Predictors of renal survival in ANCA-associated vasculitis.
Validation of a histopathological classification schema and review of the literat

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INTRODUCTION / BACKGROUND

In 2010 an international working group of renal pathologists proposed a histopathological classification of ANCA-associated glomerulonephritis based on four general categories of lesions: focal, crescentic, mixed and sclerotic. They performed a validation study on 100 biopsies from patients with diagnosis of ANCA-associated vasculitis included in different randomised studies. The study shows that the phenotypical order of the above mentioned classes corresponds to the order of severity of renal function impairment at presentation, at 1 year and at 5-year follow-up. Since the paper of Berden *et al.* validation studies were performed in Japan, China, Australia, the United States, Europe, and Turkey. We have analysed retrospectively data from 93 patients who underwent renal biopsy at our centre with a diagnosis of ANCA-associated vasculitis to test the classification proposed.

METHODS

From January 1995 to December 2011 93 patients with newly diagnosed ANCA-associated small-vessel vasculitis and renal involvement were admitted to our Renal Unit. All patients received induction therapy with steroids (89.3% three methylprednisolone pulses followed with oral prednisone and 10.7% with oral prednisolone 1–2 mg/kg/day for 1–2 months than gradually reduced). In 82 patients (82%) oral cyclophosphamide 1.5–2 mg/kg/day was added to steroids and continued for a median of 7.5 months. In the other 11 patients azathioprine 2 mg/kg/day was added to prednisone. In addition, 12 patients (12.9%), received a course of plasma exchange. The statistical package S-Plus was used to analyse sample data. For continuous variables, the non-parametric Wilcoxon test was used. Cross-tabulated data were analysed by Chi-square test, or by Fisher's exact tes. Survival curves were drawn using the Kaplan-Meier estimate and compared using the log-rank test. The association of the histological classification and other clinical and histological features was evaluated with a multivariate Cox regression analysis.

RESULTS / ANALYSIS

Renal and patient outcome: After a mean follow-up of 62.7±62.9 months 36 patients (38.7%) had normal renal function, 10 patients (11%) had chronic renal insufficiency, 33 (35.5%) were on chronic dialysis and 14 patients (15%) died. Twelve other patients died in median 12.3 months after starting dialysis. **The pure kidney survival rate (without ESRD) was 83% at 1 year, 66% at 5 years, and 60% at 10 years. Patient survival was 92% at 1 year, 84% at 5 years and 81% at 10 years** (Fig. 1).
Histopathological classification and renal survival of histological classes: Twenty biopsies (21%) were classified as Focal, 28 (30%) as Crescentic, 36 (39%) as Mixed and 9 (10%) as Sclerotic (Table II). **Focal and Mixed classes had the same and the best renal outcome in comparison to the other classes** with a renal survival, respectively, of 88% and 94% at 1 year; of 82% and 81% at 5 years; of 82 and 75% at 10 years (p=0.7). **The renal outcome of Crescentic and Sclerotic groups were not different and the worst**, their renal survival was respectively 66% and 68.5% at 1 year, 37% and 51% at 5 years, and 37% and 25% at 10 years (p=0.9). The outcome of the crescentic group was significantly worse than that of the focal group (p=0.015) and from that of the mixed group (p=0.03). The outcome of the sclerotic group was significantly worse than that of the focal group (p=0.04) and from that of the mixed group (p=0.05) (Fig. 2).
Predictors of renal outcome: The univariate analysis is shown in Table 1.
At multivarite analysis several histological and clinical features emerged as indipendent predictors of ESRD (Tables 3).

Histological features	RR	IC	P		Clinical and histological features	RR	IC	P
Less than 20% of normal glomeruli	3.38	1.32-8.65	0.011		Serum Creatinine	1.11	1.03-1.21	0.009
Circumferential crescents	1.02	1.002-1.03	0.026		Arteial hypertension	5.54	1.6-18.8	0.06
Tubulointerstitial fibrosis	1.88	1.16-3.04	0.01		Less than 20% of normal glomeruli	3.05	1.17-7.93	0.022

Table III : Multivariate analysis; RR Relative risk; IC Confidence intervals

Five studies reported the 5 year renal survival of the four classes (Fig. 3). Only in one of these studies did the order of the survival of the four classes correspond to that reported by Berden *et al.*
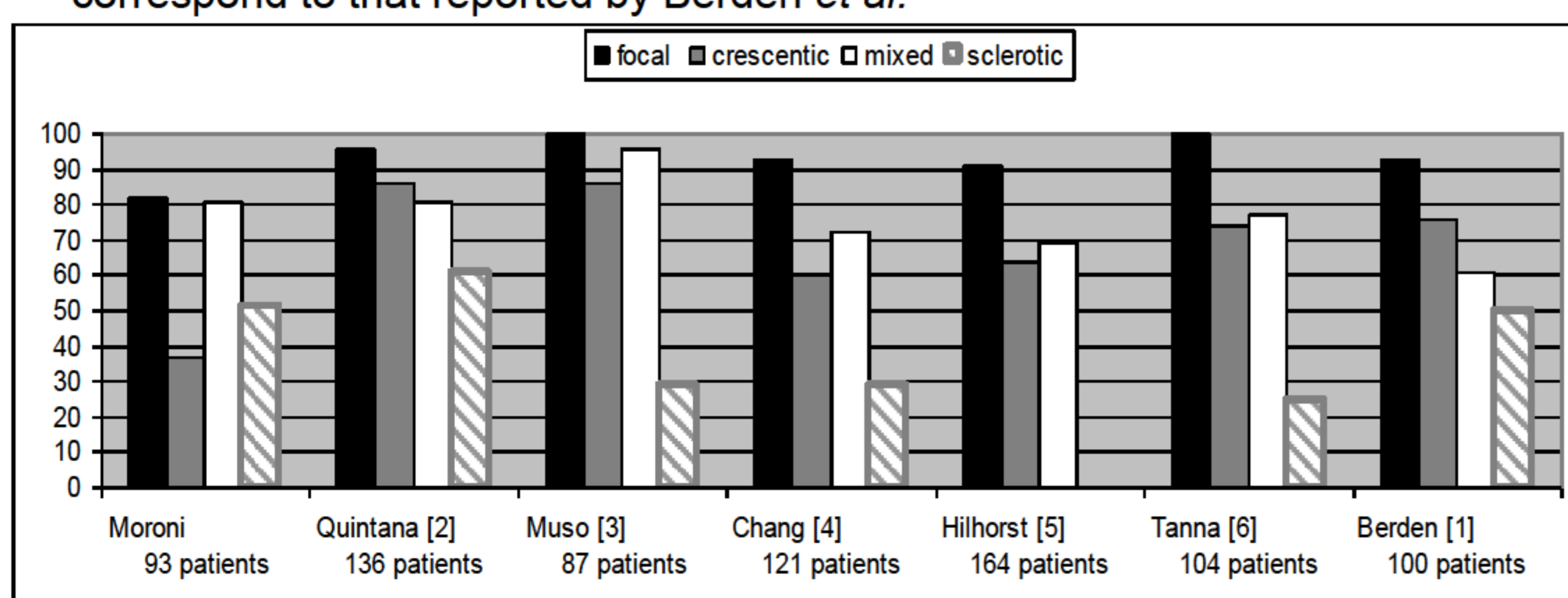
Figure 3: Renal survival of focal, crescentic, mixed and sclerotic histological classes of our studies and of the published studies who reported renal survival at 5 years.

	All patients 93 patients	ESRD 33 patients	No ESRD 60 patients	P
Follow-up months	62.7±62.9	33.15±48.0	78.3±64.9	0.0001
Female/male	44 /49	13/20	31/29	0.08
Age at diagnosis of vasculitis	58.4 ± 16.5	63±9.1	57±17.4	0.057
MPO positivity PR3 positivity ANCA negativity	46.3% 39.0% 14.6%	41.4% 44.8% 13.8%	49.1% 35.8% 15.1%	0.7
MPA GPA Kidney limited	36.5% 41.2% 10.7%	30% 39% 30%	40% 43% 17%	0.5
Arterial hypertension	52 (55.9%)	72.7%	46.7%	0.001
Serum creatinine mg/dl Serum creatinine ≥1.2mg/dl 87 patients	5.6 ± 4.4	8.3± 5.1	4.1±2.9	0.00001
GFR at diagnosis ml/min	23.2 ± 30.3	10.5±9.3	30.2±35.3	0.001
Proteinuria g/day Nephrotic syndrome 12 patients	1.9 ± 3.2	3.2± 5.05	1.3±1.6	0.03
Hemoglobin g/dl Hemoglobin <12.5 mg/dl 89 patients	9.6 ± 1.7	9.4± 1.4	9.8±1.8	0.2
Eosinophils %	3.2 ± 4.9	3.0± 3.5	3.2±5.5	0.6
Erythrocyte sedimetation rate	84.6 ± 33.3	92.05± 31.3	81.6±33.9	0.8
C reactive protein mg/dl	9.3±9.2	12.8± 10.4	7.8±8.3	0.01
C3 mg/dl	110.5 ± 29.5	100.9± 28.2	115.5±29.4	0.03
C4 mg/dl	31.1 ± 9.9	32.95± 10.0	30.3±9.9	0.39
Serum albumine g/dl	3.2 ± 0.7	3.25± 0.7	3.25±0.7	0.4
Number of urinary erythrocytes/HPF	63.5 ± 38.1	65.95±38.3	57.1± 37.9	0.26
Histological features				
Normal glomeruli N°(%)	8±12 (27.7%)	3.4±4.9 (14%)	7.5± 5.8 (53%)	0.004
Sclerotic glomeruli N° (%)	4.4±4.8 (19.3%)	5.3±6.4 (22.7%)	4±3.7 (17.5%)	0.17
Total Crescents. N° (%)	(46±5.7)	(53±28.8)	(34.4±27.8)	0.0007
Cellular crescents %	35±31	47.3±31.8	28±27.9	0.0007
Circumferential celluar crescents %	21±29.7	24.8±25.1	12.5±22.1	0.001
Vascular necrosis	18%	21.1%	17%	0.6
Moderate/severe interstitial inflammation	55.9%	75%	45%	0.02
Moderate/severe tubulointerstitial fibrosis	10.7%	21%	5%	0.002

Table I: Clinical, histological and therapeutical characteristics at presentation of all patients and of patients who developed and of those who did not develop end stage renal disease. Legend ESRD: end stage renal disease, GFR: glomerular filtration rate, MPA:microscopic polyangiitis, GPA: granulomatosis with polyangiitis, HPF: high power field.
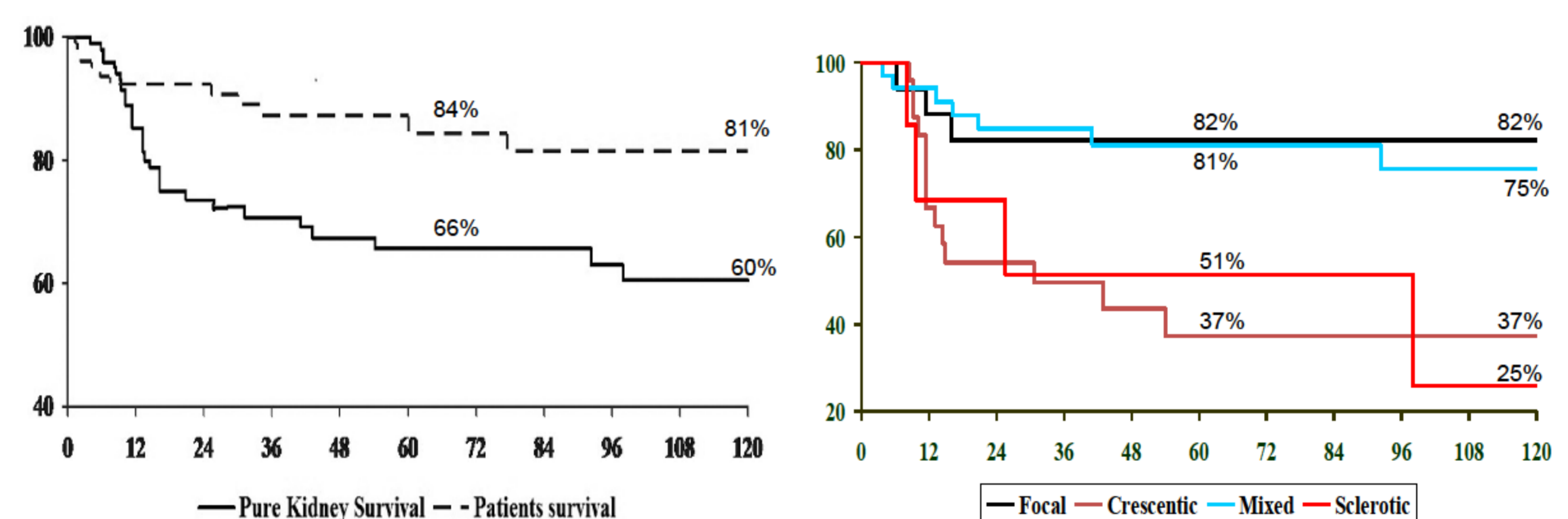
Figure 1: Kaplan-Meier estimates of patient (dashed line) and of survival without end-stage renal disease probability censored for death (solid line) in ANCA-associated renal small-vessel vasculitis.
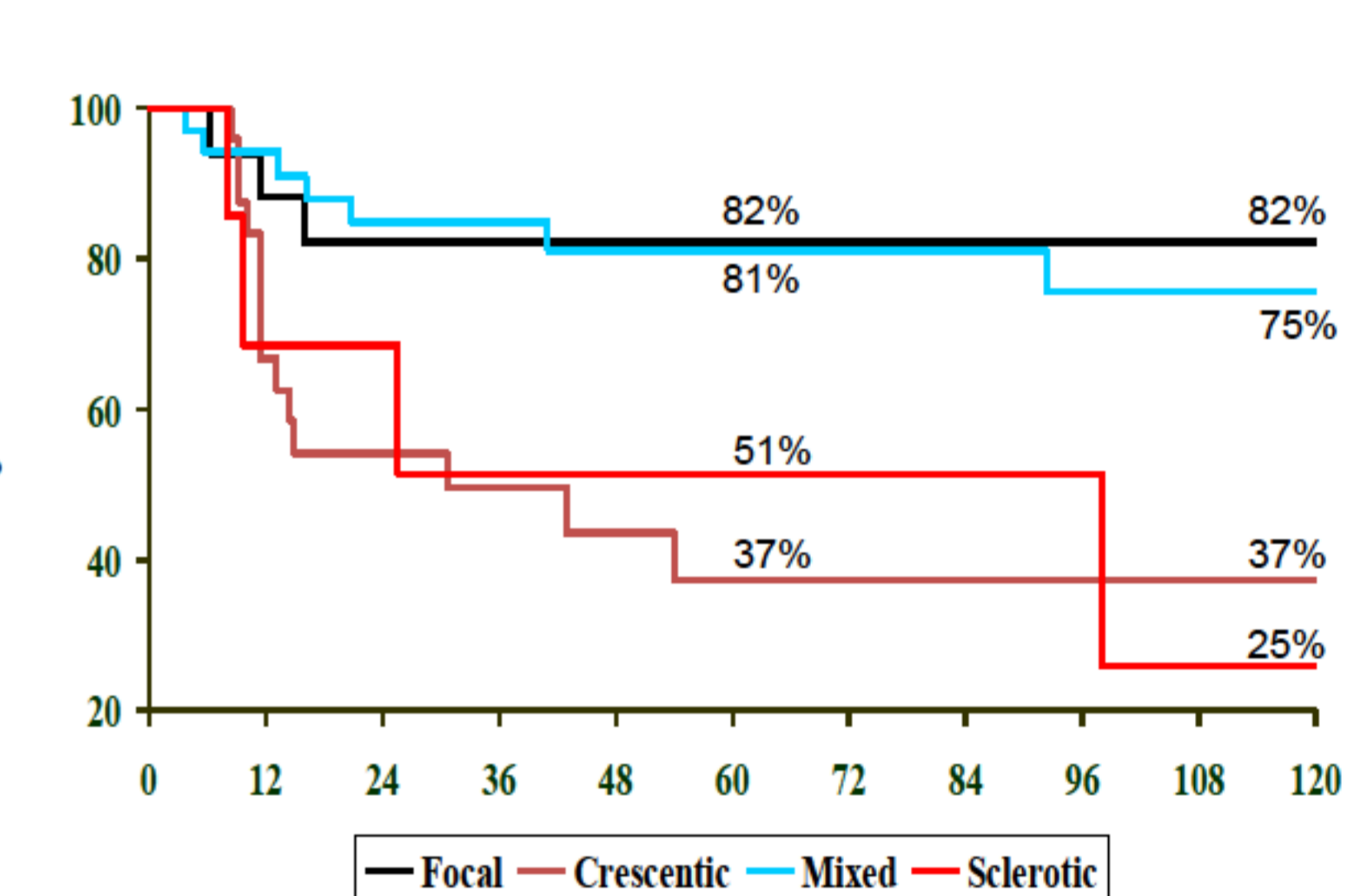
Figure 2: Kaplan-Meier estimates of survival without end-stage renal disease of the crescentic, mixed and sclerotic groups. p=0.00001, Focal vs. crescentic p=0.0015, Focal vs. sclerotic p=0.04, Focal vs. mixed p=0.07, Crescentic vs. mixed p=0.03, Crescentic vs. sclerotic p=0.9, Mixed vs. sclerotic p=0.05.

	Focal	Crescentic	Mixed	Sclerotic	P
Number of patients	20	28	36	9	
Number of glomeruli	20.6±8.2	20.8±11.5	24.3±13.5	20.8±13.4	Ns
Normal glomeruli n %	13.0±5.6 63±12.8	2.9±3.0 12.2±11.8	5.7±4.9 24.9±14.7	1.9±2.0 7.8±7.6	0.0000
Less than 20% normal glomeruli n patients (%)	20 (100%)	20 (71%)	13 (36%)	8 (88.8%)	0.0000
Crescentic glomeruli n %	2.8±3.4 13.7±14.0	15.3±8.7 75.6±17.3	5.4±5.2 20.3±13.5	3.0±2.3 13.5±9.7	0.0000
Circumferential cellular n crescents %	2.2±4.5	42.7±27.6	7.3±9.7	7.6±9.4	0.0002
Glomeruli with segmental necrosis %	9±9.8	34.4±27.9	15.8±17.2	6±8.9	0.006
Globally sclerotic glomeruli n %	2.6±2.2 12.3±8.9	2.6±3 11.6±8.9	5.1±4.7 19.7±13.2	11.8±8 58±9.5	0.002
Vascular fibrinoid necrosis n (%)	3 (15%)	9 (32%)	6 (16.6%)	0	0.1
Moderate/Severe Interstitial inflammation n (%)	7 (35%)	20 (71%)	18 (50%)	8 (88%)	0.01
Moderate/severe tubulointerstitial fibrosis n (%)	5 (25%)	6 (21.4%)	14 (38.8%)	8 (88%)	0.002

Table II: Histological features at kidney biopsy of the patients assigned to different glomerular classification groups.

CONCLUSIONS / RECOMMENDATIONS

In our cohort, the proposed histological classification was not predictive of renal prognosis. The focal and the mixed classes had the same prognosis and a significantly better renal outcome than both the crescentic and the sclerotic classes. At multivariate analysis among the histological features only less than 20% of normal glomeruli defines the renal prognosis together with renal function and arterial hypertension at baseline.

REFERENCES

1. BERDEN AE, FERRARIO F, HAGEN EC *et al.*: Histopathologic Classification of ANCA associated Glomerulonephritis. *J Am Soc Nephrol* 2010; 21: 1628-36.
2. QUINTANA LF, PERÉZ NS, De SOUSA E *et al.*: ANCA serotype and histopathological classification for the prediction of renal outcome in ANCA-associated glomerulonephritis. *Nephrol Dial Transplant* 2014; 29: 1764-9.
3. MUSO E, ENDO T, ITABASHI M *et al.*: Evaluation of the newly proposed simplified histological classification in Japanese cohorts of myeloperoxidase-anti-neutrophil cytoplasmic antibody-associated glomerulonephritis in comparison with other Asian and European cohorts. *Clin Exp Nephrol* 2013; 17: 659-62.
4. CHANG DY, WU LH, LIU G, CHEN M, KALLENBERG CG, ZHAO MH: Re-evaluation of the histopathologic classification of ANCA-associated glomerulonephritis: a study of 121 patients in a single center. *Nephrol Dial Transplant* 2013; 27: 2343-9.
5. HILHORST M, WILDE B, van BREDA VRIESMAN P, van PAASSEN P, COHEN TERVAERT JW: Estimating renal survival using the ANCA-associated GN classification. *J Am Soc Nephrol* 2013; 24: 1371-6.
6. TANNA A, GUARINO L, TAM FW *et al.*: Long-term outcome of anti-neutrophil cytoplasm antibody-associated glomerulonephritis: evaluation of the international histological classification and other prognostic factors. *Nephrol Dial Transplant* 2014; 0:1-8.