The Spectrum of Biopsy-Proven Glomerular Diseases in a Tertiary Hospital in Southern Brazil

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Abstract

Background

The prevalence and distribution of glomerular diseases differs between countries, and the indication to perform a kidney biopsy varies in each center. In this study, we assessed the prevalence of primary and secondary glomerulopathies based on histological diagnosis, and their correlation with demographic and clinical data were evaluated.

Methods

It was included in the study 1051 kidney biopsies retrospectively reviewed between the years 2000 to 2018. Demographic, clinical and laboratory data of patients were assessed. The prevalence of primary glomerulonephritis (PG) and secondary glomerulopathies (SG), as well as tubulo-interstitial diseases (TID), hereditary nephropathies (HN) and other diagnosis, were described. The frequency of primary and secondary glomerulopathies was evaluated by age group, and their temporal variation in three time periods (2000–2005, 2006–2011, and 2012–2018) were reported.

Results

The prevalence of SG predominated (52.4%) followed by PG (29.6%), other diagnoses (10.7%), TID (6.6%) and HN (1.1%). In primary forms, focal segmental glomerulosclerosis (FSGS) prevailed (37.3%), followed by IgA nephropathy (IgAN, 24.4%), membranous nephropathy (MN, 18.6%) and minimal change disease (MCD, 8.4%). Lupus nephritis (LN, 41.1%) had the highest frequency in SG, and in sequence diabetic kidney disease (DKD, 17.8%), systemic vasculitis (SV, 10.2%) and secondary FSGS (2nd FSGS, 10%). Nephrotic syndrome was the most common clinical presentation in PG, and also in DRD and 2nd FSGS, whereas in IgAN and SV the nephritic syndrome was the main form of presentation. In the age group between 18–50 years, LN, FSGS and IgAN predominated, between 51–65 years the proportion of DKD and 2nd FSGS increased, and SV were more found in patients > 65 years. The temporal variation of PG in three time periods showed a statistically significant increase in IgAN ($p = 0.001$) and a reduction in FSGS ($p < 0.001$). In SG, there were a reduction in LN ($p = 0.027$) and increase in DKD ($p < 0.001$), with a tendency to decrease of 2nd FSGS ($p = 0.053$).

Conclusions

In this kidney biopsy registry, FSGS and IgAN were the prevalent diagnoses in PG, and LN and DKD in SG. Nephrotic syndrome was the major indication for biopsy. When comparing the temporal variation of glomerulopathies, there was a reduction in FSGS and an increase in IgAN in PGs, and in SGs a reduction of LN with an increase in cases of DKD.

Background

The prevalence of chronic kidney disease (CKD) has increased worldwide, and recent data show that glomerulopathies are the third leading cause of terminal chronic kidney disease in Brazil, after arterial

hypertension and diabetes mellitus¹. As glomerular diseases have different clinical and laboratory manifestations, renal biopsy becomes a decisive approach for the diagnosis of each glomerulopathy, thus defining therapeutic management and establishing the prognosis based on the degree of activity and chronicity of glomerular and tubulointerstitial changes^{2,3}.

The indications for renal biopsy and their distinct histopathological profile both in primary and secondary glomerulopathies, as well as genetic and tubulointerstitial diseases, have been described in recent studies^{2,4-7} showing variations in their prevalence over time. Through percutaneous renal biopsy, information from optical microscopy and immunofluorescence define an etiological diagnosis, or in some conditions suggest it based on clinical presentation and anatomopathological findings^{2,3}. However, there is an epidemiological discrepancy in different countries and continents, associated with heterogeneous populations, ethnic differences, criteria for biopsy indication, environmental factors and socioeconomic restrictions specific to developing countries².

The prevalence of glomerulopathies varies throughout the world. IgA nephropathy (IgAN) is the most common primary glomerulopathy in Asian countries^{8,9} and in some European countries^{10,11}, while in Brazil¹²⁻¹⁴ and the United States^{4,15,16} focal segmental glomerulosclerosis (FSGS) is the prevalent glomerulopathy. A metanalysis of the epidemiology of glomerulonephritis in Africa showed a higher prevalence of minimal change disease (MCD) and FSGS¹⁷. In secondary glomerulopathies, studies have shown a higher prevalence of lupus nephritis (LN), diabetic kidney disease (DKD) and pauci-immune systemic vasculitis^{8,11,18,19}, but with variations in its frequency over two decades^{6,7,15}.

Temporal variation per period has been observed in the incidence rate of glomerular diseases, both in primary and secondary forms. Studies that evaluated two or more decades show an increasing trend in the prevalence of FSGS^{7,16,20}, MCD^{8,21}, DKD^{7,15}, pauci-immune systemic vasculitis^{6,7} and LN⁶, and also a temporal trend in the prevalence of NlgA^{6,9,19,20} and membranous nephropathy (MN)^{8,20}. There are records of differences related to ethnicity, with Asians having more cases of NlgA^{8,18}, afrodescendants of FSGS and caucasians of MN¹⁶. Additionally, variations related to the age group with regard to the distribution of histological types have been widely described^{6,7,18,19}.

Due to the heterogeneity of the Brazilian population in relation to geographic distribution, ethnic differences, temporal trends and age range, these parameters certainly interfere in the prevalence and also the spectrum of glomerular diseases around the country. In this study, we describe the histopathological diagnoses defined by renal biopsies performed at our center, relating primary and secondary glomerulopathies to the presentation syndromes, clinical and laboratory characteristics, age group and their prevalence over time.

Methods

Study Design

Retrospective study that evaluated native kidney biopsies performed in patients aged 18 years or older, between 2000 and 2018 at Hospital de Clínicas de Porto Alegre (HCPA), determining the demographic profile, the form of the clinical presentation and the histopathological diagnosis of the renal disease. All data were obtained through the review of the patient medical record, and were recorded anonymously. Patients underwent renal biopsy performed by the Nephrology Department or the Radiology Department of HCPA, during the period described.

Patients who underwent biopsy by Radiology were located through a query processed by the Computer Technology System of HCPA.

The clinical, laboratory and histopathological data of all patients were registered in a database, and the histology was reviewed from the Renal Biopsy Registry of the Nephrology Service and the patient medical record. All methods were carried out in accordance with relevant guidelines and regulations of HCPA. This study was approved by the Hospital de Clínicas de Porto Alegre Research Ethics Committee and the Institutional Review Board under number 3.159.116. The informed consent form was waived by the Research Ethics Committee and the Institutional Review Board as it was a retrospective study of data analysis, and a confidentiality term was signed by the research team for data access to patient medical record.

Clinical and Laboratory Data

The clinical variables analyzed included: name, age at the time of biopsy, age group (18–35, 36–50, 51–65 and > 65 years), sex, ethnicity, date of biopsy, weight, and presence systemic arterial hypertension (SAH) and diabetes mellitus (DM). The clinical presentation syndromes were searched in the medical records based on the clinical and laboratory data of the patients at the time of the biopsy, and defined in eight categories: 1) non-nephrotic proteinuria (< 3.5 g/day); 2) hematuria (≥ 3 red blood cells per high power field in qualitative urine examination); 3) nephrotic or subnephrotic proteinuria and hematuria together; 4) nephrotic syndrome (proteinuria > 3.5 g/day, serum albumin < 3.0 g/dL, edema, with or without dyslipidemia); 5) nephritic syndrome (non-nephrotic proteinuria < 3.5 g/day, hematuria, arterial hypertension, with or without loss of renal function); 6) nephrotic and nephritic syndrome together; 7) proteinuria with loss of renal function (serum creatinine > 1.20 mg/dL for men and > 1.10 mg/dL for women); 8) isolated loss of renal function, without proteinuria and/or hematuria.

Laboratory variables were obtained by exams closest to the date of the renal biopsy, not exceeding the limit of three months before or after the procedure. Serum creatinine, estimated glomerular filtration rate (eGFR) evaluated using the Modification of Diet in Renal Disease (MDRD) formula until 2009, and after 2009 using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula, 24-hour proteinuria or proteinuria-creatininuria index (IPC) in urine sample, presence of hematuria in urinary sediment, serum albumin, total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides. The serological variables evaluated were: complement C3, complement C4, anti-nuclear factor (ANA), anti-DNAs, anti-neutrophil cytoplasmic antibody (ANCA), anti-glomerular basement membrane antibody (anti-MBG), anti-HIV, anti-HCV, HBsAg, cryoglobulins and serum protein immunoelectrophoresis.

Classification of Glomerulopathies by Histological Type

Glomerulopathies were divided into four categories: primary, secondary, hereditary nephropathies and tubulointerstitial diseases. The primary glomerulonephritis included minimal change disease, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis (MPGN), IgA nephropathy, membranous nephropathy, and mesangial proliferative glomerulonephritis (MesPGN). Secondary glomerulopathies were categorized as lupus nephritis, diabetic kidney disease, systemic vasculitis including ANCA-associated vasculitis, anti-glomerular basement membrane disease and cocaine-associated vasculitis; secondary FSGS (2nd FSGS) including HIV-associated nephropathy (HIVAN), obesity-associated glomerulopathy, drug-induced glomerulopathies, and other pathologies manifested by 2nd FSGS; secondary membranoproliferative glomerulonephritis (2nd MPGN) including hepatitis C virus associated glomerulonephritis and cryoglobulinemic vasculitis; thrombotic microangiopathy (TMA); monoclonal gammopathies including amyloidosis (A), multiple

myeloma (MM) and light chain deposition disease (LCDD), described together as A-MM-LCDD; and other glomerulopathies, including post-infectious glomerulonephritis, secondary membranous nephropathy, HIV-associated nephropathy other than FSGS, Henoch-Schönlein purpura, Sjögren's syndrome and hypertensive nephrosclerosis. Renal biopsies that are not framed in the diagnoses described above were classified as other diagnoses: normal kidney, terminal kidney, biopsy without a conclusive diagnosis, or non-representative biopsy.

Tubulo-interstitial diseases included acute tubulo-interstitial nephritis (ATIN), chronic tubulo-interstitial nephritis (CTIN) and acute tubular necrosis (ATN). In hereditary diseases, thin basement membrane disease (TBMD), Alport's syndrome and Fabry's disease were evaluated.

Percutaneous Renal Biopsy

Renal biopsies were guided in real time by ultrasound. Biopsies performed by the Nephrology Service were performed with a 16G needle, and by the Radiology Service with an 18G needle. The histological sections were placed in buffered formalin for light microscopy and stained with Hematoxylin and Eosin (HE), Schiff's Periodic Acid (PAS), Periodic Schiff-Methenamine (PASM) and Masson Trichrome (TM). The frozen fragment in liquid nitrogen was evaluated by immunofluorescence using antibodies against IgG, IgA, IgM, C3 and C1q immunoglobulins, against Kappa and Lambda light chains, and fibrinogen. For selected cases, according to clinical indication (e.g. hereditary nephropathy), electronic microscopy was executed.

The total number of glomeruli on optical microscopy and immunofluorescence were evaluated, and the percentage of interstitial fibrosis and tubular atrophy (IFTA), that were quantified as: no fibrosis, fibrosis in < 25%, 25–50% or > 50% of the sample. Biopsies in which the diagnosis was not established due to insufficient or inadequate histological material, were considered as non-representative.

Statistical Analysis

Data were presented as absolute frequency and percentage, mean $\pm$ standard deviation (SD), or median and interquartile range. The association between categorical variables was analyzed using the Chi-square test or Fisher's exact test. The Kolmogorov-Smirnov and Shapiro-Wilks tests were employed to determine the normality of the variables. The independent t test or ANOVA was used for symmetric variables, and the Mann-Whitney or Kruskal-Wallis test for asymmetric variables. The distribution of primary and secondary glomerulopathies by age group and their prevalence in the three observation periods (2000–2005, 2006–2011 and 2012–2018) were analyzed using the Chi-square test. All analyzes were performed using the SPSS software (version 21.0, SPSS Inc., Chicago, IL). The level of significance established was P value less than 0.05.

Results

A total of 1051 renal biopsies were performed from January 2000 to December 2018. The demographic and clinical data of the patients are shown in Table 1. The distribution was similar between genders, and there was a predominance of caucasians, representing 85,5% of cases. The most frequent presentation syndrome was nephrotic syndrome, followed by proteinuria, proteinuria and hematuria and nephritic syndrome. SAH was present in 83.3% of the 706 patients who had this information available, as well as DM in 26.3% of 693 cases. The number of biopsies performed by Nephrology (51.2%) and Radiology (48.8%) had a similar frequency, and only 2.8% of the biopsies were non-representative. Most biopsies had mild fibrosis, with IFTA < 25% described in 44.7%

of cases, and in 30.3% IFTA was moderate (between 25–50%); IFTA > 50% indicating severe fibrosis was found in 25% of the biopsies.

In Fig. 1, the distribution of histological findings of the 1051 biopsies was presented. There was a predominance of secondary glomerulopathies, followed by primary glomerulopathies, tubulointerstitial diseases, hereditary nephropathies, and other diagnoses, including biopsies with normal kidney, terminal kidney, biopsy without a conclusive diagnosis, non-representative biopsy, or diagnoses that did not fit into the previous categories. Of the 24 patients diagnosed with hypertensive nephrosclerosis, 7 cases were included in secondary glomerulopathies in which 2nd FSGS was detected in addition to arterionephrosclerosis; the remaining 17 patients were excluded because the anatomopathological study showed only arterionephrosclerosis with medial thickening of the vascular wall, arteriolar hyaline deposits, and intimal fibrosis.

Table 1
Clinical and demographic data

	N(%)
Total	1051
Age	44.9 ± 16.1 ¹
Sex (M/F)	
Male	495(47.1)
Female	556(52.9)
Ethnicity	
caucasian	899(85.5)
afro-descendant	148(14.9)
amerindian	4.0(0.4)
Clinical syndromes ²	
proteinuria	205(21.5)
hematuria	10(1)
proteinuria and hematuria	194(20.4)
nephrotic syndrome	366(38.4)
nephritic syndrome	160(16.8)
nephritic and nephrotic syndrome	18(1.9)
Loss of renal function ³	616(63.7)
Systemic arterial hypertension ⁴	588(83.3)
Diabetes mellitus ⁵	182(26.3)
Renal biopsy by executor	
Nephrology	538(51.2)
Radiology	513(48.8)
Total number of glomeruli on OM	15 ± 9.5
IFTA percentage	
Without fibrosis	132(14.3)
<25%	413(44.7)
25–50%	280(30.3)
>50%	98(10.6)

	N(%)
Non-representative biopsies	29(2.8)

¹mean±standard deviation; ²N=953; ³N=967; ⁴N=706; ⁵N=693; OM: optical microscopy; IFTA: interstitial fibrosis and tubular atrophy.

In primary glomerulopathies (Fig. 2), the most frequent diagnosis was FSGS, followed by IgAN, MN, MCD, MPGN and MesPGN. In secondary glomerulopathies (Fig. 3), LN prevailed, followed by DKD, systemic vasculitis, 2nd FSGS, A-MM-LCDD, 2nd MPGN, and TMA. Other secondary glomerulopathies accounted for 6.4%. The frequencies of each LN histological classes are presented in Fig. 4, showing a predominance of diffuse and focal proliferative lupus nephritis, followed by membranous nephropathy. Among tubulointerstitial diseases (Fig. 5), ATN was prevalent, followed by CTIN and ATIN.

Figure 6 shows the distribution of primary glomerulopathies according to the clinical syndrome. The percentage value in each glomerular pathology described below considers the number of patients with this specific clinical manifestation. Nephrotic syndrome was prevalent in MCD (95.8%) and MN (86.3%), and in about half of the cases of FSGS (53.4%) and MPGN (52.6%). Presentation by nephritic syndrome was more associated with IgAN (38.4%). Isolated hematuria was uncommon, identified only in MesPGN (9.1%) and IgAN (1.4%). Proteinuria with hematuria predominated in MPGN (36.4%) and IgAN (30.1%).

Figure 7 shows the distribution of secondary glomerulopathies. In LN, 37% of the cases had nephrotic syndrome, nephritic syndrome, or a mixture of nephrotic/nephritic syndrome as the clinical and laboratory manifestation, and in 41.8% of patients the presentation was proteinuria and hematuria together. Nephrotic syndrome was prevalent in patients with DKD (74.2%), 2nd MPGN (60%) and A-MM-LCDD (55.2%), and nephritic syndrome was observed in 72.5% of cases of systemic vasculitis, 36.8% of TMA and 27.3% of other secondary glomerulopathies. Proteinuria with loss of renal function occurred in one third of patients with TMA (31.6%), in A-MM-LCDD (27.6%) and 2nd FSGS (22.6%). Loss of renal function as the only clinical manifestation was infrequent, observed in only 5.7% in 2nd FSGS and in 4% of patients with 2nd MPGN.

Demographic, clinical and laboratory data of primary glomerulopathies are shown in Table 2. Considering the four age groups, MCD predominated in patients aged 18–35 years, while FSGS, MPGN, IgAN and MesPGN were more prevalent in the 18–35 and 36–50 years. Between 36–50 and 51–65 years, MN was the most frequent glomerulopathy. There was a higher prevalence of women in cases of MCD, and of men in cases of FSGS and IgAN, with a similar distribution in other pathologies. The white race predominated in all primary glomerulopathies (> 90%), but in MCD 19.2% of patients were of African descent. Nephrotic proteinuria and hypoalbuminemia were the most common clinical presentations in MCD, FSGS, MN and MPGN, while in IgAN and MesPGN the prevalence of subnephrotic proteinuria were more frequently found. In primary glomerulonephritis, changes in serological markers were found in serum C3 levels, with lower values in patients with MPGN ($p < 0.001$), and also for HBsAg in IgAN and MesPGN ($p = 0.022$). The other serological markers had no statistical difference ($p > 0.05$) when comparing all primary diseases.

Table 2
Demographic, clinical and laboratory parameters in primary glomerulonephritis

	MCD	FSGS	MN	MPGN	IgAN	MesPGN	P value
Age (years, %)							0.012 ¹
18–35	57.7	40.5	20.7	30.4	51.3	50	
36–50	19.2	27.6	24.1	26.1	26.3	33.3	
51–65	19.2	25	37.9	21.6	17.1	8.3	
>65	3.8	6.9	17.2	21.8	5.3	8.3	
Sex (%)							0.03
Female	73.1	39.7	50	56.5	31.6	58.3	
Male	26.9	60.3	50	43.5	68.4	41.7	
Ethnicity (%)							0.647
Caucasian	80.8	89.7	91.4	95.7	93.4	91.7	
Afro-descendant	19.2	9.5	8.6	4.3	5.3	8.3	
Amerindian	0	0.9	0	0	1.3	0	
DM (%)	10	9.7	14.7	6.7	11.3	0	0.960
SAH (%)	63.6	84.2	94.1	93.3	81.5	83.3	0.173
Weight	72 ± 12	73 ± 15	73 ± 19	79 ± 10	78 ± 15	65 ± 10	0.395 ²
Serum creatinine	0.8 (0.5–1.5)	1.5 (1.0–2.0)	0.9 (0.8–1.3)	2.0 (1.2–3.1)	1.7 (1.1–2.2)	1,1 (0.7–2.3)	< 0,001 ³
eGFR	101 (46–124)	56 (34–90)	72 (46–103)	38 (18–60)	47 (31–81)	66 (37–109)	0.001
Proteinuria	7.7 (5.6–8.8)	4.6 (2.3–7.3)	7.0 (4.3–9.9)	7.8 (2.4–9.7)	1.9 (1.1–3.7)	1.6 (0.7–2.6)	< 0.001
Serum albumin	2.1 ± 0.9	2.9 ± 0.9	2.5 ± 0.7	2.5 ± 0.7	3.8 ± 0.7	3.8 ± 0.6	< 0.001
Total Cholesterol	421 (321–522)	257 (187–392)	282 (199–344)	236 (194–317)	198 (155–233)	180 (160–225)	< 0.001
Triglycerides	221 (179–279)	179 (117–277)	194 (134–284)	235 (139–339)	130 (99–219)	176 (80–191)	0.006
C3 ^a	143 ± 34.5	126 ± 31.3	134 ± 27.4	99 ± 43.3	114 ± 29	114 ± 33.3	< 0.001

	MCD	FSGS	MN	MPGN	IgAN	MesPGN	P value
C4 ^b	38.8 ± 13.9	34.5 ± 12.5	34.8 ± 14.6	29.2 ± 20.2	30.5 ± 11.7	28 ± 12	0.266
Anti-HIV (N,%) ^c	1(6.7)	0	1(2.6)	0	1(1.9)	0	0.413
Anti-HCV (N,%) ^d	1(6.7)	1(1,2)	1(2,6)	0	4(7,3)	0	0.370
HbsAg (N,%) ^e	0	0	0	0	4(7.3)	1(12.5)	0.022

¹N(%): Chi-square test; ²Mean±standatrd deviation: ANOVA; ³Median (interquartile range): Kruskal-Wallis test.

Number of patients with measured sorological parameters: ^aC3: 197; ^bC4: 197; ^canti-HIV: 214; ^danti-HCV: 216; ^eHbsAg: 214.

DM: diabetes mellitus; SAH: systemic arterial hypertension; eGFR: estimated glomerular filtration rate; MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; MN: membranous nephropathy; MPGN: membranoproliferative glomerulonephritis; IgAN: IgA nephropathy; MesPGN: mesangial proliferative glomerulonephritis

In secondary glomerulopathies (Table 3), LN predominated in patients under 35 years old, DKD at 36–50 years, and systemic vasculitis over 50 years. Secondary FSGS had a higher prevalence between 36–65 years, in 2nd MPGN between 51–65 years, and in A-MM-LCDD above 50 years. Lupus nephritis and TMA predominated in women, and 2nd MPGN and other secondary glomerulopathies in men. Secondary forms prevailed in caucasians, but in afro-descendants there were a higher frequency of DKD, 2nd FSGS, A-MM-LCDD and other pathologies. Laboratory and serological exams showed statistical difference according to the data presented in Table 3, where ANA ($p < 0.001$; N = 533) and anti-DNAs ($p = 0.035$; N = 450) were prevalent in LN, and ANCA titers ($p = 0.011$; N = 305) prevailed in systemic vasculitis (data not shown in Table 3).

Figure 8 and Fig. 9 show the distribution of primary and secondary glomerulopathies by age group. There was a statistical difference in the percentages by age group, both in primary ($p = 0.012$) and in secondary forms ($p < 0.001$). In primary glomerulonephritis, there was a higher prevalence of FSGS and IgAN between 18–35 years, also observed between 36–50 years. Between 51–65 years, FSGS and MN had a higher prevalence, and there was a decrease in IgAN in relation to previous frequencies. Above 65 years, the number of patients submitted to renal biopsy was lower (29%), and in this age group, FSGS and MN predominated. In secondary glomerulopathies, LN was prevalent in patients between 18–35 and 36–50 years. Between 51–65 years DKD predominated, and in patients over 65 years systemic vasculitis and A-MM-LCDD were the prevalent pathologies, and there was an increase in 2nd FSGS.

Table 3
Demographic, clinical and laboratory parameters in secondary glomerulopathies

	LN	DKD	SV	S-FSGS	S-MPGN	TMA	A-MM-LCDD	Others	P value
Age (years; %)									< 0.001 ¹
18–35	58.9	10.6	18.5	18.9	24	45	10	26.5	
36–50	26.5	21.3	18.5	37.7	24	40	13.3	17.6	
51–65	11.9	57.4	33.3	34	48	5	40	44.1	
>65	2.7	10.6	29.6	9.4	4	10	36.7	11.8	
Se (%)									< 0.001
Female	85.4	43.6	51.9	43.4	36	75	60	32.4	
Male	14.6	56.4	48.1	56.6	64	25	40	67.6	
Ethnicity (%)									0.007
Caucasian	84	76.6	94.4	75.5	84	95	76.7	70.6	
Afro-descendant	16	23.4	5.6	22.6	12	5	23.3	29.4	
Amerindian	0	0	0	1,9	4	0	0	0	
DM (%)	8.9	100	22.9	28.6	15.8	9.1	5.9	25	< 0.001
SAH (%)	71.4	95.4	80.6	90.5	78.9	81.8	94.1	96	< 0.001
Weight	68 ± 16	78 ± 17	74 ± 18	72 ± 15	73 ± 19	87 ± 31	64 ± 13	81 ± 14	0.007 ²
Serum creatinine	0.8(0.6–1.1)	2.8 (1.4–4.5)	3.1(2.2–5.5)	2.0 (1.2–3.5)	1.8 (1.4–3.2)	4.1(3.1–6.6)	2.9 (0.9–4.9)	1.5 (1.0–2.3)	< 0.001 ³
eGFR	98 (62–120)	22 (13–50)	19 (9.9–25)	32 (16–53)	37 (18–48)	13 (8.3–17)	21 (11–69)	47 (24–82)	< 0.001
Proteinuria	2.1(0,7–4.2)	6.0 (3.7–9,2)	1.5 (0.9–3.2)	2.5 (1.5–6.5)	5.0 (2.9–6.7)	1.9 (1.4–3.0)	4.8 (2.5–8.6)	3.5 (1.1–6.2)	< 0.001
Serum albumin	3.0± 0.7	2.8 ± 0.6	3.2 ± 0.6	3.2 ± 1.0	2.5 ± 0.8	3.2 ± 0.6	2.9 ± 1.0	2.9 ± 0.8	0.009

	LN	DKD	SV	S-FSGS	S-MPGN	TMA	A-MM-LCDD	Others	P value
Total Cholesterol	229 (176–284)	197 (158–239)	217 (150–255)	208 (172–288)	199 (123–284)	171 (157–227)	220 (181–261)	242 (186–287)	0.081
Triglycerides	170 (114–255)	170 (121–270)	159 (108–165)	250 (172–418)	170 (129–257)	219 (116–375)	170 (127–203)	127 (107–274)	0.011
C3 ^a	72 ± 33	125 ± 33	121 ± 31	120 ± 40	92 ± 41	110 ± 34	119 ± 31	108 ± 47	< 0.001
C4 ^b	12 ± 11	35 ± 13	29 ± 13	30 ± 13	21 ± 12	30 ± 11	41 ± 20	27 ± 18	< 0.001
Anti-HIV (N,%) ^c	2 (1.2)	11 (12.4)	0	30(58.8)	6 (24)	1 (6.7)	0	8(24.2)	< 0.001
Anti-HCV (N,%) ^d	3 (1.7)	26 (29.5)	4 (7.8)	9 (18)	18 (75)	2 (11.8)	1 (3.7)	10 (30.3)	< 0.001
HbsAg (N,%) ^e	1 (0.6)	1 (1.2)	0	6 (12)	5 (20)	0	2 (7.4)	0	< 0.001

¹N(%): Chi-square test; ²Mean±standatrd deviation: ANOVA; ³Median (interquartile range): Kruskal-Wallis test.

Number of patients with measured sorological parameters: ^aC3: 455; ^bC4: 455; ^canti-HIV: 461; ^danti-HCV: 465; ^eHbsAg: 461.

DM: diabetes mellitus; SAH: systemic arterial hypertension; eGFR: estimated glomerular filtration rate); LN: lupus nephritis; DKD: diabetic kidney disease; SV: systemic vasculitis; S-FSGS: secondary focal segmental glomerulosclerosis; S-MPGN: secondary membranoproliferative glomerulonephritis; TMA: thrombotic microangiopathy; A-M-LCDD: amyloidosis, multiple myeloma, light chain deposition disease; Others: other secondary glomerulopathies.

The temporal variation of primary and secondary glomerulopathies in the three time periods showed a significant increase in the percentage of IgAN ($p = 0.001$) and a reduction in cases of FSGS ($p < 0.001$), with no difference in MCD, MN, MPGN and MesPGN ($p < 0.05$) (Fig. 10). In secondary glomerulopathies, the reduction in LN ($p = 0.027$) and increase in DKD ($p < 0.001$) were significant, with a tendency to decrease of 2nd FSGS ($p = 0.053$) (Fig. 11). There was no difference in the variation of systemic vasculitis, 2nd MPGN, TMA, A-MM-LCDD and other pathologies over time.

In the period from 2000 to 2018, the Nephrology and Radiology departments performed 538 and 513 renal biopsies, respectively. When comparing renal biopsies by performer, the total number of glomeruli in optical microscopy was significantly higher in biopsies done by nephrologists (median and interquartile range: 15[10–22]) compared to those performed by radiologists (12[8–16]), $p < 0.001$. However, there was no difference in the

total number of glomeruli in immunofluorescence (4[2–7] and 3[2–6] respectively; $p = 0.320$), or in the number of non-representative biopsies ($N = 14$ and $N = 15$ respectively; $p = 0.568$).

Discussion

This study showed the distribution of demographic, clinical and laboratory data and histopathological diagnoses of 1051 patients who underwent renal biopsies in the years 2000 to 2018 at our center. The histological diagnosis showed that secondary glomerulopathies represented more than half of the sample (52.4%) followed by primary glomerulonephritis (29.6%), and in sequence other pathologies, tubulo-interstitial disease and hereditary nephropathies.

Nephrotic syndrome was prevalent in clinical presentation and indicated renal biopsy mainly in primary forms, but also in some secondary glomerulopathies. Studies have shown a higher frequency of nephrotic syndrome in different glomerulopathies, mainly MCD, FSGS and MN^{2,6,12,21,22} data also described in systematic reviews¹⁷, and mainly as a clinical presentation of primary glomerulopathies^{16,18}. In IgAN, nephritic syndrome and proteinuria/hematuria prevailed, in agreement with other studies^{6,18,19,21}. In secondary forms, nephrotic syndrome and proteinuria/hematuria were prevalent in LN, nephrotic syndrome in DKD, nephrotic syndrome and proteinuria with loss of renal function in 2nd FSGS and monoclonal gammopathies, and nephritic syndrome in systemic vasculitis. These findings are in disagreement with those described in some studies^{6,12,14,19,23}, what can be associated with different clinical and laboratory criteria for indicating renal biopsy between countries or states of a country, in which the prevalence of primary and secondary glomerulopathies has a significant variability.

In primary glomerulonephritis, FSGS was the prevalent histology, followed by IgAN, MN, MCD and MPGN, with frequencies similar to those described in Brazilian registries^{12–14,24} and in North and South American countries^{4,5,16,25}. In the study by Polito et al¹², the prevalence of FSGS, MN, IgAN, MCD and MPGN were 24.6%, 20.7%, 20.1%, 15.5% and 4.2%, respectively, which was similar to that described by Malafronte et al¹³ who reported frequencies of 29.7%, 20.7%, 17.8%, 9.1% and 7% for the same pathologies. Sim et al¹⁶ described a higher frequency of FSGS, followed by MN, MCD and IgAN, with an increase in FSGS and IgAN over 12 years in the follow-up. Barrera-Herrera et al²⁵ also reported a higher prevalence of FSGS and IgAN in the spectrum of primary glomerular diseases.

IgA nephropathy has a distinct epidemiological profile in different countries and continents. In Asia, its predominance is notorious, as described in several studies^{8,9,18,19}. Yang et al⁸ reported a higher prevalence of IgAN followed by MPGN, MN and MCD, with FSGS described in only 4.6% of cases. In South Korea⁹ the data are similar with IgAN in 28.3%, and in Taiwan Chiu et al¹⁸ also reported this highest prevalence (26%). In Japan²⁶ IgAN predominated as well, clinically manifested by chronic nephritic syndrome. In Europe, IgAN is also described as prevalent in some countries, such as Italy²⁷, Czech Republic¹¹ and Poland¹⁰.

Lupus nephritis was the prevalent etiology in secondary glomerulopathies, as shown in Fig. 3 and Fig. 6, representing 41.1% of the cases, followed by DKD and systemic vasculitis. Analyzing the histological class of NL, classes III and IV (63%) and class V (17.8%) predominated, in a total of 80.8% of cases. The prevalence of LN in our study did not differ from publications of other countries^{5,11,19,28}. In Brazil, Polito et al¹² analyzed 9617 renal biopsies and LN was found in 42.3%, followed by post-infectious glomerulonephritis (20.4%) and DKD (10.1%). In

the publication by Malafonte et al¹³, LN was reported in 66.2% in secondary forms, with post-infectious glomerulonephritis (12.5%) and DKD (6.2%) in sequence. These data reflect the higher frequency of LN in several countries and also in Brazil, showing similarity with our findings concerning the prevalence of secondary glomerulopathies.

Diabetic kidney disease was the second pathology in terms of frequency in secondary glomerulopathies. Usually, renal biopsy was indicated in patients with type 2 diabetes mellitus in the presence of atypical conditions to rule out a non-diabetic kidney disease, thus defining another pathology with a potential indication of immunosuppression. These criteria included abrupt nephrotic proteinuria, acute loss of renal function not compatible with the evolution of diabetes, short-term diabetes (less than 5 years), absence of diabetic retinopathy, and/or signs and symptoms of a systemic disease. Fiorentino et al²⁹ in a pooled meta-analysis assessing 48 studies who analysed renal biopsies in patients with diabetes, reported that the prevalence of DKD, non-diabetic renal disease and mixed forms ranged from 6.5 to 94%, 3 to 82.9%, and 4 to 45.5% of the overall diagnosis, respectively. The most frequent non-diabetic nephropathy was IgAN, with a variation between 3% and 59% followed by MN (7–35%), FSGS (17–37.7%) and ATIN (18–48.8%).

In a recent study, O'Shaughnessy et al⁵ evaluated 29 centers involving 42,603 patients, showing a higher prevalence of FSGS and DKD in the USA/ Canada, IgAN and FSGS predominated in Europe, in Asia IgAN and LN, and in Latin America LN (38.1%) and FSGS (15.8%). Our results showed similarity with Latin America for LN (41.1%), but the prevalence of FSGS was much higher in our sample (37.3%). Considering the temporal variation that we found over three periods, DKD is in agreement with the findings of the USA/Canada, and IgAN with those described in the European and Asian continents.

Demographic data showed a predominance of caucasians (85.5%) over afrodescendants (14.1%), which was attributed to the ethnic profile of the southern region of Brazil. It is well known that there are differences in race in different regions of Brazil, and also worldwide. As an example, O'Shaughnessy et al⁵ reported the frequency of caucasians and afrodescendants in the USA/ Canada (54.2% and 31.4%) and in Europe (98.2% and 0.8%), pointing to variations in countries on different continents. The number of centers involved in these registrations was wide, with 10 centers in the USA/Canada and 14 centers in Europe. However, data on ethnicity in Asia and Latin America were more restricted, with only 2 centers in Asia and 3 centers in Latin America, which limits comparisons in these regions.

The prevalence of each glomerulopathy varies by age group in different countries^{6,15,18,22}. The frequencies described in these studies for primary glomerulonephritis are IgAN and FSGS between 18–50 years, and FSGS and MN between 51–65 and > 65 years. In the secondary forms LN was prevalent between 18–35 years, DKD and 2nd FSGS between 36–60 years, and systemic vasculitis and monoclonal gammopathies over 65 years of age. These prevalences are compatible with those described in our study, for all age groups and for each age group analyzed apart.

The temporal variation of glomerulopathies is widely explored in many studies, usually assessed in the last four decades. Over three time periods, we observed a significant reduction in FSGS and an increase in IgAN in the primary forms, and in the secondary, there was a reduction in LN and an increase in DKD, with a minor and non-significant variation in the other glomerulopathies. Studies have shown different temporal trends in both primary and secondary glomerulopathies. The data described by Sim et al¹⁶ between 2000–2011 showed an increase in

the frequency of FSGS and IgAN, and minor temporal variations with stabilization in pauci-immune vasculitis, MPGN, MCD and MN. In the study by Garau et al⁶, an increase in IgAN, MN, LN and DKD was observed between 1990–2014, with a decrease in FSGS after 2004. Brkovic et al³⁰ comparing the periods 1987–2006 and 2007–2014 reported an increase in MN and reduction in non-IgA mesangioproliferative nephropathy, with no change in other primary glomerulopathies. Dos-Santos et al³¹ showed an increase in the prevalence of FSGS between 1975–2006, and of LN and MN between 2006–2015, with a tendency for FSGS to decrease in this last period. It is likely that these temporal variations correlate with the heterogeneity of biopsy indication in different centers, changes in the population profile (for example, increasing age and ethnic variations), changes in lifestyle and socioeconomic diversity, influencing the epidemiological status of glomerulopathies and their variation over the years.

The degree of chronicity in the histopathology also has a significant prognostic value. Adjusting for demographic, laboratory data and clinicopathological diagnosis, Srivastava et al³² showed a higher risk of kidney disease progression in association with inflammation in the non-fibrous interstitium, moderate to severe tubular atrophy, interstitial fibrosis and global glomerulosclerosis, and also with arterial and arteriolar sclerosis. In our study, we did not perform this analysis based on the percentage of IFTA, global glomerulosclerosis or arteriolar damage described in renal histologies, something to be explored in a future study.

Our study has limitations. As this is a retrospective study, the review of medical records in some patients showed incomplete demographic, clinical and laboratory data. It is a single center study, so it may not represent the real prevalence of other centers. In addition, our center performs kidney biopsy for patients referred from other centers, limiting the access to information in some cases, such as the clinical syndrome that indicated the biopsy and the clinical and laboratory data. However, of the 1051 patients included in this registry, the majority had accessible data in our center medical records, or by data reported by physicians of external centers. In addition, all biopsies were interpreted and reported by experienced nephropathologists, allowing an etiological diagnosis that defined the type of glomerulopathy, or its non-representativeness.

Conclusions

In this kidney biopsy registry demographic and clinical data and the spectrum of renal histology of 1051 biopsies between the years 2000 to 2018 were described. FSGS and IgAN were the most found diagnoses in primary glomerulonephritis, and LN and DKD in secondary glomerulopathies. Nephrotic syndrome was the major indication for biopsy, followed by proteinuria and proteinuria associated with hematuria. When comparing the temporal evolution of those glomerulopathies over three periods, there was a reduction in the frequency of FSGS and an increase in IgAN in the primary forms, and in secondary glomerulopathies a reduction of LN with an increase in cases of DKD.

Abbreviations

CKD – chronic kidney disease; IgAN – IgA nephropathy; focal segmental glomerulosclerosis – FSGS; MCD – minimal change disease; LN – lupus nephritis; DKD – diabetic kidney disease; MN – membranous nephropathy; HCPA – Hospital de Clínicas de Porto Alegre; SAH – systemic arterial hypertension; DM – diabetes mellitus; eGFR: estimated glomerular filtration rate; MDRD – Modification of Diet in Renal Disease; CKD-EPI – Chronic Kidney Disease-Epidemiology Collaboration; IPC – proteinuria/creatininuria index; ANA – anti-nuclear factor; ANCA –

anti-neutrophil cytoplasmic antibody; anti-GBM – anti-glomerular basement membrane disease; MPGN - membranoproliferative glomerulonephritis; MesPGN – mesangial proliferative glomerulonephritis; 2nd FSGS – secondary FSGS; HIVAN – HIV-associated nephropathy; 2nd MPGN: secondary membranoproliferative glomerulonephritis; TMA – thrombotic microangiopathy; A: amyloidosis; MM – multiple myeloma; LCDD – light chain deposition disease; ATIN – acute tubule-interstitial nephritis; CTIN: chronic tubulo-interstitial nephritis; ATN – acute tubular necrosis; TBMD – thin basement membrane disease; HE – Hematoxylin and Eosin; PAS – Schiff's Periodic Acid; PASM – Periodic Schiff-Methenamine; TM – Masson Trichrome; IFTA – interstitial fibrosis and tubular atrophy

Declarations

Ethics approval and consent to participate

This study was approved by the Hospital de Clínicas de Porto Alegre Research Ethics Committee and the Institutional Review Board under number 3.159.116. The informed consent form was waived by the Research Ethics Committee and the Institutional Review Board as it was a retrospective study of data analysis, and a confidentiality term was signed by the research team for data access to patient medical record.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article. The datasets used and/or analysed during current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

All authors contributed equally to the present work, had made substantial contributions to the conception, design, analysis, interpretation of data, and have drafted the manuscript. All authors have read, agreed and approved the final manuscript as submitted, are qualified for authorship and take full responsibility for its content.

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Figures

Figure 1

Presentation of the percentage of primary and secondary glomerulopathies, hereditary diseases, tubulointerstitial diseases and other diagnoses based on 1051 kidney biopsies performed between the years 2000 and 2018. Tubulointerstitial diseases: acute tubulointerstitial nephritis, chronic tubulointerstitial nephritis, acute tubular necrosis; Hereditary diseases: Alport syndrome, Fabry disease, thin basement membrane disease; Others: normal kidney, terminal kidney, biopsy without diagnosis, non-representative biopsy.

Figure 2

Frequency of primary glomerular diseases (N=311). FSGS: focal segmental glomerulosclerosis, MPGN: membranoproliferative glomerulonephritis, GN: glomerulonephritis; mesangial proliferative GN: mesangial proliferative glomerulonephritis

Figure 3

Frequency of secondary glomerular diseases (N=530). FSGS: focal segmental glomerulosclerosis, MPGN: membranoproliferative glomerulonephritis, HCV: hepatitis C virus, LCDD: light chain deposition disease, Systemic vasculitis: ANCA-associated vasculitis, cocaine/levamisole associated vasculitis, anti-glomerular basement membrane disease; Secondary FSGS: HIV-associated nephropathy (HIVAN), obesity-related glomerulopathy, other secondary FSGS; MPGN to other diseases: hepatitis C virus associated glomerulonephritis, cryoglobulinemia vasculitis; Others: postinfectious glomerulonephritis, secondary membranous nephropathy, HIV-associated nephropathy not related to FSGS, Henoch-Schönlein purpura, Sjögren syndrome, and hypertensive nephrosclerosis.

Figure 4

Frequency of the classes of lupus nephritis (N=219).

Figure 5

Frequency of tubulointerstitial renal disease (N=69).

Figure 6

Distribution of the presentation of clinical syndromes according to each primary glomerulonephritis. $P<0.001$ (Fisher's Exact Test, Chi-Square Test); the proportion of some of the primary glomerulonephritis differ significantly from each other in the clinical presentation form at the 0,05 level. MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; MN: membranous nephropathy; MPGN: membranoproliferative glomerulonephritis; IgAN: IgA nephropathy; MesPGN: mesangial proliferative glomerulonephritis.

Figure 7

Distribution of the presentation of clinical syndromes according to each secondary glomerulopathy. $P<0.001$ (Fisher's Exact Test, Chi-Square Test); the proportion of some of the secondary glomerulopathies differ significantly from each other in the clinical presentation form at the 0,05 level. LN: lupus nephritis; DKD: diabetic kidney disease; SV: sytemic vasculitis; S-FSGS: secondary focal segmental glomerulosclerosis; S-MPGN: secondary membranoproliferative glomerulonephritis; TMA: thrombotic microangiopathy; A-M-LCDD: amyloidosis, multiple myeloma, light chain deposition disease.

Figure 8

Frequency of primary glomerular diseases by age category. FSGS: focal segmental glomerulosclerosis, MPGN: membranoproliferative glomerulonephritis, GN: glomerulonephritis. Percentage values (%) according to each age category and relative to each disease, respectively: minimal change disease, FSGS, membranous nephropathy, idiopathic MPGN, IgA nephropathy, and mesangial proliferative GN: 18-35 years (N=126): 11,9; 37,3; 9,5; 5,6; 31; 4,8. 36-50 years (N=81): 6,2; 39,5; 17,3; 7,4; 24,7; 4,9. 51-65 years (N=75): 6,7; 38,7; 29,3; 6,7; 17,3; 1,3. >65 years (N=29): 3,4; 27,6; 34,5; 17,2; 13,8; 3,4.

Figure 9

Frequency of secondary glomerular diseases by age category. FSGS: focal segmental glomerulosclerosis; MPGN: membranoproliferative glomerulonephritis; HCV: hepatitis C virus; LCDD: light chain deposition disease.

Percentage values (%) according to each age category and relative to each disease, respectively lupus nephritis, diabetic kidney disease, systemic vasculitis, secondary FSGS, MPGN secondary to HCV and other diseases, thrombotic microangiopathy, amyloidosis, multiple myeloma, LCDD, and others: 18-35 years (N=186): 69,4; 5,4; 5,4; 3,2; 4,8; 1,6; 4,8; 5,4. 36-50 years (N=132): 43,9; 15,2; 7,6; 15,2; 4,5; 6,1; 3,0; 4,5. 51-65 years (N=157): 16,7; 34,6; 11,5; 11,5; 7,7; 0,6; 7,7; 9,6. >65 years (N=55): 10,9; 18,2; 29,1; 9,1; 1,8; 3,6; 20; 7,3.

Figure 10

Prevalence of primary glomerular diseases according to three time periods, from 2000 to 2005, 2006 to 2011 and 2012 to 2018. Comparing the time periods for each glomerulonephritis, statistical significance was found for FSGS ($p < 0.001$) and IgAN ($p = 0.001$); $p > 0.05$ for MCD, MN, MPGN and MesPGN. MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; MN: membranous nephropathy; MPGN: membranoproliferative glomerulonephritis; IgAN: IgA nephropathy; MesPGN: mesangial proliferative glomerulonephritis.

Figure 11

Prevalence of secondary glomerular diseases according to three time periods, from 2000 to 2005, 2006 to 2011 and 2012 to 2018. Comparing the time periods for each glomerulopathy, statistical significance was found for LN ($p=0.027$), DKD ($p<0.001$), and a trend to S-FSGS ($p=0.053$); $p>0.05$ for SV, S-MPGN, TMA, A-MM-LCDD and Others. LN: lupus nephritis; DKD: diabetic kidney disease; SV: systemic vasculitis; S-FSGS: secondary focal segmental glomerulosclerosis; S-MPGN: secondary membranoproliferative glomerulonephritis; TMA: thrombotic microangiopathy; A-M-LCDD: amyloidosis, multiple myeloma, light chain deposition disease.