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Received: 29 June 2025

Revised: 23 Sep 2025

Accepted: 1 Nov 2025

Published: 10 March 2026

Renal histopathology spectrum in the biopsy-proven native kidney diseases of adult Iranian population, southern Iran: 2019-2024

Abstract

Background: Renal diseases strongly influence global health burden and healthcare costs, especially for countries with low and middle socio-demographic indices. This study aimed to provide data on kidney disorder patterns and compare results with our previous analysis of biopsy-proven renal diseases to determine how the pattern is changing in our region.

Methods: This cross-sectional analysis of 2,392 native renal biopsies was performed from 2019 to 2024 at the Namazi Hospital, a tertiary referral healthcare center in Shiraz, Iran.

Results: Of 2,392 native kidney biopsies, primary glomerulonephritis was the most common finding, with the leading diagnosis of membranous glomerulonephritis (MGN), followed by focal segmental glomerulosclerosis (FSGS), and mesangioproliferative GN (MesGN). For secondary GN, lupus nephritis (LN), diabetic nephropathy, and amyloidosis were prominent. Lupus nephritis was the only female-predominant subtype ($p < 0.001$). Significant male predominance was observed in MGN ($p < 0.001$), IgA nephropathy ($p < 0.001$), Amyloidosis ($p < 0.05$), and hypertensive nephropathy ($p < 0.05$), whereas most other renal biopsy subtypes showed no statistically significant gender differences ($p > 0.05$). Age-related analysis showed that LN was the predominant finding in patients < 45 years, whereas MGN was the most common among older patients ($P < 0.001$).

Conclusion: Comparing the proportions of biopsy results with our previous analysis revealed that FSGS and LN decreased dramatically, while MGN, Diabetic nephropathy, IgA nephropathy, and tubulointerstitial diseases showed increasing trends. These data provided essential clues for further studies on organizing renal health goals.

Keywords: Biopsy, Glomerulonephritis, Kidney disease, Lupus nephritis, Nephropathy.

Citation:

Akbari M, Malekmakan L, Sanjarian S, Pakfetrat M. Renal histopathology spectrum in the biopsy-proven native kidney diseases of adult Iranian population, southern Iran: 2019-2024. Caspian J Intern Med 2026; 17(2): 403-411.

Renal diseases are serious contributors to global health, morbidity, mortality, cardiovascular disease, and healthcare costs, especially for countries with low and middle socio-demographic indices, a developmental measurement (1). By 2030, the number of patients requiring renal replacement therapy (RRT) is expected to increase to 5,439 million worldwide, mainly in developing areas such as Asia and Africa. Moreover, it is estimated that between 2,284 and 7,083 million individuals who could have been kept alive with RRT in 2010 died because RRT could not be accessed (2). Clinical information and laboratory tests cannot distinguish the underlying pathology. By considering the advantages of this invasive procedure against its possible complications, renal biopsy assists in making definitive diagnoses, improving treatment, and understanding disease progression or prognosis (3, 4). The biopsy-proven nephropathies and their different patterns have been published in other countries (5-7).



Based on the published evidence, the overall prevalence of chronic kidney disease (CKD) was about 11.6% in 2014 and 15.4% in 2018 in Iran, which is higher than the worldwide CKD prevalence at those times (8, 9). Also, a meta-analysis showed 360 per million population as a pooled prevalence of ESRD in the Middle East (10). The two leading causes of CKD in the general Iranian population were hypertension and diabetes from 2009 till recently (11). Our previous report described the clinical and histopathological patterns of biopsy-proven renal diseases from January 2011 to December 2017, demonstrating that three major GNs are lupus nephritis (LN), membranous glomerulonephritis (MGN), and focal segmental glomerulosclerosis (FSGS) (8). The current study aimed to provide data on the variations in kidney diseases diagnosed by renal biopsy in a nephrology unit at the referral hospital from 2019 to 2024.

Methods

Study design and population: This cross-sectional study of 2,392 native renal biopsies included patients who underwent kidney biopsy in a nephrology unit at the referral hospital, a tertiary referral healthcare center, from March 2019 to February 2024. This study obtained data from electronic databases and hardcopy records of kidney biopsy reports. All study participants gave written consent. Approval was obtained before the start of the study by the ethics committee (IR.SUMS.REC.1402.203). Assuming that no contraindication was defined by the attending physician, renal tissue specimens were received by performing a percutaneous needle biopsy. Only the first biopsy was included in this analysis for patients with multiple biopsies. Biopsy specimens were studied with light microscopy using staining techniques, including hematoxylin and eosin (H&E), Periodic acid-Schiff (PAS), Jones and Masson trichrome, and immunofluorescence microscopy technique identifying immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM), and complement component 3 (C3). At the pathologist's discretion, biopsies were selectively investigated with electron microscopy and Congo red staining. Renal biopsies were performed for clinical indications, most commonly nephrotic syndrome, nephritic syndrome, rapidly progressive glomerulonephritis (RPGN), asymptomatic urinary abnormalities, acute kidney injury, and CKD. Our approach to categorizing samples was based on the classification proposed by another study (9), which divided biopsy results into five classes: (i) primary GN (PGN), such as minimal change disease (MCD), MGN, FSGS, IgA

nephropathy (IgAN), membranoproliferative GN (MPGN), Mesangioproliferative GN (MesGN), crescentic GN (CGN), proliferative endocapillary GN (PEGN), and unclassified GN. A PGN diagnosis was considered if there was no evidence of multisystemic disease at the time of biopsy; (ii) secondary GN (SGN) such as lupus nephritis (LN), Henoch-Schönlein purpura nephritis (HSPN), amyloidosis, hemolytic uremic syndrome (HUS) and diabetic nephropathy (DN), obesity-related glomerulopathy, anti-GBM nephritis, Alport syndrome, and GN associated with infectious diseases; (iii) tubulointerstitial diseases, consisting acute and chronic tubulointerstitial nephritis (TIN), acute tubular necrosis, oxalosis, and light chain cast nephropathy; (iv) vascular diseases, including thrombotic microangiopathy (TMA) and hypertensive nephrosclerosis, and (v) miscellaneous, including entities that were challenging to classify, unclassified nephropathies, and normal histopathological findings. We add the global sclerosis category to describe chronic, irreversible changes observed on biopsy samples. We only considered primary FSGS cases, due to limitations in genetic testing and incomplete clinical histories; considering secondary or genetically related FSGS cases was not possible. Crescentic GN cases without any evidence of systemic disease were classified under primary GN. Cases associated with systemic diseases, such as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, were classified as secondary GN.

Our study comprised all patients who underwent renal biopsy within the selected period. Biopsies of transplanted kidneys, re-biopsies, patients aged ≤ 18 , patients with incomplete records, insufficient renal tissue for evaluation, and missing histologic diagnosis were excluded.

Statistical analysis: We used a standard Excel database to store data and calculated statistical analysis using SPSS software version 18.0. Categorical variables are described as absolute numbers and percentages, and the continuous variables are reported as the mean \pm standard deviation. The distribution of each histopathological diagnosis across gender and age groups was compared using a chi-square test for independence. P-values < 0.05 are set as statistically significant. Chi-square test and Fisher's exact test were performed to evaluate changes in diagnosis proportions between the two-time frames.

Results

Patients' characteristics: Three thousand nine hundred eighty-five patients had a renal biopsy performed at the Namazi Hospital during the specified period. Based on the

exclusion criteria, 2392 eligible patients with native kidney biopsy data remained. The age range at the time of renal biopsy varied from 18 to 88 years, with a mean of 43.4±14.8 years (41.9±14.0 for females and 44.9±15.5 for males, $p < .001$). MGN, IgA nephropathy, Amyloidosis, and hypertensive nephropathy showed significant male predominance ($p < 0.05$), while Lupus nephritis was significantly female-predominant ($p < 0.001$). All other subtypes showed no significant gender differences ($p > 0.05$).

Histopathological findings: As depicted in figure 1, PGN was the most common pathological finding, accounting for 42.0% (1005 cases), followed by SGN (21.1%, 504 cases)

and tubulointerstitial diseases (7.7%, 183 cases). The leading histological diagnosis for PGN is MGN (447 cases), followed by FSGS (172 cases) and MesGN (167 cases) (44.5%, 17.1%, and 16.6% of the PGN population, respectively). LN (363 cases) was the most frequent diagnosis for SGN, followed by DN (97 cases) and amyloidosis (36 cases) (72.0%, 19.2%, and 7.1% of the SGN population, respectively). Other less prevalent biopsy results are noted in table 1. In all histopathological subtypes, excluding MesGN, LN, DN, and TMA, the number of males was higher than that of females ($P < 0.001$) (table 1). The mean age of patients with LN and TMA was the youngest (37.1±10.9 and 39.00±12.3, respectively).

Table 1. Age and gender distribution of 2392 renal biopsy results conducted from March 2019 to February 2024 in Shiraz, Iran.

Glomerular Diseases	n (% of total population)	Age (years), Mean ±SD	Gender ratio (M: F)	P-value (gender)	Gender Predominance
Primary GN Subtypes					
MGN	447 (18.7)	47.6±14.9	1.5: 1	<0.001	Male
FSGS	172 (7.2)	42.6±14.7	1.3: 1	> 0.05	—
MesGN	167 (7.0)	41.4±13.2	0.8: 1	> 0.05	—
CGN	79 (3.3)	44.3±15.5	1.1: 1	> 0.05	—
IgAN	70 (2.9)	39.8±11.2	2.7: 1	<0.001	Male
Diffuse active proliferative GN	39 (1.6)	41.5±15.1	1.1: 1	> 0.05	—
MPGN	27 (1.1)	43.9±20.7	1.3: 1	> 0.05	—
Others	4 (0.2)	26.5±5.8	0.3: 1	> 0.05	—
Total	1005 (42.0)	44.5±14.9	1.3: 1	<0.001	Male
Secondary GN Subtypes					
Lupus Nephritis	363 (15.2)	37.1±11.0	0.2: 1	< 0.001	Female
Diabetic Nephropathy	97 (4.1)	50.1±14.1	1.0: 1	> 0.05	—
Amyloidosis	36 (1.5)	60.6±11.1	2.0: 1	< 0.05	Male
Others	8 (0.3)	32.7±11.0	3.0: 1	> 0.05	—
Total	504 (21.1)	41.2±14.0	0.4: 1	<0.001	Female
Tubulointerstitial Diseases					
Acute TIN	80 (3.3)	49.5±16.4	1.1: 1	> 0.05	—
Acute Tubular injury and necrosis	53 (2.2)	47.0±14.0	1.8: 1	> 0.05	—
Chronic TIN	50 (2.1)	44.5±17.9	1.3: 1	> 0.05	—
Total	183 (7.6)	47.4±16.2	1.3: 1	> 0.05	—
Vascular					
Hypertensive	11 (0.5)	42.5±17.2	10.0: 1	< 0.05	Male
TMA	10 (0.4)	39.0±12.3	0.7: 1	> 0.05	—
Total	21 (0.9)	40.8±14.9	2.0: 1	< 0.05	Male
Global Sclerosis	137 (5.7)	41.0±14.7	1.1: 1	> 0.05	—
Miscellaneous	542 (22.7)	42.7±14.9	1.0: 1	> 0.05	—

SD: standard deviation, M: F: male to female ratio, GN: glomerulonephritis, MGN: membranous glomerulonephritis, FSGS: focal segmental glomerulosclerosis, MesGN: Mesangioproliferative glomerulonephritis, CGN: crescentic glomerulonephritis, IgAN: immunoglobulin A nephropathy, MPGN: membranoproliferative glomerulonephritis, TIN: tubulointerstitial nephritis, TMA: thrombotic microangiopathy, miscellaneous: entities that were challenging to classify, unclassified nephropathies, and normal histopathological findings.

Table 2 demonstrates age-related variations in renal biopsy subtypes. LN was the predominant finding in patients aged <45 years (81.8% of LN cases occurred in this age group), whereas MGN was more common in older patients ($P < 0.001$). IgAN also demonstrated a strong predilection for younger patients, with 71.3% of cases diagnosed before 45 years ($P < 0.001$). In contrast, Diabetic Nephropathy and Amyloidosis were significantly associated with older age, with over 60% of DN and more than 90% of amyloidosis cases occurring in patients ≥ 46

years ($P < 0.001$ for both). Changes were observed by comparing this study with our previous one, conducted at the exact center during a different period, revealing a statistically significant decline in the frequencies of FSGS, MPGN, and LN ($P < 0.001$). Except for MGN, amyloidosis, and Global Sclerosis that remained statistically unchanged ($P > 0.05$), other histopathologies such as CGN, IgAN, and DN increased statistically ($P < .05$) during these time frames (table 3 and figure 3).

Table 2. Distribution of the histological pattern of 2392 renal biopsy results according to different age groups from March 2019 to February 2024 in Shiraz, Iran.

Renal Biopsy Results	Age groups, n (% of total population of subtype)				Total	P-value
	< 30 Years (n= 503)	31-45 Years (n= 929)	46-60 Years (n= 573)	> 60 Years (n= 387)		
Primary GN Subtypes					1005	
MGN	63 (14.1)	142 (31.8)	146 (32.7)	96 (21.4)	447	<0.001
FSGS	36 (21.0)	71 (41.2)	41 (23.8)	24 (14.0)	172	> 0.05
MesGN	41 (24.5)	65 (39.0)	44 (26.3)	17 (10.2)	167	> 0.05
CGN	14 (17.7)	34 (43.0)	14 (17.7)	17 (21.6)	79	> 0.05
IgAN	10 (14.2)	40 (57.1)	16 (23)	4 (5.7)	70	<0.001
Diffuse active proliferative GN	10 (25.6)	16 (41.0)	7 (18.0)	6 (15.4)	39	> 0.05
MPGN	7 (26.0)	10 (37.0)	3 (11.0)	7 (26.0)	27	> 0.05
Secondary GN Subtypes					504	
Lupus Nephritis	99 (27.3)	198 (54.5)	56 (15.5)	10 (2.7)	363	<0.001
Diabetic Nephropathy	13 (13.4)	23 (23.7)	35 (36.1)	26 (26.8)	97	<0.001
Amyloidosis	0	3 (8.3)	14 (38.9)	19 (52.8)	36	<0.001
Tubulointerstitial diseases					183	
Acute TIN	11 (13.7)	22 (27.5)	21 (26.3)	26 (32.5)	80	<0.001
Acute Tubular injury and necrosis	8 (15.1)	16 (30.2)	18 (33.9)	11 (20.8)	53	> 0.05
Chronic TIN	11 (22.0)	18 (36.0)	5 (10.0)	16 (20.0)	50	< 0.01
Vascular					21	
Hypertensive	4 (36.3)	2 (18.2)	3 (27.3)	2 (18.2)	11	> 0.05
TMA	3 (30.0)	4 (40.0)	2 (20.0)	1 (10.0)	10	> 0.05
Global Sclerosis	41 (30.0)	52 (38.0)	25 (18.2)	19 (13.8)	137	> 0.05
Miscellaneous	127 (23.4)	207 (38.2)	122 (22.5)	86 (15.9)	542	> 0.05

GN: glomerulonephritis, MGN: membranous glomerulonephritis, FSGS: focal segmental glomerulosclerosis, MesGN: Mesangioproliferative glomerulonephritis, CGN: crescentic glomerulonephritis, IgAN: immunoglobulin A nephropathy, MPGN: membranoproliferative glomerulonephritis, TIN: tubulointerstitial nephritis, TMA: thrombotic microangiopathy.

Table3. Comparison of the proportions of common glomerular biopsy results between different periods at the same center, in Shiraz, Iran.

Glomerular Diseases	2011- 2017 n (%)	2019- 2024 n (%)	P-value
Primary GN Subtypes			
MGN	231 (17.0%)	447 (18.7%)	> 0.05
FSGS	188 (13.9%)	172 (7.2%)	<0.001
MesGN	128 (9.5%)	167 (7.0%)	< 0.01
CGN	27 (2.0%)	79 (3.3%)	<0.05
IgAN	11 (0.8%)	70 (2.9%)	< 0.001
Diffuse active proliferative GN	7 (0.5%)	39 (1.6%)	< 0.01
MPGN	57 (4.2%)	27 (1.1%)	<0.001
Total	774 (57.1%)	1005 (42.0%)	
Secondary GN Subtypes			
Lupus Nephritis	332 (24.5%)	363 (15.2%)	<0.001
Diabetic Nephropathy	20 (1.5%)	97 (4.1%)	<0.001
Amyloidosis	15 (1.1%)	36 (1.5%)	> 0.05
Total	392 (28.9%)	504 (21.1%)	
Tubulointerstitial diseases			
Acute TIN	33 (2.5%)	80 (3.3%)	> 0.05
Acute Tubular injury and necrosis	7 (0.5%)	53 (2.2%)	< 0.001
Chronic TIN	11 (0.8%)	50 (2.1%)	< 0.01
Total	56 (4.1%)	183 (7.6%)	
Global Sclerosis	80 (5.9%)	137 (5.7%)	> 0.05

GN: glomerulonephritis, MGN: membranous glomerulonephritis, FSGS: focal segmental glomerulosclerosis, MesGN: Mesangioproliferative glomerulonephritis, CGN: crescentic glomerulonephritis, IgAN: immunoglobulin A nephropathy, MPGN: membranoproliferative glomerulonephritis, TIN: tubulointerstitial nephritis.

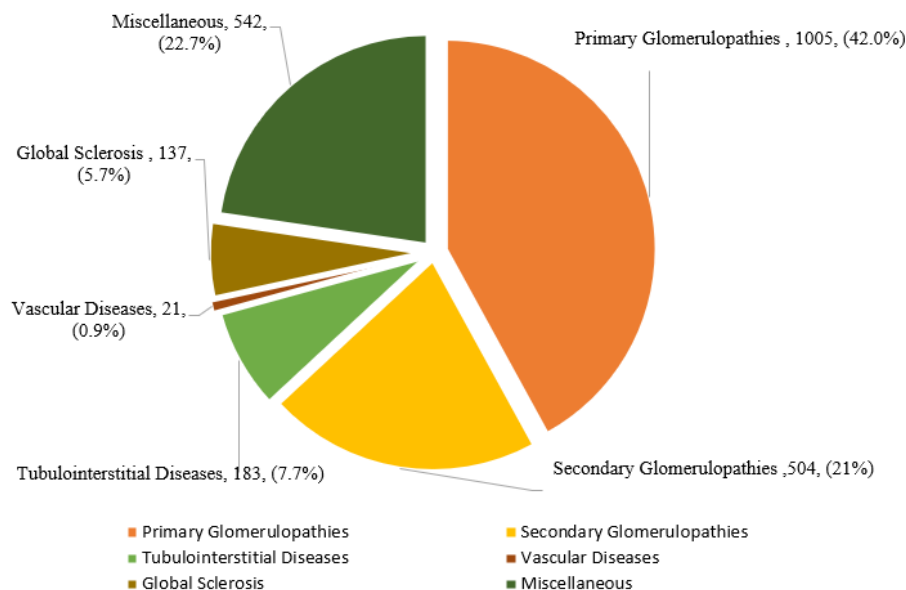


Figure 1. The histological distribution of kidney biopsies in 2392 patients. The frequencies of the groups are shown in numbers and percentages.

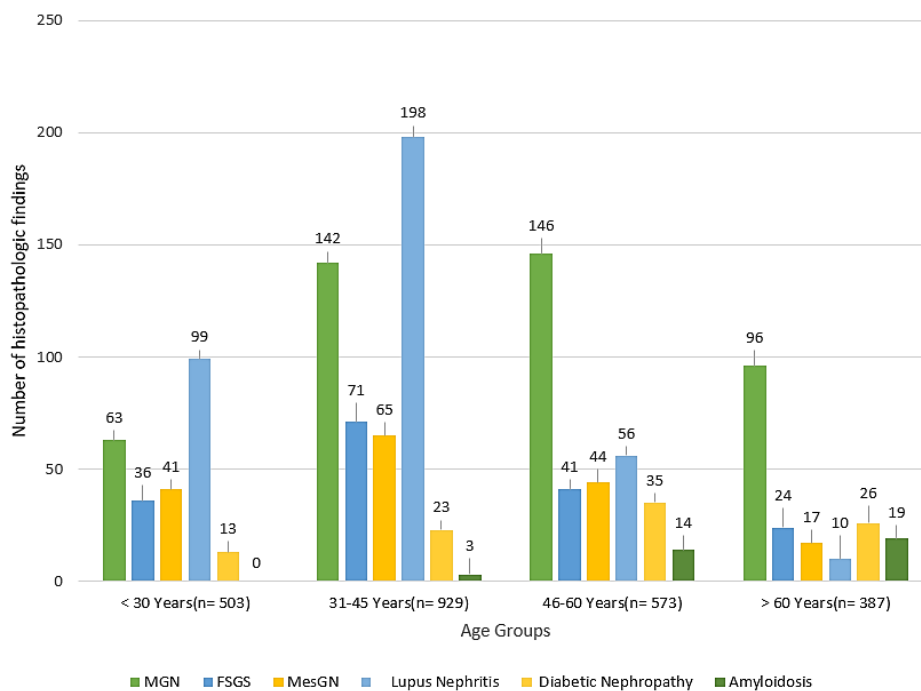


Figure 2. Distribution of the histological pattern of some renal biopsy results among different age groups. MGN: membranous glomerulonephritis, FSGS: focal segmental glomerulosclerosis, MesGN: Mesangioproliferative glomerulonephritis.

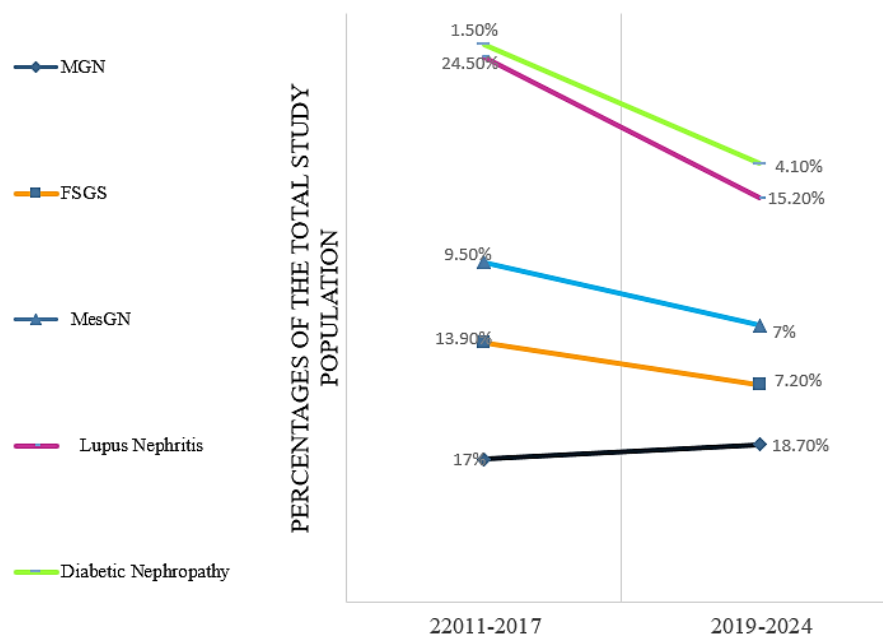


Figure 3. Comparison of the change in the trends of common glomerular biopsy results between different periods at the same center, in Shiraz, Iran. MGN: membranous glomerulonephritis, FSGS: focal segmental glomerulosclerosis, MesGN: Mesangioproliferative GN.

Discussion

Insights into the epidemiological aspects of renal diseases, including all subtypes, provide critical information to improve healthcare burdens. This analysis revealed the

distribution of histopathological diagnoses of 2,392 eligible patients with native kidney biopsy data who underwent renal biopsies from 2019 to 2024 at our center in Shiraz, Iran, one of the leading tertiary referral healthcare centers.

PGN was the most common pathological finding, followed by SGN and tubulointerstitial diseases. The leading histological diagnosis for PGN is MGN, followed by FSGS. LN and diabetic nephropathy were the most frequent diagnoses for SGN. Our analyses indicate changes in the distribution of histopathological subtypes across age groups compared to our previous study (2011–2017). In the current cohort, more than half of MGN and DN cases occurred in patients aged ≥ 46 years, whereas in the previous study, the majority of these cases were in patients aged < 45 years, indicating an upward shift in age for these conditions (8).

By comparing the proportions of common glomerular biopsy results between our current and previous study, held in different periods but at the same center, a dramatic shift in the pattern of some results can be observed. For instance, FSGS, MPGN, and LN decreased dramatically over these two periods, contrary to MGN and DN, which slightly increased. These disparities may result from differences in age distribution. Twenty-one percent of the current study population is aged ≤ 30 , which is 50% for our previous investigation (the mean age of 43.4 ± 14.8 compared to 33.2 ± 16.4 for the study mentioned above). A Spanish study has reported a gradual decrease in the incidence of LN from 104 patients/year to 86 patients/year over the 26-year study period. The frequency of diagnosis of LN significantly decreased in the period 2014–2019 (7% of total biopsies) compared with the previous years (9.6% from 1994 to 2013) (12). In contrast, a Danish population-based study observed no significant fluctuations in the incidence rates of LN between 1995 and 2011. The study also reported higher overall incidence rates for LN among women than among men, particularly in younger and middle-aged individuals (13). In our study, FSGS was the second most common PGN, following MGN as the most prevalent. This result is consistent with a 12-year survey conducted on the Iranian population from 2006 to 2018 (11). Sim et al. (14), in a large kidney biopsy cohort of a considerably racially and ethnically diverse United States population, with a 12-year observation period, FSFG was the most prevalent glomerulonephropathy (38.9%) among all races and ethnic groups, including Asians and Hispanics. In contrast, in China, Wang et al. (15) noted a decreasing trend in the proportion of FSGS (9.46% in 2008–2013 and 6.47% in 2014–2018), which was significantly lower than the American population.

Except for MesGN, LN, DN, and TMA, men were more frequently affected by most of the kidney diseases in our study. In a survey by O'Shaughnessy et al. (16), the glomerular disease subtype distributions by gender were noted. They confirmed LN as the most common glomerular

disease among women and IgAN as the most common among men. IgAN was the fifth most common PGN in our analysis. Contrary to this, IgAN represents the most frequently occurring primary, biopsy-proven GN in other national investigations, including Australia, the Czech Republic, and Japan (17–19). Recent genome-wide association studies have recognized multiple susceptibility loci for IgAN. Therefore, discrepancies could be due to geographic variation in the genetic risk for IgAN, which is highest for East Asians and Native Americans, intermediate for Middle Easterners and Europeans, and lowest for Africans (20). In Iranian studies, a Middle Eastern country, IgAN was not mentioned as the most common expected cause of GN (8, 11). Similar to Bahrain, Saudi Arabia, and other Arab countries (21–23). Moreover, systematic screening for urinary abnormalities is another cause of this geographic variation (24).

LN was the most commonly reported pathology among the SGN in our analysis, followed by DN. LN was also the most frequent SGN in Kuwait (25), northwest China (26), and western Switzerland (7). In our study, men were more frequently affected by kidney diseases, except for example, LN, in which there was female predominance. Female preponderance was evident in LN, mainly affecting women of childbearing age (27, 28). Goto et al. (29) found LN predominant in women of most ages, which was most frequently diagnosed in patients aged 20–29 and 30–39 years.

DN was the second most frequent pathology among the SGN in this investigation. Non-diabetic kidney diseases (NDKD) could develop alone or combined with DN in patients with type 2 diabetes mellitus (T2DM). Prasad et al. (30) analyzed clinical, laboratory, and pathological features in 538 patients with T2DM, of which 70% had NDKD (50% had pure NDKD and 20% had NDKD with DN). Among patients with NDKD, the most common pathology was acute tubulointerstitial nephritis, followed by infection-related GN. Similarly, in a systematic analysis of 48 studies, the prevalence of non-diabetic renal damage was reported to be significantly high, up to 82.9% of the overall diagnoses, which highlights the importance of renal biopsy as a diagnostic tool in these patients (31).

Our study also has limitations. It mainly focused on the histopathological spectrum, established based on the renal biopsy results and available clinical data at the time of biopsy, and under the pathologist's discretion. Due to a need for more documentation, the study did not investigate the clinical details and the reasons for biopsies in the present analysis. Moreover, the lack of genetic testing and comprehensive clinical information restricts our ability to

consider secondary and genetic forms of FSGS. This kidney biopsy analysis, drawn from a large population in southern Iran, demonstrated MGN as the most prevalent glomerulonephropathy. MGN was most prevalent among those above 46 years old, with a peak incidence in the 46 to 60-year-old age group. We found a dramatic shift in the proportion of FSGS, MPGN, and LN compared to our previous analysis. However, LN remains the leading SGN diagnosis. We also observed shifts in the age distribution of biopsy results across subtypes. This data provides critical clues for further studies on organizing renal health plans.

Acknowledgments

The authors would like to express their sincere gratitude to the institution for the support provided throughout this research.

Funding: The authors received no financial support for this research, authorship, and/or publication of this article.

Ethics approval: The study was done following the Declaration of Helsinki, and all experiments were performed according to the relevant guidelines and regulations. All study participants gave written consent. The consent obtained from all participants was informed. Approval was obtained before the start of the study by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1402.203).

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

Authors' contribution: Mohammadreza Akbari: Conceptualization, Resources, Visualization, Investigation. Leila Malekmakan: Conceptualization, Resources, Visualization, Investigation, Methodology, Validation, Writing - Original Draft, Writing - Review & Editing, Project administration, Supervision. Sahar Sanjarian: Methodology, Software, Formal analysis, Investigation, Resources, Writing - Original Draft, Writing - Review & Editing, Visualization. Maryam Pakfetrat: Conceptualization, Resources, Visualization, Investigation, Methodology, Validation, Writing - Original Draft, Writing - Review & Editing, Project administration, Supervision.

Consent for publication: Not applicable

Availability of data and materials: The datasets generated during and/or analyzed during the current study are not publicly available due to privacy/ethical restrictions, but are available from the corresponding author on reasonable request.

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