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

Supplementary Material:

Methods:

Patients and Study Design

Patients underwent a full clinical history and physical examination at baseline diagnostic visit to specialist centers. Biochemical assessment included estimation of eGFR using the CKD epidemiology collaboration (2009 CKD-EPI creatinine) formula,[1] proteinuria quantification by 24-hour urinary protein measurement, evaluation of hematologic parameters including serum free light chain assay (freelite), serum and urine electrophoresis and immunofixation and echocardiography.

Presence of cardiac amyloidosis

The presence of cardiac amyloidosis was determined according to ISA consensus criteria,[2] namely left ventricular hypertrophy with inter-ventricular septal thickness >12 mm and N-terminal pro b-type natriuretic peptide (NT-proBNP) >332 ng/L. Due to the known poor specificity of these criteria in patients with Chronic Kidney Disease (CKD), those in whom echocardiography did not show apical sparing on global longitudinal strain (GLS) measurement [3] despite meeting wall thickness and NT-proBNP criteria for cardiac amyloidosis underwent additional contrast-enhanced CMR imaging to determine presence or absence of cardiac amyloidosis. Mayo disease stages were determined using the 2004 staging criteria.[4]

Hematologic response at 6 months

Very Good Partial Response (VGPR) was defined as absolute difference between involved and uninvolved free light chains (dFLC) <40 mg/L in patients with baseline dFLC ≥50 mg/L and Complete Response (CR) as negative serum and urine immunofixation and normal free

light chain (FLC) ratio. For patients with a low dFLC burden defined by a pre-treatment dFLC >20 mg/L but <50mg/L, a reduction in dFLC to <10 mg/L was considered to be a VGPR, as previously described.[5, 6]

References

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Supplementary Table 1A. Baseline characteristics of patients in test and validation cohorts

Variable		
	Test (NAC) Cohort (N=1935)	**Validation (Italy) Cohort (N=438)**
Age at diagnosis, years	66 (58-72)	66 (60-74)
Male Gender (n, %)	1128 (58)	226 (52)
Serum Creatinine, µmol/L	93 (72-137)	106 (72-173)
eGFR, ml/min/1.73 m^2 (CKD-EPI)	71 (44-93)	57 (30-87)
Serum Albumin, g/L	29 (24-35)	Data Not Available
Proteinuria, g/24 h	5.2 (2.6-8.2)	4.29 (2.12-7.6)
Cardiac involvement (n, %)	977 (52)	242 (55)
NT-proBNP, ng/L	1142 (349-4322)	Data Not Available
Mayo stage (2004) I/II/III (%)	21/27/52	56/16/28
dFLC, (mg/L)	138 (53-359)	116 (42-405)
CKD stages, I/II/III/IV (%)	29/31/27/13	22/25/28/25
Progression to RRT, n (%)	338 (17)	117 (29)
ASCT during follow up (n, %)	164 (8.5)	43 (9.8)
First line Treatment (n)		
ASCT	25	15
Bortezomib based	1090	223
IMID based	439	10
Mel based	188	66
Alkylating agent	20	0
Anthracycline based	73	2
Treatment of IgM clone	74	23
Daratumumab based	6	15
Other	20	0
Uncertain	0	84

Numbers show median and IQR unless specified in the table. eGFR: estimated Glomerular filtration rate; CKD-EPI: Chronic kidney disease epidemiology equation; NT-proBNP: N-terminal pro b-type natriuretic peptide; dFLC: difference between involved and uninvolved free light chains; CKD: Chronic Kidney Disease; RRT: Renal replacement therapy; ASCT: Autologous stem-cell transplant

Supplementary Table 1B. Baseline characteristics of test cohort stratified by revised Renal Stage

	All patients n=1935	Stage 1 n= 665	Stage 2A n= 686	Stage 2B n= 268	Stage 3 n= 316	p-value
Age, years	66 (58-72)	66 (58-71)	64 (56-71)	70 (64-76)	68 (61-74)	<0.001
Male gender, n (%)	1128 (58%)	350 (53%)	426 (62%)	163 (61%)	189 (60%)	0.003
Cardiac amyloidosis, n (%)	977 (52%)	384 (59%)	274 (41%)	156 (60%)	163 (53%)	<0.001
eGFR, ml/min/1.73 m^2	70.5 (44-93)	83 (66-96)	85 (69-100)	33 (24-40)	32 (24-41)	<0.001
dFLC, mg/L	138 (53-359)	178 (64-498)	117 (47-273)	146 (60-450)	120 (47-285)	<0.001
Serum albumin, g/L	29 (24-35)	34 (29-39)	24 (21-28)	36 (32-40)	27 (22-31)	<0.001
Proteinuria, g/24h	5.2 (2.6-8.2)	2.5 (1.3-3.8)	8.1 (6.5-10.4)	2.5 (1.3-3.4)	8.3 (6.6-11.4)	<0.001
NT-proBNP, ng/L	1142 (349- 4322)	1446 (360-4815)	558 (204-2004)	3043 (870-8435)	1887 (710-6250)	<0.001
Proportion progressing to RRT, n (%)	338 (17%)	36 (5%)	125 (18%)	54 (20%)	123 (39%)	<0.001
Died, n (%)	1180 (61%)	403 (61%)	367 (53%)	185 (69%)	225 (71%)	<0.001
Patient survival (months)	59 (11-151)	59 (11-153)	82 (22-177)	33 (5-119)	48 (8-99)	<0.001

Values are expressed as median and interquartile range (IQR) unless specified in the table. eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FLC, free light chains; dFLC, difference between involved and uninvolved FLC; RRT: Renal replacement therapy.

Supplementary Table 2. Univariable analysis of predictors of progression to renal replacement therapy (RRT) at the time of diagnosis in the test cohort

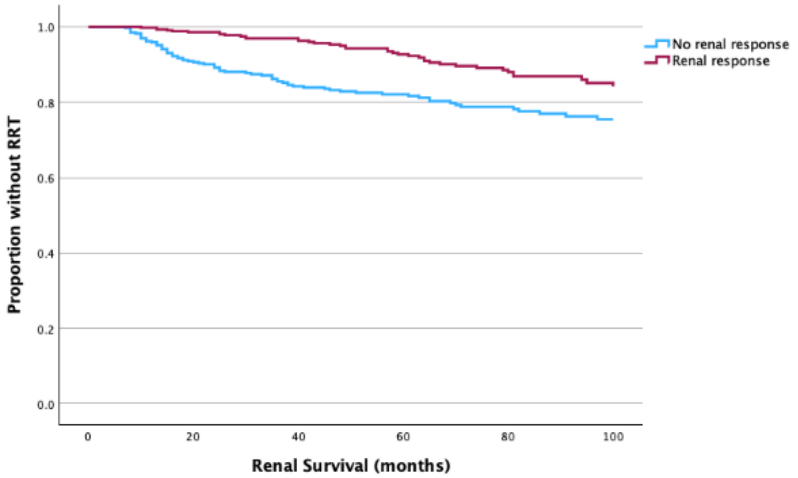
Variable		
	HR (95% CI)	**p value**
Age, years	0.98 (0.97-0.99)	**0.001**
Male Gender	1.25 (1-1.55)	**0.048**
eGFR, ml/min/1.73 m^2	0.974 (0.97-0.978)	**<0.001**
Serum albumin, g/L	0.95 (0.93-0.96)	**<0.001**
Proteinuria, g/24h	1.08 (1.07-1.1)	**<0.001**
Log NT-proBNP	1.30 (1.09-1.55)	**0.003**
Mayo stage III	1.41 (1.09-1.83)	**0.009**
Log dFLC	1.05 (0.89-1.23)	0.55
Echo LVPW >12mm at diagnosis	1.11 (0.89-1.38)	0.34
Cardiac amyloidosis	1.19 (0.95-1.48)	0.13
Palladini Renal stages		
Stage 1	Ref	
Stage 2	3.65 (2.55-5.23)	**<0.001**
Stage 3	10.63 (7.32-15.43)	**<0.001**
Revised Renal stages		
Stage 1	Ref	
Stage 2A	3.25 (2.24-4.71)	**<0.001**
Stage 2B	5.13 (3.36-7.83)	**<0.001**
Stage 3	10.66 (7.35-15.48)	**<0.001**
Kastritis Renal stages		
Stage 1	Ref	
Stage 2	1.93 (1.15-3.25)	**0.01**
Stage 3	7.35 (4.5-12)	**<0.001**

eGFR: estimated Glomerular filtration rate; NT-proBNP: N-terminal pro b-type natriuretic peptide; dFLC: difference between involved and uninvolved free light chains; LVPW: Left ventricular posterior wall.

<u>Supplementary Figure 1</u>: Landmark Kaplan-Meier analyses at 6 months evaluating death-censored renal survival at 100 months among a sub-group of patients from the test cohort who achieved a deep hematologic response (CR- Complete response or VGPR- Very good partial response) at 6 months applying three models to define Renal Response (A, B, C) and Renal Progression (D, E, F).

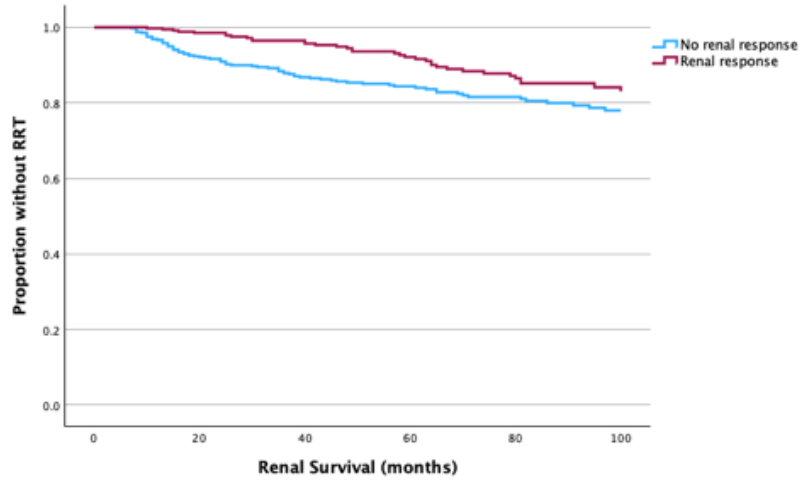
(A) Revised model comparing Renal Responders and Renal non-Responders, $p<0.001$. **(B)** Palladini model comparing Renal Responders and Renal non-Responders, $p=0.006$. **(C)** Kastritis model comparing Renal Responders and Renal non-Responders, $p<0.001$. **(D)** Revised model comparing Renal Progressors 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 ($p<0.001$).

(A)



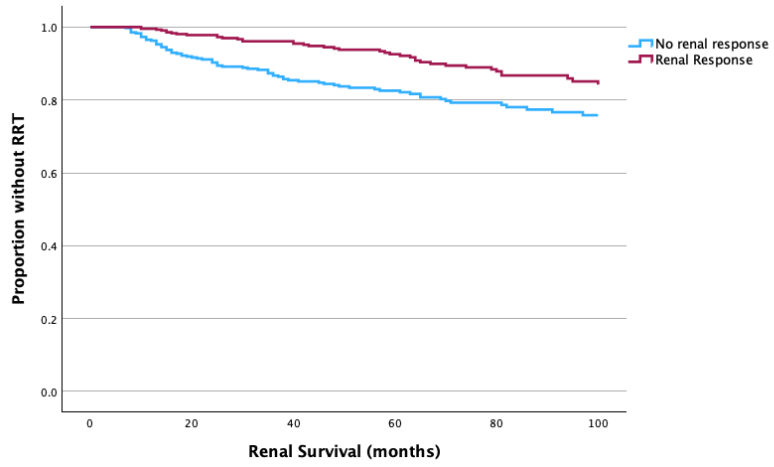
Numbers at risk						
Non-responders	397	329	253	187	135	89
Responders	440	385	313	227	156	92

(B)



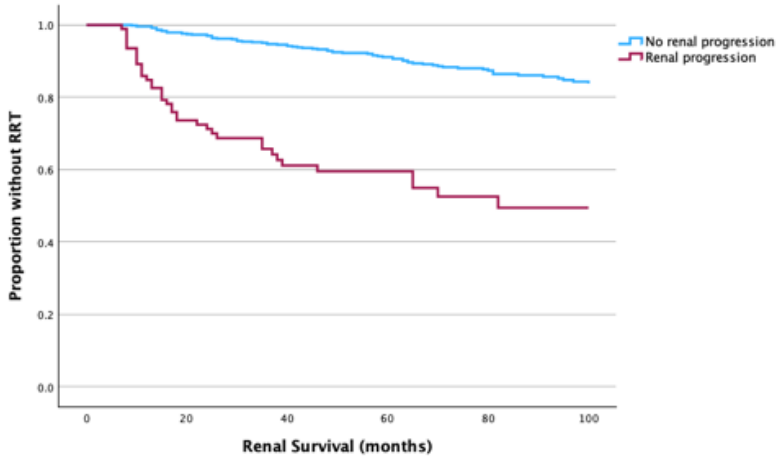
Numbers at risk						
Non-responders	484	408	314	232	159	104
Responders	353	306	252	182	132	77

(C)



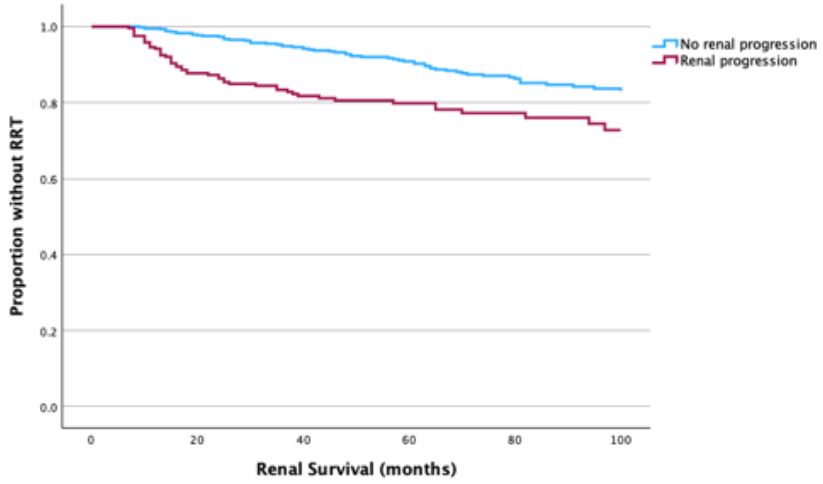
Numbers at risk						
Non-responders	410	344	260	191	132	84
Responders	427	370	306	223	159	97

(D)



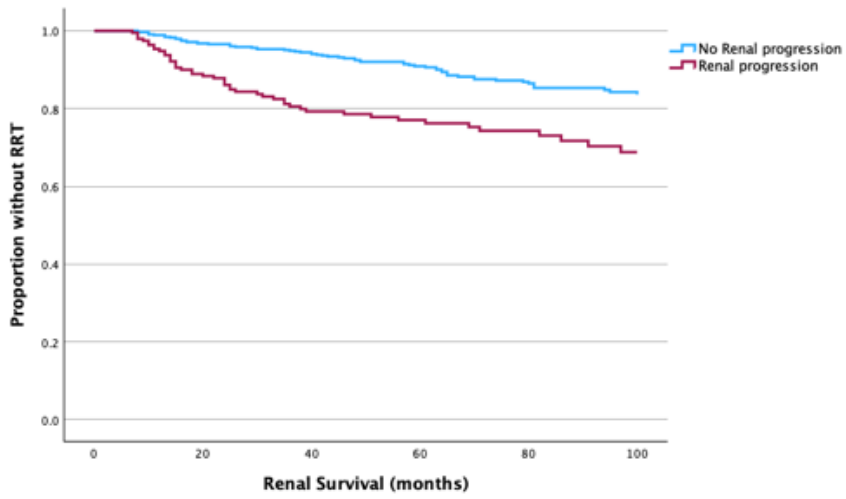
Numbers at risk						
Non-Progressors	744	652	526	387	275	169
Progressors	93	62	40	27	16	12

(E)



Numbers at risk						
Non-Progressors	594	517	419	307	227	142
Progressors	243	197	147	107	64	39

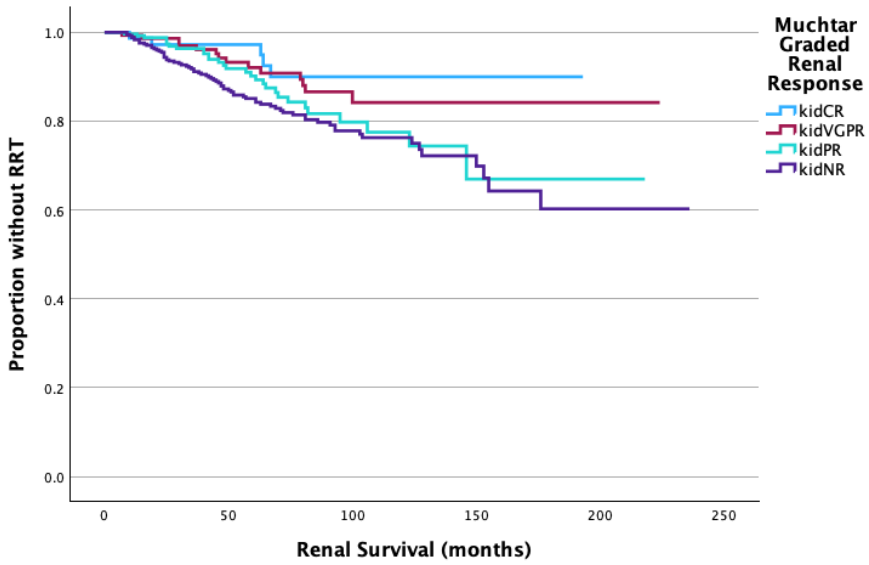
(F)



Numbers at risk						
Non-Progressors	641	553	447	322	230	141
Progressors	196	161	119	92	61	40

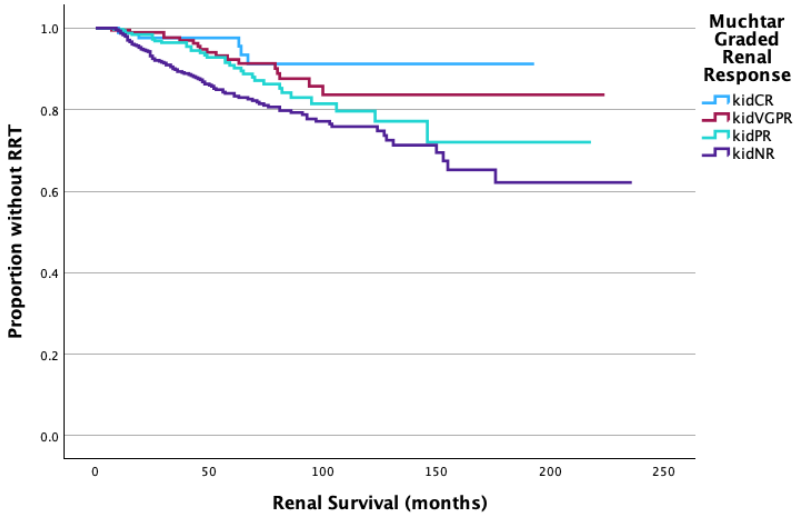
<u>Supplementary Figure 2</u>: Six-month Landmark Kaplan-Meier analyses of death-censored renal survival stratified by grade of renal response according to Muchtar *et al*
(A) Muchtar graded response criteria using Palladini definition of renal non-progressors (N=920); Log-rank; p=0.02. **(B)** Muchtar graded response criteria using revised definition of renal non-progressors (N=1178); log rank; p<0.001.
(kidCR = 24-hour UP ≤200 mg, kidVGPR = >60% reduction in 24-hour UP, kidPR = 31%-60% reduction in 24-hour UP, kidNR = ≤30% reduction in 24-hour UP)

(A)



Numbers at risk						
kidCR	77	49	18	5	0	0
kidVGPR	149	94	36	14	3	0
kidPR	264	126	39	7	1	0
kidNR	430	255	102	30	9	0

(B)



Numbers at risk						
kidCR	88	57	22	5	0	0
kidVGPR	192	122	41	16	4	0
kidPR	333	161	50	12	1	0
kidNR	565	322	121	38	10	0

<u>Supplementary Figure 3:</u> Renal survival (left) and patient survival (right) according to presence (Green) or absence (Blue) of cardiac amyloidosis at diagnosis among patients from the test cohort.

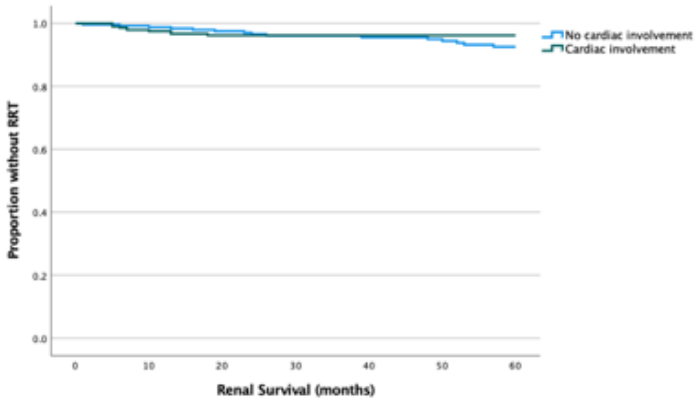
(A) Renal Stage 1: Renal survival (*p*-value=0.36); Patient survival (*p*<0.001)

(B) Renal Stage 2A: Renal survival (*p*-value=0.11); Patient survival (*p*<0.001)

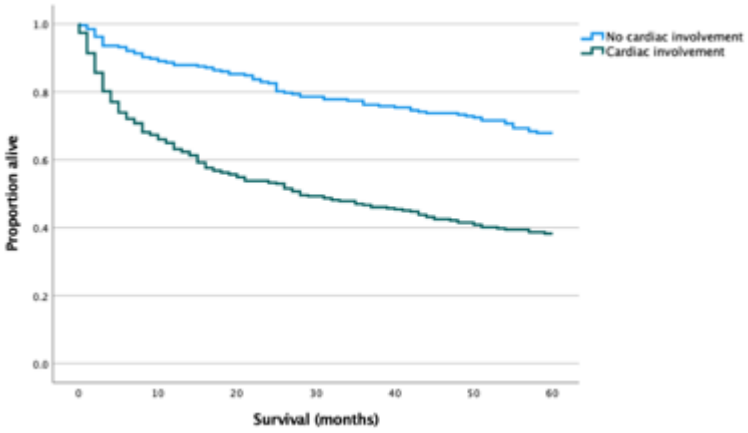
(C) Renal Stage 2B: Renal survival (*p*-value=0.14); Patient survival (*p*<0.001)

(D) Renal Stage 3: Renal survival (*p*-value =0.28); Patient survival (*p*<0.001).

(A) Renal Stage 1

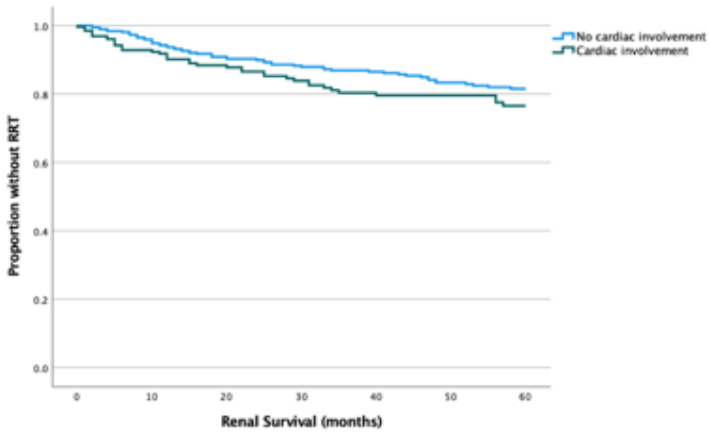


Numbers at risk							
Non-Cardiac	267	236	217	194	180	163	137
Cardiac	384	252	198	169	144	120	94

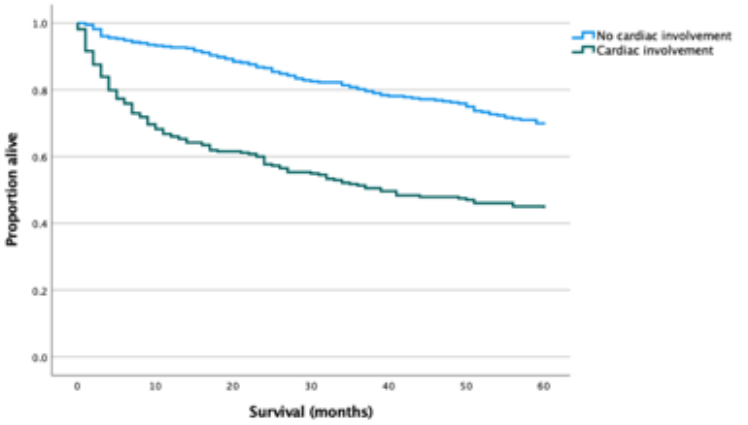


Numbers at risk							
Non-Cardiac	267	238	221	200	184	167	144
Cardiac	384	257	204	173	147	123	97

(B) Renal Stage 2A

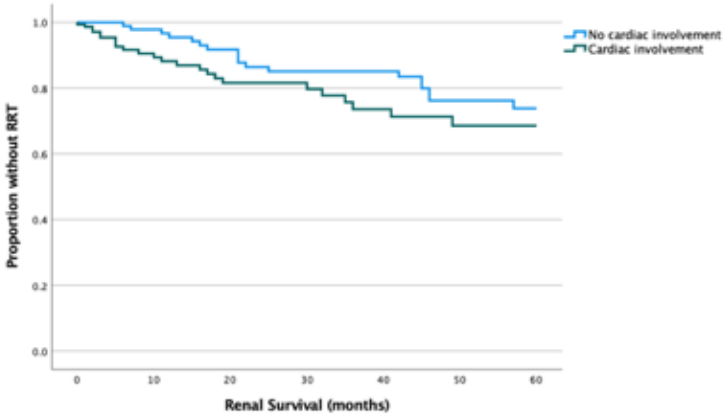


Numbers at risk							
Non-Cardiac	387	346	297	257	227	197	170
Cardiac	274	178	145	122	99	89	71

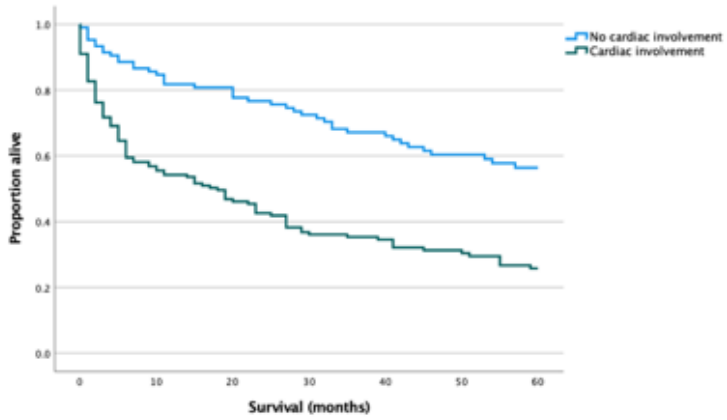


Numbers at risk							
Non-Cardiac	387	359	327	287	259	234	200
Cardiac	274	190	161	139	114	104	87

(C) Renal Stage 2B

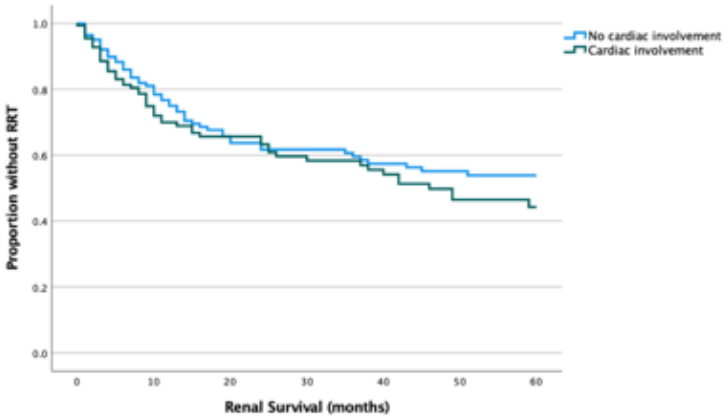


Numbers at risk							
Non-Cardiac	106	86	72	59	54	39	29
Cardiac	156	78	54	43	32	24	17

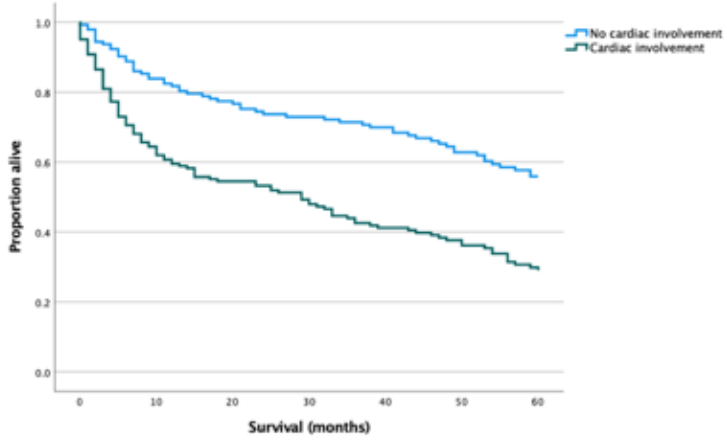


Numbers at risk							
Non-Cardiac	106	88	79	68	61	50	39
Cardiac	156	87	66	51	43	35	28

(D) Renal Stage 3



Numbers at risk							
Non-Cardiac	144	94	67	59	52	44	35
Cardiac	163	78	57	45	40	28	20



Numbers at risk							
Non-Cardiac	144	118	105	97	92	76	63
Cardiac	163	105	87	74	60	51	37