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Original Article

ORIGINAL ARTICLE

Adding 6-month parameters for the prediction of kidney prognosis in ANCA-associated glomerulonephritis

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ABSTRACT

Background. Antineutrophil-cytoplasmic antibody (ANCA)-associated vasculitis (AAV) with kidney involvement (AAV-GN) frequently evolves to end-stage kidney disease (ESKD) despite aggressive immunosuppressive treatment. Several risk scores have been used to assess renal prognosis. We aimed to determine whether kidney function and markers of AAV-GN activity after 6 months could improve the prediction of ESKD.

Methods. This retrospective and observational study included adult patients with AAV-GN recruited from six French nephrology centers (including from the Maine-Anjou AAV registry). The primary outcome was kidney survival. Analyses were conducted in the whole population and in a sub-population that did not develop ESKD early in the course of the disease.

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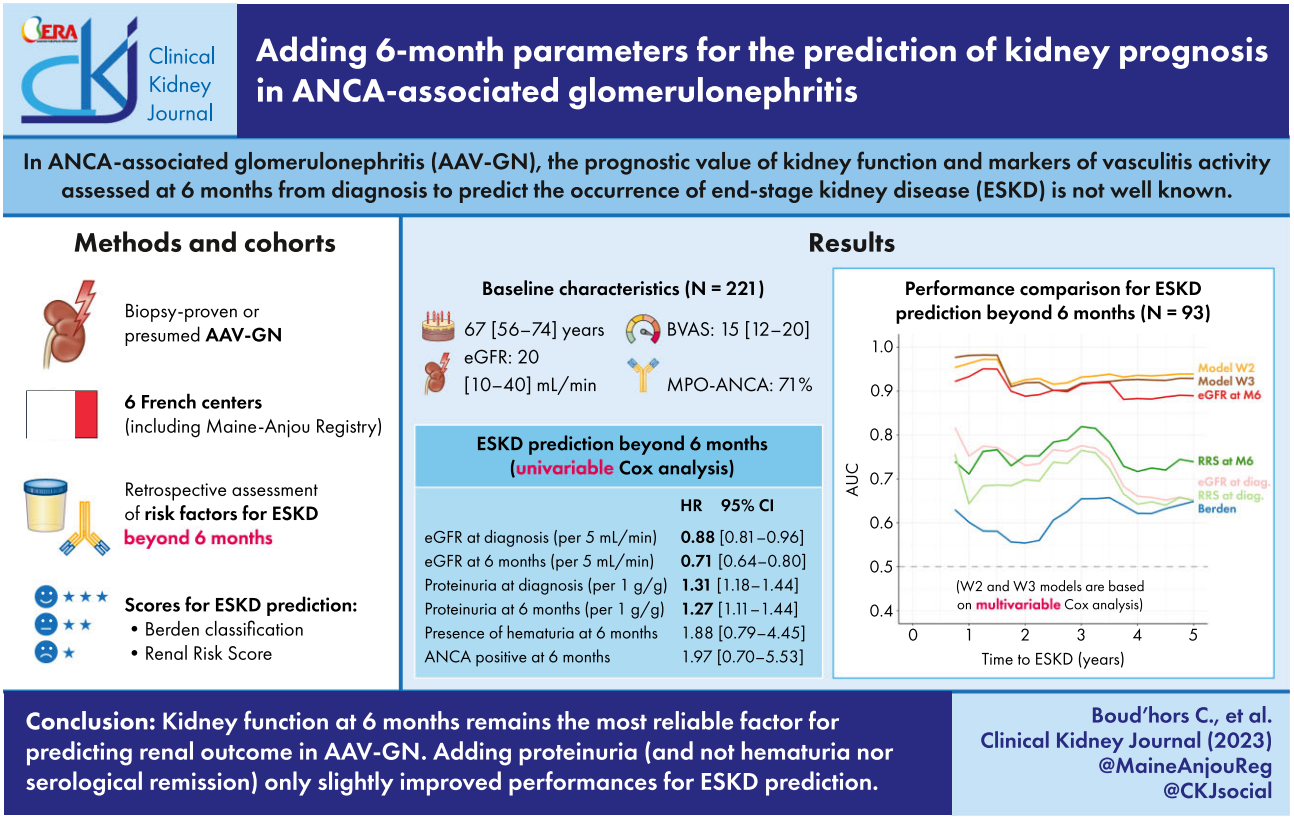
Results. When considering the 102 patients with all data available at diagnosis, Berden classification and Renal Risk Score (RRS) were not found to be better than kidney function [estimated glomerular filtration rate (eGFR)] alone at predicting ESKD (C-index = 0.70, 0.79, 0.82, respectively). Multivariables models did not indicate an improved prognostic value when compared with eGFR alone.
When considering the 93 patients with all data available at 6 months, eGFR outperformed Berden classification and RRS (C-index = 0.88, 0.62, 0.69, respectively) to predict ESKD. RRS performed better when it was updated with the eGFR at 6 months instead of the baseline eGFR. While 6-month proteinuria was associated with ESKD and improved ESKD prediction, hematuria and serological remission did not.
Conclusion. This work suggests the benefit of the reassessment of the kidney prognosis 6 months after AAV-GN diagnosis. Kidney function at this time remains the most reliable for predicting kidney outcome. Of the markers tested, persistent proteinuria at 6 months was the only one to slightly improve the prediction of ESKD.

GRAPHICAL ABSTRACT



Keywords: ANCA, ESKD, glomerulonephritis, prognosis, renal function

INTRODUCTION

Kidney involvement in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is particularly common, occurring in 70%–100% of cases [1]. Corticosteroids and immunosuppressive treatment must then be started as soon as possible [2]. Despite treatment, kidney injury leads to end-stage kidney disease (ESKD) in up to 40% of patients by 5 years [3]. Estimating the risk of progression to ESKD is thus a daily concern for nephrologists in order to select the most appropriate treatment and organize subsequent patient care. Several prognostic factors have been identified as associated with ESKD, such as advanced age or the severity of kidney involvement at diagnosis [4]. Some histological parameters are consensually associated with ESKD while others remain a matter of debate [5]. Based on these clinical, biological and histological factors, risk scores have been developed: the Berden histopathological classification [6] and the Renal Risk Score (RRS) [7]. The Mayo Clinic Chronicity score has also been evaluated in ANCA-associated glomerulonephritis (AAV-GN) [8, 9]. Other parameters associated with ESKD and not included in these scores have been identified: relapses involving the kidneys [10], proteinuria [11], anemia [11], lymphopenia [12] and serological remission [13].

Two types of patients reach ESKD over the disease course: those with severe kidney involvement at diagnosis, requiring early kidney replacement therapy (KRT) without further recovery despite treatment; and those who progress to ESKD during follow-up [14]. In this latter group, reclassifying the risk of ESKD a few months after the diagnosis may help improve AAV-GN management. Even if the definition of kidney response varies

Table 1: Baseline characteristics of the cohorts.

	Whole cohort, N = 241	WEE, N = 221	Early ESKD, N = 20
Baseline characteristics			
Male gender	151 (63)	138 (62)	13 (65)
Age (years)	67 (56–74)	67 (56–74)	72 (62–77)
Diabetes	26 (11)	25 (11)	1 (5.0)
Disease activity			
BVAS	15 (12–20)	15 (12–20)	17 (13–20)
Renal involvement	241 (100)	221 (100)	20 (100)
Pulmonary involvement	105 (44)	94 (43)	11 (55)
Neurological involvement	35 (15)	32 (15)	3 (15)
ENT involvement	85 (36)	81 (37)	4 (20)
Biological presentation at diagnosis			
Hemoglobin (g/dL)	9.90 (8.7–11)	10.00 (8.8–11.1)	8.60 (7.50–9.90)
CRP (mg/L)	54 (18–142)	50 (18–140)	94 (26–166)
ANCA-positive	233 (97)	214 (98)	19 (95)
MPO-ANCA	163 (71)	150 (71)	13 (68)
PR3-ANCA	66 (29)	60 (29)	6 (32)
Kidney function at diagnosis			
Creatinine (μmol/L)	248 (134–391)	226 (124–365)	656 (405–1002)
eGFR (mL/min)	20 (10–40)	23 (12–42)	5 (5–5)
Proteinuria (g/g)	1.30 (0.67–2.70)	1.20 (0.61–2.52)	2.80 (1.50–4.64)
Presence of hematuria	211 (92)	193 (91)	18 (95)
Pathological findings			
Kidney biopsy	215 (92)	199 (93)	16 (80)
% normal glomeruli	30 (13–50)	33 (16–52)	4 (0–8)
% crescentic glomeruli	38 (25–59)	37 (23–60)	42 (33–50)
% sclerotic glomeruli	14 (5–33)	12 (5–28)	50 (36–58)
Berden classification			
Focal	59 (29)	59 (31)	0 (0)
Crescentic	77 (37)	73 (38)	4 (25)
Mixed	41 (20)	39 (21)	2 (12)
Sclerotic	29 (14)	19 (10)	10 (62)
IF/TA (%)	20 (8–35)	20 (8–30)	30 (20–70)
RRS at diagnosis			
Low	38 (34)	38 (38)	0 (0)
Medium	49 (44)	46 (46)	3 (23)
High	25 (22)	15 (15)	10 (77)
RRS at 6 months			
Low	40 (38)	40 (43)	0 (0)
Medium	52 (49)	49 (53)	3 (23)
High	14 (13)	4 (4.3)	10 (77)

Data are presented as median (1st–3rd quartile) or *n* (%).
ENT: ear–nose–throat; CRP: C-reactive protein; MPO: myeloperoxidase; PR3: proteinase 3.

from a study to another, there is a consensus on the need to accurately assess this response [15]. We therefore sought to evaluate whether kidney function and selected markers of glomerulonephritis activity at 6 months could be good prognostic tools in a cohort of patients that did not develop ESKD early in the course of the disease. We first identified factors associated with ESKD and proposed various models for ESKD prediction. Then, we compared the performance of these models (including 6-month parameters) with preexisting scores.

MATERIALS AND METHODS

Selection of patients

This multicenter retrospective study included adult patients with AAV-GN from (i) the Maine-Anjou AAV registry, and (ii) Tours and Poitiers University Hospitals. The Maine-Anjou AAV registry [12, 13, 16] includes all successive AAV-GN patients diagnosed between 2000 and 2020 in four nephrology departments across central western France (Angers University hospital, Le Mans, Cholet and Laval General Hospitals). AAV-GN patients from Tours and Poitiers University Hospitals were consecutively diagnosed between 2003 and 2020. AAV diagnosis was based on the revised 2012 Chapel Hill Consensus Conference [17]. AAV-GN diagnosis was based on active kidney involvement (active urinary sediment with hematuria, proteinuria and/or impaired kidney function) and, in most cases, confirmed by kidney biopsy showing pauci-immune glomerulonephritis. Patients with <6 months of follow-up were excluded from the present study.

Data collection

Collected data at diagnosis are listed in Tables 1 and 2. Glomerular filtration rate was estimated (eGFR) by the Chronic Kidney Disease Epidemiology Collaboration research group equation

Table 2: Therapeutic management and outcomes.

	Whole cohort, N = 241	WEE, N = 221	Early ESKD, N = 20
Therapeutic management Induction			
Plasma exchange	58 (24)	50 (23)	8 (40)
Intravenous corticosteroids	203 (85)	184 (84)	19 (95)
Oral corticosteroids	234 (99)	214 (99)	20 (100)
Cyclophosphamide	177 (74)	158 (72)	19 (95)
Rituximab	50 (21)	49 (22)	1 (5.3)
Maintenance			
Corticosteroids	235 (98)	215 (98)	20 (100)
Rituximab	126 (53)	123 (57)	3 (15)
Azathioprine	112 (47)	103 (47)	9 (45)
Follow-up duration (months)	59 (30–111)	61 (32–113)	28 (20–74)
Kidney replacement therapy (KRT)			
At least once during follow-up	81 (34)	61 (28)	20 (100)
KRT within 30 days from diagnosis	44 (18)	25 (11)	19 (95)
KRT duration			
Never	159 (66)	159 (72)	0 (0)
Less than 3 months	19 (7.9)	19 (8.6)	0 (0)
More than 3 months (ESKD)	62 (26)	42 (19)	20 (100)
Biological parameters at 6 months			
Creatinine (μmol/L)	136 (110–204)	136 (110–204)	
eGFR (mL/min)	36 (20–54)	38 (24–55)	
ΔeGFR M0–M6		+10 (1–20)	
Proteinuria (g/g)	0.70 (0.26–1.46)	0.64 (0.26–1.44)	4.37 (3.58–5.15)
Presence of hematuria	69 (54)	65 (54)	4 (50)
CRP (mg/L)	4 (4–10)	4 (4–10)	8 (7–36)
ANCA-positive at 6 months	83 (70)	78 (68)	5 (100)
Relapses	75 (32)	71 (33)	4 (20)
With kidney involvement	47 (62.7)	45 (63.4)	2 (10)
Kidney survival			
ESKD during follow-up	62 (26)	42 (19)	20 (100)
ESKD at diagnosis	18 (7.5)	0 (0)	18 (90)
Overall survival (death)	66 (28)	55 (25)	11 (55)

Data are presented as median (1st–3rd quartile) or *n* (%).
CRP: C-reactive Protein; M0: at diagnosis; M6: at 6 months.

[18]. Berden's histopathological classification was assessed for every kidney biopsy [6]. The RRS [7] was assessed for patients from the Maine-Anjou Registry after quantification of interstitial fibrosis and tubular atrophy (IF/TA) by the same pathologist (M.-C.C.) for the purpose of the study. At 6 months, the following data were collected: creatinine, eGFR, C-reactive protein, proteinuria, hematuria (defined by >10 erythrocytes/mm^3 on urinalysis) and ANCA status (positive in indirect immunofluorescence and/or quantitative enzyme immunoassay, or negative using both techniques).

Definitions and outcomes

ESKD was defined as the need for KRT for at least 3 months or the need for kidney transplantation. The primary outcome of our analysis was kidney survival, i.e. the time to reach ESKD. Early ESKD was defined as ESKD occurring during the first 6 months of follow-up. Since the goal of this study was to evaluate the contribution of 6-month parameters in establishing the prognosis of AAV-GN, analyses were conducted in the whole population and also in a sub-population that did not develop early ESKD [hereafter called the without-early-ESKD (WEE) cohort].

Statistical analysis

Continuous variables were described with median (1st–3rd quartile); categorical variables were described with count and percentage. Correlations between continuous variables were assessed using Pearson's correlation coefficient. For the estimation of death-censored kidney survival, a Kaplan–Meier analysis was performed, and survival curves were compared with a log-rank test.

Cox proportional hazards regression analysis was performed to examine factors associated with the occurrence of ESKD (death-censored kidney survival). Multivariable Cox regression analysis included all parameters with a *P*-value <.1 in the univariable analysis or parameters judged as clinically relevant. To improve the multivariable models, variable selection was performed using manual step-by-step backward selection with a removal criterion of $P > .1$. Variance inflation factor (VIF) was computed to check the absence of collinearity against dependent variables. Hazard ratios (HR) with 95% confidence intervals (CI) were reported.

Several performance indices were used for the assessment of the predictive values of each variable, model or classification: (i) global C-index [19], (ii) time-dependent area under receiving

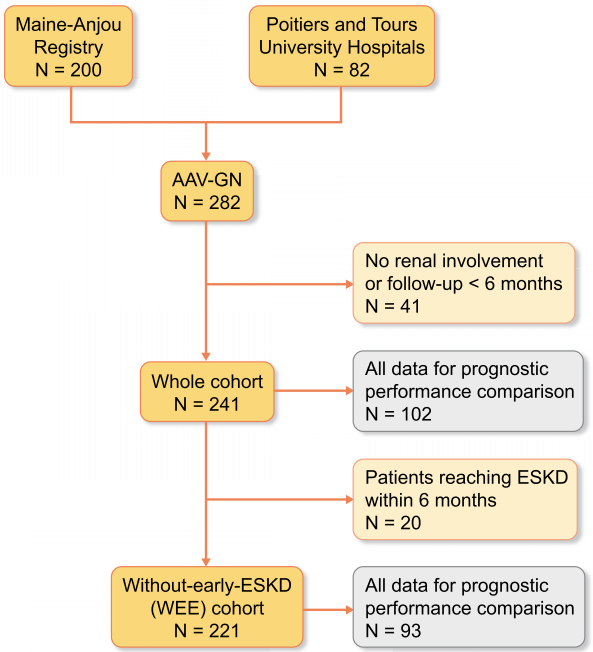


Figure 1: Flowchart of the study.

operating curve (AUROC) [20] and (iii) time-dependent Brier score [21]. The C-index and the AUROC measure the discrimination of a model (ranging from 0 to 1, higher is better). The Brier score assesses prediction error of a model (ranging from 0 to 1, lower is better).

For the determinants of the eGFR at 6 months, a linear regression analysis was performed with a methodology similar to the Cox analysis described above. Beta coefficients with 95% CI were reported.

No imputation of missing data was performed. Statistical analyses were performed using the R software v4.0 with the following packages: *survival*, *survminer*, *pec*, *timeROC* and *performance*. All tests were two-sided, and a *P*-value <.05 was considered statistically significant.

Ethical issues

The Maine-Anjou Registry has been declared and authorized by the "Commission Nationale Informatique et Libertés" (agreement number 2018-MR03-02). Patients gave their non-opposition for their participation to this research. This study was approved by the local ethics committee of Angers University Hospital (2022-044).

RESULTS

Baseline characteristics of patients

Two hundred and forty-one patients were included in the present study ("whole cohort"). Twenty (8.3%) experienced early ESKD and were excluded from the "WEE" cohort (Fig. 1). Baseline characteristics of these cohorts are shown in Tables 1 and 2.

In the WEE cohort, 62% were male, with a median age of 67 (56–74) years. Median Birmingham Vasculitis Activity Score (BVAS) was 15 (12–20), 43% of patients had pulmonary and 37% ear–nose–throat involvement. Some 214 patients (98%) were ANCA-positive, 150 (71%) had anti-myeloperoxidase and 60 (29%) had anti-proteinase 3. At diagnosis, median eGFR was 23 (12–42) mL/min, median proteinuria was 1.20 g/g (0.61–2.52) and 193 patients (91%) had hematuria. The induction treatment included corticosteroids for most patients in addition with cyclophosphamide (72%) or rituximab (22%). These baseline characteristics were similar to those of the whole cohort.

Follow-up data and evolution at 6 months

The median follow-up in the WEE cohort was 61 (32–113) months. Twenty-five patients (11%) required KRT within the first 30 days after diagnosis, but none developed ESKD afterwards. In this cohort, at 6 months, median eGFR was 38 (24–55) mL/min, median proteinuria was 0.64 (0.26–1.44) g/g and 65 (54%) patients still had hematuria. ANCA remained detectable for 78 (68%) patients. During this follow-up, 42 patients (19%) reached ESKD, 55 (25%) died and 71 (33%) experienced a relapse, including 45 (63%) with kidney involvement (of which 4 occurred before 6 months). ESKD-free survival is shown in Supplementary data, Fig. S1. Except for data pertaining to ESKD, there was no major difference when compared with the whole cohort (Tables 1 and 2).

Kidney survival according to current classifications and eGFR stages

Berden histopathologic classification was strongly associated with kidney survival ($P < .0001$, Fig. 2A). In the whole cohort, the focal class had the best kidney prognosis, and the sclerotic class had the worst. In the WEE cohort, the focal class kept the best kidney prognosis, but the three other classes had a more similar prognosis ($P = .0081$, Fig. 2B). RRS was also strongly associated with kidney survival ($P < .0001$, Fig. 2C and D). The low-risk group had the best kidney prognosis both in the whole and the WEE cohort. Lastly, kidney survival was strongly associated with eGFR, either at diagnosis in the whole cohort ($P < .0001$, Fig. 2E) or at 6 months in the WEE cohort ($P < .0001$, Fig. 2F).

Performance of classifications and eGFR for kidney survival prediction (at diagnosis)

In the whole cohort, comparison of eGFR at diagnosis, Berden classification and RRS performance for ESKD prediction could be made for the 102 patients for whom all data were available. The C-index was the highest for the eGFR alone (0.82, 95% CI 0.75–0.90), followed by the RRS (0.79, 95% CI 0.70–0.88) and the Berden classification (0.70, 95% CI 0.61–0.79) (Table 3). The eGFR also had the best prognostic performance overtime of these three models when using the AUC and the Brier score. Berden classification showed the poorest performance (Fig. 3A and B and Supplementary data, Table S1).

Performance of classifications and eGFR for kidney survival prediction (at 6 months)

In the WEE cohort, comparisons could be made for 93 patients. In this cohort, the eGFR at 6 months had the best discriminatory power (C-index = 0.88, 95% CI 0.80–0.96). C-index was lower for the RRS (0.69, 95% CI 0.56–0.81) and for the Berden classification (0.62, 95% CI 0.52–0.73) (Table 3). When the RRS was updated with the eGFR at 6 months (but not for the two other histopathological parameters), it performed better than the RRS at diagnosis

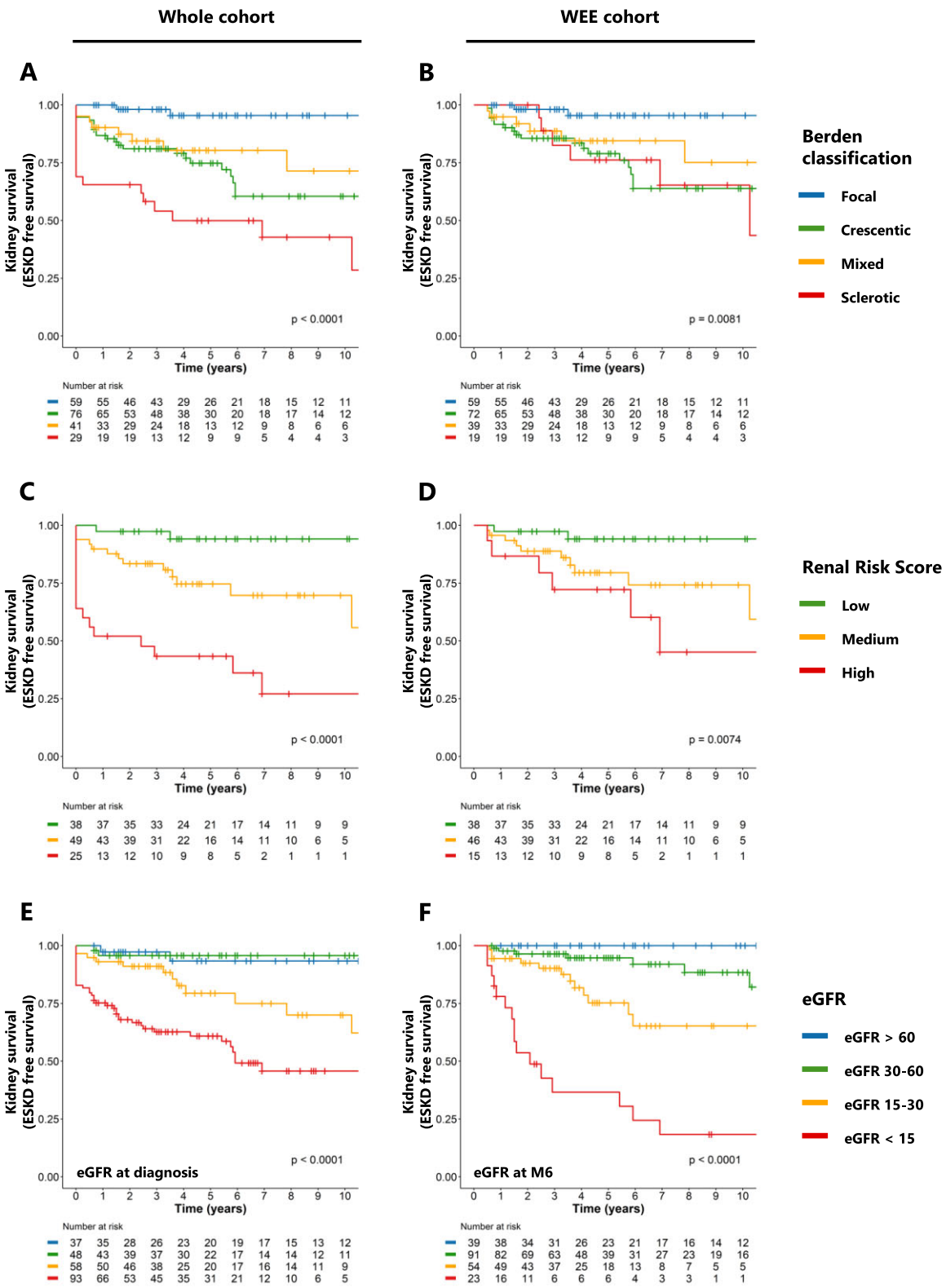


Figure 2: Kidney survival according to scores and kidney function. Kidney survival according to Berden classification in the whole cohort (**A**) or in the WEE cohort (**B**); according to RRS in the whole cohort (**C**) or in the WEE cohort (**D**); according to kidney function estimated with eGFR, either at diagnosis (**E**) in the whole cohort or at 6 months in the WEE cohort (**F**).

Table 3: C-index values for ESKD prediction.

		For each isolated variable or model			Only for patients with all variables available and selected models		
		N	C-index	95% CI	N	C-index	95% CI
Prediction of ESKD, whole cohort at diagnosis	Berden	205	0.70	0.62–0.79	102	0.70	0.61–0.79
	RRS	112	0.81	0.73–0.89		0.79	0.70–0.88
	eGFR at diagnosis	236	0.77	0.71–0.84		0.82	0.75–0.90
	Model D1	201	**0.81**	0.75–0.87		**0.84**	0.77–0.91
	Model D2	187	0.79	0.71–0.87			
	Model D3	201	**0.81**	0.75–0.87			
	Model D4	186	**0.81**	0.74–0.89		0.83	0.75–0.91
Prediction of ESKD, WEE cohort at M6	Berden	189	0.60	0.52–0.68	93	0.62	0.52–0.73
	RRS with eGFR at diagnosis	99	0.70	0.58–0.82		0.69	0.56–0.81
	RRS with eGFR at M6	93	0.74	0.63–0.84		0.74	0.63–0.84
	eGFR at diagnosis	216	0.70	0.61–0.79		0.71	0.60–0.82
	eGFR at M6	207	0.83	0.77–0.90		0.88	0.80–0.96
	Model W1	135	0.88	0.82–0.95			
	Model W2	181	0.89	0.84–0.94		**0.92**	0.85–0.98
	Model W3	95	**0.91**	0.83–0.98		0.91	0.84–0.99
	Model W4	135	0.88	0.82–0.95			

The C-index values for ESKD prediction were first computed for each variable or pathological scores or models individualy (varying number of patients, *N*). Second, the C-index values were computed for patients with data available regarding all variables of interest and selected models ($N = 102$ in the whole cohort, at diagnosis; $N = 93$ in the WEE cohort, at 6 months).
Bold type indicates the best values.
M6: at six months.

(C-index = 0.74, 95% CI 0.63–0.84) (Table 3). The same was observed using AUC and Brier score, with the highest AUC and the lowest Brier score overtime for the 6 months eGFR, a better performance for the RRS updated at 6 months (vs RRS at diagnosis) and the lowest AUC and the highest Brier score for the Berden classification (Fig. 3C and D, and Supplementary data, Table S1).

Prognostic factors of kidney survival in the whole cohort (at diagnosis)

Supplementary data, Table S2 shows variables associated with ESKD in the whole cohort. Glomerular involvement, eGFR (HR = 0.82 per 5 mL/min increment, 95% CI 0.75–0.89, *P*-value <.001, Fig. 2E) and the amount of proteinuria (HR = 1.27 per 1 g/g increment, 95% CI 1.18–1.36, *P*-value <.001, Supplementary data, Fig. S2A) were the most strongly associated with kidney survival.

Several multivariable models with non-redundant variables were then built. The four best models are presented in Table 4. Their performances were very similar (Table 3 and Supplementary data, Table S1). The best models (D1 and D4) were retained for further comparisons (Fig. 3A and B). The Model D1 included percentage of crescentic and sclerotic glomeruli, eGFR at diagnosis and proteinuria. When considering the 102 patients for whom all data were available (variables and models), it had a high C-index (0.84, 95% CI 0.77–0.91), a high AUC (0.90, 0.88, 0.81) and a low Brier score (0.08, 0.10, 0.14) at 1, 2 and 5 years, respectively, for the prediction of ESKD. The Model D4, which included proteinuria and hemoglobin at diagnosis, KRT within 30 days and Berden classification, also performed well with a high C-index (0.83, 95% CI 0.75–0.91), a high AUC (0.94, 0.86, 0.81) and a low Brier score (0.06, 0.09, 0.14) at 1, 2 and 5 years, respectively, for the prediction of ESKD.

Overall, eGFR alone (and newly developed models) were more performant for the prediction of ESKD, in comparison with Berden classification or RRS (Table 2, Supplementary data, Table S1, and Fig. 3A and B). Newly developed models had better prediction error (Fig. 3B) but similar discriminatory power (Fig. 3A) than eGFR alone.

Prognostic factors of kidney survival in the WEE cohort (at 6 months)

Supplementary data, Table S3 shows variables associated with ESKD in the WEE cohort. There was no association between kidney survival and the persistence of hematuria nor with ANCA positivity at 6 months. In contrast, eGFR (HR = 0.71 per 5 mL/min increment, 95% CI 0.64–0.80, *P*-value <.001, Fig. 2F) and the amount of proteinuria (HR = 1.27 per 1 g/g increment, 95% CI 1.11–1.44, *P*-value <.001, Supplementary data, Fig. S2B) were strongly associated with kidney survival. Of note, proteinuria at 6 months significantly correlated with the percentage of normal or crescentic glomeruli, but not with the percentage of sclerotic glomeruli or with IF/TA (Supplementary data, Fig. S2C).

As described above for the whole cohort, several multivariable models with non-redundant variables were then built. The four best models are presented in Table 5. Their performances were very similar (Table 2 and Supplementary data, Table S1). The best models (W2 and W3) were retained for further comparisons (Fig. 3C and D). The Model W2 included sex, percentage of crescentic glomeruli, eGFR at 6 months and variation of eGFR between diagnosis and 6 months. When considering the 93 patients for whom all data were available (variables and models), it had a high C-index (0.92, 95% CI 0.85–0.98), a high AUC (0.96, 0.93, 0.94) and a low Brier score (0.03, 0.04, 0.06) at 1, 2 and 5 years, respectively, for the prediction of ESKD. The Model W3 included sex, eGFR at diagnosis and at 6 months, IF/TA and proteinuria at diagnosis. It also had a high C-index (0.91, 95% CI 0.84–0.99), high AUC (0.98, 0.92, 0.93) and low Brier score (0.02, 0.04, 0.06) at 1, 2 and 5 years, respectively, for the prediction of ESKD.

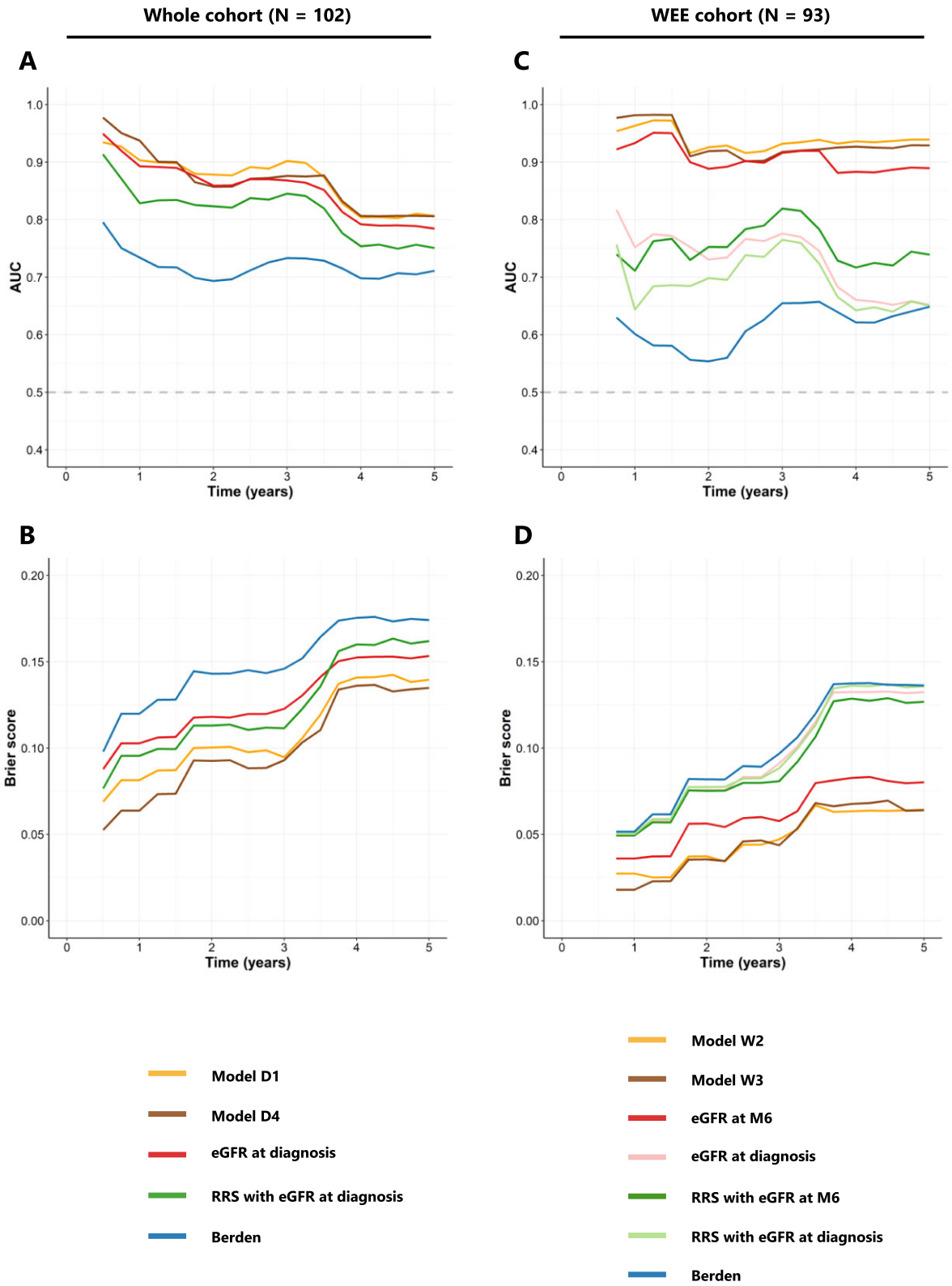


Figure 3: Performance of scores and models for the prediction of ESKD. Comparison of the prognostic performance of scores, models and eGFR for the prediction of ESKD in the whole cohort (**A**, **B**) or in the WEE cohort (**C**, **D**) using AUC (A–C) and Brier score (B–D). Performance for ESKD prediction was computed for patients with data available regarding all variables of interest and selected models ($N = 102$ in the whole cohort, at diagnosis; $N = 93$ in the WEE cohort, at 6 months).

Table 4: Multivariable Cox analysis for the determination of factors associated with ESKD in the whole cohort (at diagnosis).

	Model D1 (*N* = 201)			Model D2 (*N* = 187)			Model D3 (*N* = 201)			Model D4 (*N* = 186)		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
% crescentic glomeruli	1.02	1.00–1.04	**.018**									
% sclerotic glomeruli	1.03	1.01–1.05	**.002**	1.02	1.00–1.03	**.010**						
eGFR at diagnosis (per 5 mL/min)	0.86	0.77–0.96	**.009**				0.85	0.76–0.95	**.004**			
Proteinuria at diagnosis	1.16	1.05–1.27	**.003**	1.19	1.07–1.31	**<.001**	1.15	1.05–1.27	**.003**	1.19	1.08–1.32	**<.001**
Hemoglobin at diagnosis				0.85	0.71–1.01	.071				0.83	0.69–1.00	**.050**
KRT within 30 days				6.45	3.51–11.8	**<.001**				6.03	3.29–11.6	**<.001**
Berden classification												
Focal												
Crescentic							2.72	0.78–9.55	.12	1.73	0.47–6.41	.4
Mixed							2.29	0.59–8.84	.2	2.73	0.70–10.7	.2
Sclerotic							5.54	1.54–19.9	**.009**	5.08	1.37–18.8	**.015**

Four multivariable Cox models have been built, named Models D1 to D4, to predict ESKD at diagnosis in the whole cohort.

Table 5: Multivariable Cox analysis for the determination of factors associated with ESKD in the WEE cohort (at 6 months).

	Model W1 (*N* = 135)			Model W2 (*N* = 181)			Model W3 (*N* = 95)			Model W4 (*N* = 135)		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Male sex	3.86	1.33–11.2	**.013**	3.74	1.63–8.58	**.002**	2.82	0.88–9.05	.082	3.86	1.33–11.2	**.013**
eGFR at diagnosis (per 5 mL/min)	1.32	1.14–1.52	**<.001**				1.47	1.14–1.90	**.003**			
eGFR at M6 (per 5 mL/min)	0.53	0.42–0.67	**<.001**	0.70	0.63–0.79	**<.001**	0.38	0.25–0.58	**<.001**	0.69	0.60–0.80	**<.001**
Proteinuria at M6	1.34	1.13–1.60	**<.001**							1.34	1.13–1.60	**<.001**
% crescentic glomeruli				1.02	1.01–1.04	**.006**						
ΔGFR M0-M6 (per 5 mL/min)				0.73	0.63–0.85	**<.001**				0.76	0.66–0.88	**<.001**
IF/TA							0.97	0.95–1.00	**0.036**			
Proteinuria at diagnosis							1.40	1.07–1.82	**0.013**			

Four multivariable Cox models have been built, named Models W1 to W4, to predict ESKD at 6 months in the WEE cohort.
M6: at 6 months.

Overall, at 6 months, eGFR alone (and newly developed models) were more performant for the prediction of ESKD, in comparison with Berden classification or RRS (even after update with 6 months eGFR) (Table 3, Supplementary data, Table S1, and Fig. 3C and D). Again, newly developed models had better prediction error than (Fig. 3D) but similar discriminatory power to (Fig. 3C) eGFR alone.

DISCUSSION

In the present study, we evaluated the prognostic value of kidney function and markers of glomerulonephritis activity at 6 months for the reassessment of ESKD risk in AAV-GN. We also proposed several models for ESKD prediction and compared them with current pathological-based classifications.

Prognosis assessment in AAV-GN is a daily concern for the clinician when choosing the appropriate immunosuppressive treatment and preparing for upcoming kidney replacement therapy. From this perspective, several classifications have emerged to identify patients that are at high risk of developing ESKD [5]. In our study, as in others [16, 22, 23], we found that the performance of the RRS was superior to the Berden classification. However, both classifications performed less well than the eGFR at diagnosis alone (suggesting that points attributed to eGFR in the RRS could be optimized).

As described by Lionaki *et al.* [14], there are two ways for patients to reach ESKD in AAV-GN: either at the outset of a severe kidney disease, without recovery despite immunosuppressive treatment, or later during the clinical course of chronic kidney disease without evidence of vasculitis activity. The WEE cohort from our study allowed us to focus on this latter group of patients. Unsurprisingly, eGFR at diagnosis and at 6 months were predictors of ESKD. We developed various models at diagnosis and at 6 months that did not show much more than a small decrease in prediction error, when compared with eGFR alone. Nevertheless, 6-month eGFR and these models had better performances than the current pathological-based classifications for ESKD prediction. Interestingly, only proteinuria at 6 months was associated with kidney survival, in contrast to hematuria or ANCA positivity (i.e. serological remission not achieved) which were not.

Studies focusing on the prognostic value of kidney function a few months after the diagnosis are rare but all were consistent with our results [24–27]. If several studies suggested that proteinuria at diagnosis was associated with kidney survival [11, 28], few were interested in persistent proteinuria after treatment. In the study by de Joode *et al.*, proteinuria at 6 months had no significant prognostic value [24]. In contrast, and consistent with our results, Benichou *et al.* reported the outcomes of 571 patients in whom a persistent proteinuria was independently associated with ESKD or death (composite outcome) in a recent *post hoc* analysis of five major trials conducted by the European Vasculitis Study Group (EUVAS) [29]. Thus, as in other glomerulopathies, strategies to lower proteinuria (such as renin–angiotensin system inhibitors, or, as suggested recently, sodium/glucose cotransporter 2 inhibitors [30]) could be of particular interest to reduce kidney failure risk, and should be evaluated in this specific population. While Gopaluni *et al.* found that patients who had not achieved remission by 6 months (defined by BVAS = 0) were at higher risk of ESKD [31], our study is congruent with previous ones, including Benichou's [29], that showed no association between persistent hematuria and ESKD [32, 33]. Interestingly, serological remission at 6 months was not associated with kidney survival, as found by another study [34], strengthening the idea that it is the evolving profile, more than the 6-month status, that is important, as our group and others demonstrated recently [13, 35, 36].

Considering these data and our results, estimating the long-term kidney prognosis of patients who do not develop ESKD early may be more accurate after the induction treatment, which ends approximately at 3–6 months from the diagnosis. The prognostic interest of kidney biopsy has largely been confirmed in AAV-GN, independently of kidney function at diagnosis [5, 22, 37, 38]. Our results raise the question of whether delayed initial biopsy or second look/repeated biopsies have a place during follow-up, for example for the assessment of disease activity within the kidney, the long-term prognosis or the management of maintenance treatment. Few studies have examined repeated follow-up biopsies in AAV-GN outside of the case of kidney relapses. Hruskova *et al.* described 17 patients who underwent systematic kidney biopsy after 1 year of treatment. They found a decrease of acute lesions associated with various degrees of stagnation or aggravation of chronic lesions [39]. More recently, another study focused on the utility of repeated kidney biopsy, for the purpose of confirming the remission of the disease after induction treatment. They found fewer acute and more chronic lesions in the interval biopsies, and these interval biopsies led to a change in immunosuppressive treatment in 75% of patients, in most cases reducing such treatment [40]. The authors described updated Berden classification and RRS score that performed better for predicting ESKD when compared with initial histologic data.

Thus, until validated biomarkers can accurately assess disease activity in AAV-GN, repeated biopsy may be effective in this regard, as is customary in kidney transplantation [41, 42] or in lupus nephritis [43–45]. For patients who persist in showing signs of vasculitis activity and acute lesions, immunosuppressive treatment could be increased. Patients with a clear progression of chronic lesions, however, may benefit from immunosuppression minimization (while accounting for extra-renal manifestations). An individual evaluation of the benefit/risk balance clearly remains necessary but the safety of kidney biopsy has largely been demonstrated in large trials [46].

Our study has several limitations, mostly due to its retrospective design that contributed to missing data. In particular, IF/TA could only be evaluated for a portion of patients. This may explain why adding this parameter in our models did not improve the prediction of ESKD while it has been proven to be independently associated with kidney outcome [5, 47]. It also underlines the known low representativeness of a few biopsy slides to assess IF/TA compared with the entire kidney parenchyma [5]. Despite the precise characteristics of the cohort, the inclusion of patients was undertaken over a long period of time and therapeutic management has changed ever since, while always following up-to-date guidelines. Despite these limitations, our study is one of the few to focus on the prognostic interest of routine biomarkers later in the course of the disease in a large Caucasian population of AAV-GN.

In summary, this work suggests the benefits of reassessing kidney prognosis a few months after diagnosis of AAV-GN, after the end of the induction treatment. Kidney function at this time remains the best parameter related to kidney outcome, but there may be a place for specific risk scores also at this time. While waiting for accurate biomarkers, the question of interval kidney biopsies has already been raised in a number of studies to date, and our results emphasize their potential use in striving to provide individualized therapeutic management.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest in relation to this article. All co-authors have seen and agree with the contents of the manuscript. The results presented in this paper have not been published previously in whole or part, except in abstract format.

AUTHORS' CONTRIBUTIONS

C.B., J.-F.A. and B.B. contributed to the study conception and design. C.B., N.F., C.S., A.D. and B.B. performed the data collection. J.R. and B.B. performed the data analysis. C.B. prepared the first draft of the manuscript. J.-F.A. and B.B. revised the manuscript. All authors contributed to patient care, and read and approved the final manuscript.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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