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ORIGINAL ARTICLE

Outcomes and risk factors in patients with crescentic glomerulonephritis: a multicenter cohort study

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Abstract

Background Patients with crescentic glomerulonephritis have a poor prognosis despite immunosuppressive therapy. This study investigated the clinicopathologic features, outcomes, and risk factors in Chinese patients with crescentic glomerulonephritis.

Methods The multicenter cohort study included consecutive individuals with crescentic glomerulonephritis and a minimum follow-up of 1 year after biopsy, observed from January 2013 to December 2020. Primary outcome was the occurrence of death or end stage kidney disease (ESKD) for surviving patients. Multivariable adjusted Cox proportional hazards model was applied.

Results Of 109 patients enrolled, 73 (67%) suffered primary outcomes, including 39 deaths, and 34 ESKDs among the 70 surviving patients, with a mean follow-up of 26 months. All 26 patients with over 90% glomeruli with crescents reached a primary outcome. Patients with type III crescentic glomerulonephritis had the worst prognosis for primary outcomes (HR, 95% CI for type I vs. type III: 0.29, 0.14–0.58; type II vs. type III: 0.44, 0.22–0.91) and a significantly faster rate of eGFR decline after adjusting for baseline variables. In patients with 75%-100% glomeruli with crescents, the risk of a primary outcome increased nearly fourfold (HR 3.96; 95% CI 2.17–7.23) compared with patients with 50–75% glomeruli with crescents after adjusting for baseline variables. Type of crescentic glomerulonephritis and percentage of cellular and total glomeruli with crescents were independent risk factors for early primary outcomes (within 6 months).

Conclusions This study provides new insights into crescentic glomerulonephritis, including a description of the worst outcomes occurring in patients with type III crescentic glomerulonephritis, and suggests that the quantification of the percentage of crescents may be of use for guiding therapeutic decisions, due to their role in identifying the risk of primary outcomes.

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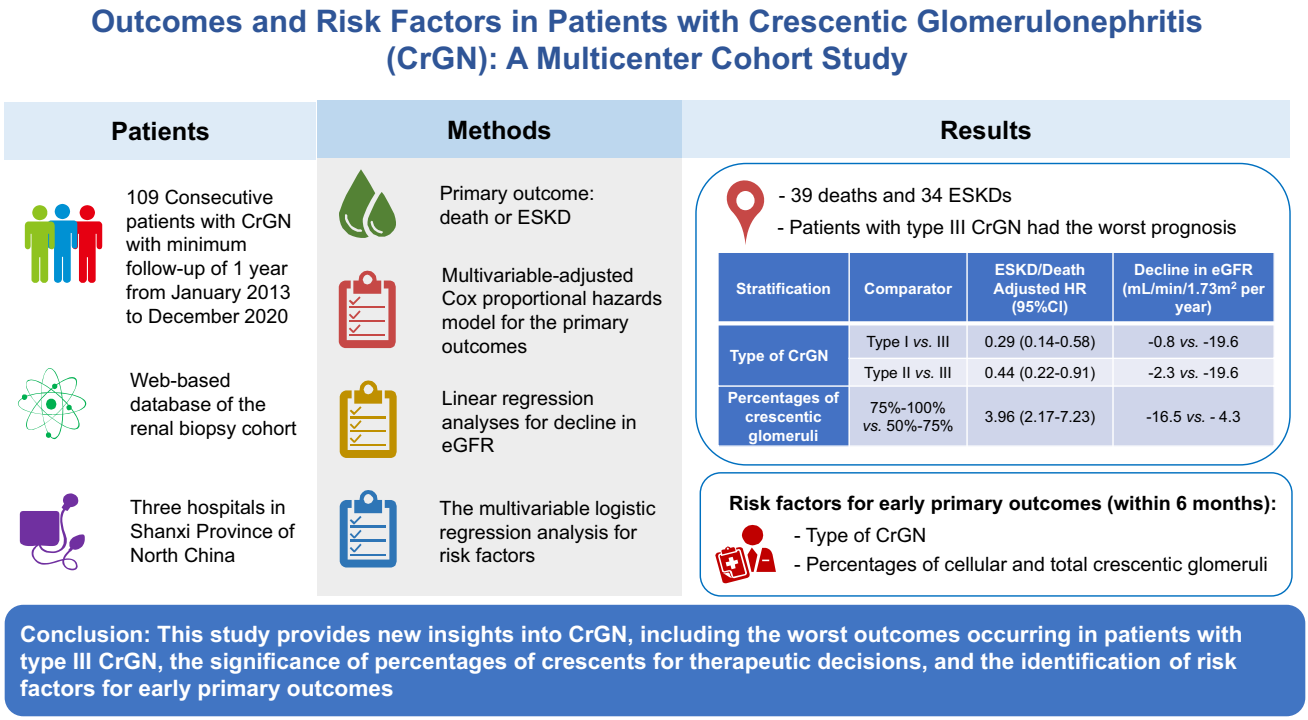
Graphical abstract



Keywords Crescentic glomerulonephritis · Chronic kidney disease · Glomerular filtration rate · Renal failure · Dialysis · End stage kidney disease

Introduction

Crescentic glomerulonephritis is the most aggressive structural phenotype in the continuum of injury that results from glomerular inflammation; it usually causes the signs and symptoms of rapidly progressive glomerulonephritis [1]. The three major immunopathologic categories of crescentic glomerulonephritis, i.e., anti-glomerular basement membrane (GBM) antibody-mediated crescentic glomerulonephritis, immune-complex-mediated crescentic glomerulonephritis, and pauci-immune crescentic glomerulonephritis, have been reported to have different frequencies and outcomes [2–5]. In two previous cohorts that included patients with anti-GBM disease, patients with 100% crescents were still dialysis-dependent at the last follow-up [6, 7]. A study from the UK found that the percentage of glomerular crescents was the only pathologic parameter associated with poor renal outcome in anti-GBM disease [7]. The association between crescents and renal function progression was also confirmed in lupus nephritis [8, 9] and IgA nephropathy [10], which are the most common associated diseases in type II crescentic glomerulonephritis [3, 11]. Several studies showed that patients with sclerotic crescents (sclerotic class) were at higher risk for end stage kidney disease (ESKD) than the focal, crescentic, and mixed classes in antineutrophil cytoplasmic antibody-associated (ANCA) glomerulonephritis [12–14]. However, in the case of crescentic glomerulonephritis, defined as having more than half of the glomeruli involved by crescents in a biopsy sample, the effects of different percentages of crescents on the prognosis and the risk factors for adverse outcomes remain unclear.

We therefore conducted a multicenter cohort study to explore the clinicopathologic features, follow-up, treatment and outcomes associated with the type of crescentic glomerulonephritis, the effect of the percentage of crescents on overall survival, and the risk factors for early ESKD and death.

Materials and methods

Study cohort

The Second Hospital of Shanxi Medical University is a general hospital in Shanxi Province of North China with 2500 beds.The pathological specimens of the consecutive patients

who underwent renal biopsy at the three hospitals involved in the study (Center Hospital of Taiyuan City, the First People's Hospital of Yangquan City, and the Second Hospital of Shanxi Medical University) were received and evaluated by the pathology department of the renal pathology center for Shanxi Province. The web-based database of the renal biopsy cohort was established in August 2015 (http://tdiga.edc-china.com.cn) and is made up of patients who underwent biopsy from January 2013 to the present. The clinical and pathologic information of patients at the time of biopsy and during follow-up was collected in the database.

All patients in the renal biopsy database were considered for inclusion. For this analysis, the patients needed to have at least 12 months of follow-up since the biopsy, or death. Patients who were diagnosed with other kidney diseases or were younger than 15 years at presentation were excluded. Patients with fewer than eight glomeruli in the biopsy specimen, patients having less than 50% glomeruli involved with crescents and patients with crescents affecting less than 50% of the area of each affected glomerulus were also excluded. The study was registered, and the protocol is available on the website of the China Clinical Trial Registry (ChiCTR2100043185, http://www.chictr.org.cn). The study was undertaken in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Second Hospital of Shanxi Medical University (No. 2015-KY-006). All patients gave written informed consent.

Clinical data and outcomes

Data were gathered prospectively, periodically controlled, and entered into the electronic database. Baseline clinical and demographic data were collected from all patients at the time of kidney biopsy. Patients with crescentic glomerulonephritis were followed up every 1–3 months as routine clinical practice, and data during follow-up were collected. Survival status, including death or ESKD, was also confirmed by telephone once every three months by the study nurse. Glomerular filtration rate (GFR) was estimated according to the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation. Mean arterial pressure (MAP) was defined as two-thirds diastolic blood pressure plus one-third systolic blood pressure. Rate of kidney function decline was expressed as the slope of estimated GFR (eGFR), which was obtained by fitting a straight line through the calculated eGFR using linear regression and the principle of least squares. Dialysis dependency at presentation was defined as the need for dialysis within 72 h of admission to the hospital.

The outcome of ESKD was defined as eGFR < 15 mL/min/1.73 m^2 or the initiation of renal replacement therapy, including hemodialysis, peritoneal dialysis, or renal transplantation. The primary outcome was death or ESKD for surviving patients. An early primary outcome is an event of ESKD or death within 6 months of the biopsy. The last date of web-based database data extraction was December 31, 2020. Right censoring was used if death or ESKD did not occur before the last date.

Biopsy specimen evaluation

The diagnosis of crescentic glomerulonephritis required two characteristics at kidney biopsy: over 50% of the glomeruli with crescents; more than 50% of the area of each glomerulus with crescents involved by the crescent itself, in serial sections of biopsy specimens. Crescentic glomerulonephritis was classified into three types according to immunofluorescence staining: type I was defined by linear deposition of immunoglobulins along the GBM; type II was defined by deposits of immune complexes in the glomeruli; type III was defined as the absence of immune complex deposition in the glomeruli.

Kidney biopsy samples were available for light microscopy evaluation for all but three patients (their specimens were lost), nonetheless, their pathology reports and medical files had sufficient information to include them in the study. The immunofluorescence results were assessed from the pathology reports. All pathologic sections were evaluated independently by one of two experienced nephropathologists who were blinded to the clinical data.

Statistical analysis

Categorical data were presented as number (percentage) and compared by Chi-squared test or Fisher's test. Continuous data were expressed as mean ± standard deviation (SD) or median (interquartile) and compared using the *t* test, one-way analysis of variance (ANOVA), or Kruskal–Wallis test. Patients were grouped by types of crescentic glomerulonephritis and percentage of crescentic glomeruli (using a cutoff of 75% based on the median). Kaplan–Meier analysis with the log-rank test was used to compare the cumulative rate of the primary outcome over time among three types of crescentic glomerulonephritis or between two groups of crescentic percentage. Multivariable-adjusted Cox proportional hazards model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of the types or the crescentic percentages with the primary outcome. Sensitivity analyses were performed using death alone or ESKD alone as the event of interest. The Fine and Gray model was calculated to account for the competing risk for death with ESKD. Linear regression analyses were used to evaluate the association of the type of crescentic glomerulonephritis or crescentic percentage with rate of eGFR decline. We imputed eGFR as 10 mL/min/1.73 m^2 at the time of ESKD onset. Relevant variables that were significant by univariable analysis were included in the multivariable

models. A 2-sided $P < 0.05$ was considered statistically significant. We performed the statistical analyses with SPSS software, version 19.0 (IBM) and Stata version 12 (StataCorp., College Station, TX).

Results

Study cohort and therapy

From January 2013 to December 2020, a total of 3,348 consecutive patients from three hospitals underwent kidney biopsy and were registered in the database. A total of 109 patients (3.4%) with crescentic glomerulonephritis were identified. Most of the patients were from Shanxi Province. Of the 109 patients considered, 20 (18.3%) were classified as with type I, 36 (33.1%) as with type II and the remaining 53 (48.6%) as with type III crescentic glomerulonephritis (Fig. 1). Table 1 displays the baseline characteristics stratified by type of crescentic glomerulonephritis and by percentage of crescentic glomeruli in the biopsy samples. Overall, patients with type III crescentic glomerulonephritis were older than those with types I and II crescentic glomerulonephritis. Patients with type I crescentic glomerulonephritis usually had the worst kidney function, the highest frequency of gross hematuria, and the largest percentage of cellular and total crescentic glomeruli.

Data on therapy and follow-up are presented in Fig. S1 and Table 2. During induction therapy, thirty-one patients (28.4%) required dialysis, including 16 patients (80%) with type I, 8 (22.2%) with type II and 7 (13.2%) with type III. All patients with type I crescentic glomerulonephritis underwent plasma exchange, and 90% received an intravenous methylprednisolone pulse. Infection occurred in 37 patients (33.9%), including six patients with type III crescentic glomerulonephritis who died due to severe

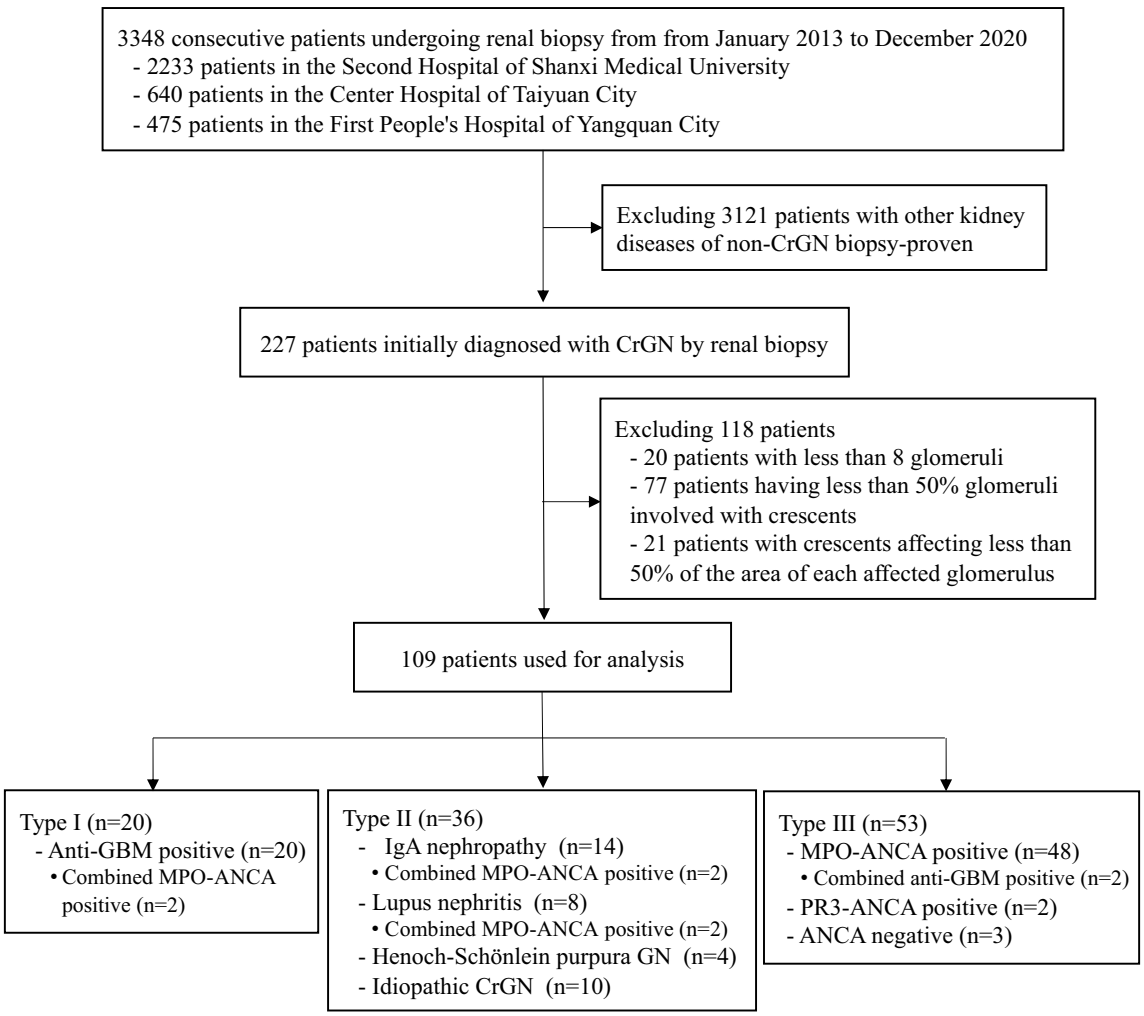


Fig. 1 Flowchart of patient selection. *ANCA* antineutrophil cytoplasmic antibody, *CrGN* crescentic glomerulonephritis, *GBM* glomerular basement membrane, *GN* glomerulonephritis, *MAP* mean arterial pressure, *MPO* myeloperoxidase, *PR3* proteinase 3

Table 1 Baseline Clinical and Histopathologic Characteristics by Type of Crescentic Glomerulonephritis and by Percentage of Crescentic Glomeruli

	Total ($n=109$)	Type of CrGN				Percentage of crescentic glomeruli		
		Type I ($n=20$)	Type II ($n=36$)	Type III ($n=53$)	*P* value	50–75% ($n=54$)	75–100% ($n=55$)	*P* value
Clinical characteristics								
Age, years	52 ± 18	39 ± 14	45 ± 20	62 ± 13	**< 0.001**	50 ± 18	54 ± 19	0.3
Male sex	49 (45)	8 (40)	14 (38.9)	27 (50.9)	0.5	20 (37)	29 (53)	0.1
BMI, Kg/m^2	23.1 ± 3.6	23.7 ± 4.2	22.2 ± 2.5	23.5 ± 3.9	0.2	23.1 ± 3.3	23.1 ± 3.9	0.9
Proteinuria, g/24 h	3.1 ± 1.9	2.9 ± 2.0	3.8 ± 2.2	2.6 ± 1.7	**0.02**	3.5 ± 2.1	2.6 ± 1.8	**0.02**
Albumin, g/L	28.1 ± 5.6	26.6 ± 2.3	26.4 ± 7.5	29.4 ± 4.5	0.05	27.5 ± 6.3	28.6 ± 4.7	0.4
Scr, mg/dL	5.1 ± 4.9	9.4 ± 9.2	3.4 ± 2.4	4.7 ± 2.8	**< 0.001**	3.7 ± 2.2	6.6 ± 6.4	**0.002**
Systolic BP, mmHg	138 (125–158)	127 (115–152)	146 (125–173)	138 (125–158)	0.1	133 (122–158)	138 (125–159)	0.8
Diastolic BP, mmHg	80 (70–94)	80 (68–97)	93 (80–106)	74 (70–81)	**< 0.001**	81 (75–96)	80 (70–87)	0.5
MAP, mmHg	99 (90–114)	96 (86–111)	108 (98–129)	96 (88–103)	**0.001**	103 (93–116)	96 (88–110)	0.3
eGFR, mL/min/1.73m^2	12.5 (7.5–29.1)	6.2 (5.5–17.7)	25.9 (11.5–37.6)	11.1 (8.0–20.5)	**< 0.001**	20.9 (8.9–34.2)	10.4 (6.9–15.2)	**0.003**
Hemoglobin, g/L	93.0 ± 18.1	90.7 ± 17.8	95.2 ± 23.6	92.4 ± 13.5	0.6	92.2 ± 18.1	93.9 ± 18.3	0.6
MPO-ANCA positive	54 (49.1)	2 (10)	4 (11.1)	48 (88.9)	**< 0.001**	24 (44.4)	30 (54.5)	0.3
PR3-ANCA positive	2 (1.8)	0 (0)	0 (0)	2 (3.7)	0.3	0 (0)	2 (3.6)	0.5
Anti-GBM positive	24 (21.8)	20 (100)	0 (0)	2 (3.7)	**< 0.001**	8 (14.8)	16 (29.1)	0.1
Dialysis dependency at presentation	12 (11)	4 (20)	6 (16.7)	2 (3.8)	**0.06**	4 (7.4)	8 (14.5)	0.4
Gross hematuria	28 (25.7)	14 (70)	10 (27.8)	4 (7.5)	**< 0.001**	14 (25.9)	14 (25.5)	1
Histopathologic features								
Number of glomeruli	19 (14–27)	19 (16–24)	16 (12–24)	19 (14–32)	0.5	16 (14–24)	19 (12–32)	0.5
Crescentic glomeruli, %	76.7 ± 15.3	84.1 ± 17.3	68.1 ± 13.5	79.5 ± 13.5	**0.02**	63.2 ± 7.3	89.8 ± 7.2	**< 0.001**
Cellular crescentic glomeruli, %	60.1 ± 26.3	80.6 ± 17.8	54.5 ± 22.5	56.2 ± 28.2	**0.02**	49.1 ± 17.3	70.4 ± 29.2	**< 0.001**
Globally sclerotic glomeruli, %	2.9 (0–25.0)	0 (0–3.9)	21.6 (0–36.4)	2.9 (0–15.8)	**0.004**	11.8 (0–28.6)	0 (0–7.7)	0.2
Patients with capillary loop necrosis	24 (22.0)	4 (20)	10 (27.8)	10 (18.9)	0.6	14 (25.9)	10 (18.2)	0.4
Patients with diffuse tubular atrophy/interstitial fibrosis[a]	51 (46.8)	4 (20)	14 (38.9)	33 (62.3)	**0.002**	20 (37)	31 (56.4)	0.06

Statistically significant differences are in bold

Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation or median (interquartile range)

ANCA antineutrophil cytoplasmic antibody, *BMI* body mass index, *BP* blood pressure, *CrGN* crescentic glomerulonephritis, *eGFR* estimated glomerular filtration rate, *GBM* glomerular basement membrane, *MAP* mean arterial pressure, *MPO* myeloperoxidase, *PR3* proteinase 3, *Scr* serum creatinine

[a]Defined as more than 50% of the tubulointerstitial area in biopsy specimen

Table 2 Therapy and Outcomes Stratified by Type of Crescentic Glomerulonephritis and Percentage of Crescentic Glomeruli at Baseline

	Total ($n=109$)	Type of CrGN			Percentage of crescentic glomeruli	
		Type I ($n=20$)	Type II ($n=36$)	Type III ($n=53$)	50–75% ($n=54$)	75–100% ($n=55$)
Mean follow up, month	26.2 ± 20.8	31.7 ± 23.2	37.9 ± 17.1	16.2 ± 17.3	17.8 ± 19.8	34.7 ± 18.3
Patients with induction therapy	**109 (100)**	**20 (100)**	**36 (100)**	**53 (100)**	**54 (100)**	**55 (100)**
Plasma exchange	35 (32.1)	20 (100)	6 (16.7)	9 (17)	16 (29.6)	19 (34.5)
Intravenous MP pulse	66 (60.6)	18 (90)	18 (50)	30 (56.6)	26 (48.1)	40 (72.7)
RRT	31 (28.4)	16 (80)	8 (22.2)	7 (13.2)	8 (14.8)	23 (41.8)
Other immunosuppression therapy[a]	52 (47.7)	4 (20)	18 (50)	30 (56.6)	30 (55.6)	22 (40)
Infection during induction therapy	37 (33.9)	6 (30)	12 (33.3)	19 (35.8)	14 (25.9)	23 (41.8)
Death within 6 months	**25 (22.9)**	**4 (20)**	**0 (0)**	**21 (39.6)**	**4 (7.4)**	**21 (38.2)**
Patients with maintenance therapy	**84 (77.1)**	**16 (80)**	**36 (100)**	**32 (60.4)**	**50 (92.6)**	**34 (61.8)**
Prednisone alone	14 (16.9)	2 (12.5)	4 (11.2)	8 (25)	9 (18)	5 (14.7)
Combined agents[b]	46 (55.4)	7 (43.8)	22 (61.1)	17 (53.1)	32 (64)	14 (41.2)
RRT	26 (31.3)	10 (62.5)	6 (16.7)	10 (31.3)	8 (16)	18 (52.9)
Outcome						
Death	39 (35.8)	6 (30)	2 (5.6)	31 (58.5)	8 (14.8)	31 (56.4)
Surviving patients	70 (64.2)	14 (70)	34 (94.4)	22 (41.5)	46 (85.2)	24 (43.6)
ESKD	34 (48.6)	10 (71.4)	10 (29.4)	14 (63.6)	14 (30.4)	20 (83.3)
CKD stage 1–2	12 (17.1)	2 (14.3)	10 (29.4)	0 (0)	10 (21.7)	2 (8.3)
CKD stage 3–4	24 (34.2)	2 (14.3)	14 (41.2)	8 (36.4)	22 (47.8)	2 (8.3)
Primary outcome[c] within 6 months	51 (47.7)	14 (70)	6 (16.7)	31 (58.5)	12 (22.2)	39 (65.5)
Mean rate of eGFR decline, mL/min/1.73m^2 per year	− 10.2 ± 20.1	− 0.8 ± 9.6	− 2.3 ± 17.8	− 19.6 ± 36.9	− 4.3 ± 23.7	− 16.5 ± 32.9

Statistically significant differences are in bold

Values for categorical variables are given as number (percentage) or percentage

CKD chronic kidney disease, *CrGN* crescentic glomerulonephritis, *eGFR* estimated glomerular filtration rate, *ESKD* end stage kidney disease, *MP* methylprednisolone, *RRT* renal replacement therapy

[a]Other immunosuppression therapy included routine dose of corticosteroids, cyclophosphamide, cyclosporine A, mycophenolate mofetil, rituximab and gamma globulin

[b]Combined agents refer to low-dose prednisone combined with one immunosuppressive agent, including azathioprine, cyclophosphamide, cyclosporine A, mycophenolate mofetil and tacrolimus

[c]Primary outcome included death and ESKD. The outcome of ESKD was defined as eGFR < 15ml/min/1.73 m^2 or the initiation of renal replacement therapy, including hemodialysis, peritoneal dialysis, or renal transplantation

pulmonary infections. Twenty-five patients (22.6%) died within 6 months, and the remaining 84 patients entered the maintenance phase, of whom 26 patients (31.3%) required dialysis.

Outcomes

Different types of crescentic glomerulonephritis

Over a mean follow-up of 26 months, 73 individuals (67%) experienced the primary outcome, including 39 patients who died and 34 patients who survived and reached ESKD (Fig. S1 and Table 2). In detail, 58.5% (31/53) of patients with type III crescentic glomerulonephritis died, while the mortality rates for types I and II were 30% (6/20) and 5.6% (2/36), respectively. Nearly half of the survivors (34/70) developed ESKD, of which type I crescentic glomerulonephritis had the highest rate (10/14), followed by type III (14/22) and II (10/34). The incidences of the primary outcome in the three types of crescentic glomerulonephritis were significantly different in the univariable analysis (log-rank test, $P<0.001$). Unadjusted associations are illustrated in Fig. S2A. Multivariable-adjusted Cox proportional hazards analysis also showed that there was a significant effect of the type of crescentic glomerulonephritis on the primary outcome after adjustment for baseline eGFR, MAP, proteinuria, and percentage of crescentic glomeruli ($P<0.001$). Patients with type III crescentic glomerulonephritis had the worst prognosis for the primary outcomes (Table 3): HR (95% CI) for type I vs. type III was 0.29 (0.14–0.58), and type II vs. type III was 0.44 (0.22–0.91). The Fine and Gray sensitivity analysis was used to assess ESKD alone with

Table 3 Comparison of Outcomes in Patients with Different Types of crescentic glomerulonephritis and Percentages of Crescentic Glomeruli

Stratification	Comparator	Primary outcomes		Death alone		ESKD alone	
		Adjusted HR (95%CI)	*P* value	Adjusted HR (95%CI)	*P* value	Adjusted HR (95%CI)	*P* value
Type of CrGN	Type I vs. Type III	0.29 (0.14–0.58)[a]	< 0.001[b]	0.21 (0.07, 0.61)[a]	0.004[a]	0.41 (0.21, 0.82)[c]	0.01[c]
	Type II vs. Type III	0.44 (0.22–0.91)[a]	0.03[b]	0.09 (0.02, 0.43)[a]	0.002[a]	0.46 (0.21, 0.97)[c]	0.04[c]
Percentage of crescentic glomeruli	75–100% vs. 50–75%	3.96 (2.17–7.23)[b]	< 0.001[b]	5.05 (2.04, 12.52)[b]	< 0.001[b]	2.93 (1.60, 5.36)[d]	< 0.001[d]

CI credible interval, *CrGN* crescentic glomerulonephritis, *ESKD* end stage kidney disease, *HR* hazard ratio, *MAP* mean arterial pressure

[a]The Cox proportional hazards model adjusted for baseline eGFR, MAP, proteinuria, and percentages of crescentic glomeruli

[b]The Cox proportional hazards model adjusted for baseline eGFR, MAP, proteinuria, and type of CrGN

[c]The Fine and Gray model adjusted for baseline eGFR, MAP, proteinuria, and percentage of crescentic glomeruli was calculated to account for the competing risk for death with ESKD

[d]The Fine and Gray model adjusted for baseline eGFR, MAP, proteinuria, and type of CrGN was calculated to account for the competing risk for death with ESKD

death as a competing risk. Significant associations were also identified between ESKD alone or death alone and the type of crescentic glomerulonephritis (Table 3, Fig. S3). A statistically significant difference in the rate of decline in eGFR was observed among types I, II and III (− 0.8, − 2.3 and − 19.6 mL/min/1.73m^2 per year, and *P* values of type I vs. type III and type II vs. type III were 0.006 and 0.04, respectively) after adjustment for baseline eGFR, MAP, proteinuria, and percentage of crescents.

Percentage of glomeruli with crescents at baseline

Of the surviving patients, 69.5% (32/46) of patients with 50–75% glomeruli with crescents had renal survival at the last follow-up, compared with 16.7% (only 4/24 patients) of those with 75–100% crescents (Fig. S1 and Table 2). All patients who had over 90% crescentic glomeruli ($n = 26$, including 8 patients with type I, 2 patients with type II, and 16 patients with type III) reached the primary outcome, among whom 14/26 died and 12/26 patients remained dialysis dependent.

The incidences of the primary outcome differed significantly between patients with 50–75% ($n = 54$) and 75–100% crescentic glomeruli ($n = 55$) ($P < 0.001$, Fig. S2B). Patients with 75–100% crescentic glomeruli had a higher risk of reaching the primary outcome than patients with 50–75% crescentic glomeruli after adjustment for baseline eGFR, MAP, proteinuria, and type of crescentic glomerulonephritis (HR 3.96; 95% CI 2.17–7.23; Table 3). The results of the sensitivity analyses for death alone and ESKD alone (death as a competing risk) were also consistent (Table 3, Fig. S3).

The rates of decline in eGFR were more rapid in patients with 75–100% crescentic glomeruli than in those with 50–75% crescentic glomeruli (− 16.5 vs. − 4.3 mL/min/1.73m^2 per year; $P = 0.02$) after adjustment for baseline eGFR, MAP, proteinuria, and type of crescentic glomerulonephritis.

Risk factors of early primary outcomes

An early primary outcome (death or ESKD within 6 months) occurred in 51 (47.7%) individuals. The baseline characteristics and therapy stratified by early primary outcome are shown in Table S1. Multivariable logistic regression analysis revealed that type of crescentic glomerulonephritis, percentage of cellular crescentic glomeruli and total crescentic glomeruli were statistically significant risk factors for an early primary outcome, whereas eGFR and proteinuria at baseline were not (Table S2).

Discussion

This multicenter cohort study of 109 patients with crescentic glomerulonephritis registered in a prospective database, allowed us to provide insights into the clinical features and outcomes of patients with crescentic glomerulonephritis. First, 73/109 (67%) patients reached the primary outcomes, including 39/109 (35.8%) deaths and 34/70 (48.6%) ESKDs in a mean follow-up of 26 months. All 26 patients with over 90% glomeruli with crescents on renal biopsy reached the primary outcome (14 deaths, and 12 ESKDs among surviving patients). Nearly seventy percent (51/73) of the primary outcomes occurred within 6 months. Second, we confirmed that patients with type III crescentic glomerulonephritis had worse prognosis and a faster eGFR decline than patients with types I and II crescentic glomerulonephritis in the multivariable-adjusted model. Third, we confirmed that in patients with 75–100% crescentic glomeruli, the risk of the primary outcome increased nearly fourfold compared

with patients with 50–75% of glomeruli with crescents after adjustment for the relevant baseline variables. Sensitivity analysis for the competing risk for ESKD and death did not alter the conclusions. Finally, we identified type of crescentic glomerulonephritis and percentage of cellular and total crescentic glomeruli as independent risk factors for early primary outcome (within 6 months).

Survival rates vary considerably across previous studies, most of which only reported renal survival (44–67%) during the follow-up period [3, 5, 15–18]. Recently, a single-center study from South China enrolled 56 patients diagnosed with crescentic glomerulonephritis who were followed up for 5 years. The results showed that 14 (25%) patients died, and 25 (44.6%) patients reached ESKD (including ESKD before death) [5]. In contrast to these studies, the rate of death and/or ESKD in the current cohort is higher. The discrepancy could be attributed to the different inclusion criteria. The definition of crescentic glomerulonephritis in our study was limited to two "fifty percent", that is, more than 50% of glomeruli involved crescents, and more than 50% of the area of each affected glomerulus was covered by crescents in serial sections of the biopsy specimen, which is different from other studies. Severe renal involvement was a characteristic of the patients included in this cohort.

There has been disagreement regarding which types of crescentic glomerulonephritis are associated with the worst prognosis in different cohorts. Several studies have shown that patients with type I crescentic glomerulonephritis have the poorest renal prognosis [3, 4, 11]. The renal prognosis of patients with type II crescentic glomerulonephritis was superior to that of patients with type III crescentic glomerulonephritis [3, 19], which contrasts with the results reported by Han et al. [20]. Regarding patient survival, no significant difference was found among the three types of crescentic glomerulonephritis [4, 11, 18]. All these existing studies on prognosis were based on univariable analysis. With the inclusion of high-risk patients and the application of a multivariable-adjusted model, our study indicated that patients with type III crescentic glomerulonephritis had the worst prognosis for the primary outcomes. Furthermore, the results of the sensitivity analyses for death alone and ESKD alone were also consistent.

As a characteristic manifestation of crescentic glomerulonephritis, crescent formation has long been recognized as an indicator of the severity of glomerular inflammation and it usually calls for urgent treatment. In our cohort, all 55 patients with 75–100% crescentic glomeruli received the routine tapering dose of prednisolone (1 mg/kg of starting dose), 40 (72.7%) patients received intravenous methylprednisolone pulses and 19 patients (34.5%) were treated with plasma exchange. However, all 26 patients with over 90% crescentic glomeruli reached the primary outcome, and only 4 patients with 75–90% crescentic glomeruli had renal survival. Thus, treatment seems to be considerably less effective in patients with 75–100% crescentic glomeruli. In 2001, Levy et al. reported that patients with anti-GBM glomerulonephritis who were dialysis-dependent at presentation and had 100% crescents on their kidney biopsy did not recover kidney function [6]. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines of anti-GBM glomerulonephritis currently suggest that patients who require initiation of dialysis and have 100% crescents or > 50% global glomerulosclerosis in an adequate biopsy sample without pulmonary hemorrhage do not require intensive treatment [21]. To date, there is a relative paucity of original studies investigating the impact of high percentages of crescents in patients with type II and III crescentic glomerulonephritis. Our study is an addition to the literature on the topic and highlights the important implications of the percentage of crescents for appropriate therapeutic decisions. The importance of a timely kidney biopsy should be further emphasized.

For patients with crescentic glomerulonephritis, the decision to initiate therapy should consider this low probability of kidney recovery and the risks of intensive immunosuppression based on their other clinical characteristics. Our study supports the significance of different proportions of crescents for supporting appropriate therapeutic decisions. Patients with 90–100% crescents in their biopsy specimens are very unlikely to recover renal function. Patients with 75–90% crescents, especially patients with type III crescentic glomerulonephritis may occasionally recover renal function with intensive treatment. Notably, the risk–benefit ratio of immunosuppression could be greater, and the treatment duration of immunosuppression should not be extended. However, in patients with active extrarenal manifestations, such as pulmonary hemorrhage, the roles of immunosuppression and plasma exchange remain pivotal [21].

Several limitations to this study need to be acknowledged. First, all biopsies were clinically decided by a nephrologist, so the results may not be generalizable to those without indications for renal biopsy. Second, although the percentage of crescents and type of crescentic glomerulonephritis were clearly related to the outcomes, adverse clinical outcomes of patients could not be consistently identified by simple criteria. Third, potential confounding factors caused by unmeasured variables always exist, which cannot be addressed by statistical models. Our findings may provide valuable insights to help clinicians, but must be interpreted and applied with caution.

In conclusion, new insights are provided by our study, including the worst renal survival and patient survival occurring in patients with type III crescentic glomerulonephritis, the significance of the percentage of crescents for supporting appropriate therapeutic decisions, and the identification

of risk factors for an early primary outcome. It is worth noting that all patients with 90–100% crescents in the current cohort suffered death and/or ESKD despite intensive immunosuppression. Further advances in treating high-risk crescentic glomerulonephritis will require multicenter collaboration to confirm the above findings.

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Availability of data and material The datasets generated and/or analyzed during the current study are not publicly available due to ethical/legal restrictions.

Declarations

Conflict of interest The authors declare that they have no competing interests.

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