Revised renal stratification and progression models for predicting long-term renal outcomes in immunoglobulin light chain amyloidosis

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Received: February 27, 2025.
Accepted: June 5, 2025.
Early view: June 26, 2025.

https://doi.org/10.3324/haematol.2025.287703

Abstract

Renal prognosis in light-chain amyloidosis (AL) is determined by categorizing patients into three renal stages at diagnosis and assessing renal response or renal progression following chemotherapy after 6 months. We evaluated, in a test (N=1,935) cohort of patients with renal AL amyloidosis who were followed for a median of 95 months, a modified 4-stage model where Renal Stage 2 was sub-categorized according to preserved (2A) or reduced (2B) estimated glomerular filtration rate (eGFR). A hybrid model for evaluation of renal progression was also introduced, using an eGFR cut-off of 30 mL/min/1.73 m^2. These models were compared with existing models; namely those of Palladini and Kastritis, and results were validated in a multicenter cohort (N=438). The risk of progression to renal replacement therapy (RRT) increased progressively across all Renal Stages of the Revised staging model (hazard ratio [HR] =3.25, HR=5.13, HR=10.66 for stages 2A, 2B and 3 respectively *vs.* stage 1; each $P<0.001$). Our revised criteria for renal response (HR=0.26, 95% confidence interval [CI]: 0.18-0.38 at 60 months) and renal progression (HR=8.15, 95% CI: 6.1-10.9) were independently predictive of RRT and outperfomed existing criteria at all follow-up time points. Renal progression was independently associated with mortality (HR=1.5, 95% CI: 1.26-1.86; $P<0.001$). The enhanced performance of these refined renal staging and response models enables timely and appropriate chemotherapy adjustment in patients with renal AL amyloidosis.

Introduction

Immunoglobulin light-chain amyloidosis (AL) is a rare multi-system disease which involves the kidneys in approximately 70% of cases and is responsible for ~1% of end stage kidney disease (ESKD) requiring renal replacement therapy (RRT).[1-3] Early diagnosis of renal AL amyloidosis, before development of irreversible organ dysfunction, coupled with achieving a rapid and deep hematologic response with anti-plasma cell or anti-B-cell therapy are key

to preserving renal and patient survival.[4,5]

Renal AL amyloidosis is typically characterized by proteinuria and/or a decreased glomerular filtration rate;[6-8] progression to end-stage kidney disease (ESKD) occurs in approximately 25% of patients.[8] Although the presence and severity of cardiac amyloidosis is the most important prognostic factor influencing patient survival in AL amyloidosis,[9,10] ESKD has a very significant burden of morbidity and renal dysfunction also contributes to prognosis.[11,12]

Renal survival in AL amyloidosis depends on several histopathological and laboratory parameters.[13] Two independent teams of investigators, led by Palladini and Kastritis, identified low estimated glomerular filtration rate (eGFR) and heavy proteinuria at the time of diagnosis to be significant predictors of ESKD. Palladini *et al.* proposed a renal AL amyloidosis staging system based on eGFR and proteinuria using cut-offs of <50 mL/min/1.73 m^2 and >5 g/day respectively (i.e., 3 stages) to predict progression to ESKD at 3 years.[2] Kastritis *et al*. introduced an alternative 3-stage model using the ratio of 24 hours (h) proteinuria to eGFR (UPr/eGFR ratio in mg/mL/min/1.73 m^2) and demonstrated better renal risk stratification in their cohort using this model.[14] However, ~50% of all patients with renal AL amyloidosis are categorized as stage 2 which represents a heterogeneous group, ranging from those with eGFR <30 mL/min/1.73 m^2 and subnephrotic proteinuria at diagnosis to patients with eGFR >90 mL/min/1.73 m^2 and nephrotic range proteinuria. Renal response was defined by Palladini at 6 months from diagnosis following administration of chemotherapy as a >30% reduction in proteinuria or a drop in proteinuria below 0.5 g/day in absence of renal progression, the latter defined as >25% decline in eGFR. In Kastritis' model, renal response was defined as reduction of 24 h UPr/eGFR ratio by at least 25% or to below 100 (if ≥100 at baseline) and renal progression was defined as ≥25% increase from baseline or to ≥100 (if <100 at baseline). However, a large meta-analysis in chronic kidney disease (CKD) showed that absolute eGFR more robustly predicts progression to ESKD than trajectory of eGFR decline over a shorter follow-up period, with a low eGFR at the time of measurement associated with a substantial risk of ESKD even in the context of minimal eGFR decline.[15] Another large CKD study showed that absolute eGFR was associated with a graded increase in ESKD risk, independently of a 25% decline over 1 year, the latter no longer associated with progression to ESKD when adjusted for the last eGFR measurement.[16] Our clinical experience in AL amyloidosis aligns with these CKD studies in that patients who are labeled as 'renal progressors' at 6 months by current criteria have not infrequently achieved a deep hematologic response and a reduction in proteinuria accompanied by restoration to good health and a 'response' in other amyloidotic organs; such patients rarely require RRT despite long-term follow-up.

Based on these considerations, we sought to evaluate in a test and a multi-center validation cohort of patients with renal AL amyloidosis who were followed for over 5 years from diagnosis; (i) whether the performance of a 4-stage system based on proteinuria and eGFR at diagnosis could improve the predictive performance for renal survival and (ii) whether the predictive performance of renal response and progression criteria at 6 months could be improved upon by use of a hybrid model (eGFR cut-off and percentage eGFR decline) rather than percentage eGFR loss from baseline alone. Additionally, we sought to evaluate the impact of cardiac amyloidosis on renal survival.

Methods

Patients and study design

A multi-center retrospective study of patients who were diagnosed with renal AL amyloidosis at the UK National Amyloidosis Center (NAC); the Careggi University Hospital in Florence; the University Hospital of Parma; the Nephrology Unit, University of Brescia, ASST Spedali Civili, Brescia; the Cattinara Hospital, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), Trieste; the Fatebenefratelli Hospital in Rome; and the Policlinico S.Orsola-Malpighi Hospital in Bologna between January 2000 and December 2022 and who fulfilled both of the following inclusion criteria: (i) histological diagnosis of AL amyloid with presence of a monoclonal light chain of the same isotype in serum and/or urine by immunofixation and/or circulating serum free light-chain (FLC) assay; (ii) renal amyloidosis as defined by the ISA consensus criteria,[17] namely non-Bence Jones proteinuria of >0.5 g/24 h. Patients were excluded from the study if they fulfilled any of the following criteria: (i) eGFR <15 mL/min/m^2 or dialysis dependent at the time of diagnosis; (ii) unfit for chemotherapy; (iii) received chemotherapy prior to diagnosis; (iv) insufficient clinical information or laboratory parameters at baseline or at follow up; (v) CKD due to non-amyloid pathology.

Renal staging criteria

Using the previously validated cut-off values for eGFR and proteinuria[2] patients were grouped into four (rather than 3) categories as follows; Renal Stage 1 - 24-h proteinuria ≤5 g/24 h and eGFR ≥50 mL/min/1.73 m^2; Renal Stage 2A - proteinuria >5 g/24 h and eGFR ≥50 mL/min/1.73 m^2; Renal Stage 2B - proteinuria ≤5 g/24 h and eGFR <50 mL/min/1.73 m^2; Renal Stage 3 - proteinuria >5 g/24 h and eGFR <50 mL/min/1.73 m^2.

Renal response criteria

Renal response was defined at 6 months from diagnosis following administration of chemotherapy as a reduction in 24 h proteinuria by at least 30% from baseline or a drop below 0.5 g/day in the absence of renal progression. Renal progression was defined as a drop in eGFR to <30 mL/min/1.73 m^2 in patients with baseline eGFR ≥45 mL/min/1.73

m^2 and >25% reduction in those with baseline eGFR <45 mL/min/1.73 m^2. Renal response and renal progression criteria were evaluated by 6 months landmark analysis. Chemotherapy was administered to all patients included in this study. Hematologic response was assessed according to the 2012 ISA criteria at 6 months after treatment initiation[18] (*Online Supplementary Appendix*).

Our renal staging and renal response/progression models were evaluated in the test (English) and validation (Italian) cohorts, and their performance was compared to that of the Palladini and Kastritis models.[2,14]

Patient and renal survival

Patient survival was defined as time from diagnosis to death or censor and renal survival (death-censored) was defined as time from diagnosis to initiation of RRT or censor, where RRT requirement was >3 months. Follow-up period was defined as the time between diagnosis and the last attendance at the specialist center. Censor date was that of the last follow-up prior to December 9, 2022.

The study was conducted in accordance with Declaration of Helsinki and approved by the relevant institutional ethics committees of participating centers. All patients provided written informed consent for publication of their anonymized data.

Statistical analysis

Patient characteristics at diagnosis were described, using median and interquartile range (IQR) or number (percentage) unless noted otherwise for continuous variables. The Kruskal-Wallis H test was used for numerical variables to ascertain difference among renal stages.

Kaplan-Meier estimates were used to generate renal and overall survival curves related to different groups across all three models, with distributions between groups compared by the log-rank test.

Proportional hazard assumptions were confirmed, and Cox proportional hazards regression models were fitted to compute hazard ratio (HR) and 95% confidence intervals (CI) with additional utilization of time-dependent covariates in multivariable analysis to robustly evaluate predictors of renal survival among renal stages. Discriminatory assessment, performed using Harrell's C-statistic and Somers' D, was achieved after splitting the dataset into training and validation sets, and fitting the respective models based on their derived prognostic indices. The models were fitted to the first cohort, and the C-statistics compared in the second cohort using a *t* test after creating Jackknife standard errors.[19] Calibration was assessed by plotting predicted risk *versus* observed risk for progression to RRT and explained variation R^2 was determined where applicable. Statistical significance was established at $P<0.05$.

Data were analyzed with the use of Stata (StataCorp. 2023. Stata Statistical Software: Release 18) and SPSS software version 28.0.

Results

Patient characteristics

Among 1,935 patients who comprised the test cohort, 1,395 (72%) had nephrotic-range proteinuria (>3 g/24 h) with a median of 5.2 g (IQR, 2.6-8.2) and 977 (52%) had cardiac amyloidosis. For analysis of renal response and progression, 576 (30%) were excluded due to death (N=359) or progression to RRT (N=91) within 6 months, or due to missing data (N=126), leaving 1,359 evaluable patients. The validation cohort (N=438) included 300 (69%) patients with nephrotic range proteinuria and 242 (55%) with cardiac amyloidosis. Of these, 280 (64%) were evaluable for renal response and progression at 6-month Landmark after excluding 68 deaths, 40 who progressed to RRT, and 50 with missing data. *Online Supplementary Table S1A, B* summarize the patient characteristics.

Median estimated follow-up in the test cohort by reverse Kaplan-Meier (KM) analysis was 95 months (95% CI: 90-99%) and in the validation cohort was 65 months (95% CI: 56-74%). In the test cohort 338 (17%) patients progressed to RRT whereas 117 (29%) in the validation cohort required RRT. Among the 338 and 117 patients who required RRT from the test and validation cohorts respectively, the median time from diagnosis to RRT by KM analysis was 15 months (IQR, 6-44) and 11 months (IQR, 6-36). Among 1,180 (61%) patients in the test cohort who died, median survival from diagnosis by KM analysis was 19 months (IQR, 5-54) and among 200 (47%) patients in the validation cohort who died, median survival was 12 months (IQR, 4-44).

Renal stage and outcomes

Death-censored renal survival was analyzed according to all three staging systems. A comparison of the three models in the test cohort with respect to incidence of progression to RRT at 1 year, 3 years, 5 years and 100 months is

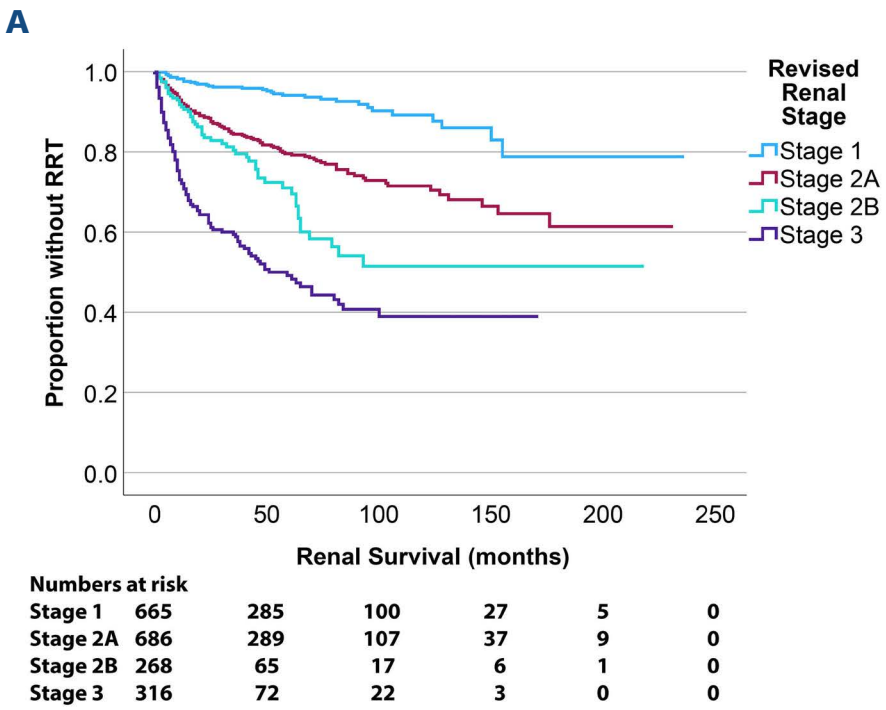
Table 1. Cumulative incidence of progression to renal replacement therapy in test cohort (N=1,935) according to Renal Stage at diagnosis by three Renal Staging models.

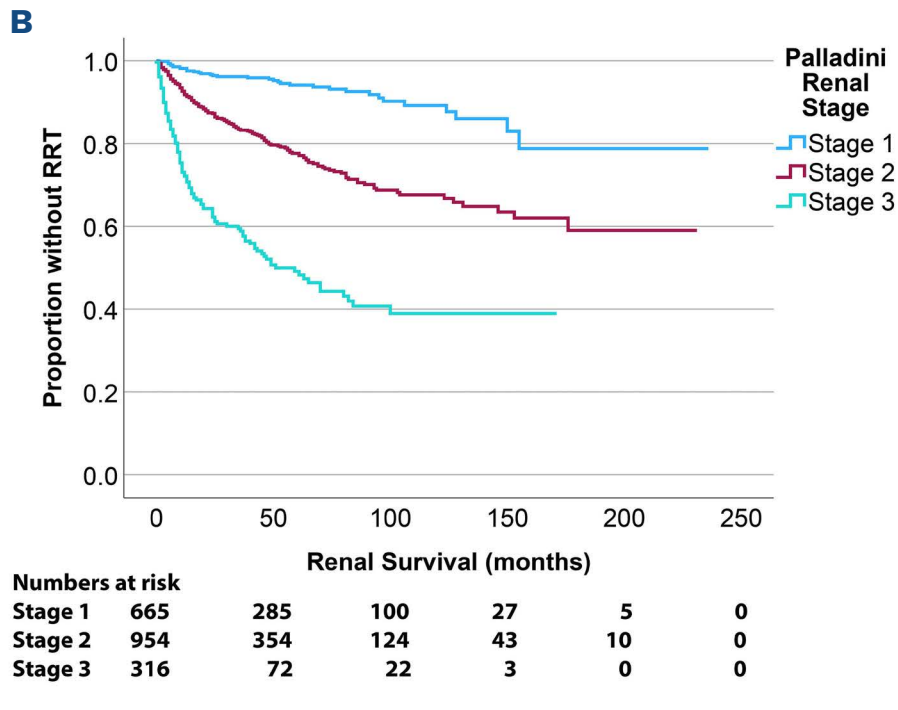
Renal Stage	Cumulative incidence of RRT, %			
	1 year	3 years	5 years	100 months
Palladini				
Stage 1	2	4	6	10
Stage 2	8	17	22	31
Stage 3	28	41	51	61
Revised Stage 2				
Stage 2A	8	16	20	27
Stage 2B	9	21	30	49
Kastritis				
Stage 1	1	3	5	11
Stage 2	4	8	12	19
Stage 3	19	32	39	48

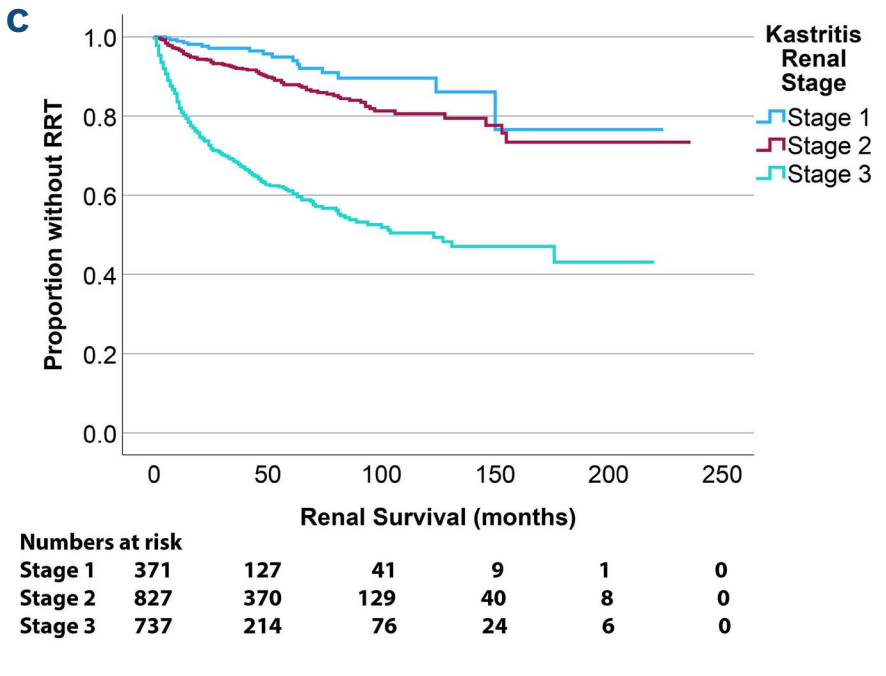
RRT: renal replacement therapy.

shown in Table 1. Univariable Cox regression analysis of predictors of progression to dialysis in the test cohort is shown in *Online Supplementary Table S2*. Multivariable Cox regression analyses were conducted using non-confounding variables stratified by presence/absence of Mayo stage III; eGFR, degree of proteinuria, serum albumin and NT-proBNP were excluded due to their role in calculation of Renal and Mayo Stages.

Applying the Revised Renal Staging system to the test cohort, 665 (34.5%) patients were stage 1, 686 (35.5%) stage 2A, 268 (14%) stage 2B, and 316 (16%) stage 3. The risk of progression to RRT increased significantly across all stages (Figure 1A; Log-rank: 1 *vs*. 2A, *P*<0.001; 2A *vs*. 2B, *P*=0.003; 2B *vs*. 3, *P*<0.001). At 5 years, cumulative incidence of RRT was 6% (stage 1), 20% (stage 2A), 30% (stage 2B), and 51% (stage 3). The 5-year C-statistic showed that the Revised model (0.763) outperformed those of Palladini (0.759) and Kastritis (0.758) (Figure 1B, C). Among stage 3 patients, those with eGFR 15-30 mL/min/1.73 m² had a higher 5-year RRT risk than those with eGFR 31-50 mL/min/1.73m² (HR=1.88; 95% CI: 1.3-2.72; *P*<0.001) after adjusting for baseline proteinuria.







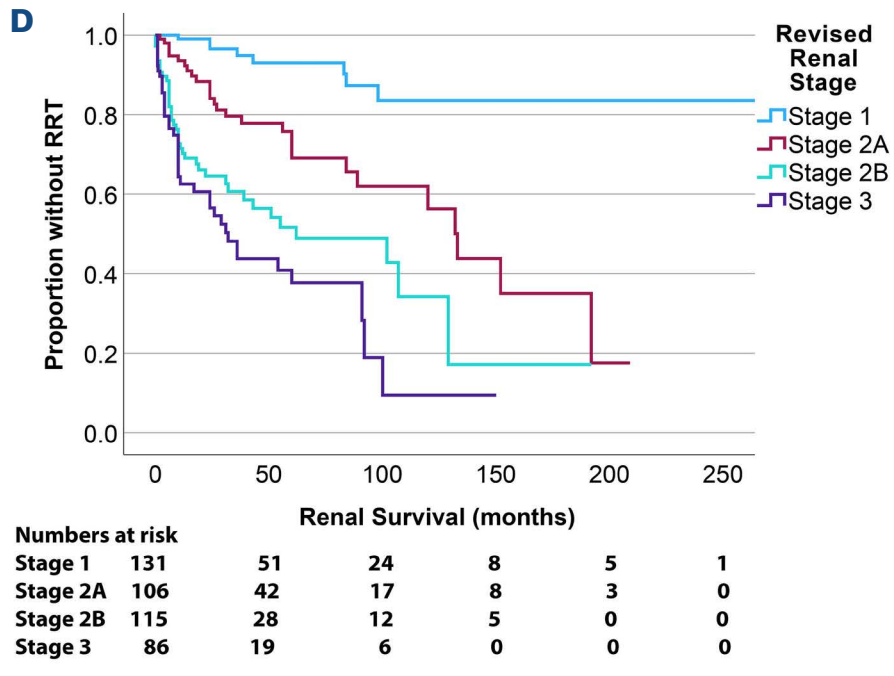


Figure 1. Kaplan-Meier analyses of time from diagnosis to renal replacement therapy in the test cohort according to three models (A, B, C) of Renal Stage and in the validation cohort (D) using the Revised Renal Stage. (A) Revised Renal Stage - stage 1: estimated glomerular filtration rate (eGFR) ≥50 mL/min/1.73 m² and proteinuria ≤5 g/24 hours (h); stage 2A: eGFR ≥50 mL/min/1.73 m² and proteinuria >5 g/24 h; stage 2B: eGFR <50 mL/min/1.73 m² and proteinuria ≤5 g/24 h; stage 3: eGFR <50 mL/min/1.73 m² and proteinuria >5 g/24 h. Log-rank; 1 *versus* 2A, *P*<0.001; 2A *versus* 2B, *P*=0.003; 2B *versus* 3, *P*<0.001. (B) Palladini Renal Stage - stage 1: eGFR ≥50 mL/min/1.73 m² and proteinuria ≤5 g/24 h; stage 2: eGFR <50 mL/min/1.73 m² or proteinuria >5 g/24 h; stage 3: eGFR <50 mL/min/1.73 m² and proteinuria >5 g/24 h. Log-rank: 1 *versus* 2, *P*<0.001; 2 *versus* 3, *P*<0.001. (C) Kastritis Renal Stage – stage 1: UPr/eGFR ratio <30; stage 2: UPr/eGFR ratio 31-99; stage 3: UPr/eGFR ratio >100. Log-rank: 1 *versus* 2, *P*=0.02; 2 *versus* 3, *P*<0.001. (D) Time to renal replacement therapy (RRT) in the validation cohort according to Revised Renal Stage. Log-rank: 1 *versus* 2A, *P*<0.001; 2A versus 2B, *P*=0.001; 2B *versus* 3, *P*=0.09.

Median time from RRT (dialysis) to death in the test cohort was 28 months (IQR, 12-56) and did not appear to be impacted by Renal Stage at diagnosis.

The 4-stage Revised model resulted in similar discriminatory C-statistic values when applied to the validation cohort. KM analysis of renal survival in the validation cohort is shown in Figure 1D.

Renal response and progression

Renal response was analyzed in a 6-month landmark analysis in 1,359 evaluable patients from the test cohort, using all three models: Revised, Palladini and Kastritis. The HR associated with renal response and renal progression for development of RRT (death-censored) at 1-year, 3-years, 5-years and 100 months along with discriminatory C-indices, using all three models, are reported in Table 2. The evaluation of discriminatory C-statistics yielded higher concordance (Harrell's C) between renal response and renal progression and absence and presence of RRT at 5 years respectively using the Revised model. KM renal survival analyses among renal responders and renal progressors with all three models are shown in Figure 2. Sub-group analyses of death-censored renal survival at 100 months in the test cohort among those who achieved deep hematologic response (very good partial reponse/complete reposnse [VGPR/CR]) at 6 months (N=837), stratified by renal response and renal progression using the three models are shown in *Online Supplementary Figure S1A-C* and *S1D-F*, respectively. At 100 months, cumulative incidence of RRT was 51%, 27% and 31% among renal progressors as defined by Revised, Palladini and Kastritis models respectively.

Renal progression according to revised criteria was independently predictive of RRT at 5 years across all four Renal Stages when deep hematologic response was incorporated into the analysis as a covariate; Renal Stage 1: HR=11.32, *P*<0.001; Renal Stage 2A: HR=9.53, *P*<0.001; Renal Stage 2B: HR=3.04, *P*<0.002; Renal Stage 3: HR=3.1, *P*<0.001. We also evaluated the renal survival at 5-years among 107 patients with low level baseline proteinuria (i.e., >0.5 g but ≤1 g/24 h) who were classified as Renal Progressors by Revised, Palladini and Kastritis criteria; the cumulative incidence of RRT was 38%, 12% and 23% respectively.

The Revised model showed very similar results and discriminatory C-statistics at all time points (1 year, 3 years, 5 years, 100 months) when it was applied to the validation cohort. The 5-year KM analyses of time from diagnosis to RRT among renal responders and renal progressors applying the Revised model to the validation cohort are shown in Figure 3A and B, respectively.

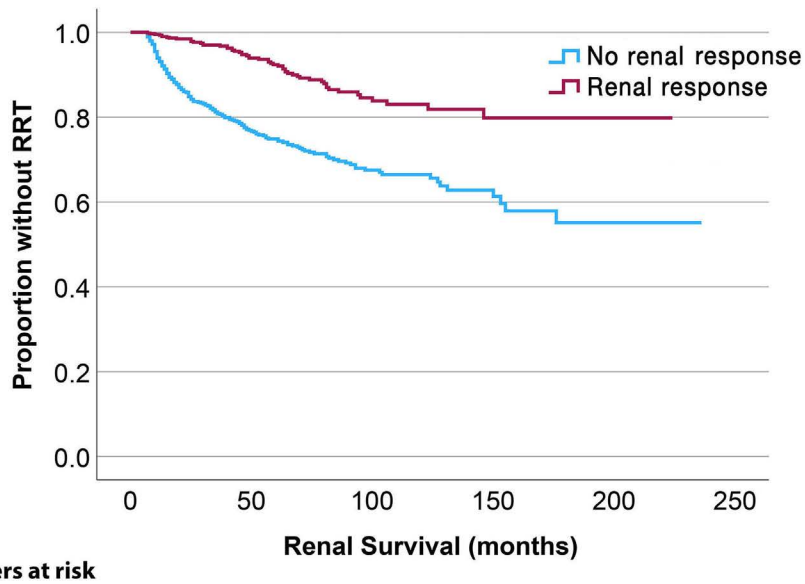
We evaluated a three-category renal prognostication model using a 6-month landmark analysis, defining 'stable renal disease' for patients meeting neither renal response nor renal progression criteria across three models. KM analyses for renal survival by response category in each model are shown in Figure 4. Multivariable Cox regression (including hematologic response) showed HR for progression to RRT at 5 years among renal progressors: 8.15 (95%CI: 6.1-10.9, *P*<0.001, Revised), 3.5 (95% CI: 2.64-4.7, *P*<0.001, Palladini), and 3.9 (95% CI: 2.9-5.17, *P*<0.001, Kastritis). For renal responders, HR were 0.26 (95% CI: 0.18-0.38, *P*<0.001, Revised),

Table 2. Hazard ratios with C-indices indicating risk of progression to renal replacement therapy at different time points among renal responders and renal progressors by 6-month Landmark analysis using three models (Revised, Palladini, Kastritis) in the test cohort (N=1,359).

Renal response, months	Revised model Responders, N=613 Non-responders, N=746		Palladini model Responders, N=490 Non-responders, N=869		Kastritis model Responders, N=598 Non-responders, N=761	
	HR (95% CI)	C-index	HR (95% CI)	C-index	HR (95% CI)	C-index
12	0.11 (0.04-0.32)	0.76	0.12 (0.013-0.39)	0.73	0.18 (0.08-0.44)	0.73
36	0.15 (0.09-0.25)	0.72	0.19 (0.11-0.33)	0.69	0.23 (0.15-0.37)	0.70
60	0.26 (0.18-0.38)	0.70	0.32 (0.22-0.48)	0.67	0.34 (0.24-0.48)	0.68
100	0.36 (0.26-0.49)	0.69	0.44 (0.32-0.61)	0.66	0.42 (0.3-0.57)	0.66
Renal progression, months	**Revised model Progressors, N=181 Non-progressors, N=1,178**		**Palladini model Progressors, N=439 Non-progressors, N=920**		**Kastritis model Progressors, N=410 Non-progressors, N=949**	
	HR (95% CI)	C-index	HR (95% CI)	C-index	HR (95% CI)	C-index
12	23.5 (12.5-44)	0.82	9.8 (4.94-19.5)	0.75	4.84 (2.75-8.5)	0.69
36	10.2 (7.3-14.1)	0.72	4.9 (3.50-6.98)	0.70	5.2 (3.7-7.35)	0.69
60	8.15 (6.1-10.9)	0.70	3.5 (2.64-4.70)	0.67	3.9 (2.9-5.17)	0.67
100	7.0 (5.42-9.2)	0.69	2.9 (2.20-3.70)	0.65	3.0 (2.36-3.96)	0.65

CI: confidence interval; HR: hazard ratio.

A



Numbers at risk						
Non-responders	746	367	135	41	10	0
Responders	613	339	112	33	5	0

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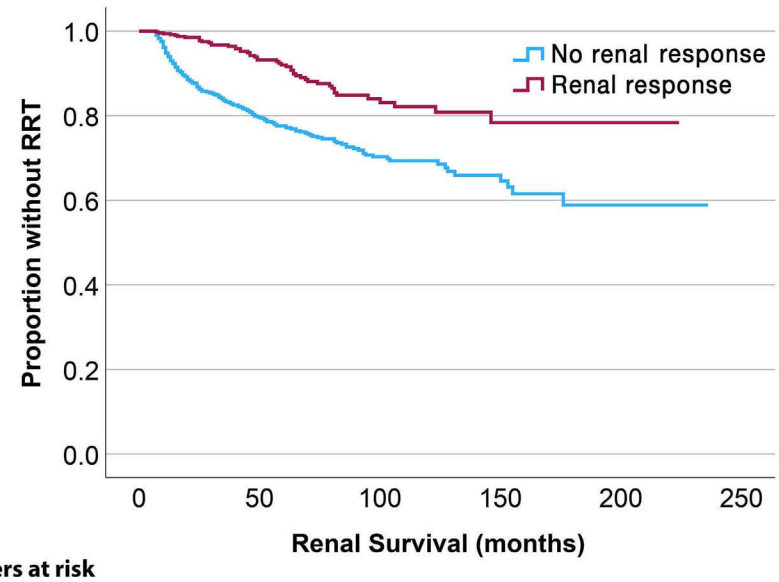
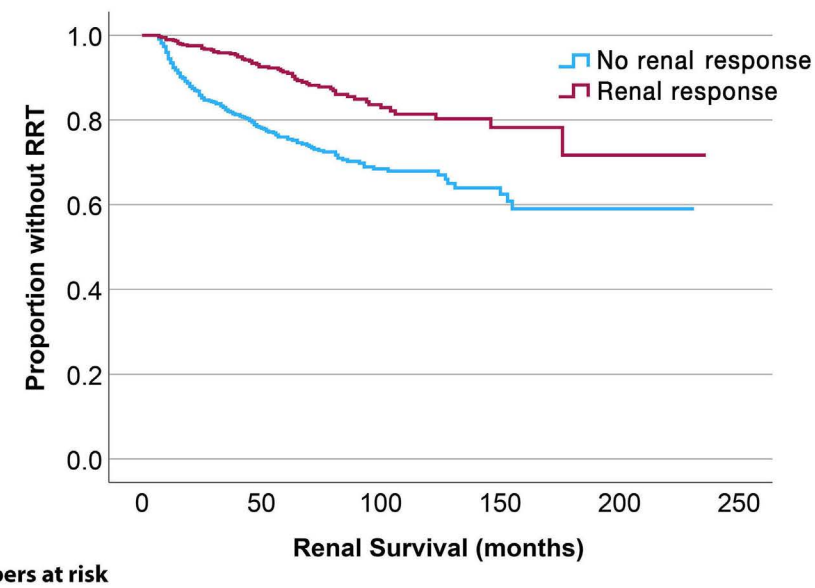


Numbers at risk						
Non-responders	869	438	154	48	11	0
Responders	490	268	93	26	4	0

C



Numbers at risk						
Non-responders	761	373	130	42	9	0
Responders	598	333	117	32	6	0

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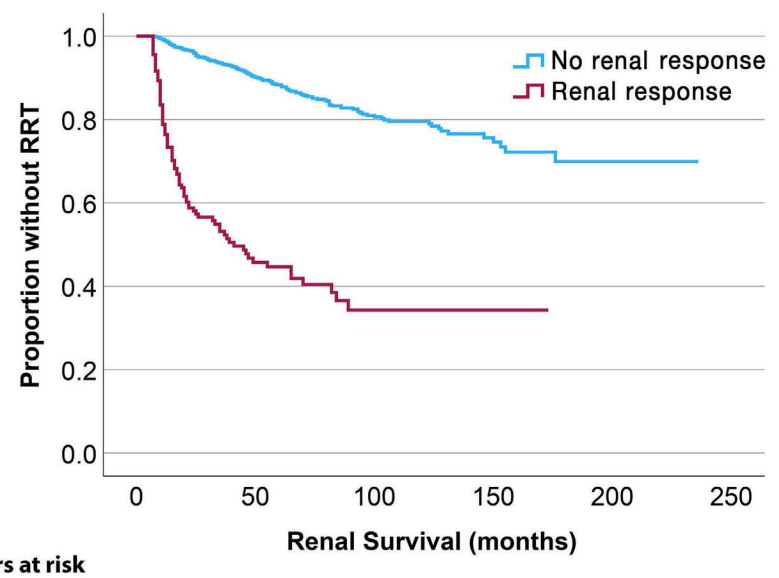

Numbers at risk						
Non-progressors	1178	662	234	71	15	0
Progressors	181	44	13	3	0	0

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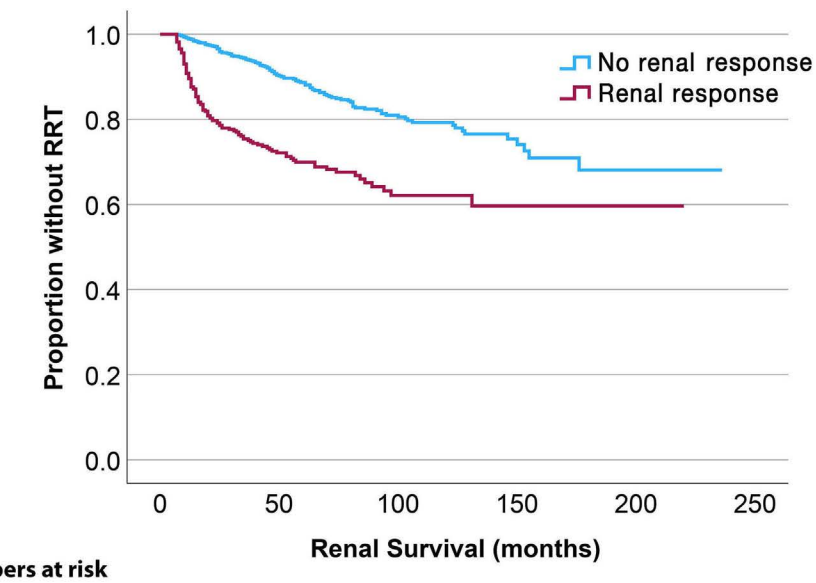

Numbers at risk						
Non-progressors	920	524	195	56	13	0
Progressors	439	182	52	18	2	0

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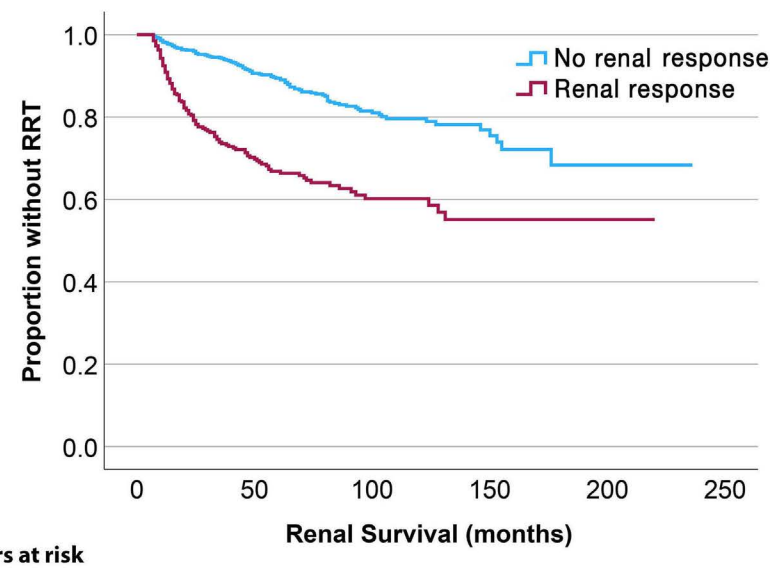

Numbers at risk						
Non-progressors	949	528	185	53	10	0
Progressors	410	178	62	21	5	0

Figure 2. Landmark Kaplan-Meier analyses at 6 months evaluating time to renal replacement therapy in the test cohort applying three models to define renal response (A, B, C) and renal progression (D, E, F). (A) Revised model comparing renal responders and renal non-responders; *P*<0.001. (B) Palladini model comparing renal responders and renal non-responders; *P*<0.001. (C) Kastritis model comparing renal responders and renal non-responders; *P*<0.001. (D) Revised model comparing renal progressors and renal non-progressors; *P*<0.001. (E) Palladini model comparing renal progressors and renal non-progressors; *P*<0.001. (F) Kastritis model comparing renal progressors and renal non-progressors; *P*<0.001. RTT: renal replacement therapy.

0.32 (95% CI: 0.22-0.48, *P*<0.001, Palladini), and 0.34 (95% CI: 0.24-0.48, *P*<0.001, Kastritis), respectively. Among 'stable renal disease' patients, HR were 0.70 (95% CI: 0.5-0.93, *P*=0.01), 0.64 (95% CI: 0.46-0.9, *P*=0.008), and 0.69 (95% CI: 0.5-0.98, *P*=0.04) by revised, Palladini, and Kastritis models, respectively. The proportion of 'renal responders' classified by revised criteria decreased across renal stages: stage 1 (43%), 2A (33%), 2B (14%), and 3 (10%); whereas proportions with 'stable renal disease' were 36%, 47%, 8%, and 9%, and those of 'renal progressors' were 10%, 30%, 23%, and 37% among stages 1, 2A, 2B and 3, respectively.

We applied Muchtar's recently published graded renal response criteria to patients who were defined at 6 months as non-progressors according to our revised renal response criteria as opposed to those defined as non-progressors according to the Palladini criteria that were utilized by Muchtar.[20] The integrity of Muchtar's model of graded renal response criteria was preserved with respect to renal survival (*Online Supplementary Figure S2*).

Impact of cardiac involvement

The influence of cardiac amyloidosis on progression to RRT (Figure 5A) and patient survival (Figure 5B) were evaluated in the test cohort. Cardiac amyloidosis did not impact progression to RRT, with 22% of patients with and 20% without cardiac amyloidosis requiring RRT at 60 months (*P*=0.12). However, cardiac amyloidosis was associated with poorer overall survival, with 60-month mortality of 63% in those with and 35% in those without cardiac amyloidosis (*P*<0.001). This effect was consistent across all four Revised Renal Stages (*Online Supplementary Figure S3*). A multivariable Cox regression 6-month Landmark analysis incorporating presence of cardiac amyloidosis, renal response and renal progression (using revised, Palladini, and Kastritis models), and hematologic response showed renal progression by revised criteria to be independently associated with mortality (HR=1.5, 95% CI: 1.2-1.86; *P*<0.001), Table 3.

Discussion

Risk-adapted therapeutic strategies in renal AL amyloidosis rely on predictive models with high sensitivity and specificity given the variable risk of ESKD progression. Current definitions of renal response and progression in AL amyloidosis,[2,14] despite their unequivocal utility, are flawed principally because they mislabel patients as 'progressors' at 6 months, despite a deep hematologic response, reduced proteinuria and minimal future risk of RRT. In addition, renal survival has previously been evaluated to 3 years in these studies but there are few data examining longer term renal prognosis. In our multicenter study, we modified the existing renal staging system at diagnosis and the renal response and progression criteria at 6 months from diagnosis developed by Palladini to enhance their performance as predictors of renal survival over a longer duration of follow-up and validated the findings in an unrelated and unselected cohort with renal AL amyloidosis. Given the increasing armamentarium of therapies available for systemic AL amyloidosis and ever improving patient outcomes generally, re-evaluating the utility of renal predictors of prognosis over a longer follow-up period, including in patients with minimal competing risk of death, is warranted. Muchtar *et al.* recently published graded renal response criteria in which renal responders were defined as renal complete (KidCR), renal very good partial (KidVGPR), renal partial (KidPR) or renal non (kidNR) responders.[20] Whilst these response criteria will undoubtedly be of immense value, particularly in renal AL amyloidosis clinical trials, the definition of renal progression utilized in Muchtar's analy-

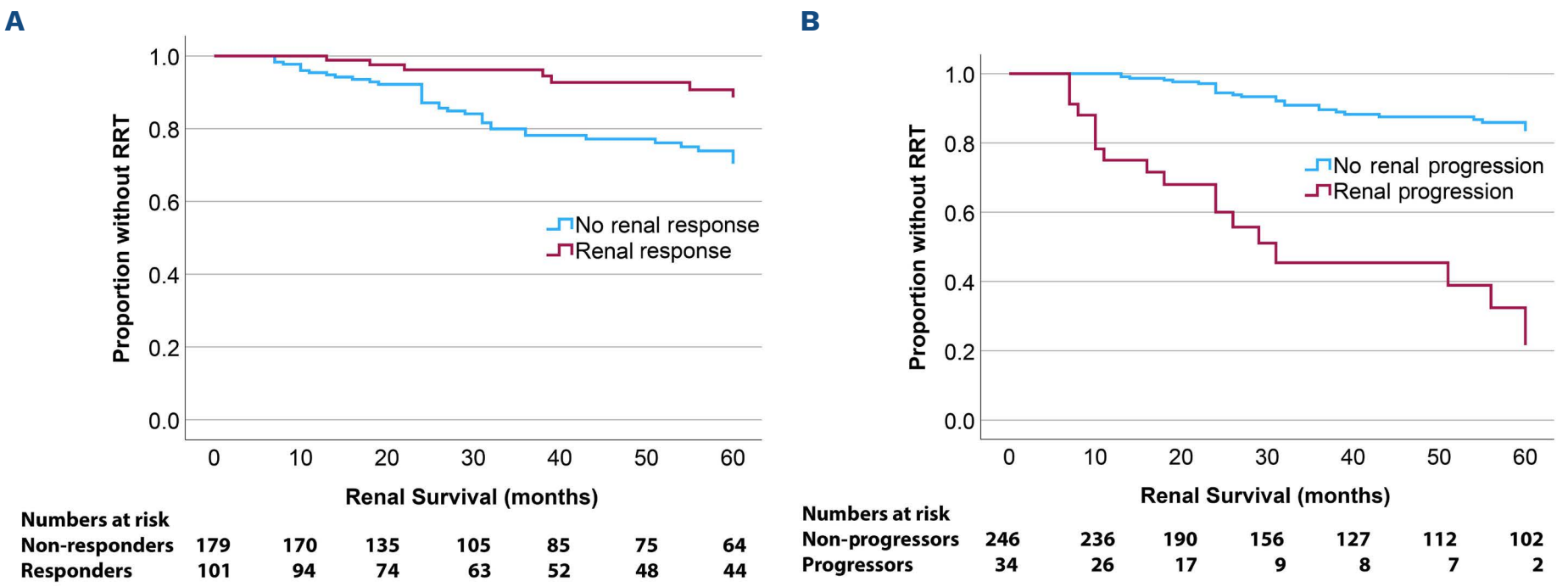

Figure 3. Landmark Kaplan-Meier analyses at 6 months of death-censored renal survival in the validation cohort. (A) Stratified by renal response *versus* no renal response (*P*=0.003). (B) Stratified by renal progression *versus* no renal progression (*P*=<0.001).

ses was that of Palladini. Importantly however, application of Muchtar's renal response criteria to 'non-progressors' as defined by our revised renal response model yielded results that were entirely consistent with respect to renal survival with those previously reported by Muchtar and colleagues. The re-categorization of Palladini Renal Stage 2 into 2A and 2B with emphasis on relative preservation or not of eGFR respectively, was able to enhance the positive and negative predictive power for risk of progression to RRT afforded by the existing staging systems. Our findings are consistent with previous studies in CKD in which segregation of early (CKD IIIA) and late (CKD IIIB) stage III CKD on the basis of eGFR has important prognostic value.[21,22] Our analyses showed significantly worse overall patient survival among patients with Renal Stage 2B than those with Renal Stage 2A AL amyloidosis and indeed no significant difference between Renal Stages 2B and 3 in terms of patient survival. Our modification of the Palladini definition of renal progression in renal AL amyloidosis - defining progression as an eGFR <30 mL/minute at 6 months for patients with CKD I-IIIA and >25% eGFR reduction for CKD IIIB-IV - more accurately predicted renal survival than a >25% eGFR reduction alone or the 24 h proteinuria/eGFR ratio. The sensitivity of our revised model (at 5 years) was 46%, compared to 25% for Palladini and 27% for Kastritis, and its negative predictive value (NPV) was 92%, compared to 72% and 74%, respectively. These findings align with the results of a large systematic review of 1.7 million participants across 35 cohorts in the CKD Prognosis Consortium showing higher ESKD incidence with greater eGFR declines.[23] Additionally, renal progression as defined by revised criteria, was independently associated with mortality, even after adjusting for known predictors of death in AL amyloidosis namely cardiac amyloidosis and sub-optimal hematologic response. Even among patients without cardiac amyloidosis, renal pogression correlated with significantly lower overall survival (median 75 *vs*. 140 months; *P*<0.001), consistent with prior reports linking eGFR decline to mortality in CKD.[21, 24] The study's "three-category" renal response model introduced "stable renal disease" for patients who didn't meet criteria for renal response or progression at 6 months. 'Stable renal disease' patients had a higher risk of progression to RRT at 100 months than renal responders (*P*<0.05 in each of the 3 models). 'Renal progressors' classified by revised

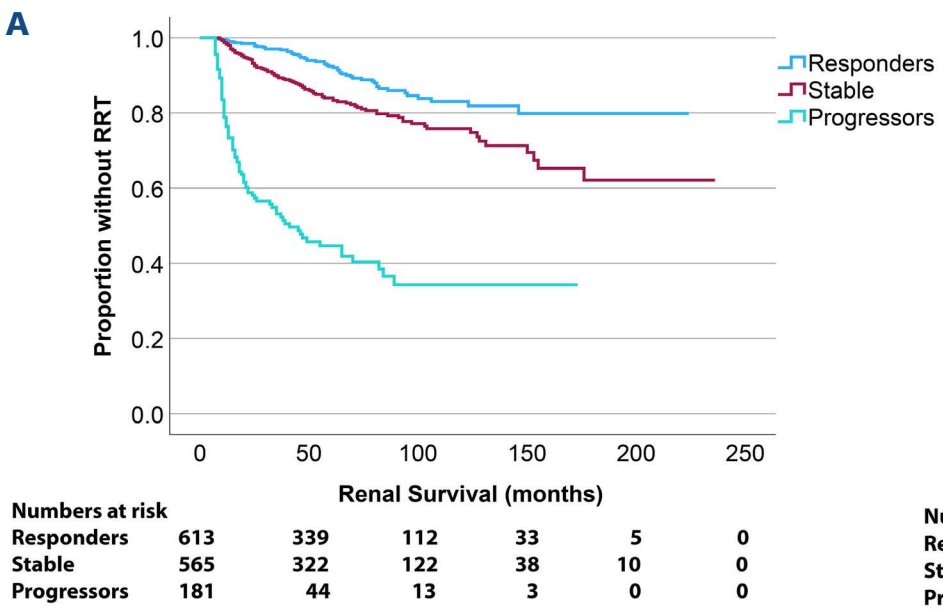

Figure 4. Landmark Kaplan-Meier analyses of death-censored renal survival in the test cohort stratified by renal response (blue), stable renal disease (red), and renal progression (green) applying each of three models to the cohort. Renal response and renal progression were defined according to each model and stable renal disease comprised all patients who were neither categorized as responders nor progressors by the respective model. (A) Revised model (Log-rank: responders *vs*. stable, *P*<0.001; stable *vs*. progressors, *P*<0.001). (B) Palladini model (Log-rank: responders *vs*. stable, *P*=0.005; stable *vs*. progressors, *P*<0.001). (C) Kastritis model (Log-rank: responders *vs*. stable, *P*=0.013; stable *vs*. progressors, *P*<0.001).

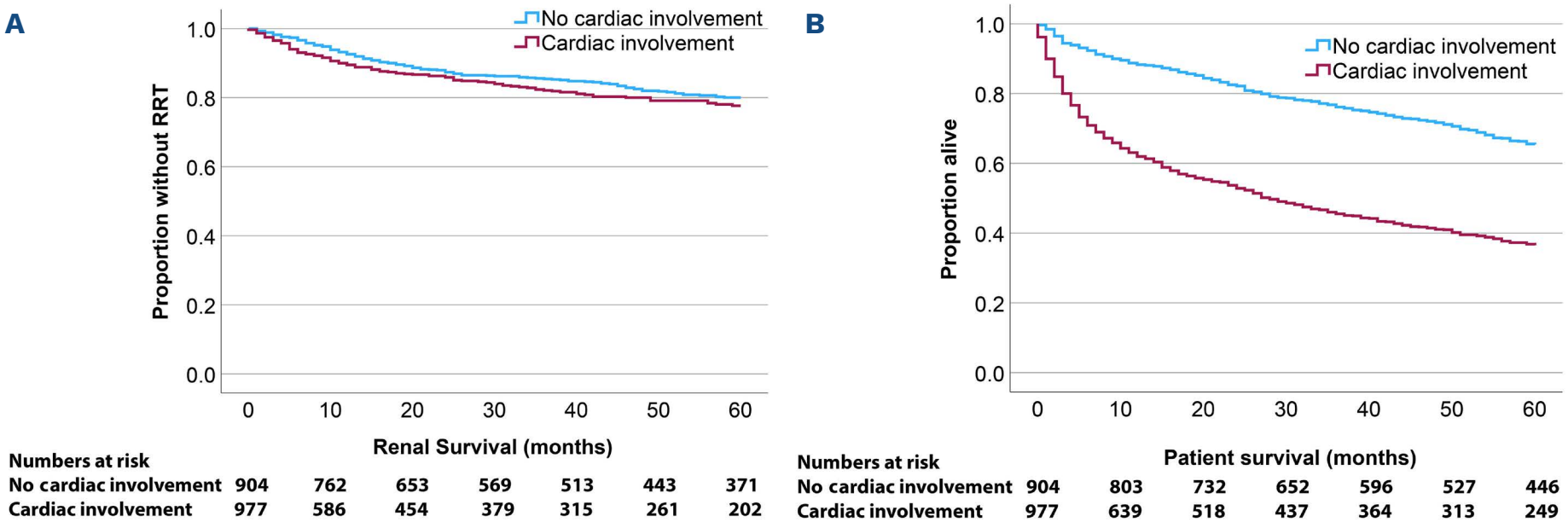

Figure 5. Renal and patient survival in the test cohort stratified by presence (red) or absence (blue) of cardiac amyloidosis at the time of diagnosis. (A) Renal survival stratified by presence or absence of cardiac amyloidosis (Log-rank; *P*=0.12). (B) Patient survival stratified by presence or absence of cardiac amyloidosis (Log-rank; *P*<0.001).

criteria had a substantially higher cumulative incidence of RRT (55%) compared to those classified by the Palladini and Kastritis models (38% and 40%).

The influence of depth of hematologic response on renal outcomes and overall survival in AL amyloidosis is well established. However, renal progressors compared to renal non-progressors as defined by the revised criteria had a shorter median time to RRT even among deep hematologic responders (median, 33; IQR, 16-69 months *vs*. median, 62; IQR, 34-96 months; *P*<0.001). Among patients who failed to achieve at least a hematologic VGPR within 6 months of starting chemotherapy, the median time to RRT among renal progressors and renal non-progressors was 13 (IQR, 10-24) and 44 (IQR, 21-76) months respectively (*P*<0.001).

This study's strength lies in its long follow-up, enabling a valid head-to-head comparison of three models for predicting long-term renal survival. However, its retrospective nature over a decade-long time span coincides with advancements in AL amyloidosis therapies. The small size of the validation cohort with a higher rate of progression to RRT represents a limitation of this study. From a clinical practice perspective, there remains an unmet need for further studies of large international cohorts with renal AL amyloidosis to assess the correlation between urine protein-to-creatinine ratio and 24-h proteinuria with the aim of integrating spot urinary protein measurements into current renal staging and response models. While our revised criteria have better sensitivity and NPV than those of Palladini and Kastritis, they remain imperfect, as some renal progressors never require RRT, and some renal responders progress to RRT, highlighting the need for better early indicators of long-term renal survival, potentially including histopathological findings at diagnosis.

In conclusion refining Renal Stage 2 by emphasizing rather than GFR over proteinuria improves the performance of existing staging systems. Adjusting Palladini's 6-month renal progression criteria to include an eGFR cut-off of <30 mL/min/1.73 m² for those presenting with eGFR ≥45 mL/min/1.73 m² more accurately predicts a future requirement for RRT. We encourage adoption of the Revised model in clinical practice to aid clinical assessment of early therapy adjustments and their impact on renal outcomes.

Table 3. Multivariable Cox regression analyses of predictors of mortality in the test cohort.

Variable*	HR (95% CI)	*P*
Presence of cardiac amyloidosis	1.74 (1.5-2)	<0.001
Deep hematologic response at 6 months	0.46 (0.4-0.54)	<0.001
Revised model		
Renal response	0.98 (0.83-1.15)	0.78
Renal progression	1.5 (1.2-1.86)	<0.001
Palladini model		
Renal response	1.01 (0.86-1.2)	0.89
Renal progression	1.1 (0.94-1.3)	0.22
Kastritis model		
Renal response	0.98 (0.83-1.15)	0.79
Renal progression	1.13 (0.96-1.34)	0.13

*Variables assessed include presence of cardiac amyloidosis at diagnosis, 6-month Landmark analysis of hematologic response, and renal response or renal progression (applied in turn) as defined by 3 models. CI: confidence interval; HR: hazard ratio.

Disclosures

No conflicts of interest to disclose.

Contributions

MUR, MA and JDG conceived the study and analyzed the data. MUR and JDG wrote the manuscript. AP performed all

statistical analyses. All other authors contributed to data collection and/or provided critical input into the manuscript. All authors reviewed and approved the final version of the manuscript.

Data-sharing statement

The authors agree to share publication-related anonymized patient data in accordance with the data sharing agreement. For original data please email the corresponding authors.

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