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## Gender difference in crescentic glomerulonephritis; an eleven-year single-center study

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### ABSTRACT

**Introduction:** Crescentic glomerulonephritis is an essential kind of glomerulonephritis. According to its rapid progression and aggressiveness, recognizing its risk factors helps to manage a better treatment and outcome.**Objectives:** This study was designed to compare demographic, laboratory, and renal biopsy findings of patients with crescentic glomerulonephritis among males and females.**Patients and Methods:** This cross-sectional study compared age, gender, types of crescentic glomerulonephritis, serum creatinine, 24-hour proteinuria, the number of crescents, and percentage of fibrosis.**Results:** Of 169 patients with crescentic glomerulonephritis, 54.4% were males, and 45.6% were females. The mean age, serum creatinine level, and 24-hour proteinuria were 37.73±15.32 years, 2.06±1.35 mg/d, and 2084.82±1170.98 mg/d, respectively. Serum creatinine level and 24-hour proteinuria were not significantly different by gender. In addition, the number of crescents had no relationship with age and 24-hour proteinuria; however, it had a significant direct relationship with serum creatinine.**Conclusion:** According to our study, lupus nephritis affected women more than men, while other forms of crescentic glomerulonephritis were more common in males. Depending on the population, a significant relationship between the number of crescent and serum creatinine was detected. The mean age of females with crescentic glomerulonephritis was significantly lower than males.

### Implication for health policy/practice/research/medical education:

In a cross-sectional study on 169 patients with crescentic glomerulonephritis, we found that the number of crescents had a significant direct relationship with serum creatinine value.

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### Introduction

Crescentic glomerulonephritis is a severe type of glomerulonephritis characterized by more than 50% crescents in renal biopsy, and leads to glomerular demolition and terminates to end-stage renal disease (ESRD) in a short period (months to weeks). Crescentic glomerulonephritis is not common however it is a rapidly progressive disease and is associated with several morbidities. This pattern appears in 10-15% of glomerulonephritis and is more common in rapidly progressive diseases (1).

The crescent is a hyperplastic lesion occupying more than 10% of the Bowman's space. Histopathologically, these lesions are glomerular damage due to parietal epithelial cell hyperplasia, leads to extra-capillary proliferation. Finally, this condition resulted to the reduction of Bowman's space causes a decrease in glomerular filtration rate (2).

Crescentic glomerulonephritis is categorized into three groups based on immunofluorescence microscopy findings. The first is anti-glomerular basement membrane (anti-GBM) disease or Goodpasture syndrome.

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Immune-complex glomerulonephritis is the second type, and it includes conditions like lupus nephritis and immunoglobulin A nephropathy (IgA nephropathy). Third, pauci-immune glomerulonephritis is also known as nephritis associated with antineutrophil cytoplasmic autoantibody (ANCA) (3).

In anti-GBM disease, autoantibody against collagen type IV causes linear deposition along the glomerular basement membrane. Around 10-15% of crescentic glomerulonephritis is an anti-GBM disease. Goodpasture syndrome usually appears as rapidly progressive glomerulonephritis with or without pulmonary involvement which can lead to ESRD (4).

Immune-complex glomerulonephritis is characterized by glomerular immune complex deposition in immunofluorescence microscopy. Around 25-30% of crescentic glomerulonephritis are immune-complex, based on targets and responses, like IgA nephropathy, lupus nephritis, and Henoch–Schönlein purpura (5,6).

Pauci-immune glomerulonephritis is a common type of crescentic glomerulonephritis (65-70%). There is no immune deposition in immunofluorescence microscopy. In addition, it is usually associated with anti-neutrophil cytoplasmic autoantibody (ANCA-associated). Based on previous studies, pauci-immune glomerulonephritis is more common in old patients (7).

According to previous studies, clinical manifestations, outcomes, and prognosis are different in each kind of crescentic glomerulonephritis (7). This study was conducted to assess the risk factors that affect the chronicity and severity of crescentic glomerulonephritis in the Iranian population among males and females.

## Objectives

We aimed to study the risk factors of crescentic glomerulonephritis in males versus females.

## Patients and Methods

### Study design

This cross-sectional study was conducted in Isfahan from July 2011 until April 2022. This study is the extension of our previous investigation in 2015 on 87 crescentic glomerulonephritis (8). In this study focused on the gender difference of this disease. This study was conducted on consecutive sampling to collect data from 169 patients with crescentic glomerulonephritis.

Patients with incomplete laboratory data and renal biopsy reports did not enter. Patients with other medical diseases (such as diabetes or amyloidosis) were excluded from the study.

Each patient had two samples; one for immunofluorescence study and another for light microscopy. For light microscopy, renal tissues were

fixed in 10% formalin for sectioning. Afterward, tissues were prepared by paraffin blocks, cut into 3  $\mu$ m, and stained with periodic acid Schiff, hematoxylin and eosin, Jones methenamine silver, and Masson's trichrome. Immunofluorescence samples were stained for IgA, IgM, IgG, C3, and C1q antibodies.

The full-house pattern (abundant granular deposits of C1q, IgG, and C3) approved the diagnosis of lupus nephritis. Accordingly, the definitive diagnosis of IgA nephropathy was accepted with the presence of granular IgA and C3 in the absence of C1q. Meanwhile, ANCA-associated glomerulonephritis was detected by the absence of IgG, C1q, and IgA deposition. In ANCA-associated glomerulonephritis few C3 deposition were interpreted as non-specific. Accordingly, linear deposition of IgG on the glomerular basement membrane was characteristic of Goodpasture syndrome. The granular deposition of C3 and IgG is considered as cryoglobulinemia in the mesangium and endocapillary space, along with morphological features and clinical data. Isolate deposition of C3 and the starry sky were characteristic of PSGN across with histological features and clinical findings. Finally, in Henoch–Schönlein purpura depositions of IgA and fibrin were existed.

### Data analysis

Patient demographic information, including age, gender, serum creatinine, 24-hour proteinuria, number of crescents, and fibrosis percentage, were entered into SPSS software (version 25). Data were presented as means  $\pm$  standard deviation or frequency (percentage) for continuous and categorical variables. The Kolmogorov-Smirnov test was conducted to evaluate the normal distribution for continuous variables. The chi-square test was conducted to compare genders, since the independent t-test was conducted to compare the mean continuous variables between the different crescents. A level of less than 0.05 was considered significant in all analysis.

## Results

In this study, out of 169 patients with crescents, 54.4% were men, and 45.6% were women, with a mean age of  $37.73 \pm 15.32$  years.

Our sample included 47.3% IgA nephropathy, 37.9% lupus nephritis, 11.2% vasculitis, and Henoch–Schönlein purpura, since 3.6% were other diseases, including cryoglobulinemia (one patient), Goodpasture syndrome (four patients), and PSGN (one patient) (Table 1).

The mean serum creatinine and 24-hour proteinuria were  $2.06 \pm 1.35$  mg/d and  $2084.82 \pm 1170.98$  mg/d, respectively. Furthermore, the mean number of crescents and percentage of fibrosis were  $2.99 \pm 3.56$  (minimum-maximum; 1-25) and  $18.18 \pm 16.89$  (minimum-

**Table 1.** Demographic and clinical characteristics of studied patients (N=169)

Variable	
Gender	
Male	92 (54.4%)
Female	77 (45.6%)
Age (y)	37.73±15.32
Serum creatinine (mg/d)	2.06±1.35
24-hour proteinuria (mg/d)	2084.82±117.98
Crescent (number)	2.99±3.56
Percentage of fibrosis	18.18±16.89
Crescentic glomerulonephritis	
IgA nephropathy	80 (47.3%)
Lupus glomerulonephritis	64 (37.9%)
Vasculitis + Henoch–Schönlein purpura	19 (11.2%)
Others*	6 (3.6%)

Data shown mean ±SD or n (%).

\* Others included cryoglobulinemia, goodpasture syndrome, and post-streptococcal glomerulonephritis.

maximum: 2.5-90%) respectively (Table 1).

Moreover, our study showed no significant correlation between the number of crescents and age or 24-hour proteinuria; however, a significant direct correlation between the number of crescents and serum creatinine was found ( $P < 0.001$  and correlation coefficient = 0.393; Table 2).

There was no significant difference between serum creatinine, 24-hour proteinuria and fibrosis percentage

**Table 2.** Correlation between the number of crescents and the study variables

Variable	Coefficient	P value
Age (y)	-0.003	0.971
Serum creatinine	0.393	<0.001
24-hour proteinuria	0.087	0.262
Fibrosis	0.086	0.266

**Table 3.** Frequency of characteristics by gender

Crescentic glomerulonephritis	Males (n=92)	Females (n=77)	P value
Age (year)	40.85±17.14	34.01±11.90	
<40	44 (47.8%)	60 (77.9%)	<0.001
≥40	48 (52.2%)	17 (22.1%)	
Creatinine (mg/d)	2.17 ± 1.46	1.94 ± 1.23	0.272
24-hour proteinuria	1940.35 ± 959.16	2257.44 ± 1368.96	0.080
Crescents (number)	17.47 ± 16.18	19.03 ± 17.77	0.552
IgA nephropathy	53 (66.3%)	27 (33.8%)	<0.001
Lupus nephritis	19 (29.7%)	45 (70.3%)	<0.001
Vasculitis and Henoch–Schönlein purpura	16 (84.2%)	3 (15.8%)	<0.001
Others	4 (66.7%)	2 (33.3%)	<0.001

among males and females ( $P > 0.05$ ; Table 3).

Our results showed that females were more likely to have lupus nephritis while males were more likely to have other disorders ( $P < 0.05$ ). Females' average age was 34.01±11.90 years, which was significantly lower than that of males, with a mean of 40.85±17.14 years ( $P < 0.001$ ). In addition, the percentage of age younger than 40 years in females was significantly higher than in males ( $P$  value<0.001; Table 3).

Moreover, 24-hour proteinuria in younger patients with a mean of 2269.63 ± 1336.02 mg/d was significantly higher than in older ones with a mean of 1789.14 ± 763.18 mg/d ( $P = 0.009$ ). However, mean serum creatinine and fibrosis percentage in young and old patients had no significant difference ( $P > 0.05$ ; Table 4).

In comparison, crescents in lupus patients were more common in younger (age below 40 years old; 45.2%) while it was more common in older patients (age over 40 years old) in vasculitis (16.9%) and Henoch–Schönlein purpura (6.2%), and also IgA nephropathy (50.8%; Table 4).

## Discussion

In China, epidemiologic data on crescentic glomerulonephritis accounted for 3.73%. This rate is higher than previously stated in this country (7,9). No precise statistics on the prevalence of this condition in Iran are available. Our study on crescentic glomerulonephritis in Iranian patients for eleven years showed that crescentic glomerulonephritis of type II was predominated (lupus and IgA nephropathy). Moreover, females were more likely to have lupus nephritis, which was more common in younger than 40 years. We also found, 24-hour proteinuria in younger patients was significantly higher than in older patients. Several other investigations had indicated that pauci-immune crescentic glomerulonephritis was the most common form (10-13). One study also noted that the immune complex type was as common as the pauci-immune type. In type II crescentic glomerulonephritis,

**Table 4.** Relationships between the age and clinical characteristics

Variable	<40 years old (n=104)	≥40 years old (n=65)	P value
Gender			
Male	48 (73.8%)	44 (42.3%)	<0.001
Female	17 (26.2%)	60 (57.7%)	
Serum creatinine (mg/d)	1.96±1.28	2.23±1.47	0.209
24-hour proteinuria (mg/d)	2269.63±1336.02	1789.14±763.18	0.009
Interstitial fibrosis (%)	16.62±15.81	20.68±18.34	0.129
Crescentic glomerulonephritis			0.027
IgA nephropathy	47 (45.2%)	33 (50.8%)	
Lupus nephritis	47 (45.2%)	17 (26.2%)	
Vasculitis and Henoch–Schönlein purpura	8 (7.7%)	11 (16.9%)	
Others	2 (1.9%)	4 (6.2%)	

IgA nephropathy was the most common primary disease, which is consistent with our results (14). We think that the geographical location and timing of the investigation may have influenced the variation in prevalence.

We concluded that younger crescentic lupus patients had more proteinuria. Chen et al found that proteinuria did not significantly correlate with renal outcome (15).

Recently, Chen et al in a study on 158 IgA nephropathy patients, evaluated the relationship between crescentic glomerulonephritis and several factors. They found no relevant correlation between age and crescent count, however a meaningful direct correlation between the number of crescents and serum creatinine was seen. This finding was consistent with our study. They also found a direct relationship between 24-hour proteinuria and the number of crescents, while our study did not mention it (16).

In another study from India, most individuals with crescentic glomerulonephritis had pauci-immune, which was more common in men, since IgA nephropathy was the most common type of immune complex crescentic glomerulonephritis, followed by post-infectious glomerulonephritis (PIGN) and lupus nephritis (17).

In another study from China on 528 patients, crescentic glomerulonephritis was seen more in females (60.6%), and lupus nephritis had the highest prevalence. It was followed by pauci-immune crescentic glomerulonephritis and IgA nephropathy, respectively (7).

According to the study by Nakakita et al in Japan on 256 patients, the mean serum creatinine in crescentic glomerulonephritis with immune-complex deposition (lupus and IgA nephropathy) had a significant difference with ANCA-related crescentic glomerulonephritis (vasculitis). However, there was no significant difference of 24-hour proteinuria in both groups was seen. In their research, the crescent percentage in ANCA-related crescentic glomerulonephritis was higher than immune-complex deposition glomerulonephritis. Their one-year follow-up indicated a poor prognosis in ANCA-

related glomerulonephritis. Correspondingly, global glomerulosclerosis and GFR were important predictors of the prognosis. They showed that IgA nephropathy had the highest prevalence, and lupus nephritis was more common in females. Likewise, the mean age of microscopic polyangiitis was 64 years, while the mean age of the immune-complex deposition group was 34 years old. Their findings were consistent with the current study; as a result, most lupus patients were under 40 years old, while most vasculitis patients were over 40 years old (5).

### Conclusion

Our study on 169 individuals with crescentic glomerulonephritis showed that, 45.6% of patients with lupus nephritis were female, and women generally had a lower mean age than men. Furthermore, no significant difference was observed in 24-hour proteinuria, creatinine, and fibrosis percentage in either gender.

In this study, 47.3% had IgA nephropathy, 37.9% had lupus nephritis, and 11.2% had vasculitis and Henoch–Schönlein purpura. Furthermore, our research showed that younger patients had more crescents (below 40 years old). Additionally, this group had considerably higher 24-hour proteinuria, and the number of crescents demonstrated a strong connection with serum creatinine.

### Limitations of the study

This research was conducted in a single laboratory and required further investigation by larger samples.

### Authors' contribution

**Conceptualization:** Hamid Nasri.

**Data curation:** Hamid Nasri.

**Formal analysis:** Asieh Maghami Mehr.

**Funding acquisition:** Hamid Nasri.

**Investigation:** Hamid Nasri, Raha Manouchehrian.

**Methodology:** Asieh Maghami Mehr, Rohollah Valizadeh.

**Project management:** Hamid Nasri.

**Resources:** Hamid Nasri.

**Supervision:** Hamid Nasri.

**Validation:** Hamid Nasri.

**Visualization:** Hamid Nasri.

**Writing—original draft:** Hamid Nasri.

**Writing—review and editing:** Hamid Nasri, Rohollah Valizadeh.

### Conflicts of interest

The authors declare that they have no competing interests.

### Ethical issues

This investigation was conducted in accordance with the Declaration of Helsinki. This study was also approved by the Ethics Committee of NIMAD (National Institute for Medical Research Development; <http://nimad.ac.ir>, in Iran; ethical code# IR.NIMAD.REC.1399.223). Accordingly, written informed consent was taken from all participants before renal biopsy or at the time of hospitalization. Besides, the authors have observed ethical issues (including plagiarism, data fabrication, and double publication).

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