# Relationship Between Severity of Renal Amyloid Deposition and Clinical Outcomes in Non-AA Amyloidosis

Aygül Çeltik[1] , Sait Şen[2] , Fatma Keklik Karadağ[1] , Güray Saydam[1] , Gülay Aşçı[1] ,
Banu Sarsık Kumbaracı[2] , Mehmet Özkahya[1] , Hüseyin Töz[1]

[1]Department of Internal Medicine, Division of Nephrology, Ege University, Faculty of Medicine, İzmir, Türkiye
[2]Department of Pathology, Ege University, Faculty of Medicine, İzmir, Türkiye

**ABSTRACT**

**Objective:** Renal involvement is a common manifestation of systemic amyloidosis. Amyloid load can be predicted by histopathological grading of amyloid deposits in renal biopsy specimens. This study aimed to determine the relationship of renal amyloid deposition grade with clinical manifestations and outcomes in patients with biopsy-proven renal non-AA amyloidosis.

**Methods:** This retrospective cohort study included 74 subjects with renal non-AA amyloidosis (52 light chain amyloidosis and 22 unclassified amyloidosis). Baseline characteristics and follow-up data were recorded. Pattern and quantity of amyloid deposition in glomeruli, interstitium, vessels, and tubulointerstitial changes were scored. Renal Amyloid Prognostic Score was obtained by addition of all scores and divided into 3 grades (Renal Amyloid Prognostic Score grades I, II, III).

**Results:** In light chain amyloidosis group, the median follow-up was 11 (4-45) months. The baseline estimated glomerular filtration rate was significantly lower among patients with Renal Amyloid Prognostic Score grade III. Death-censored Renal survival was significantly lower among patients with Renal Amyloid Prognostic Score grade III. Renal Amyloid Prognostic Score grade III was a significant predictor of lower renal survival. Patient survival was not significantly different according to Renal Amyloid Prognostic Score grade. Receiving autologous stem cell transplantation treatment was associated with better patient survival. The type of amyloid could not be determined in 22 patients. In this group, baseline estimated glomerular filtration rate was significantly lower in patients with Renal Amyloid Prognostic Score grade III.

**Conclusions:** In patients with light chain amyloidosis, baseline renal function is associated with Renal Amyloid Prognostic Score grade. Renal survival is significantly lower in patients with the highest Renal Amyloid Prognostic Score grade. However, patient survival is not significantly different according to Renal Amyloid Prognostic Score grade.

**Keywords:** AL amyloidosis, grading, renal biopsy, prognosis

## INTRODUCTION

Amyloidosis is characterized by the deposition of insoluble amyloid fibrils in various organs.[1] The most common types are immunoglobulin-related amyloidosis and amyloid A (AA) amyloidosis. Immunoglobulin-related amyloidosis is caused by malignant plasma cell clone-producing amyloidogenic light chains (AL amyloidosis) and rarely heavy chain (AH amyloidosis) or both (AHL).[2] Classification of renal amyloidosis is based on these precursor proteins. The most definitive methods for the detection of amyloid type are immunofluorescence and immunohistochemistry. However, accurate identification of amyloid types could not be done in 3-16% of cases using these traditional methods.[3,4] For these cases, laser microdissection/mass spectrometry is used in some tertiary centers. These cases were mainly diagnosed as AL, AA, and ALECT2 (leukocyte chemotactic factor 2) after evaluation with mass spectrometry.[3]

In Türkiye AA amyloidosis is relatively more common among patients with systemic amyloidosis when compared to AL amyloidosis. The underlying reason may be higher incidence of rheumatologic diseases (particularly FMF) and chronic infections, as well as ethnic differences.[5,6]

Amyloidogenic precursor proteins aggregate extracellularly, disturb the structure of tissues and subsequently the functions of affected organs. The type of affected organ and degree of amyloid accumulation may determine clinical manifestations and outcomes.[7] Renal involvement is common and presents with proteinuria and renal failure. It is a major determinant of morbidity and mortality.[8] Relationship between amount and localization of amyloid deposits and clinical findings, morbidity, and mortality was evaluated previously. Results were conflicting due to a lack of standardized methods for the assessment of renal involvement.[9-12]

In order to standardize the histopathological evaluation and grading of renal amyloidosis, a scoring and grading system was defined to evaluate the pattern and quantity of amyloid deposition in each compartment of the renal together with tubulointerstitial changes.[6] In this study, our aim was to investigate the association of baseline clinical manifestations and outcomes with the renal amyloid prognostic score and grade in patients with renal non-AA amyloidosis.

### METHODS

Our study is a retrospective cohort study that included subjects with biopsy-proven renal non-AA amyloidosis. All native renal biopsies obtained between January 2005 and December 2019 were retrospectively reviewed. We identified 92 subjects with renal non-AA amyloidosis. Of 92 subjects, 18 patients were excluded: 14 were referred from other hospitals and 4 had inadequate data. Demographic findings including age and gender; laboratory data including serum creatinine, serum albumin, 24-hour urine protein or spot urine protein/creatinine ratio, and bone marrow biopsy findings at the time of renal biopsy were recorded from electronic medical reports. Treatment regimens and outcome data were obtained.

All renal biopsy specimens were obtained by ultrasound-guided needle-biopsy, embedded in paraffin, and cut into 4-6 μm sections. The sections were stained with hematoxylin and eosin, periodic acid–Schiff, Masson's trichrome, Jones methamine silver, and Congo red and evaluated by light microscopy (LM). For immunohistochemical (IHC) evaluation, paraffin-embedded tissue sections were stained with antibodies to AA, fibrinogen alpha, transthyretin, kappa, lambda, and lysosome by a fully automated device (Benchmark XT, Ventana Medical Systems, Tucson, Ariz, USA). Cryosections were stained with polyclonal FITC-conjugated antibodies to kappa, lambda, immunoglobulin (Ig)G, IgA, IgM, C1q, C3c, and fibrinogen (1/20 dilution, DAKO, Glostrup, Denmark) for immunofluorescence microscopy (IF).

Congo red stain was performed for the detection of amyloid deposits and assessed by LM. Amyloid was identified as eosinophilic deposits which demonstrated apple-green birefringence under polarized light (Figure 1). AL amyloidosis was determined by IF, IHC, and laboratory findings. Unclassified (UC) amyloidosis was defined when IHC and IF revealed equivocal or inconclusive results together with laboratory findings. All biopsies were evaluated according to the renal amyloidosis scoring and grading system previously described by Sen and Sarsik.[6] Pattern and quantity of amyloid deposition in glomeruli, interstitium, vessels, and tubulointerstitial changes were scored (Table 1 and 2). By adding all scores of glomerular, vascular, and tubulointerstitial involvement, a renal amyloid prognostic score (RAPS) was obtained.
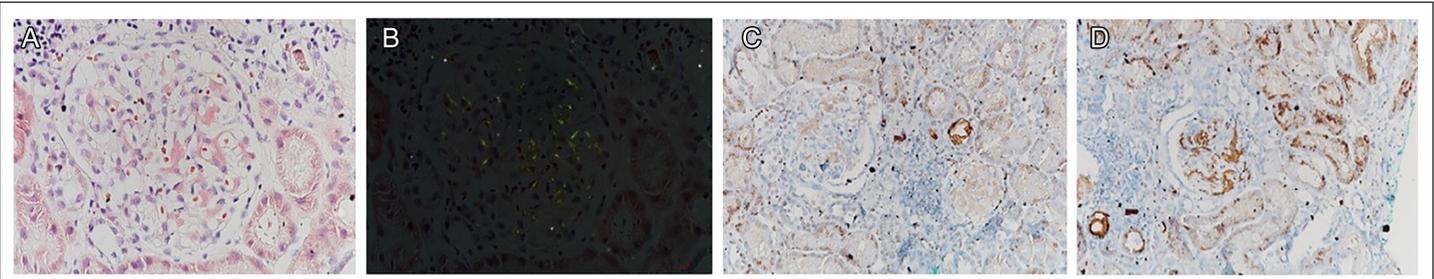
All patients with AL amyloidosis underwent bone marrow aspiration and biopsy with Jamshidi needles from the iliac crest. After fixation with Hollant, bone marrow biopsy specimen was stained with hematoxylin and eosin, Congo red, and periodic acid–Schiff reagent. Immunohistochemical analysis was done with Ventana automatic machine for kappa, lambda, and immunoglobulins. Plasma cell monoclonality was defined as a $\kappa/\lambda$ ratio of more than 3 ($\kappa$ clone) or less than 1 ($\lambda$ clone). Plasma cell percentages were assessed on immunoperoxidase-stained sections for $\kappa$ and $\lambda$ immunoglobulins and Wright–Giemsa-stained aspirate smears. Amyloid deposits were stained Congo red and detected by apple-green birefringence under polarized light. Multiple myeloma was diagnosed according to International Myeloma Working Group criteria.[13]

The estimated glomerular filtration rate (eGFR) was calculated by using CKD-EPI equation.[14] End-stage renal disease (ESKD) was defined as a requirement of renal replacement therapy (KRT).

Primary outcomes were renal and patient survival. The follow-up period was defined as the duration from renal biopsy to last visit or death. Renal survival was calculated from the date of biopsy to the initiation of KRT. Patients who died without requiring KRT were censored for analysis of renal survival (death-censored renal survival).

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### MAIN POINTS

- In patients with light chain amyloidosis, renal function at the time of biopsy was inversely associated with RAPS grade.
- Renal survival was lower among patients with the highest RAPS grade.
- Patient survival was not associated with RAPS grade in patients with light chain amyloidosis.

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**Figure 1.** Glomerular amyloid deposits are stained with Congo red (A) and show apple-green birefringence under polarized light (B). Immunohistochemical stain is negative for kappa light chain (C) and positive for lambda chain (D). All images were taken at 200×.

## Statistical Analysis

Categorical variables were presented as percentages and compared with the chi-square test. Normality of distribution was assessed using the Kolmogorov–Smirnov test. Continuous variables were presented as mean ± standard deviation or median and interquartile ranges. Continuous variables were compared with one-way analysis of variance or Mann–Whitney *U* test according to the distribution of normality. Ordinary regression analysis was performed for estimating the relationship between age, gender, baseline eGFR, proteinuria, and RAPS grade. Kaplan–Meier analysis was used for the evaluation of death-censored renal survival and patient survival. Cox-regression analyses adjusted by age, gender, baseline GFR, baseline proteinuria, treatment regimens, and RAPS grade were applied for the evaluation of risk factors for death-censored renal survival and patient survival. A *P* value <.05 was statistically significant. All statistics were performed with Statistical Package of Social Science software version 14.0 for Windows.

## RESULTS

Among 74 patients, 52 had AL amyloidosis. In 22 patients, amyloid deposition was unclassified (UC amyloidosis). Baseline characteristics and clinical findings are presented in Table 3.

## AL Amyloidosis

### Baseline Clinical Findings

The mean age of the patients was 60 ± 10 years. Twenty-five patients were male. Median eGFR and proteinuria were 66 (24-99) mL/min/1.73 m$^2$ and 6.0 (3.7-9.8) g/day, respectively (Table 4).

All patients had a bone marrow biopsy. All except two patients were diagnosed with AL amyloidosis by a renal biopsy initially and bone marrow evaluation was done subsequently. Thirteen patients were diagnosed with multiple myeloma. Amyloid deposits were also detected in bone marrow biopsies of 34 patients.

Patients were divided into 3 groups according to RAPS grade. At the time of diagnosis, baseline eGFR was significantly lower among patients with RAPS grade III when compared to patients with RAPS grade I (*P* = .002). Serum albumin and proteinuria were not significantly different according to RAPS grades (*P* = .913 and *P* = .098, respectively). In ordinary regression analysis adjusted by age, gender, and proteinuria, eGFR was significantly associated with RAPS grade III (hazard ratio = 0.97, 95% CI: 0.95-0.99, *P* = .009).

**Table 1.** Scoring of Histopathological Findings in Renal Biopsies

| Definition | Abbreviation | Definition | Score |
|---|---|---|---|
| Class of glomerular amyloid deposition | GAP | 0: absent, 1: hilar, 2: minimal mesangial, 3: focal mesangial, 4: mesangiocapillary, 5: membranous, 6: global sclerotic | 0-6 |
| Percentage of glomerular amyloid deposition | GA | 0: absent, 1: 1%-10%, 2: 11%-25%, 3: 26%-50%, 4: 51%-75%, 5: 76%-100% | 0-5 |
| Vascular amyloid deposition | VA | 0: absent, 1: minimal 2: focal, 3: moderate, 4: severe | 0-4 |
| Interstitial amyloid deposition | IA | 0: absent, 1: minimal 2: focal, 3: moderate, 4: severe | 0-4 |
| Interstitial fibrosis and tubular atrophy | Ifib | 0: absent, 1: 1%-10%, 2: 11%-25%, 3: 26%-50%, 4: 51%-100% | 0-4 |
| Interstitial inflammatory infiltration | Iinf | 0: absent, 1: 1%-10%, 2: 11%-25%, 3: 26%-50%, 4: 51%-100% | 0-4 |
| Glomerular sclerosis | GS | 0: absent, 1: 1%-10%, 2: 11%-25%, 3: 26%-50%, 4: 51%-100% | 0-4 |

**Table 2.** Renal Amyloid Prognostic Score (RAPS) and Grades

| Grades | Definition | RAPS (GAP+GA%+VA+IA +Ifib+Iinf+GS) |
|---|---|---|
| I | Early renal amyloidosis | 1-7 |
| II | Late renal amyloidosis | 8-15 |
| III | Advanced renal amyloidosis | 16 or higher |
| RAPS, renal Amyloid Prognostic Score. | | |

## Follow-Up Data

Seventeen patients had autologous stem cell transplantation (ASCT) with a melphalan-based conditioning regimen (melphalan 200 mg/m$^2$ or 140 mg/m$^2$/day), and 29 patients were treated with bortezomib-based regimens. Six patients could not receive chemotherapy due to comorbidities and poor performance status. Distributions of RAPS grades were not different between the patients who underwent ASCT and who received a bortezomib-based treatment regimen only.

The median follow-up was 11 (4-45) months. Twelve patients developed ESKD at a median of 7 (2-28) months and all underwent hemodialysis. Median baseline eGFR was 35 (10-83) mL/min/1.73 m$^2$ for patients who developed ESKD and 68 (36-103) mL/min/1.73 m$^2$ for patients who did not develop ESKD ($P$ = .041). Renal Amyloid Prognostic Score grade was III in 13% of patients who did not develop ESKD and in 50% of patients who progressed to ESKD.

Death-censored renal survival rates were 64%, 77%, and 45% for RAPS grades I, II, and III, respectively (Figure 2). Renal survival

**Table 3.** Baseline Clinical Findings and Follow-Up Data of All Patients

| | AL Amyloidosis (n = 52) | UC Amyloidosis (n = 22) |
|---|---|---|
| Baseline characteristics | | |
| Age (years) | 60 ± 10 | 60 ± 14 |
| Gender (male) (n, %) | 25 (48) | 10 (45.4) |
| Serum creatinine (mg/dL) | 1.02 (0.74-2.42) | 3.66 (1.52-5.84) |
| eGFR (mL/min/1.73 m$^2$) | 66 (24-99) | 14 (10-37) |
| Serum albumin (g/dL) | 2.5 (2.3-3.1) | 2.5 (2.1-3.1) |
| Proteinuria (g/day) | 6.0 (3.7-9.8) | 6.0 (4.2-9.9) |
| Outcome | | |
| Follow-up (months) | 11 (4-45) | 23 (7-53) |
| Requirement of RRT | 23.1% | 68.1% |
| Patient survival at fifth year | 30.9% | 24.8% |

Data are expressed as mean ± standard deviation, median (interquartile range), n (%). AL, amyloidosis, eGFR, estimated glomerular filtration rate; light-chain amyloidosis; UC, amyloidosis, unclassified amyloidosis; KRT, renal replacement therapy.

**Table 4.** Baseline Demographical Features and Clinical Findings of Patients with AL Amyloidosis

| | RAPS Grade I (n = 15) | RAPS Grade II (n = 26) | RAPS Grade III (n = 11) | P |
|---|---|---|---|---|
| Age (years) | 58 ± 12 | 60 ± 10 | 63 ± 9 | .479 |
| Gender (male) (n, %) | 8 (53.3) | 10 (38.4) | 7 (63.6) | .334 |
| Serum creatinine (mg/dL) | 0.89 (0.70-1.18) | 0.94 (0.70-2.93) | 2.28 (1.26-3.95) | .024* |
| eGFR (mL/min/1.73 m$^2$) | 91 (49-106) | 67 (22-101) | 27 (11-66) | .029** |
| Serum albumin (g/dL) | 2.5 (2.3-3.2) | 2.6 (2.2-3.1) | 2.5 (1.8-3.1) | .913 |
| Proteinuria (g/day) | 5.9 (4.4-11.4) | 5.2 (1.5-8.3) | 8.3 (5.0-13.6) | .098 |

*$P$ = .002 for grade I vs. III, **$P$ = .005 for grade I vs. III
Data are expressed as mean ± standard deviation, median (interquartile range), n (%). AL, amyloid light chain eGFR, estimated glomerular filtration rate; light chain amyloidosis; RAPS, Renal Amyloid Prognostic Score.
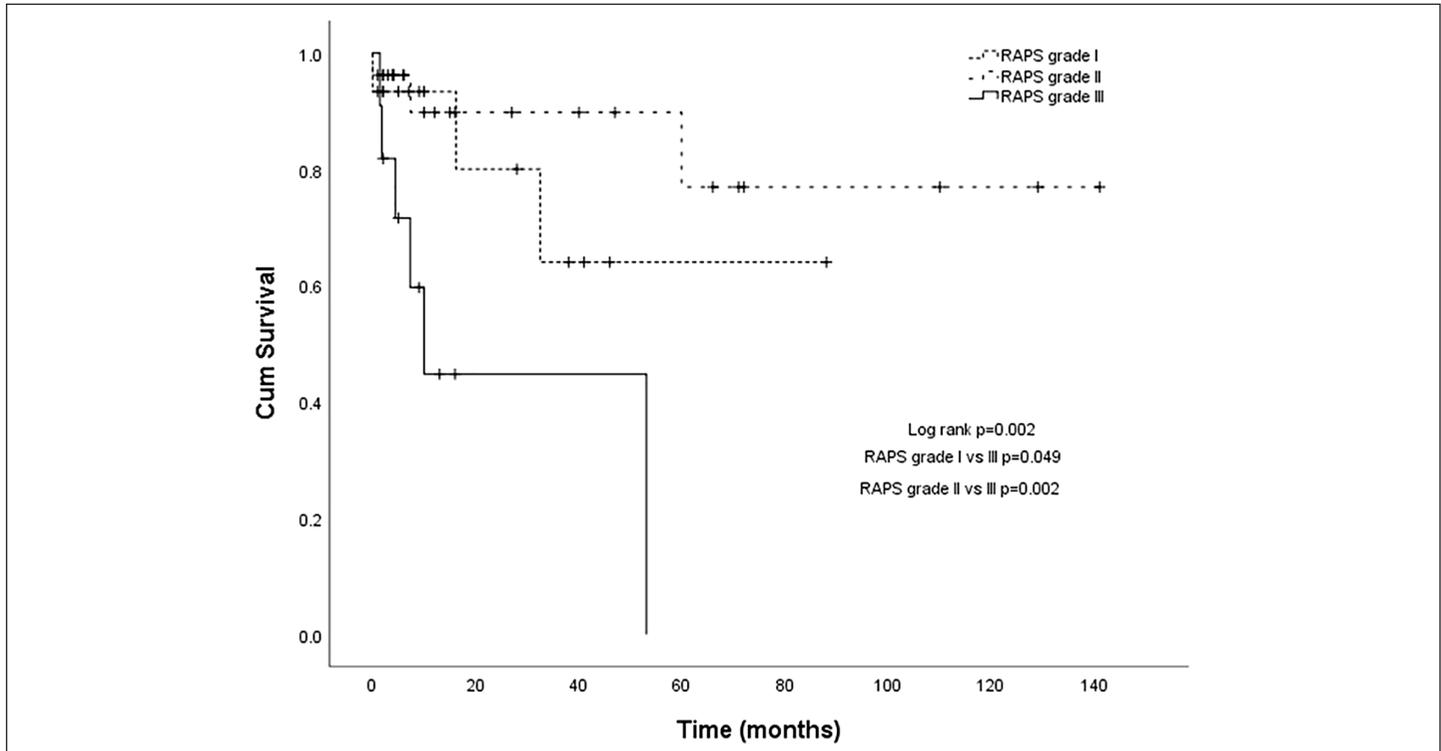
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rate was significantly lower among patients with RAPS grade III when compared to those with RAPS grades I and II ($P$ = .002). Patients who underwent ASCT had better renal survival when compared to those who received CT ($P$ = .049). In Cox regression analysis adjusted by age, gender, baseline eGFR, baseline proteinuria, different treatment regimens (ASCT or CT), and RAPS grade, RAPS grade III was associated with lower renal survival rate (RR: 7.47, 95% CI 1.37-40.3, $P$ = .02).

Patient survival rates were 37%, 25%, and 24% for RAPS grades I, II, and III during follow-up, respectively ($P$ = .575). The survival of patients who underwent ASCT was better than those who received bortezomib-based regimens ($P$ = .013). Cox regression analysis adjusted by age, gender, baseline eGFR, proteinuria, RAPS grade, and treatment regimens for patient survival showed that only receiving ASCT treatment was associated with better patient survival (RR: 0.41, 95% CI 0.17-0.98, $P$ = .04).

## UC Amyloidosis

In 22 patients, amyloid deposits were not classified. The mean age was 60 ± 14 years. Ten patients were male. At the time of biopsy, median serum creatinine and proteinuria were 3.66 (1.52-5.84) mg/dL and 6.0 (4.2-9.9) g/day, respectively (Table 5). There were seven patients with RAPS grade II and 15 patients with RAPS grade III. Baseline eGFR was significantly lower among patients with RAPS grade III ($P$ = .012). Baseline proteinuria levels were not significantly different according to RAPS grade ($P$ = .227).

The median follow-up was 23 (7-53) months. Among seven patients with RAPS grade II, only two patients required KRT and

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**Figure 2.** Death-censored renal survival according to RAPS grades in AL amyloidosis group. AL, amyloid light chain; RAPS, Renal Amyloid Prognostic Score.

both underwent KRT at the time of diagnosis. Out of 15 patients with RAPS grade III, 13 underwent KRT (11 patients started KRT within the first month of diagnosis and the other two patients underwent dialysis at 2 and 25 months after diagnosis). The patient survival was 59.2 % in first year and 24.8% in fifth year.

## DISCUSSION

We retrospectively evaluated clinical findings and outcomes of patients with biopsy-proven renal non-AA amyloidosis (52 AL and 22 unclassified amyloidosis). The relationship between these parameters and a histopathological scoring and grading system was assessed. We demonstrated that increased RAPS

grade was correlated with lower baseline eGFR but not with baseline proteinuria in patients with AL amyloidosis. Renal survival was associated with the severity of renal amyloidosis, whereas patient survival was not in AL amyloidosis group.

In amyloidosis, amyloidogenic precursors undergo extracellular misfolding and aggregation into amyloid fibrils in affected organs. The rate of aggregation depends on the plasma concentration of precursor proteins which is determined by secretion and turnover. Amyloid deposits lead to the malfunctioning of organs primarily by disturbing the structure of tissues.[7,15] Therefore, amyloid load which can be defined as degree, pattern, and localization of amyloid deposition in renal biopsy specimen may correlate with the severity of clinical manifestations. In our study, we evaluated renal amyloid load according to a histopathological scoring and grading system. The grading system was associated with renal function and outcome in patients with AA amyloidosis.[16] Baseline eGFR was lower in patients with RAPS grade III; however, proteinuria was not different according to RAPS grade in AL amyloidosis group. In some previous studies, amyloid load was associated with the degree of renal failure and proteinuria at the time of diagnosis. Amyloid-positive area in renal tissue was associated with renal function in patients with AL amyloidosis.[11] Yao et al[12] found that the amount of glomerular AL amyloid was positively associated with proteinuria and renal failure.

In retrospective studies, baseline eGFR and proteinuria were associated with outcomes in AL amyloidosis. Castano

**Table 5.** Baseline Demographical Features and Clinical Findings of Patients with UC Amyloidosis

|  | RAPS Grade II (n = 7) | RAPS Grade III (n = 15) | P |
|---|---|---|---|
| Age (years) | 58 ± 13 | 60 ± 15 | .763 |
| Gender (male) (n, %) | 5 (71.4) | 5 (33.3) | .095 |
| Serum creatinine (mg/dL) | 1.59 (0.90-4.16) | 3.89 (2.92-6.18) | .032 |
| eGFR (mL/min/1.73 m²) | 35 (16-90) | 14 (9-21) | .012 |
| Serum albumin (g/dL) | 2.2 (1.9-2.4) | 2.8 (2.1-3.2) | .083 |
| Proteinuria (g/day) | 8.4 (5.1-10.3) | 5.1 (3.8-9.0) | .227 |

Data are expressed as mean ± standard deviation, median (interquartile range), n (%). eGFR, estimated glomerular filtration rate; RAPS, Renal Amyloid Prognostic Score; UC amyloidoisis, unclassified amyloidosis.

et al[9] showed that severe glomerular amyloid deposition is indicative of poor patient survival among 35 patients with AA and AL amyloidosis. The risk for overall death increased as the renal amyloid load increased.[12] An overall amyloid score was strongly correlated with the development of ESKD among 39 patients with renal AL amyloidosis.[17] Recently, 2 clinical renal staging systems based on eGFR and proteinuria were validated for AL amyloidosis. Both demonstrated that decreased eGFR and increased proteinuria were predictors of poor renal outcomes. However, the renal staging was not significantly associated with patients' survival.[18-20] It is reasonable to assume that renal amyloid load may be correlated with the severity of renal staging and be a predictor of renal and patient survival. Histopathological grading of amyloid load can be interpreted easily by the evaluation of renal biopsies. However, histopathological evaluation of renal biopsies has not been incorporated into previous clinical staging systems for AL amyloidosis.[18,19] In our study, RAPS grade includes overall amyloid load and tubulointerstitial changes. Patients with highest RAPS grade had the worst renal survival. At the time of diagnosis, renal histopathological amyloid grading may be useful for predicting renal outcomes along with clinical and laboratory findings. In contrast, we did not demonstrate a relationship with patient survival, indicating that the degree of amyloid burden in the renal does not have a major prognostic impact on the survival of patients with AL amyloidosis. However, receiving ASCT was associated with better patient survival. In AL amyloidosis, patient outcome is mainly influenced by many factors such as age, co-morbidities, and extrarenal organ involvement including heart and treatment modalities.

The classification of systemic amyloidosis is based on the precursor proteins that are essential for treatment and prognosis. The most definitive methods for the determination of amyloid type are IHC and IF, but the distinction between amyloid types may still be difficult in some cases. IF microscopy staining can be negative for immunoglobulins with deleted or modified epitopes.[21] Additionally, amyloid deposits occasionally exhibit non-specific immunostaining due to contamination with serum proteins, interaction of reagent and amyloid proteins, or humoral reaction against amyloid fibrils.[22,23] In previous studies, the amyloid type could not be determined in 3%-16% of cases.[3,4] In our cohort, IF, IHC and laboratory findings, of patients were inadequate to determine amyloidosis type in 22 patients. In a previous study, 15.6% of cases were evaluated with mass spectrometry and 45% of them had AL, 17% had ALECT2, and 12% had AA amyloidosis.[3] Immunoglobulin-related or AA amyloidosis is likely to account for most cases in the UC group. In nearly 70% of patients with UC amyloidosis, RASPS grade was III, suggesting that they were diagnosed at an advanced stage. Therefore, nearly 60% of them required KRT within the first month of diagnosis.

This study has several limitations. Small sample size and retrospective design are the main limitations. We could not classify amyloidosis in 22 patients due to lack of mass spectrometry which is the gold standard for the typing of amyloidosis. We were unable to diagnose ALECT2 amyloidosis in our study. Patients with advanced glomerular amyloid deposits might have AFib amyloidosis, but fibrinogen staining was negative. In addition, interstitial dominant amyloid deposits compatible with AApo amyloidosis were not detected in our cohort.

## CONCLUSIONS

The degree of amyloid load in the renal is associated with baseline eGFR in patients with AL amyloidosis. RAPS grade is significantly associated with the progression of ESKD but not associated with patients' survival in AL amyloidosis. Histopathological findings in renal biopsy may be considered for the prediction of renal survival in AL amyloidosis patients with renal involvement.

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