Modified histopathological classification with age-related glomerulosclerosis for predicting kidney survival in ANCA-associated glomerulonephritis

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Research Article

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Abstract

Background

The histopathological classification of ANCA-GN divides patients into four groups based on signs of glomerular injury. However, this classification did not consider age-related glomerulosclerosis. In this study, we aimed to compare the prediction of renal survival between Berden's ANCA-GN histopathological classification and ANCA-GN histopathological classification modified with age-related glomerulosclerosis.

Methods

Between January 2004 and December 2019, 65 patients diagnosed with ANCA-GN were enrolled. Demographic, laboratory, and histopathologic findings were retrospectively analyzed. Renal survival analyzes were compared according to classical and modified ANCA-GN histopathological classifications. The multivariate Cox regression analysis for the factors affecting renal survival was performed.

Results

In Berden's ANCA-GN histopathological classification, 15 patients were in the focal group, 21 in the crescentic, 21 in the sclerotic, and 8 in the mixed group. The ANCA-GN histopathological classification model generated statistically significant predictions for renal survival ($p = 0.022$). When the histopathological classification was modified with age-related glomerulosclerosis, 8 of the 9 patients previously classified in the sclerotic group were classified in the mixed and 1 in the crescentic groups. Modification of histopathological classification with age-related glomerulosclerosis increases the statistical significance in renal survival analysis ($p = 0.009$). The multivariate Cox regression analysis showed that the disease-related global sclerotic glomeruli percentage and serum creatinine level were the significant independent factors.

Conclusion

Modification of Berden's ANCA-GN histopathological classification model with age-related glomerulosclerosis may increase the statistical significance of the histopathological classification model.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a multisystemic vasculitis group with necrotizing involvement in small vessels. Vasculitis in this group are granulomatous polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatous polyangiitis (EGPA) [1]. The incidence of AAV increases with age and is most common in the 6th decade [2]. Typical renal

involvement of AAV is in the form of rapidly progressing pauci-immune necrotizing and crescentic glomerulonephritis (GN) [3]. The most common findings of kidney involvement are hematuria, proteinuria, and renal failure. Kidney involvement is approximately 90% and 80% in MPA and GPA, respectively [4]. Renal involvement is associated with a high risk of morbidity and mortality and poor prognosis.

Berden et al. developed a histopathological classification model for ANCA-GN [5]. Kidney involvement is divided into four subgroups in this classification according to glomerular involvement in biopsy: Focal (≥ 50% normal glomeruli), crescentic (≥ 50% crescentic glomeruli), sclerotic (≥ 50% global sclerotic glomeruli), and mixed (< 50% normal, < 50% crescentic, < 50% sclerotic glomeruli). Many studies have been conducted investigating the relationship between histopathological classification and renal survival. Studies have shown that the focal group is associated with a good prognosis and the sclerotic group with a poor prognosis. Inconsistent results were obtained in studies on kidney prognosis when mixed and crescent groups were compared. The crescentic group was associated with a better renal prognosis in some studies [5–7], while in others the mixed group was associated with a better renal prognosis [8, 9]. No significant difference was found between the crescentic and mixed groups in terms of renal survival in many studies [10–16]. However, these studies did not consider age-related glomerulosclerosis. Since ANCA-GN is an advanced age disease, we think that age-related glomerulosclerosis should also be considered in this classification. Histological findings of chronic kidney disease (CKD) are global glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arteriosclerosis, which can be defined together as nephrosclerosis [17]. Glomerulosclerosis, one of the chronic histopathologic findings, is seen in CKD but is also part of the natural course of aging, and its incidence increases with advanced age [18]. Aging-related glomerulosclerosis has been demonstrated in numerous autopsy studies [19, 20]. Kremers et al. obtained data estimating the age-related global sclerotic glomerular number in their study [21].

We aimed to compare the prediction of renal survival between Berden's ANCA-GN histopathological classification and ANCA-GN histopathological classification modified with age-related glomerulosclerosis.

Material And Methods

Renal biopsies performed in the Division of Nephrology, Bursa Uludag University Faculty of Medicine, between January 2004 and December 2019 were analyzed retrospectively. The following variables were extracted from medical records in all participants: age, gender, ANCA types, GFR, serum creatinine, albumin, hematuria, proteinuria, complete blood count, neutrophil/lymphocyte ratio (NLR), erythrocyte sedimentation rate (ESR), c- reactive protein (CRP), rheumatoid factor (RF), immunoglobulins, C3c, C4, histopathological findings, lung involvement, co-morbid diseases, plasmapheresis requirement and treatment regimens. Sixty-five patients diagnosed with pauci-immune crescentic glomerulonephritis by kidney biopsy and clinically supported the diagnosis of AAV were included in the study. Epidemiological and clinical information was obtained from medical records. All biopsies were performed before initiation of therapy or during the first days of induction therapy. Kidney biopsies were evaluated by light microscopy and immunofluorescence analysis. It was confirmed that hematoxylin and eosin,

methenamine silver, periodic acid-Schiff, and Masson trichrome dyes were used in the pathological evaluation of kidney biopsies. Renal biopsies were classified as sclerotic, focal, crescentic, and mixed according to the Berden's histopathological classification and algorithm [5].

Clinical diagnoses are based on the 2012 International Chapel Hill Consensus Conference Nomenclature of Vasculitides [1]. Patients were grouped as GPA and MPA according to their diagnosis. ANCA tests were performed using both indirect immunofluorescence and ELISA tests. The estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

Patients were grouped as focal, crescentic, sclerotic, and mixed according to their histopathological classification. The QxMD calculator (https://qxmd.com/calculate/calculator_2/glomerulosclerosis-on-biopsy-2015) was used to estimate age-related glomerulosclerosis. The estimated age-related sclerotic glomeruli were calculated by the QxMD calculator using age and the total glomeruli in the biopsy. Disease-related glomerulosclerosis was estimated by subtracting the number of estimated age-related sclerotic glomeruli from the number of global sclerotic glomeruli. Because of biopsies without sclerotic glomeruli, reclassification was performed without subtracting the number of sclerotic glomeruli from the total number of glomeruli. The histopathological classification of the cases was re-evaluated by taking the number of disease-related sclerotic glomeruli in the ANCA-GN histopathological classification instead of sclerotic glomeruli.

All patients received induction therapy consisting of intravenous methylprednisolone combined with intravenous pulse cyclophosphamide followed by oral corticosteroids. Dose adjustment for cyclophosphamide was made according to renal function. After achieving remission, maintenance therapy with azathioprine or rituximab was given.

Total renal survival was considered as a prognostic criterion. Renal survival was defined as the time to end-stage renal failure requiring renal replacement therapy (RRT). Renal survival analysis was done as death-censored. If the patients who died during the follow-up did not receive RRT at the time of death, the event was deemed not to have occurred. Renal survival, which required dialysis from the time of admission, was accepted as zero.

The Shapiro–Wilk test was used to assess whether the variables followed normal distribution. Variables were reported as mean ± SD, median (minimum:maximum) values and n (%). According to the normality test results, Kruskal-Wallis test and Anova test were used to compare groups. Categorical variables were compared by Chi square test, Fisher's exact test and Fisher-Freeman-Halton test. To estimate survival times Kaplan-Meier method was performed and the log-rank test was used to compare survival times across groups. Cox regression analysis was performed to determine the factors affecting mortality. $p < 0.05$ values were considered statistically significant. SPPS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) software was used for performing the statistical analysis.

The study was initiated after the approval of the Bursa Uludag University Faculty of Medicine Clinical Research Ethics Committee (29.03.2016, 2016-5/6).

Results

The demographic, laboratory, histopathologic, and clinical findings of the patients are given in table 1. The mean age of the patients was 51 ± 14.3 years, and 39 (60%) were male. 34 (52%) of the patients were diagnosed as MPA, 31 (48%) as GPA. 27 (41.5%) of the patients were p-ANCA / MPO positive, 27 (41.5%) were c-ANCA / PR3 positive, and 11 (17%) were ANCA negative. The mean number of glomeruli in biopsies was 16.1 ± 9.4. The number of glomeruli was 3 to 9 in 27.7% of kidney biopsies. Median follow-up length is 59.3 (0.6 – 204.9) months. In the first year after admission, 25 patients developed ESRD and needed RRT. During the total follow-up period, 33 patients progressed to ESRD, and mean duration from diagnosis to the start of RRT was 13.18±4.2 months. Plasmapheresis was applied to 12 patients, 6 of whom were in the crescentic group and 6 in the sclerotic group.

In Berden's ANCA-GN histopathological classification, 15 patients were in the focal group, 21 in the crescentic, 21 in the sclerotic, and 8 in the mixed group. When the histopathological classification was modified with age-related glomerulosclerosis, 8 of the 9 patients previously classified in the sclerotic group were classified in the mixed and 1 in the crescentic groups (Table 2). During the total follow-up period, ESRD developed in 5 of 9 patients whose histopathological classification changed.

In univariate analyses, the ANCA-GN histopathological classification model generated statistically significant predictions for renal survival **(p=0.022)** (Figure 1). It is seen that the focal group has the best renal survival, while the sclerotic group has the worst. There was no significant difference in renal survival between the crescentic and mixed groups (p=0.639). Modification of histopathological classification with age-related glomerulosclerosis increases the statistical significance in renal survival analysis **(p=0.009)**. 1- and 5-year cumulative ESRD-free survival rates are 59.7% and 46.4%, respectively.

The univariate Cox regression analysis was performed for age, gender, diagnosis, percentage of normal glomeruli, percentage of global sclerotic glomeruli, percentage of disease-related global sclerotic glomeruli, percentage of cellular crescentic glomeruli, histopathological class, modified histopathological class, pANCA, cANCA, GFR, serum creatinine, albumin, hematuria, proteinuria, white blood cell, neutrophil, lymphocyte, hemoglobin, platelet, NLR, ESH, CRP, RF, IgG, IgA, IgM, C3c, C4, presence of HT, presence of DM, lung involvement and plasmapheresis requirement. The percentage of normal glomeruli, percentage of global sclerotic glomeruli, percentage of disease-related global sclerotic glomeruli, histopathological class, modified histopathological class, GFR, and creatinine were included in the multivariate Cox regression model. Multivariate analysis showed that disease-related global sclerotic glomeruli percentage and creatinine were the only factors affecting renal survival. In order to determine the factors affecting mortality, a cox regression analysis was performed and the results are presented in table 3. Variables that provide $p<0.25$ condition in the univariable cox regression were included in the multivariable cox regression model and the obtained model was found to be significant ($p<0.001$). It was determined that

an increase of 1% in disease-related global sclerotic glomeruli percentage increased the risk of ESRD by 1.02 times, and an increase of 1 mg/dL in serum creatinine increased the risk of ESRD by 1.36 times **(p=0.006, and p<0.001, respectively)**.

Discussion

In our study, we confirmed that Berden's ANCA-GN histopathological classification model can predict the risk of ESRD with univariate analyses in the Turkish population. The focal group had the best renal survival and the sclerotic group had the worst. The crescentic and mixed groups had poorer renal survival from the focal group and better renal survival from the sclerotic group, but there was no statistically significant difference between the crescentic and mixed groups. We demonstrated that the classification could change when considering the age-related disease-independent sclerotic glomeruli.

Glomerulosclerosis, which is an expected finding in CKD, can also be seen independent to CKD, and its incidence increases with advanced age. Autophagy-mediated glomerular damage mechanisms with aging have been demonstrated. Failure to clean damaged organelles and proteins in cells results in podocyte damage, and these disorders have been termed age-related nephropathy. It is not possible to distinguish age-related global glomerulosclerosis from immunological causes. However, the data obtained from the Kremers et al. study enables the estimation of the number of these sclerotic glomeruli due to the natural course of age [21]. ANCA-GN is an advanced age disease and is generally seen in the 6th decade [2]. It is inevitable to have global sclerotic glomeruli associated with disease-independent aging in these patients. Sclerotic glomeruli in these patients may also be related to co-morbid diseases such as hypertension that increases with age. These factors can accelerate glomerulosclerosis regardless of age and vasculitic process. It should be noted that sclerotic glomeruli, which are the most important prognosis markers in ANCA-GN, may develop as a result of these processes. Podocyte loss and increase in parietal epithelial cell proliferation have been shown with aging in experimental studies [22]. Podocyte loss is the most important pathological marker determining the development of glomerulosclerosis [23]. We think that not all global sclerotic glomeruli in kidney biopsies obtained from ANCA-GN patients should be evaluated as disease-related, and it would be more meaningful to evaluate the number of disease-related sclerotic glomeruli by modifying with age-related glomerulosclerosis. This approach can reduce the unnecessary use of immunosuppressants with more accurate prognosis prediction. The proposal of Brix et al. to consider tubulointerstitial damage and renal functions together with glomerular involvement in the prognosis shows us the dynamic change in ANCA-related vasculitis classification [24].

The multivariate Cox regression analysis showed that Berden's histopathological classification and the modified histopathological classification did not significantly affect renal survival, which may be due to the small number of our study. However, the percentage of disease-related global sclerotic glomeruli, the main difference in the modified histopathological classification, was found to have a significant effect on renal survival, unlike the percentage of global sclerotic glomeruli, supporting that after modification of Berden's ANCA-GN histopathological classification model with age-related glomerulosclerosis, the statistical significance of the histopathological classification model may be increased.

Some limitations of our study merit comment, including the retrospective design, the small number of patients, the inclusion of biopsies with 3 to 9 glomeruli, and the histopathological scoring only based on data from the first biopsy interpretation by a nephropathologist. Berden et al. reported that there should be at least ten glomeruli from the biopsy material for histopathological classification [5]. However, it has been shown that biopsies containing 3 to 9 glomeruli can also be used for this classification [15]. Based on this study and due to the small number of patients in our cohort, we included kidney biopsies with 3 to 9 glomeruli in our study.

In conclusion, we think that modifying ANCA-GN histopathological classification with age-related glomerulosclerosis may increase the prognostic value of histopathological classification. Studies in larger patient populations may better reveal the importance of age-related glomerulosclerosis in the ANCA-GN histopathological classification.

Declarations

Conflicts of interest: The authors have declared that no conflict of interest exists.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (IRB approval number 2016-5/6) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Tables

Table 1 Demographic, laboratory, histopathologic, and clinical findings of the patients

	Focal, n=15	*Crescentic,* n=21	*Mixed,* n=8	*Sclerotic,* n=21	p-value
Age, *years*	50.9 (32:68)	47.5 (21:70)	56.4 (51:72)	54.9 (21:75)	0.346[a]
Male / female, *n (%)*	9 (60) / 6 (40)	15 (71.4) / 6 (28.6)	5 (62.5) / 3 (37.5)	10 (47.6) / 11 (52.4)	0.465[b]
MPA / GPA, *n (%)*	8 (53.3) / 7 (46.7)	9 (42.9) / 12 (57.1)	2 (25) / 6 (75)	15 (71.4) / 6 (28.6)	0.106[b]
ANCA, *n (%)*					
p-ANCA / MPO	7 (46.7)	6 (28.6)	4 (50)	10 (47.6)	0.538[b]
c-ANCA / PR3	7 (46.7)	10 (47.6)	4 (50)	6 (28.6)	0.538[b]
ANCA negative	1 (6.7)	5 (23.8)	0	5 (23.8)	0.294[b]
eGFR, *mL/min/1.73m^2*	26 (7:116)	21 (5:149)	19.5 (6:62)	15 (4:103)	0.153[a]
Creatinine, *mg/dL*	2.3 (0.8:8.2)	2.9 (0.7:10.3)	3.4 (1.3:7)	4.3 (0.6:10.7)	0.189[a]
Albumin, *g/dL*	3.14 ± 0.4	2.91 ± 0.59	2.98 ± 0.79	3.11 ± 0.48	0.581[c]
Leukocyte, *10^9/L*	12.7 (7.81:44.38)	11.15 (5.32:28.37)	13.66 (5.86:16)	11.44 (4.44:18.56)	0.644[a]
Neutrophil, *10^9/L*	9.125 (5.73:43)	8.535 (4.72:24.56)	11.905 (3.41:15.51)	8.553 (3.41:15.51)	0.581[a]
Lymphocyte, *10^9/L*	2.055 (0.69:3.38)	1.645 (0.901:2.73)	1.245 (0.602:2.7)	1.830 (0.61:7.7)	0.249[a]
NLR	4.6 (3.2:61.4)	5.3 (3.1: 16.5)	7.8 (4.4:23.1)	4.7 (1.8:12.7)	0.171[a]
Hemoglobin, *g/dL*	10.2 (6.7:12.4)	9.7 (8:14.6)	10.7 (9:12.5)	9.6 (6.5:17.1)	0.417[a]
Platelet, *K/µL*	365 (233:665)	382 (116:836)	359 (104:542)	245 (137:621)	0.102[a]
CRP, *mg/dL*	7.6 (0.3:33)	11.9 (0.3:21.1)	8 (1.4:25.4)	4.2 (0.2:51.5)	0.053[a]
ESR, *mm/hr*	71.6±27.1	69.8±33.7	59.6±30.2	47.1±29	0.092[c]

IgG, *mg/dL*	1445 (679:2520)	1395 (866:2500)	946 (627:1640)	1275 (544:1710)	0.097[a]
IgA, *mg/dL*	189 (146:599)	249 (106:613)	139.5 (24.9:225)	188 (95:472)	0.100[a]
IgM, *mg/dL*	66.3 (36:120)	71.9 (28.9:144)	59.2 (34.4:121)	73.9 (38.3:203)	0.802[a]
C3c, *mg/dL*	137±19.5	140±23.9	123.3±16.7	106.8±16.5	**<0.001[c]**
C4, *mg/dL*	27.9±11.5	30.7±10.5	31.8±3.8	24.7±6.9	0.226[c]
RF, *IU/mL*	48.4 (9.2:452)	20.7 (9.6:203)	-	28.4 (8.8:243)	0.309[a]
Proteinuria, *mg/24 h*	1070 (331:4778)	2500 (597:8160)	1581 (800:6857)	1985 (291:6831)	0.089[a]
Hematuria, *RBC/HPF*	27 (5:331)	85 (1:724)	38.5 (0:1025)	40 (1:225)	0.563[a]
Normal glomeruli, *%*	65 (50:100)	13 (0:40)	36.7 (16.7:44.4)	0 (0:25)	**<0.001[a]**
Cellular crescentic glomeruli, *%*	30 (0:50)	69.2 (53.3:100)	38,8 (27.3:44.4)	17.4 (0:50)	**<0.001[a]**
Sclerotic glomeruli, *%*	11.8 (0:41.7)	8.7 (0:46.7)	27.8 (11.1:45.5)	73.9 (50:100)	**<0.001[a]**
Lung involvement	11 (73.3)	7 (33.3)	5 (62.5)	8 (38.1)	0.073[b]
Hypertension	5 (33.3)	3 (14.3)	5 (62.5)	2 (9.5)	**0.013[b]**
Diabetes mellitus	2 (13.3)	1 (4.8)	0	3 (14.3)	0.608[b]
Plasmapheresis requirement	0	6 (28.6)	0	6 (28.6)	**0.033[b]**

MPA: microscopic polyangiitis, *GPA:* granulomatous polyangiitis, *ANCA:* anti-neutrophil cytoplasmic antibody, *MPO:* myeloperoxidase, *PR3:* proteinase 3, *eGFR:* estimated glomerular filtration rate, *NLR:* Neutrophil/lymphocyte ratio, *CRP:* c-reactive protein, *ESR:* erythrocyte sedimentation rate, *IgG:* immunoglobulin G, *IgA:* immunoglobulin A, *IgM:* immunoglobulin M, *RF:* rheumatoid factor, *RBC:* red blood cell, *HPF:* high power field

The data were expressed as mean ± standard deviation, median (minimum:maximum) and n(%).

a: Kruskal-Wallis test, b:Fisher Freeman Halton, c: Anova test

Table 2 Distribution of patients according to ANCA-GN histopathological classifications

	ANCA-GN Histopathological Classification, *n (%)*	Modified ANCA-GN Histopathological Classification, *n (%)*
Focal	15 (23.1)	15 (23.1)
Crescentic	21 (32.3)	22 (33.8)
Sclerotic	21 (32.3)	12 (18.5)
Mixed	8 (12.3)	16 (24.6)

ANCA-GN: Anti-neutrophil cytoplasmic antibody associated glomerulonephritis

Table 3 Determination of the factors affecting mortality

	Univariable Cox Regression Model			Multivariable Cox Regression Model		
	Wald	**HR (95%CI)**	**p-value**	**Wald**	**HR (95%CI)**	**p-value**
Age	0	1 (0.97:1.03)	0.992			
Diagnosis						
GPA	0.36	0.81 (0.41:1.61)	0.550			
Percentage of normal glomeruli	8.86	0.97 (0.95:0.99)	**0.003**			
Percentage of GSG	10.34	1.02 (1.01:1.03)	**0.001**			
Percentage of disease-related GSG	5.07	1.04 (1.01:1.08)	**0.024**	7.59	1.02 (1.01:1.03)	**0.006**
Histopathological classification						
Focal	5.90	0.26 (0.08:0.77)	**0.015**			
Crescentic	3.09	0.49 (0.22:1.09)	**0.079**			
Mixed	2.82	0.35 (0.09:1.19)	**0.093**			
Modified histopathological classification						
Focal	7.43	0.20 (0.06:0.64)	**0.006**			
Crescentic	4.09	0.42 (0.18:0.97)	**0.043**			
Mixed	4.63	0.35 (0.13:0.91)	**0.031**			
Creatinine	22.71	1.36 (1.20:1.55)	**<0.001**	19.42	1.36 (1.18:1.55)	**<0.001**
eGFR	6.09	0.97 (0.95:0.99)	**0.014**			

HR: hazard Ratio, *CI:* confidence Interval, *GPA:* granulomatous polyangiitis, *GSG:* global sclerotic glomeruli, *eGFR:* estimated glomerular filtration rate

Figures

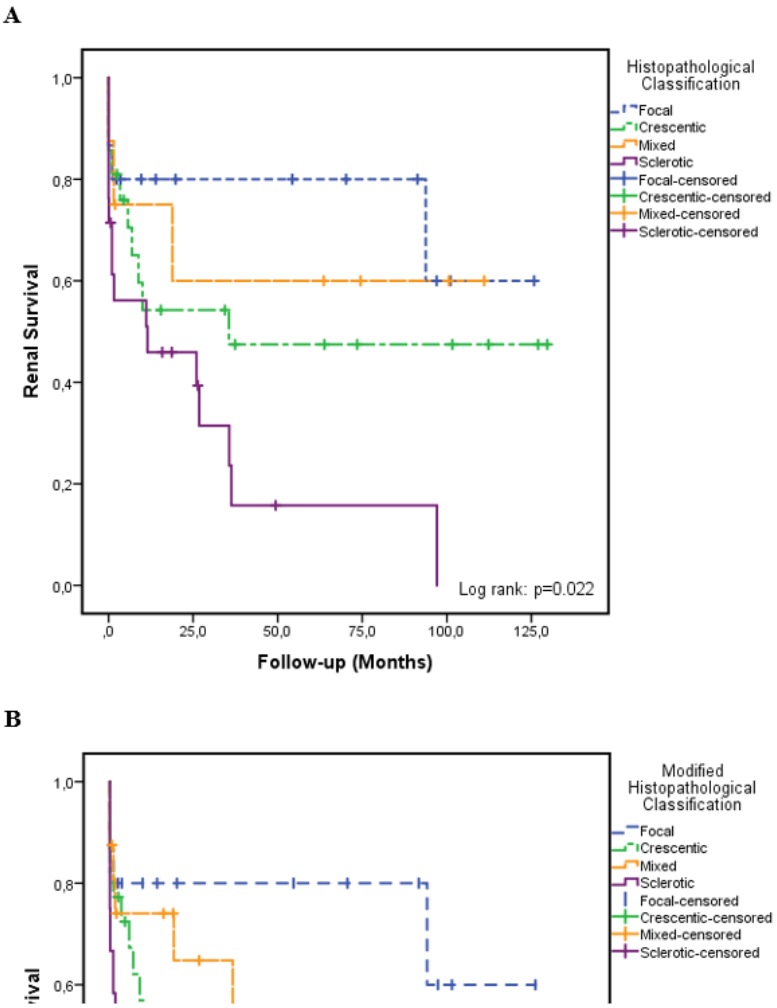

Figure 1

Kaplan-Meier plots showing cumulative risk of ESRD with ANCA-GN histopathological classification models