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Evaluation of Long-term Outcomes and its Related Factors in Patients with Immune-complex Mediated Glomerulonephritis: A 20-Year Historical Cohort Study in Iran

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Introduction. Immune-complex mediated glomerulonephritis (IC-GN) has a poor prognosis and commonly leads to kidney failure This study reports 20-year experience with the long-term outcomes of 222 Iranian IC-GN patients.
Methods. This single-center historical cohort study was conducted on patients who underwent kidney biopsies from 1998 to 2018 in Hasheminejad Kidney Center (HKC). Initial demographic, clinical, laboratory, and pathology data were extracted from the glomerulonephritis registry of HKC. Follow-up data was obtained by reviewing hospital and outpatient files, as well as phone calls. The primary outcomes were end-stage kidney disease (ESKD) and death, and the secondary outcomes were complete remission, partial remission, and stable chronic kidney disease.
Results. A total of 222 patients, (141 (63.5%) males, 81 (36.5%) females, mean age: 37.76 ± 15.71 years), were diagnosed with IC-GN. The most common causes were IgA nephropathy and lupus nephritis. Among all, 60.2% progressed to ESKD, 15.5% died, 13.1% achieved complete, and 18.5% achieved partial remission. The overall one-, three-, five-, and ten-years kidney survival rates were 52%, 42%, 38%, and 27%, respectively, with a significant difference between the IC-GN subtypes ($P < .001$). The highest kidney survival rate was found in lupus nephritis. Significant independent predictors of ESKD were the percentage of interstitial fibrosis and tubular atrophy (adjusted hazard ratio (aHR) = 1.022 [95% confidence interval (CI) = 1.012-1.033]), percentage of active crescents (aHR = 4.002 [95% CI = 2.066-7.752]), and initial serum creatinine level (aHR = 1.073 [95% CI = 1.035-1.112]) ($P < .001$ for all).
Conclusion. There was a significant difference between the long-term survival of IC-GN types. Histopathologic features, and higher initial serum creatinine levels, were important predictors of poor outcome.

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INTRODUCTION

Crescentic glomerulonephritis is a severe condition marked by rapid decline in kidney function and distinctive glomerular changes in kidney biopsy. A key feature is crescent formation in the glomeruli, resulting from the focal disruption of the glomerular basement membrane. This disruption allows leukocytes and other mediators to enter Bowman's space, leading to the proliferation of epithelial cells, macrophage invasion, and the

formation of cellular crescents.[1,2]

The severity of crescentic glomerulonephritis depends on the underlying immunological process, the extent of crescent formation, and the presence of circumferential crescents. Based on immunofluorescent microscopy, Crescentic GN is classified into three types: Type I (anti-glomerular basement membrane (GBM) antibody disease), Type II (immune-complex mediated crescentic glomerulonephritis (IC-GN)), and Type III (pauci-immune crescentic glomerulonephritis).[3] Immune-complex mediated crescentic glomerulonephritis includes a range of primary and secondary glomerular diseases including IgA nephropathy, membranoproliferative glomerulonephritis (MPGN), and postinfectious glomerulonephritis (PIGN). Alternatively, glomerulonephritis may be part of a systemic immune-complex disease, such as systemic lupus erythematosus, cryoglobulinemia, or IgA vasculitis.[1,4]

Immune-complex mediated crescentic glomerulonephritis can lead to end-stage kidney disease (ESKD). The risk of ESKD and poor treatment outcomes is associated with factors such as initial serum creatinine level, the need for dialysis at treatment onset, disease duration, the extent of glomerulosclerosis and interstitial fibrosis/tubular atrophy (IF/TA).[1,4-6] Delayed immunosuppressive treatment can exacerbate glomerular damage and promote interstitial and glomerular fibrosis, resulting in a less favorable response to therapy.[7-9]

Understanding the prognosis of crescentic glomerulonephritis and its related clinical and pathological factors can guide individualized treatment and improve patient outcomes. However, studies from Asian countries have yielded varying and often inconclusive results, most of them being retrospective and including small sample sizes and short follow-up periods of 6-36 months.[4,5,10-12]

To the best of our knowledge, this is the first study in Iran which reporting the 20-year analysis of long-term outcomes and clinical and pathological characteristics of IC-GN patients from Hasheminejad Kidney Center (HKC), a referral kidney center in Tehran, Iran.

MATERIALS AND METHODS

Patients and data

This single-center historical cohort study was conducted at Hasheminejad Kidney Center (HKC) on patients diagnosed with IC-GN who underwent kidney biopsy between 1998 and 2018. The study was approved by the Ethics Committee of Iran University of Medical Sciences (Ethics Code: 1399.324).

Eligibility criteria included age over 18 years old, having a biopsy with at least 10 glomeruli including one crescentic glomerulus, and immunoglobulins and complement components staining with an intensity greater than 1+ on immunofluorescent microscopy. Additionally, a minimum of six months was needed to have elapsed from the diagnosis. Exclusion criteria included patients under 18 years or those with incomplete data.

Data on demographics, clinical and laboratory findings, and initial kidney biopsy pathology were retrieved from the Glomerulonephritis Registry database of HKC and Health Information System records. The assessed pathology features included crescent type, the presence of endocapillary proliferation, tuft necrosis, rupture of Bowman's capsule, mesangial proliferation, interstitial neutrophil infiltration, the ratio of crescentic to total glomeruli, percentage of active crescents, global sclerosis, and IF/TA. Classification and diagnosis were made based on biopsy findings and serological assessments, retrospectively. Follow-up was conducted through hospital records, outpatient files, and phone contact to record treatment outcomes and final laboratory results.

Primary and secondary outcomes

The primary outcomes were ESKD and death. The secondary outcomes included complete remission, partial remission, and stable chronic kidney disease (CKD). Complete remission was defined as a serum creatinine level below 1.4 mg/dL and a 24-hour urine protein less than 400 mg. Partial remission was defined as a 50% reduction in both serum creatinine (if it was more than 2.3 mg/dL at baseline) and 24-hour urine protein levels, at the last follow-up.[10] Stable CKD was defined as no change in serum creatinine levels during the last year of the follow-up.

Statistical analysis

The normality of continuous variables was assessed using Q-Q plots, histograms, skewness, and kurtosis indices. Descriptive statistics (mean

and standard deviation or median and interquartile range) were used for continuous variables, while frequency and percentage were used for categorical variables. Differences between groups were analyzed with independent sample t-tests or one-way ANOVA for parametric data, and Mann-Whitney U or Kruskal-Wallis tests for non-parametric data. Post hoc pairwise comparisons were performed using Scheffe and Tamhane's T2 tests. Chi-square or Fisher's exact tests were used for categorical variables.

Survival analysis was performed using the Kaplan-Meier method, and survival curves were plotted for overall patient survival (time to death) and overall kidney survival (time to ESKD). Survival rates at one, three, five, and ten years, and median survival times were reported. The Cox proportional hazards model assessed the impact of variables on ESKD development. Variables with a P-value less than 0.200 in univariable analysis were included in multivariable models. Risk factors were reported with crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI). Statistical significance was defined as P-value < .05.

Data was analyzed using IBM SPSS Statistics for Windows, version 15.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 222 patients with IC-GN were included in the study. The cohort consisted of 141 males (63.5%) and 81 females (36.5%), with a mean age of 37.8 ± 15.7 years. 72.4% of patients were hypertensive, 37.9% were on dialysis at diagnosis, and 60.2% progressed to ESKD. Positive tests for P-ANCA, C-ANCA, ANA, and anti-dsDNA were observed in 5.4%, 6.3%, 14.5%, and 14.5% of patients, respectively. The most common IC-GN subtypes were IgA nephropathy (38.2%), lupus nephritis (20.3%), and unclassified IC-GN (30.2%). The conditions accompanying IC-GN included nephrotoxic drug use (21.2%), diabetes mellitus (4.5%), infection (4.1%), and malignancy (1.8%). Nephrotoxic drug use was more common in IgA nephropathy (30.6%) and unclassified IC-GN (17.9%). Infections related to immunosuppressive therapy were observed in 10.4% of patients, with higher rates in lupus nephritis (17.8%) and unclassified IC-GN (13.4%) (Supplementary Table 1).

Significant differences in pathological features were found among IC-GN subtypes ($P < .001$) (Table 1). Lupus nephritis had the highest rates of endocapillary proliferation and interstitial neutrophil infiltration, but the lowest rate of diffuse crescents. IgA nephropathy had the lowest rates of tuft necrosis and interstitial neutrophil infiltration, with the highest rate of mesangial proliferation. MPGN showed the highest rate of diffuse crescents, while unclassified IC-GN had the highest rate of tuft necrosis and lowest rates of endocapillary and mesangial proliferation. Capsular rupture was noted only in unclassified cases. Post hoc analysis showed significant differences in the ratio of crescentic-to- total glomeruli between lupus nephritis and MPGN ($P = .02$), and IgA nephropathy and MPGN ($P = .021$). Differences in the percentage of active crescents were significant between lupus nephritis and MPGN ($P = .002$), lupus nephritis and unclassified IC-GN ($P < .001$), and IgA nephropathy and unclassified IC-GN ($P = .001$). The percentage of global sclerosis differed significantly between IgA nephropathy and lupus nephritis ($P < .001$), unclassified IC-GN and lupus nephritis ($P = .005$), and IgA nephropathy and MPGN ($P = .039$). The percentage of IF/TA also differed significantly between unclassified IC-GN and lupus nephritis ($P = .006$) (Table 1).

The rates of complete remission, partial remission, stable CKD, ESKD, and death were 13.1%, 18.5%, 11.3%, 60.2%, and 15.5%, respectively. Significant differences were observed in remission rates (partial and complete) ($P = .01$), ESKD rates ($P < .001$), and mortality rates ($P = .04$) between different types of IC-GN. No significant difference was found in stable CKD rates ($P = .21$). Lupus nephritis had the highest remission rates, while the highest stable CKD rate was found in IgA nephropathy. PIGN and MPGN had the highest ESKD and mortality rates (Table 2).

The overall patient survival rates were 91%, 88%, 83%, and 79% at one, three, five and ten years, respectively. Kidney survival rates were 52%, 42%, 38%, and 27% at similar time points. The Wilcoxon test showed significant differences in median patient survival rate (Wilcoxon $W = 10.160$, $P = .038$) and median kidney survival rate (Wilcoxon $W = 24.425$, $P < .001$) among IC-GN subtypes. Lupus nephritis and IgA nephropathy had the highest patient survival rates, with lupus nephritis showing the highest kidney survival rate

Supplementary table 1. Associated medical conditions with IC-GN

Variable	IgA-N (n = 85)	lupus-N (n = 45)	PIGN (n = 10)	MPGN (n = 15)	Idiopathic (n = 67)	Total (n = 222)
Associated condition						
Infection (No. (%))	3 (3.5)	0 (0)	0 (0)	1 (6.7)	5 (7.5)	9 (4.1)
Nephrotoxic drug use (No. (%))	26 (30.6)	6 (13.3)	1 (10.0)	2 (13.3)	12 (17.9)	47 (21.2)
Collagen Vascular Disease (No. (%))	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.5)	1 (0.5)
Diabetes mellitus (No. (%))	3 (3.5)	1 (2.2)	1 (10.0)	1 (6.7)	4 (6.0)	10 (4.5)
Familial disease (No. (%))	2 (2.4)	0 (0)	0 (0)	0 (0)	1 (1.5)	3 (1.4)
Other diseases (No. (%))	0 (0)	0 (0)	0 (0)	2 (13.3)	0 (0)	2 (0.9)
Malignancy (No. (%))	3 (3.5)	0 (0)	1 (10.0)	0 (0)	0 (0)	4 (1.8)
Positive HCV antibody (No. (%))	1 (1.2)	0 (0)	0 (0)	1 (6.7)	1 (1.5)	3 (1.4)
Positive HBs antigen (No. (%))	3 (3.5)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1.4)
Positive HIV antibody (No. (%))	1 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.5)
Latent tuberculosis (No. (%))	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.5)	1 (0.5)
Hypertension (No. (%))	63 (74.1)	27 (60.6)	7 (70.0)	12 (80.0)	46 (68.7)	155 (69.8)
Infection due to immunosuppressive use (No. (%))	5 (5.9)	8 (17.8)	0 (0)	1 (6.7)	9 (13.4)	23 (10.4)

Abbreviations: MPGN, membranoproliferative glomerulonephritis; PIGN, postinfectious glomerulonephritis; IgA-N, Immunoglobulin A nephropathy; Lupus-N, lupus nephritis.

Table 1. Pathological characteristics of patients with IC-GN

Variable	Unclassified (n = 67)	MPGN (n = 15)	PIGN (n = 10)	IgA-N (n = 85)	Lupus-N (n = 45)	*P*
Crescents						
Diffuse (No. (%))	34 (50.7)[1]	10 (66.7)	4 (40.0)	16 (18.8)	5 (11.1)	< .001¥
Focal (No. (%))	33 (49.3)	5 (33.3)	6 (60.0)	69 (81.2)	40 (88.9)	
Endocapillary proliferation						
Positive (No. (%))	23 (34.3)	8 (53.3)	5 (50.0)	40 (47.1)	41 (91.1)	< .001¥
Negative (No. (%))	44 (65.7)	7 (46.7)	5 (50.0)	45 (52.9)	4 (8.9)	
Mesangial proliferation						
Positive (No. (%))	19 (28.3)	6 (40.0)	6 (60.0)	66 (77.6)	28 (62.2)	< .001¥
Negative (No. (%))	48 (71.7)	9 (60.0)	4 (40.0)	19 (22.4)	17 (37.8)	
Tuft necrosis						
Positive (No. (%))	18 (26.9)	1 (6.7)	1 (10.0)	3 (3.5)	4 (8.9)	< .001¥
Negative (No. (%))	49 (73.1)	14 (93.3)	9 (90.0)	82 (96.5)	41 (91.1)	
Capsular rapture						
Positive (No. (%))	13 (19.4)	0 (0)	0 (0)	0 (0)	0 (0)	< .001Ÿ
Negative (No. (%))	54 (80.6)	15 (100)	10 (100)	85 (100)	45 (100)	
Interstitial neutrophil infiltration						
Positive (No. (%))	3 (4.5)	1 (6.7)	3 (30.0)	1 (1.2)	31 (68.9)	< .001¥
Negative (No. (%))	64 (95.5)	14 (93.3)	7 (70.0)	84 (98.8)	14 (31.1)	
Crescentic to total glomeruli ratio, % (Median [IQR])	49 [46]	51 [47]	39 [48]	14 [25]	15 [19]	< .001†,1
Active crescents, % (Median [IQR])	56 [48]	75 [58]	40 [49]	24 [51]	16 [39]	< .001†,2
Global sclerosis, % (Median [IQR])	24 [51]	16 [36]	28 [52]	34 [47]	6 [24]	< .001†,3
IF/TA, % (Mean ± SD)	37.0 ± 23.4	38.0 ± 23.6	30.0 ± 21.2	30.4 ± 21.2	18.8 ± 21.9	< .001‡,4

Abbreviations: ESKD, end-stage kidney disease, MPGN, membranoproliferative glomerulonephritis; PIGN, postinfectious glomerulonephritis; IgA-N, Immunoglobulin A nephropathy; Lupus-N, lupus nephritis; IF/TA, Interstitial fibrosis/Tubular atrophy.
[1]Tamhane's T2 posthoc: $P_{\text{Lupus-N, MPGN}} = .02$, $P_{\text{IgA-N, MPGN}} = .021$
[2]Tamhane's T2 posthoc: $P_{\text{Lupus-N, MPGN}} = .002$, $P_{\text{IgA-N, Unclassified}} = .001$, $P_{\text{Lupus-N, Unclassified}} < .001$
[3]Tamhane's T2 posthoc: $P_{\text{Lupus-N, IgA-N}} < .001$, $P_{\text{Lupus-N, Unclassified}} = .005$, $P_{\text{IgA-N, MPGN}} = .039$
[4] Scheffe post hoc:$P_{\text{Lupus-N, Unclassified}} = .006$
†Kruskal Wallis test
‡One-way ANOVA test
¥Chi-square test
ŸFisher's Exact test

(Table 2). Kaplan-Meier survival analysis indicated significant differences in diagnosis-to-death (Log Rank $\chi2 = 10.072$, $P = .039$) and diagnosis-to-ESKD intervals (Log Rank $\chi2 = 31.445$, $P < .001$) (Figure 1).

Table 2. Outcomes of patients with IC-GN

Variable	Total (n = 222)	Unclassified (n = 67)	MPGN (n = 15)	PIGN (n = 10)	IgA-N (n = 85)	Lupus-N (n = 45)	*P*
Remission							
Complete (No. (%))	29 (13.1)	7 (10.4)	0 (0)	2 (20.0)	6 (7.1)	14 (31.1)	
Partial (No. (%))	41 (18.5)	12 (17.9)	1 (6.7)	1 (10.0)	17 (20.0)	10 (22.2)	.01†
No remission (No. (%))	155 (68.5)	48 (71.6)	14 (93.3)	7 (70.0)	62 (72.9)	21 (46.7)	
Stable CKD							
Yes (No. (%))	25 (11.3)	5 (7.5)	0 (0)	0 (0)	14 (16.5)	6 (13.3)	.21†
No (No. (%))	197 (88.7)	62 (92.5)	15 (100)	10 (100)	71 (83.5)	39 (86.7)	
ESKD							
Yes (No. (%))	133 (60.2)	51 (76.1)	12 (80.0)	8 (80.0)	47 (55.3)	15 (34.1)	< .001‡
No (No. (%))	88 (39.8)	16 (23.9)	3 (20.0)	2 (20.0)	38 (44.7)	29 (65.9)	
Kidney, life table							
1-year survival, %	52	36	23	50	53	81	
3-year survival, %	42	22	16	50	47	67	
5-year survival, %	38	22	16	33	40	67	< .001†
10-year survival, %	27	9	-	-	33	55	
Median survival, months	27.08	10.92	8.70	60.00	32.57	168.00	
Death							
Yes (No. (%))	34 (15.5)	15 (23.1)	4 (26.7)	3 (30.0)	7 (8.2)	5 (11.1)	.04‡
No (No. (%))	186 (84.5)	50 (76.9)	11 (73.3)	7 (70.0)	78 (91.8)	40 (88.9)	
Death, life table							
1-year survival, %	91	85	86	80	96	93	
3-year survival, %	88	81	77	69	95	93	
5-year survival, %	83	77	63	69	89	89	.038†
10-year survival, %	79	65	63	-	89	89	
Median survival, months	180.00	180.00	180.00	96.00	156.00	168.00	

Abbreviations: MPGN, membranoproliferative glomerulonephritis; PIGN, postinfectious glomerulonephritis; IgA-N, Immunoglobulin A nephropathy; Lupus-N, lupus nephritis; ESKD, end-stage kidney disease; CKD, chronic kidney disease.
†Fisher's Exact test
‡Chi-square test
¥Wilcoxon test

Independent factors significantly associated with progression to ESKD are shown in Supplementary Table 2. Multivariable analysis identified percentage of IF/TA, active crescents, and initial serum creatinine as significant independent predictors of ESKD ($P < .001$). For each unit increase in these factors, the likelihood of ESKD increased by 1.022 (95% CI = 1.012-1.033), 4.002 (95% CI = 2.066-7.752), and 1.073 (95% CI = 1.035-1.112), respectively (Table 3). Additionally, In IgA nephropathy subgroup, higher initial serum creatinine levels (aHR: 1.326 [95% CI: 1.102-1.595], $P = .003$) and the presence of active crescents (aHR: 1.088 [95% CI: 1.012-1.169], $P = .022$) predicted ESKD, while initial hemoglobin levels and endocapillary proliferation were inversely associated with risk of ESKD (aHR: 0.693 [95% CI: 0.508-0.944], $P = .020$ and aHR: 0.112, [95% CI: 0.016-0.798], $P = .029$, respectively). Furthermore, in lupus nephritis subgroup, male sex was the only significant independent predictor of progression to ESKD (aHR: 5.345 [95% CI: 1.234-23.147], $P = .025$) (Table 3).

DISCUSSION

This study aimed to assess the clinical and pathological characteristics of IC-GN in Hasheminejad Kidney Center as a main referral kidney center in Iran, and to investigate its' long-term kidney outcomes and survival in a sample of 222 patients.

Our study found that IgA nephropathy was the most common cause of IC-GN, followed by lupus nephritis and unclassified IC-GN. This is consistent with previous studies by Nagaraju *et al.*, Rampelli *et al.*, and Lin *et al.*, which also reported IgA nephropathy as the most common cause of IC-GN.[5,11,13] In contrast, Rianthavorn *et al.* found lupus nephritis to be the most common cause in a study of 72 children with crescentic glomerulonephritis.[14] Similarly, Wu *et al.* reported IgA nephropathy

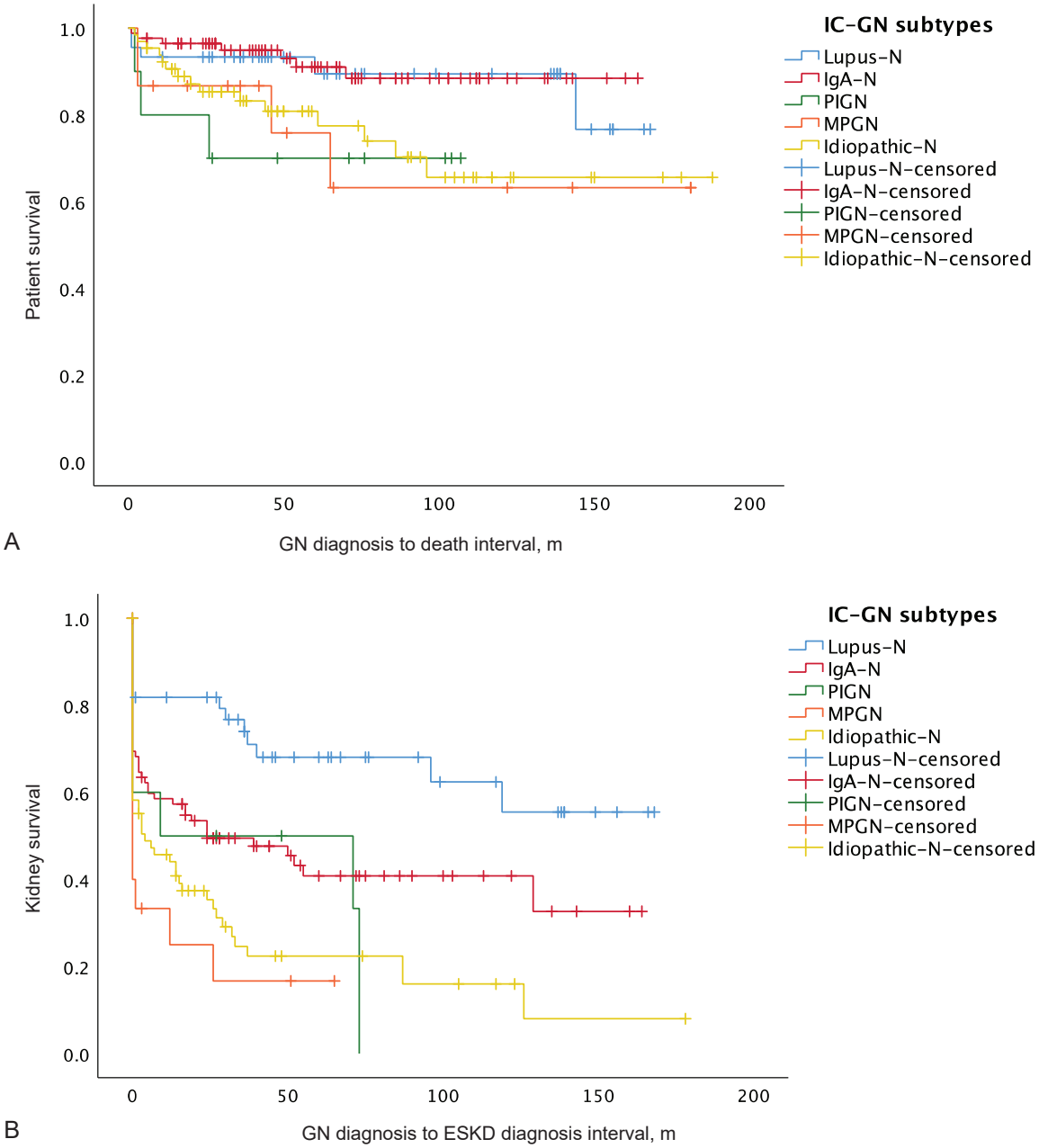

Figure 1. Kaplan-Meier plot of (A) diagnosis-to-death and (B) diagnosis-to-ESKD intervals categorized by IC-GN subtypes

and lupus nephritis as the predominant subtypes IC-GN in a study on 49 patients.[15] Faye *et al.* also reported lupus nephritis as the most frequent cause of IC-GN.[16]

The rate of ESKD in our cohort was 60.2%. Lin *et al.* reported a rate of 51% in a study of 106 patients with crescentic glomerulonephritis, which is close to our findings.[13] However, in another study by Chen *et al.* reported a lower rate of 23%.[4] Variations in reported rates, ranging from 25% to 48.6% in other studies, might be attributed to shorter follow-up periods compared to ours.[5,11,14,17] Additionally, factors such as higher percentages of active crescents, sclerosed glomeruli, and interstitial inflammation, or delay in initiating treatment might contribute to these differences.

Univariable analysis identified significant risk factors for the development of ESKD in IC-GN patients, including initial hemoglobin, 24-hour urine protein and creatinine levels,

Supplementary table 2. Correlation between demographic, clinical, pathological, laboratory characteristics, and medication used with ESKD in patients with IC-GN

Variable	ESKD (n =133)	No ESKD (n = 88)	*P*
Age, year (Mean ± SD)	38.26 ± 15.78	37.27 ± 15.58	.65†
Gender			
Male (No. (%))	90 (67.7)	51 (58.0)	.14‡
Female (No. (%))	34 (32.3)	37 (42.0)	
Hypertension			
Positive (No. (%))	108 (85.0)	46 (54.1)	< .001‡
Negative (No. (%))	19 (15.0)	39 (45.9)	
Crescents type			
Diffuse (No. (%))	56 (42.4)	12 (14.0)	< .001‡
Focal (No. (%))	76 (57.6)	74 (86.0)	
Hemoglobin, g/dL (Mean ± SD)	9.54 ± 2.15	11.44 ± 2.43	< .001†
Initial serum creatinine, mg/dL (Median [IQR])	6.60 [6.05]	1.90 [1.95]	< .001¥
Initial urine protein, mg/24h (Median [IQR])	3975.0 [4350.0]	3231.0 [2747.0]	.024¥
Crescents to total glomeruli ratio, % (Median [IQR])	36 [0.29]	11 [0.20]	< .001¥
Active crescents, % (Median [IQR])	53 [0.47]	13 [0.19]	< .001¥
Global sclerosis, % (Median [IQR])	40 [0.50]	11 [0.25]	< .001¥
IF/TA, % (Mean ± SD)	40.38 ± 22.06	15.69 ± 15.08	< .001†
Medication used			
Cyclophosphamide (No. (%))	58 (43.6)	33 (37.5)	.40‡
Prednisolone (No. (%))	113 (85.0)	86 (97.9)	.002‡
Mycophenolate (No. (%))	34 (25.6)	51 (58.0)	< .001‡
Tacrolimus (No. (%))	0 (0)	8 (9.1)	< .001Ÿ
Azathioprine (No. (%))	10 (7.5)	22 (25.0)	< .001‡
Rituximab (No. (%))	4 (3.0)	6 (6.8)	.20Ÿ
Cyclosporine (No. (%))	3 (2.3)	9 (10.2)	.01Ÿ
Plasmapheresis (No. (%))	3 (2.3)	2 (2.3)	1.00Ÿ

Abbreviations: ESKD, end-stage kidney disease; IF/TA, Interstitial fibrosis/Tubular atrophy.
†Independent t- test
‡Chi-square test
¥Mann-Whitney U test
ŸFisher's Exact test

Table 3. Multivariable Cox Proportional-Hazards regression for defining significant independent predictors of ESKD in patients with IC-GN, lupus nephritis and IgA nephropathy

Predictor	aHR	95% CI		Wald statistic	*P*
		Lower	Upper		
All IC-GN patients (n = 222)					
IF/TA, %	1.022	1.012	1.033	18.340	< .001
Active crescents, %	4.002	2.066	7.752	4.002	< .001
Initial serum creatinine, mg/dL	1.073	1.035	1.112	1.073	< .001
IgA nephropathy patients (n = 85)					
Initial serum creatinine, mg/dL	1.326	1.102	1.595	8.907	.003
Initial serum hemoglobin, g/dL	0.693	0.508	0.944	5.394	.020
Endocapillary proliferation	0.112	0.016	0.798	4.771	.029
Active crescents, %	1.088	1.012	1.169	5.240	.022
Lupus nephritis patients (n = 45)					
Male sex	5.345	1.234	23.147	5.025	.025

Abbreviations: IF/TA, Interstitial fibrosis/Tubular atrophy; aHR, adjusted hazard ratio; CI, confidence interval.

hypertension, use of immunosuppressive drugs, diffuse type crescentic glomerulonephritis, and specific histopathologic features (i.e., the ratio of crescentic-to-total glomeruli, active crescents percentage, global sclerosis percentage, and IF/TA). Multivariable analysis, however, found the

initial serum creatinine levels, IF/TA, and active crescents percentage as independent prognostic factors, reflecting irreversible changes and disease severity.[18] These findings have been widely reported in previous studies. Rampelli *et al.* identified high blood pressure, high initial serum creatinine levels, and higher percentages of fibrocellular crescents as predictors of poor outcomes in 37 patients with crescentic glomerulonephritis, 77% of whom had IC-GN.[11] Similarly, Faye *et al.* reported high initial serum creatinine levels, need for dialysis, oliguria, and higher percentages of fibrous and fibrocellular crescents to be associated with poor kidney prognosis.[16] Lim *et al.* found that ESKD was associated with several histopathologic characteristics, including the percentage of normal glomeruli, higher arteriosclerosis grade, sclerotic histopathologic class, severe tubular atrophy, and tertiary lymphoid organ formation.[17] Other studies also support the association of high serum creatinine levels and need for dialysis at presentation with worse kidney prognosis in crescentic glomerulonephritis.[5,14,15] For instance, Piyaphanee *et al.*, in a cohort of patients with rapidly progressive glomerulonephritis with 50.7% PIGN, noted that acute need for dialysis, high serum creatinine levels, high crescentic-to-total glomeruli ratio, and high IF/TA were linked to ESKD, though only the latter two variables were independently associated with ESKD in multivariable analysis.[19]

In multivariable survival analysis, higher initial serum creatinine levels and the presence of active crescents were significant predictors of ESKD among patients with IgA nephropathy. Initial hemoglobin levels and endocapillary proliferation were inversely associated with ESKD risk. This is consistent with a study of 619 Chinese patients with IgA nephropathy, in which lower serum hemoglobin was an independent risk factor for ESKD.[20] Similarly, Lv *et al.* found initial serum creatinine at biopsy to be the only an independent risk factor for ESKD in crescentic IgA nephropathy patients.[21] Additionally, the multivariable survival analysis in the subset of patients with lupus nephritis showed that male sex was the only significant predictor of ESKD, supported by a meta-analysis of 25 studies identified a trend indicating that male patients with severe lupus nephritis are more likely to develop ESKD.[22]

Our study showed kidney survival rates of 52%, 42%, 38%, and 27% at one, three, five, and ten years, respectively. These findings are consistent with Wu *et al.*, who reported a kidney survival rate of approximately 25% after 50 months,[15] and Lin *et al.*, with a 5-year rate of about 30%.[13] However, the kidney survival rates of our cohort were lower than those reported by Chen *et al.* (70.1% at 5 years), as well as rates from pediatric IC-GN cohorts, where survival rates were reported as 79.5%, 58.8%, and 58.8% at 1, 5, and 10 years, respectively.[4] Similarly, a study from China reported a 5-year survival rate of 83.3%.[23] We assume this to be due to baseline differences between the studies. For example, higher initial average serum creatinine concentrations at diagnosis, as well as higher proportion of patients with serum ANCA positivity, may contribute to lower IC-GN survival rates. Additionally, less intensive immunosuppressive treatment may impact kidney survival. Moreover, differences in inclusion criteria, disease severity at diagnosis, and population-specific characteristics can partly explain the variation in survival outcomes observed between this and the other studies.

We found significant differences in kidney and patient survival among IC-GN subtypes, with lupus nephritis and IgA nephropathy showing the best prognosis and PIGN and MPGN the worst. Although data is scarce for kidney and patient survival in IC-GN subtypes, long-term prognosis varies among histological types of crescentic glomerulonephritis. Rianthavorn *et al.* noted significant differences in kidney survival rates among pediatric patients based on various histological classifications, including focal, crescentic, mixed, and sclerotic entities.[14] Lin *et al.* found that patients with IgA nephropathy had fewer glomeruli affected by cellular crescents and more normal glomeruli compared to other IC-GN subtypes (i.e., lupus nephritis or ANCA-associated glomerulonephritis),[13] findings that were also observed in the present study. Additionally, lupus nephritis patients may have a better kidney outcome, especially in late-onset cases.[24,25] On the other hand, in PIGN, Streptococcus and Staphylococcus are common causative organisms. While PIGN in children often results in complete remission, adult cases, particularly in the elderly or those with comorbid conditions, may progress to ESKD at higher rates.[26-28] Moreover, MPGN has a poor prognosis due to the lack of specific treatments and the frequent presence of impaired

kidney function at diagnosis.[29,30] Studies show five- and ten-year kidney survival rates of 33.3% and 16.7% for primary MPGN, and 79% renal failure at the time of diagnosis with 43.5% progression to ESKD after a mean follow-up of 51.9 months.[29,30] Nonetheless, large cohorts of specific IC-GN etiologies with long follow-up periods are needed to yield more data for renal and patients' survival.

Interestingly, our cohort revealed positive P-ANCA and C-ANCA tests in 5.4% and 6.3% of cases, respectively. Specifically, P-ANCA positivity was found in nine idiopathic and three lupus nephritis cases, while C-ANCA positivity was observed in eight idiopathic cases, three with IgA nephropathy, two with lupus nephritis, and one with MPGN. While ANCA positivity is typically associated with pauci-immune crescentic glomerulonephritis, occurring in approximately 90% of cases and contributing to the nomenclature of ANCA-associated vasculitis,[31] there is growing evidence of ANCA positivity in patients with IC-GN. This overlap syndrome, where ANCA positivity coexists with IC-GN, has been documented in cases of IgA nephropathy,[32,33] PIGN,[34] and MPGN.[35] Such cases usually present with lower ANCA and CRP titers compared to typical ANCA-associated vasculitis, and they tend to lack pulmonary involvement. However, these patients frequently exhibit more severe proteinuria and are more likely to develop necrotizing or crescentic lesions.[32,36,37] Generally, this phenomenon may address the need for careful evaluation of ANCA-positive IC-GN cases as their clinical presentation may differ from the classical ANCA-associated vasculitis.

Our study had several limitations. First, it was conducted at a single center and therefore the results may not be applicable to the Iranian population. Second, there were insufficient sample sizes for certain IC-GN subtypes, specifically PIGN and MPGN. Third, due to the use of a historical cohort design, some data was inevitably missing, although the percentage of missing data was less than 30% for all variables. Particularly, a key limitation of our study is that approximately 30% of cases remained unclassified. This may be attributed to limitations in diagnostic techniques, incomplete clinical data, or the retrospective nature of the study, which potentially limited the identification of specific underlying etiologies in some patients. As such, certain cases were categorized as idiopathic IC-GN, as further serology or pathologic findings did not show a clear pathologic entity. Finally, due to the retrospective nature of the study and the broad spectrum of disease presentations, it was difficult to assess the specific impact of various therapies, as treatment regimens varied across histologic classes. Some patients did not respond to their initial regimen and switched to another, further complicating the evaluation of treatment effects. Additionally, we were unable to compare the effects of different immunosuppressive treatments on outcomes, as a randomized clinical trial would be more suitable for such an assessment.

Conclusion: Our study showed the significance of certain histopathologic features in predicting the outcome of IC-GN. Specifically, a high percentage of active crescents and IF/TA, along with elevated initial serum creatinine levels, are important prognostic factors. Moreover, our findings suggest that different etiologies of IC-GN have varying long-term survival rates. These identified features could be utilized to personalize and monitor treatment plans.

Recommendations and Further Research

We recommend future research to be conducted with larger sample sizes, particularly including more cases with MPGN and PIGN, and comparison of the outcomes of IC-GN with those of anti-GBM antibody GN and pauci-immune crescentic GN patients.

DECLARATIONS

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Author contributions

The study was designed by Dr. Shahrzad Ossareh and Dr. Shiva Shahnazari. Data was collected from Glomerulonephritis Registry of HKC, which was developed by Dr. Shahrzad Ossareh. Dr. Shiva Shahnazari and Dr. Mitra Mehrazma collected the data. Dr. Shadi Naderian performed data analysis. Dr. Shiva Shahnazari drafted the manuscript. Dr. Shahrzad Ossareh critically revised the drafted manuscript and supervised the manuscript preparation.

Authorship

All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship. They take full responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

Competing interests

The authors declare that they have no competing interests.

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Availability of data and materials

The corresponding author can provide the data upon request, with permission from the third party.

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