01
λ FLC, *n* (%)	58 (78.4)	45 (77.6)	13 (81.3)	0.999
dFLC, mg/L	103 (37.3, 154)	99.7 (36.1, 164)	108 (58.8, 128)	0.823
NT-proBNP, pg/ml	837 (161, 2685)	529 (121, 2563)	1046 (819, 6764)	0.022
cTnT, ng/ml	0.02 (0.02, 0.03)	0.02 (0.02, 0.03)	0.02 (0.02, 0.03)	0.798
LVEF	58.0 (55.0, 60.0)	58.0 (56.0, 60.0)	56.5 (54.8, 59.0)	0.241
IVST, mm	10.5 (9.00, 13.0)	10.0 (9.00, 12.9)	11.8 (9.75, 13.0)	0.345
Cardiac involvement, *n* (%)	47 (63.5)	32 (55.2)	15 (93.8)	0.005
Mayo 2012 stage				0.644
I, *n* (%)	27 (36.5)	23 (39.7)	4 (25.0)	
II, *n* (%)	20 (27.0)	14 (24.1)	6 (37.5)	
III, *n* (%)	18 (24.3)	14 (24.1)	4 (25.0)	
IV, *n* (%)	9 (12.2)	7 (12.1)	2 (12.5)	
Delay from symptom onset, months	6 (2, 12)	5 (2, 12)	9.5 (2.5, 33)	0.180
Amyloid score	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	3.00 (3.00, 4.00)	0.021
Mesangial deposition, *n* (%)	69 (93.2)	53 (91.4)	16 (1.0)	0.513
Capillary deposition, *n* (%)	6 (8.1)	5 (8.6)	1 (6.3)	0.999
Interstitial deposition, *n* (%)	31 (41.9)	20 (34.5)	11 (68.8)	0.014
Vascular deposition, *n* (%)	61 (82.4)	47 (81.0)	14 (87.5)	0.818
Hematologic VGPR or better	32 (43.2)	25 (43.1)	7 (43.8)	0.963
Renal response	32 (43.2)	29 (50.0)	3 (18.8)	0.025
VGPR or better and Renal response	18 (24.3)	16 (27.6)	2 (12.5)	0.189
Death	23 (31.1)	13 (22.4)	10 (62.5)	< 0.01

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was applied to calculate the eGFR

Hematologic and renal response were evaluated at 3 months

Hb hemoglobin; *TBIL* total bilirubin; *ALB* albumin; *ALP* alkaline phosphatase; *CHO* cholesterol; *HDL* high-density lipoprotein; *LDL* low-density lipoprotein; *CysC* cystatin c; *eGFR* estimated glomerular filtration rate; *UA* uric acid; *24UTP* 24-h urine total protein; *FLC* free light chain; *rFLC* ratio of κ and λ FLC; *dFLC* difference between involved FLC and uninvolved FLC; *NT-proBNP* n-terminal pro-brain natriuretic peptide; *cTnT* cardiac troponin t; *LVEF* left ventricular ejection fraction; *IVST* interventricular septum; *VGPR* very good partial response

Pathological features

The varied degrees of renal pathology are also presented in Fig. 2. In our cohort, the median AS was 3 (2, 4) and patients who experienced kidney events had higher AS ($P=0.021$). Mesangial was the area where amyloid deposition is most commonly found, with just 5 (6.8%) patients having no amyloid deposition there, and 33 (44.6%) patients had more than 2 + amyloid deposition. Besides, both vascular and interstitial were the common areas with mild amyloid deposition.

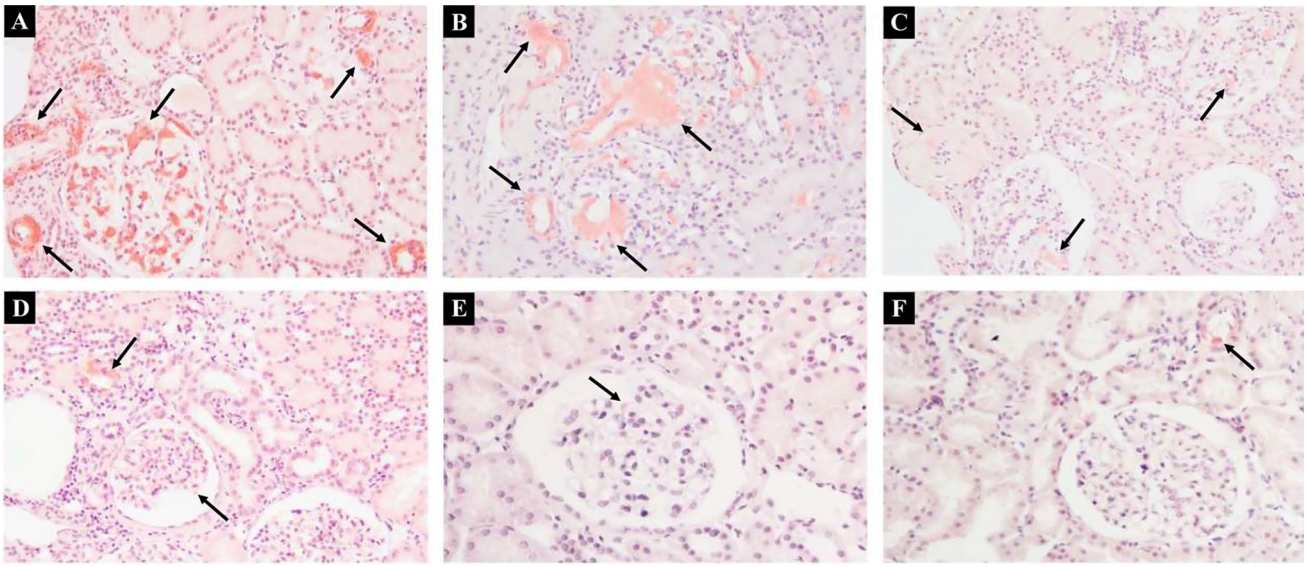

Fig. 2 Pathological results of enrolled patients. Black arrows showed Congo Red depositions. Representative slides showing the different amyloid scores. $A=7$ (200 x), $B=6$ (400 x), $C=3$ (Mesangial and interstitial, 200 x), $D=3$ (Mesangial and vascular, 200 x), $E=1$ (Mesangial, 400 x), $F=1$ (No depositions was found in Mesangial, 400 x)

Clinical outcomes

At 3 months, 32 (43.2%) patients achieved hematologic VGPR or better. There was no difference among the patients with or without kidney events in terms of that. Meanwhile, RR was also achieved in thirty-two patients. Patients who did not experience kidney events were more likely to obtain RR ($P=0.025$). Moreover, RR and hematologic VGPR or better were achieved simultaneously in 18 (24.3%) patients, and no difference observed between the two groups (Table 1). Following a median follow-up of 24.7 (11.9, 50.7) months, 23 (31.1) patients died due to disease progression and ten patients had kidney events ($P<0.01$) (Table 1). Of the 16 (21.6%) patients who had kidney events, 11 patients progressed to ESRD and 5 patients had progression in renal function. According to the competing risk model, the rate of kidney events in 12-, 36- and 60-months were 17.9%, 21.3% and 24.1%, while the incidence of death were 11.5%, 18.3% and 21.2%, respectively (Supplemental Fig. 1).

Risk factors affecting kidney events

In order to simplify the competing risk model, dFLC, NT-proBNP and cardiac troponin t (cTnT) were dichotomized according to Mayo 2012 staging system, respectively. The Spearman analysis was also conducted to remove variables with correlation coefficients greater than 0.75. Then, AS, total bilirubin, CysC, eGFR, 24UTP, Cardiac involvement and RR were selected by univariate competing risk model. Finally, AS (HR = 1.63, 95%CI 1.03–2.59, $P=0.039$) and eGFR (HR = 0.96, 95% CI 0.93–0.99, $P=0.012$) were identified as independent risk factors affecting kidney events in multivariate competing risk model (Supplemental Table 1).

The optimal thresholds estimated for AS and eGFR were 2.0 and 61.93875 mL/min/1.73m^2 according to MSRS, respectively. Then, all patients were divided into high-risk group or low-risk group based on those values, and the Kaplan–Meier curve was made. By log-rank test, we can find higher AS (Supplemental Fig. 2A), and lower eGFR (Supplemental Fig. 2B) had more chances of kidney events.

The development and validation of the novel renal staging system

A key eGFR threshold of 60 mL/min/1.73m^2 and a key threshold of 2 for AS were set to establish the renal staging system, leading to the categorization of all patients into three groups. Additionally, patients were stratified into three groups based on previous research findings [11, 12], with the outcomes summarized in Table 2. As we can see, all renal staging systems were effective in distinguishing patients with different risks for adverse kidney events. The renal staging systems formulated by Palladini et al. and our study had more power in identifying the patients with the greater probability of kidney events, while the renal staging systems proposed by Kastritis et al. and our study had a better performance in identifying patients with stable renal function.

Meanwhile, the cumulative hazard curves based on different renal staging systems are presented (Fig. 3A–C) and indicated the great performance of them. The C-index of renal staging systems proposed by Palladini et al. and

Table 2 Rate of kidney outcomes according to different staging systems

Renal staging system	Rate of kidney events			*P* value
	12-months (%)	36-months (%)	60-months (%)	
Staging system A				< 0.01
eGFR ≥ 50 and 24UTP < 5000 (*N* = 53)	13.9	16.9	21.5	
eGFR < 50 or 24UTP ≥ 5000 (*N* = 20)	26.2	33.5	33.5	
eGFR < 50 and 24UTP ≥ 5000 (*N* = 1)	100.0	100.0	100.0	
Staging system B				< 0.01
24UTP/eGFR < 30 (*N* = 35)	0.0	4.8	12.1	
24UTP/eGFR 30–99 (*N* = 29)	28.6	33.4	33.4	
24UTP/eGFR ≥ 100 (*N* = 10)	50.0	50.0	50.0	
Staging system C				< 0.01
AS ≤ 2 and eGFR ≥ 60 (*N* = 27)	0.0	0.0	0.0	
AS > 2 or eGFR < 60 (*N* = 39)	19.6	30.4	39.1	
AS > 2 and eGFR < 60 (*N* = 8)	75.0	75.0	75.0	

eGFR estimated glomerular filtration rate, mL/min/1.73m^2; *24UTP* 24-h urine total protein, mg; *AS* amyloid score

Kastritis et al. were 0.60 (95% CI, 0.47–0.74) and 0.757 (95% CI, 0.67–0.84), respectively. The renal staging system formulated by our study had a greater C-index of 0.81 (95% CI, 0.73–0.89), which meant the greater performance than both of them ($P < 0.01$). In addition, the five-fold internal cross-validation also indicated the stable C-index of renal staging system formulated by our study at 12-, 36- and 60-months (Supplemental Fig. 3). Finally, the DCA was performed to confirm the great clinical decision benefits of our renal staging system (Fig. 3D–F). At 12-months, the renal staging system proposed by Palladini et al. was most limited, while the renal staging system formulated by our study had the greatest benefit over other staging systems at 60-months.

Discussion

To the best of our knowledge, this study is the first to explore the key risk factors for adverse kidney events from renal pathological characteristics, baseline clinical indicators and early treatment responses in renal AL amyloidosis patients. By competing risk models, eGFR and AS were identified as independent risk factors for adverse kidney events. And the AS was validated in Asian renal AL amyloidosis patients. Furthermore, a novel renal staging system was developed by incorporating renal pathological characteristics, which was proven its great performance.

As the gold standard for assessing renal function, the eGFR was also identified as an independent risk factor for adverse kidney events. In individuals with renal involvement, the decreased eGFR appeared in the advanced phase of irreversible damage of FLCs to kidney and was associated with higher AS [11]. Besides, the decreased eGFR seems to be related to prerenal kidney injury brought on by cardiac involvement [17]. In our study, patients who experienced kidney events had a relatively longer delay in diagnosis, more cardiac involvement, and higher NT-proBNP levels, which was consistent with the above ideas. Hence, identification of renal AL amyloidosis as soon as possible and mitigation of the renal burden resulting from cardiac involvement may offer insights into preventing unfavorable renal outcomes.

As a rare plasma cell disorder, prognostic studies of AL amyloidosis patients with renal involvement are lacking and the specialized pathological scoring tool for these patients had not been proposed until 2017. The scoring tool proposed by Rubinstein et al. indicated that AS is useful indicators for judging the progression to ESRD in AL amyloidosis within 12 months [10]. Furthermore, AS was associated with poor renal outcomes in another study [11]. However, the effectiveness of AS in Asian patients remained to be tested. In our research, AS was also firstly validated its prognostic effect on the occurrence of renal adverse events in Chinese patients. The values of AS in our research were lower than those in previous studies, and the optimal threshold of AS for predicting adverse kidney events was only 2. According to previous research, 37% of AL amyloidosis patients were diagnosed 1 year after the onset of symptoms and 69% of patients visited 3 or more physicians before the confirmation of AL amyloidosis [18]. Therefore, correctly identifying AL amyloidosis is frequently delayed. Actually, the median delay from symptom onset to kidney biopsy was only approximately six months in our cohort, which is considerably shorter than the time required in other international studies [19], suggesting a relatively timely diagnosis and less renal damage from amyloid protein. This was also validated by the fact that patients in our cohort had better renal function than in the original study which the median eGFR was

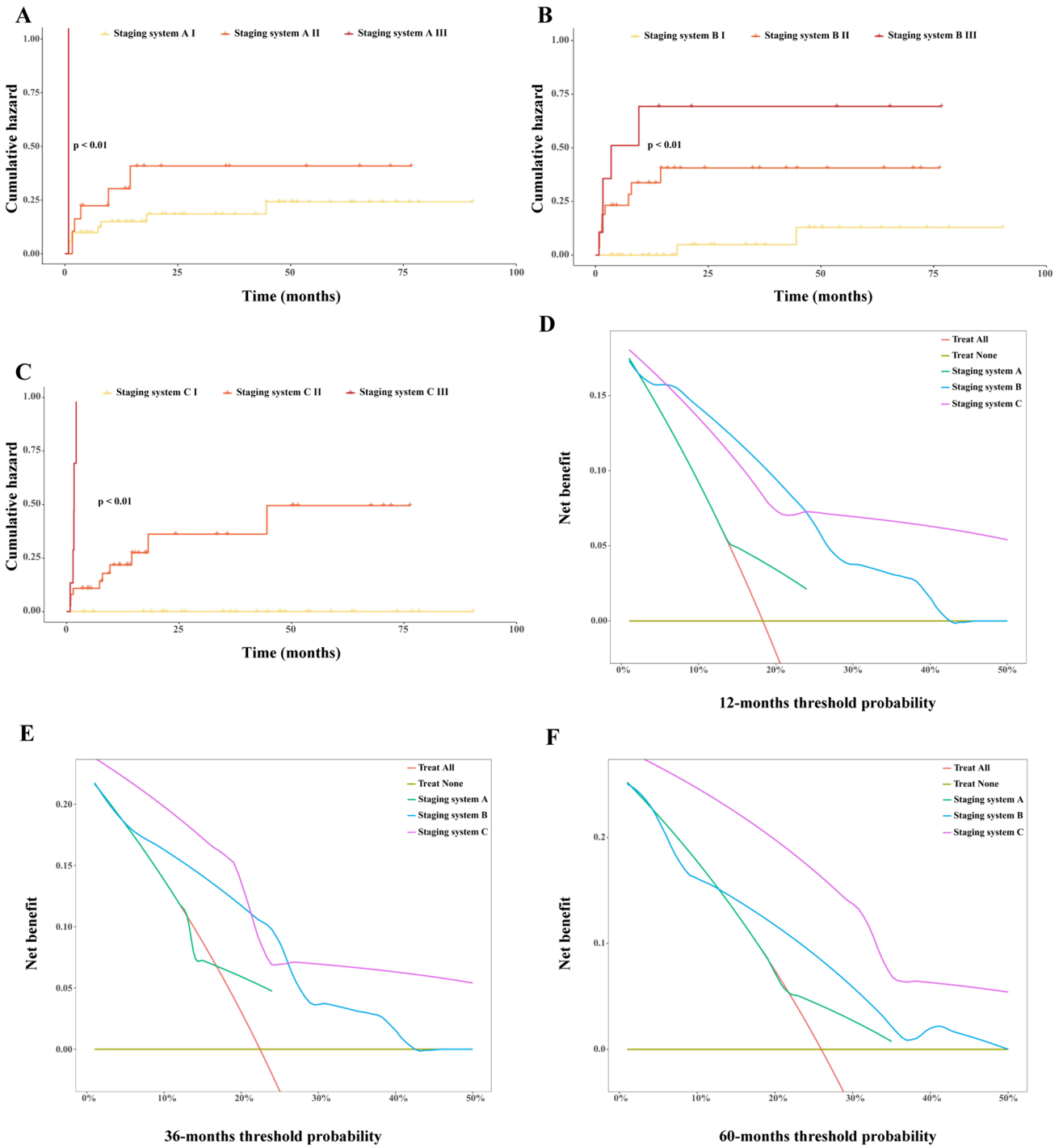

Fig. 3 The cumulative hazard curves and clinical decision curves based on different staging systems. *AS* amyloid score; *eGFR* estimated glomerular filtration rate; *24UTP* 24-h urine total protein. **A**, **B** and **C** are cumulative hazard curves of different staging systems; **D**, **E** and **F** are clinical decision curves of different staging systems. Staging system A I was defined as eGFR ≥ 50 mL/min/1.73m^2 and 24UTP < 5000 mg; Staging system A II was defined as eGFR < 50 mL/min/1.73m^2 or 24UTP ≥ 5000 mg; Staging system A III was defined as eGFR < 50 mL/min/1.73m^2 and 24UTP ≥ 5000 mg; Staging system B I was defined as 24UTP/eGFR < 30 mg/mL/min/1.73m^2; Staging system B II was defined as 24UTP/eGFR among 30-99 mg/mL/min/1.73m^2; Staging system B III was defined as 24UTP/eGFR ≥ 100 mg/mL/min/1.73m^2; Staging system C I was defined as AS ≤ 2 and eGFR ≥ 60 mL/min/1.73m^2; Staging system C II was defined as AS > 2 or eGFR < 60 mL/min/1.73m^2; Staging system C III was defined as AS > 2 and eGFR < 60 mL/min/1.73 m^2

only 61 mL/min/1.73 m^2 [10]. Besides, the kidney being the most commonly affected organ rather than the heart in China [20, 21], the popularization of renal biopsy and referral center bias may be reasonable for this discrepancy too.

Most importantly, a novel renal staging system was formulated by incorporating AS and eGFR. These two indicators used have been recognized by international peers. The eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation, which was recommended in the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [22]. As a pathological assessment tool for AL amyloidosis patients with renal involvement, AS has also been validated [11]. Therefore, we think our conclusions could be extrapolated to diverse ethnic or geographic groups. Compared with previous renal staging system based on 24UTP [12, 13], the staging system proposed by our study may prevent staging inaccuracies caused by fluctuations in 24UTP due to different test methods. By comparing C-index and DCA of our staging system and previous systems, our renal staging system proved its better performance in predicting the occurrence of ESRD or progression in renal function, helping clinical doctors make early medical decisions and taking intervention measures in advance. Besides, the threshold of eGFR in our staging system was consistent with the current criteria for the evaluation of chronic kidney disease, which further enhanced the clinical practice of our staging system.

Hematological VGPR or better has long been the therapeutic goal for patients with AL amyloidosis, but its applicability to patients with specific organ involvement has been challenged. In our cohort, hematologic VGPR or better and RR even to simultaneous RR and hematologic VGPR or better were not identified as significant factors in preventing adverse kidney events in renal AL amyloidosis patients, which underscored the damage due to amyloid deposition and scarring injury may be hard to reverse by current therapy. Nevertheless, there is currently no recommended regimen for AL patients with renal involvement. This phenomenon could potentially be attributed to the pre-existing multi-organ involvement in the majority of patients upon diagnosis. Furthermore, the organ response exhibits a considerably slower pace compared to the hematologic response, thereby prompting previous studies to refrain from designating it as the primary observation endpoint. While it is true that a more favorable hematologic response is associated with a more profound organ response [23, 24], it is imperative to acknowledge the existence of a subgroup of patients who do not derive any advantages from such hematologic response [7, 8, 25, 26]. Furthermore, renal pathology changes may persist despite hematologic improvement [9, 25, 26], implying ongoing renal damage. Consequently, it is imperative to promptly verify the effectiveness of novel therapies aimed at eliminating amyloid deposits in affected organs, such as CAEL-101 or NEOD001 [27, 28].

Meanwhile, our study also has some limitations. At first, due to the biases of single center retrospective studies and rarity of renal AL amyloidosis, the number of patients included in our study was relatively modest with no external validation. However, the reliability of our study was ensured by regular follow-up, strict data management, and internal cross-validation. In addition, as we mentioned above, our cohort had a relatively low degree of renal burden and the threshold for pathology score was derived to be lower than that of other studies. To obtain the most accurate threshold, a prospective study with a large cohort of patients from multi-center was taken into the agenda. Eventually, our study shifted its focus towards ESRD or renal progression, rather than solely on the occurrence of ESRD. As a result, our staging system may exhibit limited predictive performance compared to the previous staging system in forecasting ESRD.

Conclusion

Our study identified risk factors from renal pathological characteristics, baseline clinical indicators, and early treatment responses for the occurrence of adverse kidney events in renal AL amyloidosis patients. Specifically, we found that only AS and eGFR were independent risk factors. Furthermore, a novel renal staging system based on AS and eGFR was formulated, which may provide prognostic guidance for these patients.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval The studies involving human participants were reviewed and approved by the Ethics Committee of Xijing Hospital (ethical number: KY20213027-1). In addition, this study was conducted in accordance with the standards of the 1964 Declaration of Helsinki and its later revisions or comparable ethical standards.

Informed consent Informed consent was not required because of the nature of the retrospective study.

References

1. Zanwar S, Gertz MA, Muchtar E (2023) Immunoglobulin light chain amyloidosis: diagnosis and risk assessment. J Natl Compr Canc Netw 21(1):83–90
2. Quock TP, Yan T, Chang E et al (2018) Epidemiology of AL amyloidosis: a real-world study using US claims data. Blood Adv 2(10):1046–1053
3. Kumar N, Zhang NJ, Cherepanov D et al (2022) Global epidemiology of amyloid light-chain amyloidosis. Orphanet J Rare Dis 17(1):278
4. Gertz MA, Dispenzieri A (2020) Systemic amyloidosis recognition, prognosis, and therapy: a systematic review. JAMA 324(1):79–89
5. Varga C, Dorbala S, Lousada I et al (2021) The diagnostic challenges of cardiac amyloidosis: a practical approach to the two main types. Blood Rev 45:100720
6. Palladini G, Schönland S, Merlini G et al (2023) The management of light chain (AL) amyloidosis in Europe: clinical characteristics, treatment patterns, and efficacy outcomes between 2004 and 2018. Blood Cancer J 13(1):19
7. Zhang P, Chen X, Zou Y et al (2022) Value of repeat renal biopsy in the evaluation of AL amyloidosis patients lacking renal response despite of complete hematologic remission: a case report and literature review. BMC Nephrol 23(1):127
8. Sloan JM (2019) Lessons in long term survival from AL amyloidosis. Br J Haematol 187(5):557–558
9. Angel-Korman A, Jaberi A, Sanchorawala V et al (2020) The utility of repeat kidney biopsy in systemic immunoglobulin light chain amyloidosis. Amyloid 27(1):17–24
10. Rubinstein S, Cornell RF, Du L et al (2017) Novel pathologic scoring tools predict end-stage kidney disease in light chain (AL) amyloidosis. Amyloid 24(3):205–211
11. Hoelbeek JJ, Kers J, Steenbergen EJ et al (2021) Renal amyloidosis: validation of a proposed histological scoring system in an independent cohort. Clin Kidney J 14(3):855–862
12. Palladini G, Hegenbart U, Milani P et al (2014) A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. Blood 124(15):2325–2332
13. Kastritis E, Gavriatopoulou M, Roussou M et al (2017) Renal outcomes in patients with AL amyloidosis: Prognostic factors, renal response and the impact of therapy. Am J Hematol 92(7):632–639
14. Gertz MA, Comenzo R, Falk RH et al (2005) Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th international symposium on amyloid and amyloidosis, Tours, France, 18–22 April 2004. Am J Hematol 79(4):319–328
15. Rajkumar SV, Dimopoulos MA, Palumbo A et al (2014) International myeloma working group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 15(12):e538–e548
16. Kumar SK, Callander NS, Adekola K, et al. Systemic Light Chain Amyloidosis, Version 2.2023, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2023;21(1):67–81.
17. Dittrich T, Benner A, Kimmich C et al (2019) Performance analysis of AL amyloidosis cardiac biomarker staging systems with special focus on renal failure and atrial arrhythmia. Haematologica 104(7):1451–1459
18. Lousada I, Comenzo RL, Landau H et al (2015) Light chain amyloidosis: patient experience survey from the amyloidosis research consortium. Adv Ther 32(10):920–928
19. Hester LL, Gifkins DM, K MB et al (2021) Diagnostic delay and characterization of the clinical prodrome in AL amyloidosis among 1523 US adults diagnosed between 2001 and 2019. Eur J Haematol 107(4):428–435
20. Chen M, Liu J, Wang X et al (2023) Diagnosis for Chinese patients with light chain amyloidosis: a scoping review. Ann Med 55(1):2227425
21. Xie W, Wang Q, Zhou F et al (2023) Clinical characteristics and prognosis of a Chinese cohort with systemic light chain amyloidosis: a single-center study. Int J Hematol 118(2):231–241
22. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2024) KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int 105(4):117–314
23. Muchtar E, Dispenzieri A, Leung N et al (2018) Depth of organ response in AL amyloidosis is associated with improved survival: grading the organ response criteria. Leukemia 32(10):2240–2249
24. Manwani R, Cohen O, Sharpley F et al (2019) A prospective observational study of 915 patients with systemic AL amyloidosis treated with upfront bortezomib. Blood 134(25):2271–2280
25. Okuyama H, Yamaya H, Fukusima T et al (2013) A patient with persistent renal AL amyloid deposition after clinical remission by HDM/SCT therapy. Clin Nephrol 79(3):233–236
26. Zeier M, Perz J, Linke RP et al (2003) No regression of renal AL amyloid in monoclonal gammopathy after successful autologous blood stem cell transplantation and significant clinical improvement. Nephrol Dial Transplant 18(12):2644–2647
27. Edwards CV, Rao N, Bhutani D et al (2021) Phase 1a/b study of monoclonal antibody CAEL-101 (11–1F4) in patients with AL amyloidosis. Blood 138(25):2632–2641
28. Huart A (2023) Birtamimab: a new amyloidosis treatment? Blood 142(14):1178–1180