

Epidemiology of kidney biopsy from regional referral center in Romania: 10-year review

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Abstract

Purpose: To provide epidemiologic data on kidney biopsy from Romania.

Methods: Retrospective observational study of kidney biopsy records for adult patients from a referral center in the north-western part of Romania, reported for 2014–2023.

Results: 556 biopsies were performed, corresponding to an incidence of 12 biopsies/m person-year with over 50% increase over the last reported year. Optimal core for optic microscopy was available in 81.4%, immunofluorescence was performed in 86.3%, and electron microscopy in 35.2% of patients. The mean age at biopsy was 47.12 years, and 53.8% were males. Indications for kidney biopsy were nephrotic syndrome in 63.1% of patients, nephritic in 25.9% of patients, asymptomatic urinary abnormalities in 2.9%, acute kidney injury/ rapid progressive renal failure in 3.6%, and chronic kidney disease in 1.4%. The most frequent diagnostic categories were membranous nephritis (14.7%), IgA nephropathy (13.9%), focal segmental glomerulosclerosis (11.1%), minimal change disease (12.2%), lupus nephritis (10.9%), vasculitis (7.6%), and membranoproliferative glomerulonephritis (8%).

The age of diagnosis increased for IgA Nephropathy over time while it decreased for membranous nephritis.

Conclusions: Our study adds data for the completion of the kidney biopsy map in our region.

Keywords: Kidney biopsy, Epidemiology, Glomerular disease.

What is new? What is important?

Data from regional kidney biopsy registries importantly contribute to information about incidence and prevalence of glomerular disease and inform about local clinical practice. Biopsy registry evaluation can influence healthcare decisions. This the first study that provides kidney biopsies data of the north-west region of Romania, from the most important referral center for kidney biopsies in Romania outside Bucharest.

INTRODUCTION

Chronic kidney disease (CKD) accounts for about 10% of the overall population, which is a major healthcare problem. One of the main causes of CKD is represented by glomerular diseases.

The gold standard for diagnosis of glomerular disease is the kidney biopsy which is employed for diagnostic reasons but also offers valuable prognostic information. Also, indications for renal biopsy expand beyond glomerulonephritis (e.g. acute or chronic unexplained decrease in renal function, tubulointerstitial syndromes).

Many factors play a role in reported figures regarding epidemiology for biopsy-amenable kidney disease, such as ethnicity, geography, socioeconomic factors, and timeframe of the reported data. National registries provide valuable data, however, in the absence of such records, the local biopsy registries could inform about clinical practice, demographics, and characteristics of biopsy-amenable kidney pathology. Here we provide biopsy data retrospectively collected for a decade in a kidney biopsy referral center from the north-western part of Romania, which completes the previously reported data from our country [1,2,3].

MATERIALS AND METHOD

In this retrospective observational study, kidney biopsy records for adult patients from the Emergency County Clinical Hospital Cluj-Napoca were reviewed for 10 years, starting January 2014 until December 2023. Seventeen records from a second kidney biopsy or samples without glomeruli were excluded. This study was approved by the Ethics Committee of the Emergency County Clinical Hospital Cluj-Napoca (3/2021), and the “Iuliu Hațieganu” University of Medicine, and Pharmacy Cluj-Napoca (142/2021) under the ethical standards of the Declaration of Helsinki.

COLLECTION OF DATA

Data were retrieved from the electronic records of the patients. Histopathological results were collected from the standardized kidney biopsy form. Optic microscopy (OM - Hematoxylin eosin, Periodic Acid Schiff, Silver, and Trichrome stain, and another staining when indicated), immunofluorescence (IF), and starting from 2021 electron microscopy (EM) if indicated, were routinely performed. OM comprised Hematoxylin eosin, Periodic Acid Schiff, Silver, and Trichrome stain as routine with other staining applied if necessary (e.g. Congo Red). Immunofluorescence included antibodies against IgG, A, M, C3, C1q, and light chains as standard. All reports judged as incomplete were reviewed by a nephropathologist for the present study. At least two cores were obtained with 16-gauge needles as per standard procedure. Direct inspection under light microscopy of the retrieved core was available from 2016 onwards which allowed for a further attempt to optimize the sample. Tissue for EM was generally obtained by section of 1-2 glomeruli from one core. EM fragments were obtained for all glomerular syndromes except anti-phospholipase A2 receptor (APLA2) positive membranous nephritis (MN), anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis, and lupus nephritis (LN) without nephrotic syndrome. EM was processed only if a definite diagnosis was not obtained by OM, and IF alone.

Data collected regarding biopsy resulted in a pattern of injury derived from the Mayo Clinic/Renal Pathology Society consensus [4], and defined as mesangial proliferative, endocapillary hypercellularity, crescentic, membranoproliferative, sclerosant, membranous, focal segmental glomerulosclerosis (FSGS), diffuse or nodular mesangial expansion, vascular, and optically normal glomeruli.

Clinical, and laboratory data were collected from the electronic records, and consisted of creatinine, urea, estimated glomerular filtration rate (eGFR), cholesterol, triglycerides, uric acid, serum albumin, total proteins, hemoglobin, C reactive protein, proteinuria, hematuria, and the presence of dysmorphic erythrocytes. Hypertension has been recorded only as a disease association, as retrospective records of blood pressure were considered unreliable. The estimated glomerular filtration rate was calculated according to the CKD-EPI 2021 formula [5]. Indications of biopsy were defined as nephrotic syndrome (association of proteinuria >3.5g/day, edema, hypoproteinemia, hypoalbuminemia), nephritic syndrome (non-nephrotic proteinuria, hematuria, with or without reduced eGFR, hypertension, and edema), asymptomatic urinary abnormalities (AUA - isolated microscopic hematuria or moderate range proteinuria), acute kidney injury (AKI) including rapid progressive renal failure (RPRF), and CKD. The number of dysmorphic red blood cells was retrieved from the lab reports but was not consistently analyzed with contrast phase microscopy.

The final diagnosis recorded for the patient after the biopsy was grouped into the following entities: FSGS, minimal change disease (MCD), LN, vasculitis, membranous MN, membranoproliferative glomerulonephritis (MPGN), postinfectious GN, IgA nephropathy (IgAN), monoclonal gammopathy of renal significance (MGRS), Alport Syndrome, Diabetic nephropathy (DN), and anti-glomerular basement membrane disease (GBM). Distinct categories were defined for vascular disease (post hypertensive nephrosclerosis or acute post hypertensive nephropathy, predominantly vascular disease as in scleroderma, anti-phospholipidic syndrome, thrombotic microangiopathy), acute tubular necrosis (ATN), tubulointerstitial nephritis (TIN).

The glomerular disease was considered primary if an etiology was not established, and secondary if etiology was clear.

STATISTICAL ANALYSIS

Qualitative variables were expressed as absolute, and/or relative frequency computed relative to the total number of cases. To represent the data as charts (Pie, Line, Bar) Microsoft Excel 2019 was used. Incidences were calculated as absolute frequencies per 10⁶ person-year. Then the average incidence per county was calculated. The geographical distribution of incidence was mapped using Microsoft Excel 2019. The yearly rate was calculated relative to the total number of cases in each year. The average yearly rate was calculated after that.

Quantitative variables were presented as arithmetic mean $\pm$ standard deviation in the case of normally distributed ones or with median (25th – 75th percentile) in the case of non-normally distributed ones. The distribution was assessed using the Shapiro-Wilk test. We tested the null hypothesis which state that there is no difference between the indication of kidney biopsy for each quantitative variable either with the Anova test or with Kraskal-Wallis's test, depend on equality of variances. The statistical analysis was conducted using SPSS 25.0.

The regression equation, the Pearson coefficient of correlation, and the coefficient of determination were used to evaluate in the number of cases over the years.

RESULTS

Over the studied period of 10 years, a total of 556 biopsies were performed. Two hundred ninety (53.8%) were men. Fifteen surrounding counties referred for kidney biopsies, in some of them

current practice consists of referral to more than one kidney biopsy center in Romania (Figure 1).

The mean incidence of 12 biopsies/m person-year when computed using only the counties where the standard clinical practice consists of referral to our center, and considering the population census 2021.

The yearly rate of biopsies was constant over the reported decade, varying between 36–60 (mean of 50.8) biopsies yearly except for the last year when 98 biopsies were performed (an increase of 51.91%).

Indications for kidney biopsy were nephrotic syndrome in 351(63.1%) patients, nephritic syndrome in 144 (25.9%) patients, AUA in 16 (2.9%) patients, AKI/RPRF in 20 (3.6%) of patients, chronic unexplained renal insufficiency in 8 (1.4%) of patients with 17 patients (3.1%) listed as other causes; proportions were fairly constant over time (Figure 2).

Baseline characteristics of patients according to the indication of kidney biopsy were presented in Table 1.

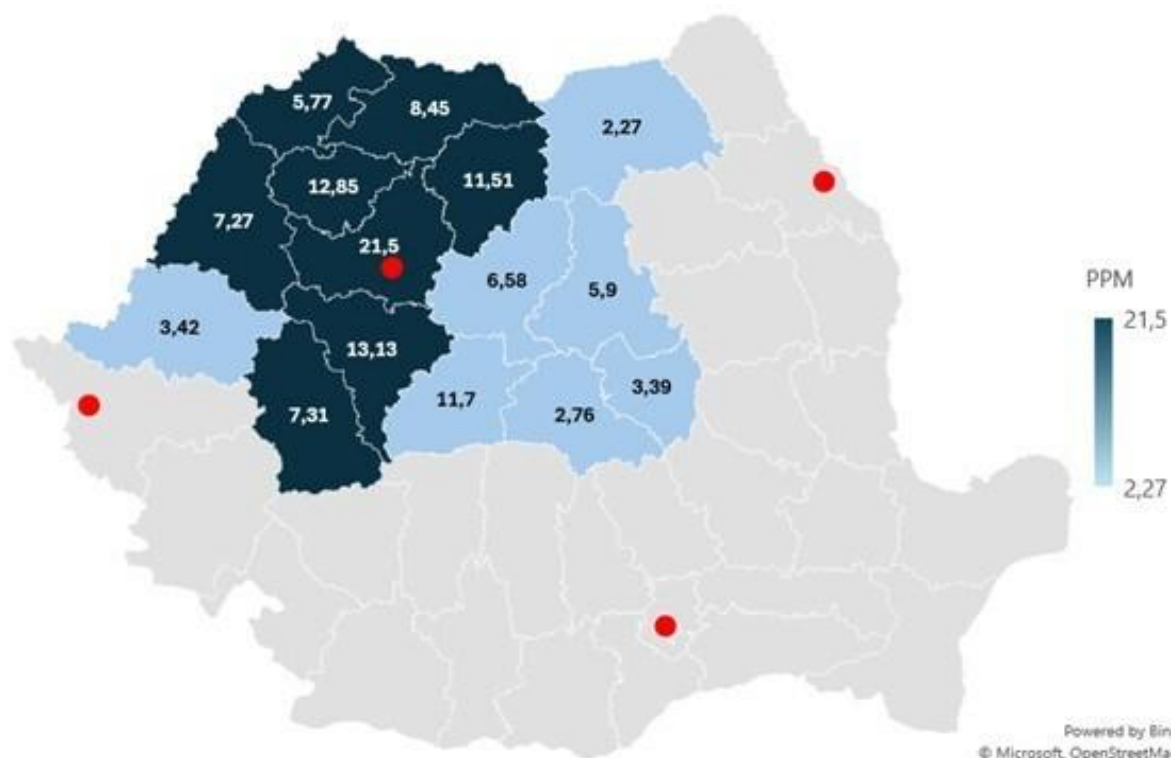


Figure 1. Referral of biopsy, and incidence.

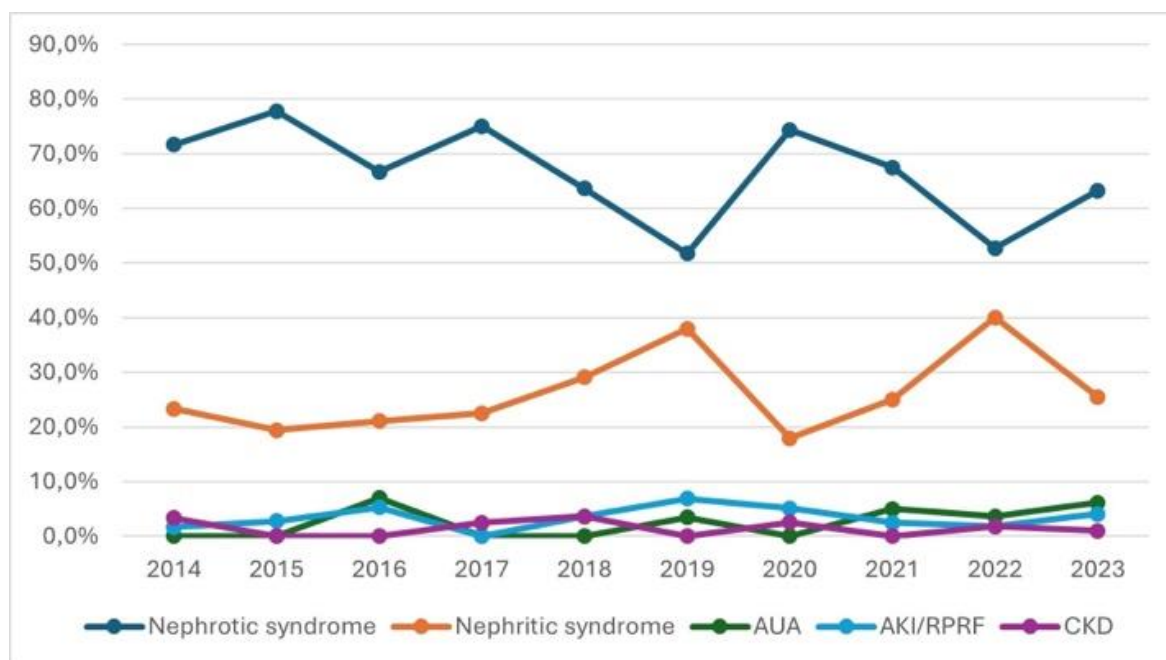


Figure 2. Distribuiton of specific diagnosis, and sex.

Table 1

Baseline characteristics of patients according to indication of kidney biopsy

	Nephrotic syndrome	Nephritic syndrome	AUA	AKI/RPRF	CKD	p
Age (years)	48 (34; 60)	45.5 (34; 56.5)	44 (36; 55.5)	57.5 (49.5; 65.5)	46.5 (33; 50)	0,03
Sex male (%)	55,6	50	56,3	45	62,5	
Serum creatinine (mg/dL)	1.23 (0.8; 2.19)	1.41 (0.89; 2.97)	1.02 (0.8; 1.28)	6.3 (2.13; 8.2)	4.65 (3.2; 7.38)	<0.001
eGFR (mL/min)	65.09 (32.04; 101.62)	57.44 (23.83; 99.52)	87.03 (53.35; 113.77)	8.45 (6.23; 28.23)	13.8 (6.27; 23.66)	<0.001
Serum albumin (g/dL)	2.56 (1.98; 3.23)	3.78 (3.3; 4.1)	3.97 (3.77; 4.12)	3.46 (2.73; 4.05)	3.8 (3.4; 3.97)	<0.001
Total serum proteins (g/dL)	5.14 (4.4; 5.91)	6.7 (6.11; 7.09)	6.47 (6.02; 6.98)	6.7 (5.97; 6.93)	7.01 (6.1; 7.93)	<0.001
Total cholesterol (mg/dL)	254 (194; 345.5)	195.5 (162; 239)	198 (156; 235)	203.5 (178.5; 238)	111 (59; 163)	<0.001
Tryglicerides (mg/dL)	175 (122; 269)	141.5 (96; 204)	130 (99; 215)	149 (121; 222.5)	115.5 (28; 203)	0,005
Uric acid (mg/dL)	6,49 (5,2; 7,72)	6,78 (5,4; 8,12)	6,72 (5,97; 9,59)	6,8 (6,21; 7,88)	6,48 (4,51; 10,32)	0,72
Hemoglobin (g/dL)	12.4 (10.8; 14.05)	11.9 (10.5; 13.8)	13.95 (13; 14.75)	10.2 (9.15; 10.75)	10.8 (9.85; 11.55)	<0.001
C-reactive protein (mg/dL)	0.41 (0.15; 0.7)	0.43 (0.13; 0.9)	0.15 (0.08; 0.49)	0.9 (0.3; 1.96)	0.7 (0.42; 4.25)	0,04
Proteinuria (g/day)	7 (4.25; 11.75)	1.52 (0.88; 2.5)	2.1 (1.42; 2.85)	0.7 (0.46; 1.68)	1.17 (0.52; 1.85)	<0.001
Hematuria (%)	< 5 p/HPF	71,3	9,6	6,6	2,9	
	5-20 p/HPF	75,0	21,9	1,5	0,5	
	20-50 p/HPF	48,3	48,3	3,4	0,0	
	>50 p/HPF	53,2	41,5	3,2	1,1	
Dysmorphic hematuria (%)	14,3	37,0	12,5	0,0	0,0	

The mean number of glomeruli was 15 ± 8.58 . A relevant fragment for diagnosis (minimum 8 glomeruli, and one vessel present) was recorded overall in 453 of biopsies (81.4%), 103 biopsies had less than 8 glomeruli. We observe a significant increase in the number of glomeruli $r=0.9$, $p<0.001$ after direct microscopic inspection of the fragment was implemented (Figure 3). IF was available in 480 (86.3%) of biopsies, and EM fragment was harvested starting in 2021 in 74.61% of patients with full work-out in 35.2%.

The predominant histologic pattern was mesangial proliferative (11.5%), endocapillary hypercellularity (9.8%), crescentic (8.2%), membranoproliferative (4.1%), sclerosing (6.5%), membranous (14.5%), FSGS (8.25%), diffuse or nodular mesangial expansion (17.4%), vascular pattern (17.3.2%), normal glomeruli (16.7%).

Baseline characteristics according to the histological pattern were presented in Table 2.

The main diagnostic categories for glomerular disease were FSGS (11,1%), MCD (12,2%), LN

(10.9%), vasculitis (7.6%), MN (14.7%), MPGN (8%), postinfectious (1.9%), IgAN (13.9%), MGRS (3.4%), Alport Syndrome (1.4%), DN (3.2%), anti-GBM disease (0.9%), vascular (2.5%), ATN (1.1%), TIN (3.8%), other (3.4%).

Overall, 53.8% of patients were males; the distribution of sex according to diagnosis was depicted in Figure 4.

Baseline characteristics of patients according to specific disease were provided in Table 3.

Analysis of specific diagnosis relative to clinical syndrome, and distribution of clinical syndromes within each specific diagnosis are provided in Table 4.

Overall, the age at diagnosis was 47.12 ± 15.64 . For IgA Nephropathy age increased over time while it decreased for MN, there were no other significant trends (Figure 5).

Fifty-seven percent of glomerular diseases were considered primary, and 43% secondary, relative frequency is depicted in Figure 6.

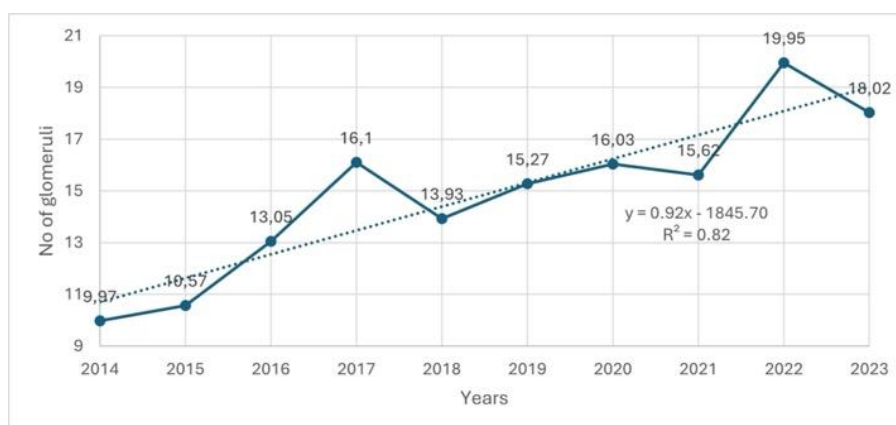


Figure 3. Primary and secondary forms of glomerular diseases.

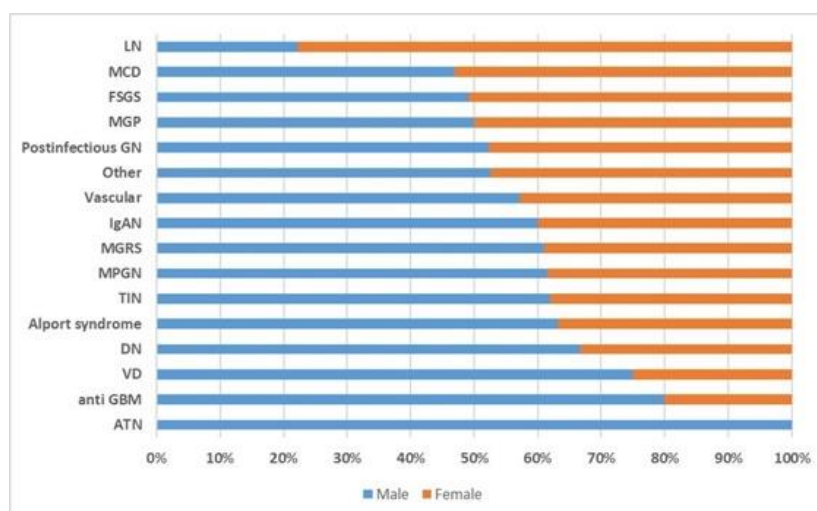


Figure 4. Distribution of specific diagnosis, and sex.

Table 2
Baseline characteristics according to histological pattern

	Normal glomeruli	Mezangiopro-liferative	Endocapillary proliferative	Crescentic	Membranopro-liferative	Sclerozant	Membranous	FSGS	Diffuse Nodular mesangial expansion	Vascular	p
Age (years)	47 (29; 59)	43 (35; 55)	46 (33; 58)	57 (44; 64.5)	52.5 (42; 61)	49 (36.5; 55.5)	53.5 (44; 63)	42 (32.5; 56.5)	45.5 (34; 54)	49 (37; 55)	0,03
Sex male (%)	55,4	51,6	26,4	70,5	54,5	60	53,8	50	55,3	41,2	
Serum creatinine (mg/dL)	0.99 (0.66; 1.67)	1.44 (0.7; 2.07)	1.5 (0.81; 3.7)	4.88 (2.33; 8)	1.57 (1.14; 2.41)	2.27 (1.7; 4.5)	0.9 (0.76; 1.48)	1.3 (0.95; 1.77)	1.21 (0.83; 1.94)	4.28 (2; 6.59)	<0.001
eGFR (mL/min)	90.48 (40.95; 114.14)	52.69 (34.67; 114.66)	58.88 (16.63; 96.66)	11.34 (6.39; 32.76)	41.06 (27.38; 62.41)	28.46 (14.29; 49.42)	82.59 (51.26; 107.82)	60.59 (42.2; 82.27)	67.73 (35.25; 106.37)	13.59 (8.41; 29.32)	<0.001
Serum albumine (g/dL)	2.32 (1.78; 2.99)	3.56 (2.95; 4)	3.31 (2.76; 3.75)	3.03 (2.65; 3.4)	3.27 (2.66; 3.57)	3.74 (3.11; 4.14)	2.39 (1.94; 3)	2.69 (1.68; 3.6)	3.33 (2.42; 3.93)	3.31 (2.88; 4.16)	<0.001
Total serum proteins (g/dL)	4.98 (4.2; 5.71)	6.23 (5.5; 6.97)	6.25 (5.34; 6.57)	6.05 (5.5; 6.74)	5.69 (5.13; 6.34)	6.48 (5.23; 7.02)	4.78 (4.22; 5.6)	4.7 (3.91; 6.24)	6.02 (5.1; 6.72)	6.27 (5.41; 6.91)	<0.001
Total cholesterol (mg/dL)	287 (226; 374)	198.5 (168; 246)	206 (166; 255)	174.5 (156; 256)	203.5 (171; 244)	211.5 (171.5; 252)	255.5 (213; 331)	333.5 (208.5; 378)	215 (185; 290)	193 (151.5; 221)	<0.001
Triglycerides (mg/dL)	172 (118; 264.5)	134 (100; 179)	162 (110; 224.5)	163 (124.5; 196.5)	170 (109.5; 264)	140 (104.5; 181)	183 (139; 267.5)	261 (193; 350)	150 (104.5; 230)	169.5 (129; 197)	0,001
Uric acid (mg/dL)	6.36±1.88	6.78±1.99	6.8±2.13	7.86±2.30	6.9±2.13	7.25±1.65	6.14±1.73	7.19±1.63	6.29±2.01	7.9±2.24	0,72
Hemoglobin (g/dL)	13 (11.8; 14.4)	12.3 (11; 13.4)	11.2 (9.9; 12.5)	10.25 (9.2; 11.4)	10.8 (9.7; 12.5)	12 (10.4; 14.4)	12.7 (11.3; 14.5)	13.2 (12.1; 14.5)	12.5 (11; 14.2)	10.1 (9.65; 10.65)	<0.001
C-reactive protein (mg/dL)	0.99 (0.66; 1.67)	1.44 (0.7; 2.07)	1.5 (0.81; 3.7)	4.88 (2.33; 8)	1.57 (1.14; 2.41)	2.27 (1.7; 4.5)	0.9 (0.76; 1.48)	1.3 (0.95; 1.77)	1.21 (0.83; 1.94)	4.28 (2; 6.59)	0,04
Proteinuria (g/day)	7.11 (3.95; 11.5)	2.68 (1.32; 5.2)	2.22 (0.88; 6.07)	2.5 (1.7; 5.12)	4.7 (1.5; 11)	2.63 (0.78; 5.14)	6.7 (3.7; 12.26)	7.8 (4.06; 13.25)	3.62 (2.04; 8.85)	3.1 (1.28; 8.55)	<0.001
< 5 p/HPF	44,7	15	13,3	12,2	4,5	24,2	31,2	38,1	27	40	
5-20 p/HPF											
Hematuria p/HPF	43,5	40	35,6	14,6	36,4	36,4	59,7	35,7	30,3	26,7	
20-50 p/HPF	9,4	15	22,2	26,8	22,7	18,2	6,5	16,7	23,6	20	
>50 p/HPF	2,4	30	28,9	46,3	36,4	21,2	2,6	9,5	19,1	13,3	
Dysmorphic hematuria (%)	5,9	25,4	36,4	32,5	45,5	15,2	10,5	9,5	23,6	20	

Qualitative variables presented as absolute frequencies, non-normally distributed quantitative variables presented as Median (IQR), normally distributed variables presented as Mean ± S

Table 3

Baseline characteristics of patients according to specific disease

	FSGS	MCD	LN	Vasculitis	MGP	MPGN	Posinfectious GN	IgAN	p
Age (years)	42 (31; 54)	44 (27; 57)	38 (29; 49.5)	62 (50; 69)	54 (44; 63)	48.5 (35; 61)	41 (28; 57)	42 (29; 51)	<0.001
Sex male (%)	49,2	47	22,2	50	61,5	52,4	60	61	
Serum creatinine (mg/dL)	1.21 (0.9; 1.81)	1 (0.64; 1.55)	0.87 (0.67; 1.82)	5.5 (3.1; 7.2)	0.9 (0.72; 1.34)	1.59 (1.06; 3.02)	1.54 (1.16; 2.46)	1.35 (0.83; 1.94)	<0.001
eGFR (mL/min)	64.02 (40.64; 91.18)	90.73 (45.27; 117.98)	92.73 (39.26; 114.52)	10.35 (6.63; 19.25)	83.04 (56.93; 108.18)	44.25 (25.27; 71.47)	59.8 (27.46; 73.33)	61.25 (39.43; 111.04)	<0.001
Serum albumine (g/dL)	2.8 (1.7; 3.57)	2.27 (1.78; 2.85)	3 (2.55; 3.59)	3.29 (2.92; 3.51)	2.5 (1.96; 3)	3.27 (2.69; 3.65)	3.84 (2.99; 4.17)	3.63 (2.9; 4.03)	<0.001
Total serum proteins (g/dL)	5.03 (3.98; 6.03)	4.76 (4.2; 5.5)	6.04 (5.1; 6.57)	6.3 (5.84; 6.95)	4.93 (4.26; 5.58)	5.65 (5.11; 6.5)	6.41 (5.62; 7.17)	6.3 (5.43; 6.8)	<0.001
Total cholesterol (mg/dL)	287 (207; 357)	301 (246; 400)	200.5 (173; 252)	169 (156.5; 229)	257.5 (217; 351)	222 (190.5; 263)	213.5 (168; 244)	211 (180; 281)	<0.001
Triglycerides (mg/dL)	211.5 (151.5; 331)	198 (130.5; 290.5)	162.5 (109; 229)	162.5 (132; 196.5)	181 (139; 267.5)	155.5 (116; 230)	118 (100.5; 185)	131 (86; 198)	0.001
Uric acid (mg/dL)	6.71 (5.49; 8)	6.26 (4.96; 8.1)	6.03 (4.98; 7.35)	7.22 (6.15; 8.99)	5.8 (4.7; 7.1)	6.65 (5.13; 8.6)	7.59 (6.26; 9.39)	6.83 (5.71; 8.32)	0.006
Hemoglobin (g/dL)	13.2 (11.85; 14.1)	13.05 (11.7; 14.5)	11.4 (10.2; 12.95)	10.4 (9.3; 11)	13.1 (11.8; 14.8)	11.6 (10; 12.7)	11.8 (9.1; 13.8)	13 (11.2; 14.3)	<0.001
C-reactive protein (mg/dL)	0.42 (0.14; 0.67)	0.2 (0.09; 0.48)	0.41 (0.19; 0.75)	1.42 (0.6; 3.71)	0.4 (0.13; 0.52)	0.43 (0.2; 0.79)	0.2 (0.09; 0.46)	0.25 (0.09; 0.57)	<0.001
Proteinuria (g/day)	7.15 (4.15; 12.68)	7.99 (4.23; 11.8)	3 (2; 6.12)	2.2 (1.3; 3.2)	6.64 (3.9; 11.52)	3.93 (1.52; 9.4)	2.42 (0.63; 2.68)	2.56 (1; 4.68)	<0.001
Hematuria (%)	< 5 p/HPF 32,8	39,1	19,3	7,5	37,7	4,8	40	13,3	
	5-20 p/HPF 44,8	48,4	42,1	15	51,9	40,5	20	32	
	20-50 p/HPF 12,1	10,9	17,5	22,5	7,8	19	30	25,3	
	>50 p/HPF 10,3	1,6	21,1	55	2,6	35,7	10	29,3	
Dysmorphic hematuria (%)	10,3	6,3	14,3	41	9,2	33,3	20	36,5	
MGRS									p
Alport syndrome									
Age (years)	55 (51; 63.5)	31 (19.5; 48.5)	43.5 (37; 53)	54.5 (47; 58)	58 (50; 60)	50 (45; 58)	49 (46; 57)	49 (39.5; 63)	<0.001
Sex male (%)	63,2	75	57,1	66,7	100	61,9	80	52,6	
Serum creatinine (mg/dL)	1.49 (1.08; 4.12)	0.99 (0.74; 1.56)	2.42 (1.01; 4.3)	1.52 (0.94; 2.27)	7.8 (4.12; 8.6)	2.28 (1.81; 3.7)	7.82 (4.13; 9.31)	2.16 (0.99; 4.21)	<0.001

Table 3 (continued)

eGFR (mL/min)	48,28 (17.08; 73.49)	92,73 (56.3; 116.68)	29,32 (13.59; 98.23)	53,27 (29.5; 87.08)	7,42 (6.6; 18.64)	28,68 (16.22; 34.51)	8,35 (5.57; 34.89)	33,94 (16.52; 80.14)	<0.001
Serum albumine (g/dL)	2,47 (2.19; 3.36)	3,85 (3.66; 3.92)	4,02 (3.38; 4.21)	2,97 (2.46; 3.59)	3,77 (2.46; 3.97)	3,78 (3.18; 4.14)	2,84 (2.59; 2.9)	3,46 (2.27; 3.99)	<0.001
Total serum proteins (g/dL)	5,23 (4.6; 5.94)	6,37 (6.2; 7.07)	6,41 (6.17; 6.91)	6,1 (5.46; 6.62)	6,95 (5.5; 7.33)	6,98 (6.2; 7.27)	5 (4.94; 5.49)	5,16 (4.9; 6.7)	<0.001
Total cholesterol (mg/dL)	271 (194; 358)	174 (143; 209)	205,5 (166; 210)	206 (151; 227)	191 (162; 199)	200 (133; 244)	180 (167.5; 265.5)	186 (160; 294)	<0.001
Triglycerides (mg/dL)	191 (111; 298)	99 (66; 159)	143 (114; 174)	104 (81; 167)	167 (113; 172)	109 (87.5; 161.5)	137 (118.5; 142.5)	172 (137.5; 213)	0,001
Uric acid (mg/dL)	4,99 (3.9; 6.89)	6,98 (6.62; 9)	7,74 (6.1; 9.37)	6,7 (5.37; 8.51)	7,21 (6.28; 7.97)	6,8 (6.3; 7.22)	7,33 (6.93; 8.66)	1,21 (0.9; 1.81)	0,006
Hemoglobin (g/dL)	11,4 (10.6; 12.5)	14,55 (12.65; 15.4)	10,1 (9.8; 13.7)	13,1 (10.9; 14.2)	11,1 (10.4; 11.5)	10,5 (9.9; 12.45)	9,8 (9.5; 11.1)	11,3 (10.3; 12.55)	<0.001
C-reactive protein (mg/dL)	0,5 (0.21; 4.58)	0,17 (0.09; 0.31)	0,35 (0.18; 1.51)	0,64 (0.33; 1.1)	1,29 (0.37; 5)	0,61 (0.32; 2.29)	3,06 (0.16; 4.72)	0,79 (0.5; 0.99)	<0.001
Proteinuria (g/day)	11,7 (6.21; 19.14)	2,19 (1.15; 2.98)	2,7 (0.5; 3.43)	6,7 (4.5; 8.19)	2,69 (1.1; 11.43)	1,23 (0.57; 5.05)	9,68 (9.55; 11.68)	2 (1.28; 5)	<0.001
Hematuria (%)	< 5 p/HPF 61,1	0	46,2	35,3	66,7	36,8	0	13,3	
	5-20 p/HPF 16,7	12,5	38,5	41,2	16,7	26,3	0	46,7	
	20-50 p/HPF 16,7	37,5	15,4	17,6	16,7	15,8	25	33,3	
	>50 p/HPF 5,6	50	0	5,9	0	21,1	75	6,7	
Dysmorphic hematuria (%)	5,6	62,5	30,8	11,8	16,7	10,5	50	6,7	

Legend: eGFR- estimated glomerular filtration rate, LN-lupus nephritis, MCD-Minimal change disease, FSGS-Focal segmental glomerulosclerosis, MN-Membranous glomerulopathy, DN-Diabetic nephropathy, IgAN- IgA Nephropathy, MGRS – Monoclonal gammopathy of renal significance, MPGN-Membranoproliferative glomerulonephritis, TIN-Tubulointerstitial nephritis, VD-Vascular disease, anti-GBM-anti-glomerular base membrane, ATN- Acute tubular necrosis.

Table 4

Specific diagnosis relative to clinical syndrome and distribution of clinical syndromes within each specific diagnosis

		Biopsy indication			
		Nephrotic syndrome	Nephritic syndrome	AUA	AKI /RPRF
FSGS	within specific diagnosis (%)	87,3	6,3	4,8	0
	within biopsy indication (%)	15,7	2,8	18,8	0
MCD	within specific diagnosis (%)	89,4	4,5	6,1	0
	within biopsy indication (%)	16,8	2,1	25	0
LN	within specific diagnosis (%)	55,9	39	3,4	1,7
	within biopsy indication (%)	9,4	16	12,5	5
Vasculitis	within specific diagnosis (%)	25	636,6	0	9,1
	within biopsy indication (%)	3,1	19,4	0	20
MGP	within specific diagnosis (%)	93,5	3,9	2,6	0
	within biopsy indication (%)	20,5	2,1	12,5	0
MPGN	within specific diagnosis (%)	64,1	30,8	2,6	2,6
	within biopsy indication (%)	7,1	8,3	6,3	5
Postinfectious GN	within specific diagnosis (%)	44,4	55,6	0	0
	within biopsy indication (%)	1,1	3,5	0	0
IgAN	within specific diagnosis (%)	39,2	59,5	1,4	0
	within biopsy indication (%)	8,3	30,6	6,3	0
MGRS	within specific diagnosis (%)	95,2	4,8	0	0
	within biopsy indication (%)	5,7	0,7	0	0
Alport syndrome	within specific diagnosis (%)	25	62,5	12,5	0
	within biopsy indication (%)	0,6	3,5	6,3	0
VD	within specific diagnosis (%)	42,9	21,4	7,1	21,4
	within biopsy indication (%)	1,7	2,1	6,3	15
DN	within specific diagnosis (%)	88,2	5,9	5,9	0
	within biopsy indication (%)	4,3	0,7	6,3	0
ATN	within specific diagnosis (%)	16,7	16,7	0	50
	within biopsy indication (%)	0,3	0,7	0	15
TIN	within specific diagnosis (%)	33,3	33,3	0	14,3
	within biopsy indication (%)	2	4,9	0	15
anti GBM	within specific diagnosis (%)	60	20	0	20
	within biopsy indication (%)	0,9	0,7	0	5
Other	within specific diagnosis (%)	56,3	18,8	0	25
	within biopsy indication (%)	2,6	2,1	0	20

LN-lupus nephritis, MCD-Minimal change disease, FSGS-Focal segmental glomerulosclerosis, MN-Membranous glomerulopathy, DN-Diabetic nephropathy, IgAN- IgA Nephropathy, MGRS – Monoclonal gammopathy of renal significance, MPGN-Membranoproliferative glomerulonephritis, TIN-Tubulointerstitial nephritis, VD-Vascular disease, MGP- Membranous glomerulopathy anti-GBM-Anti-glomerular base membrane, ATN- Acute tubular necrosis.

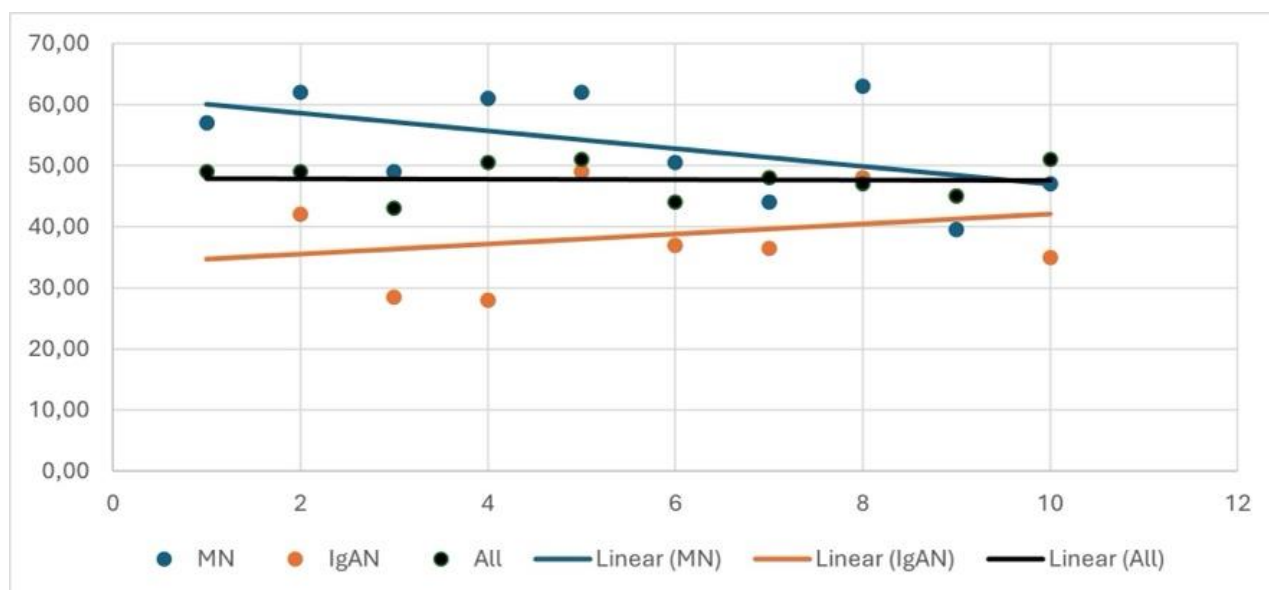


Figure 5. Time-trend for MN, and IgAN.

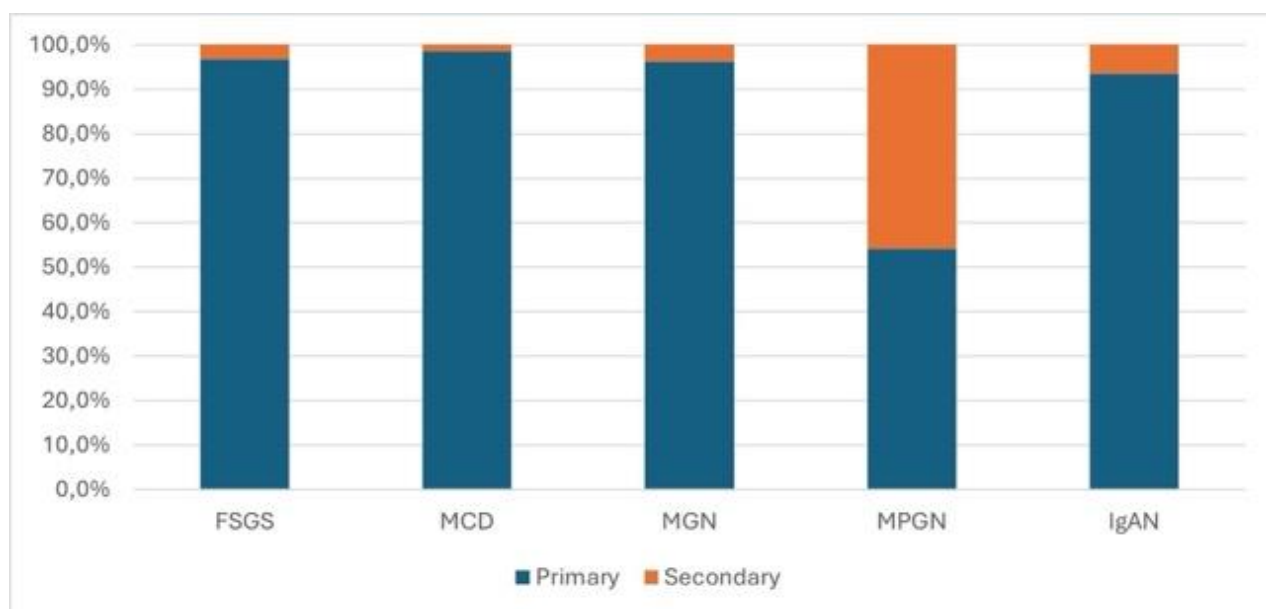


Figure 6. Primary and secondary forms of glomerular diseases.

DISCUSSION

The incidence of kidney biopsies in the north-western part of Romania is 12 biopsies/m person-year, derived only from counties that refer kidney biopsies to our center. This is lower than in most other registries worldwide, with figures over 25 [6,7] up to 250 biopsies/m person-year [8,9,10] being reported. Socio-economic conditions, cultural background, addressability, and timeframe studied might play a role but even in other eastern European countries wide differences are reported ranging from 3.9 biopsies/m person-year in Serbia

[11] to 61 biopsies/m person-year in Poland [12]. When comparing to the recently reported study from the “Carol Davila” University of Medicine and Pharmacy, the incidence is comparable with our figure (12 biopsies/m person-year in our report versus 14.75). Addressability varies however widely across the reported region, as depicted in Figure 1. From 5.7 in some counties (exclusively referring to our center), up to 21.5 in the county of Cluj – where the referral center for biopsies is located. The same experience is reported in the “Carol Davila” University of Medicine and Pharmacy [3] with up to 35 times more biopsies

performed for the residents of Bucharest. One explanation is the number of nephrologists in different counties: up to 40 nephrologists/county in university centers like Cluj, 100 in the capital Bucharest whereas only 1-2 nephrologists are available in other counties or, extreme cases without a permanently employed nephrologist, which surely influences addressability.

The likely explanation for the dramatic increase in the incidence of biopsies in the last period (an increase of 51%) is a heightened awareness regarding kidney disease in Romania, but also the availability, starting in 2021 of EM in our center which increased the referral rate. The tendency is maintained in the current year (54 biopsies/6 months) – unpublished data.

The main indication for kidney biopsy was nephrotic syndrome (63% of cases), followed by nephritic syndrome (25%), figures that are comparable to those reported in other biopsy registries [1,11]. However our findings are disagreement with reports from Spain (reporting 35% nephrotic, and 6% nephritic syndrome) [12], Czechia (39% nephrotic, and 30% nephritic) [13] or Poland (45% nephrotic, and 13% nephritic) [14]. These differences result from varied definitions, mainly for nephritic syndrome, and AUA, (e.g. in the Polish registry for nephritic syndrome decreased eGFR was mandatory).

The mean age at biopsy was 47.19 ± 15.54 years old which is in line with other registries [6,13], however younger than some newer reports [15]. The mean age at diagnosis was similar for most clinical syndromes at presentation (Table 1).

The other differences noted in baseline characteristics according to the indication of kidney biopsy are easily inferred from the respective syndromes, regarding proteinuria, eGFR, etc.

There was a male prevalence for kidney biopsies with two exceptions: for the nephritic syndrome, males, and females were equally represented (with the higher prevalence of IgA nephropathy in men counterbalanced by lupus nephritis in women), and a higher prevalence for female patients in the AKI group. The male prevalence is constantly reported in all biopsy registries worldwide [3,6,14], and the word is still out wheather this represents a truly higher prevalence of glomerular disease amenable to biopsy in males or if psychosocial factors play a role.

Only a minority of patients had hematuria described as dysmorphic with a higher percentage for nephritic syndrome. However, contrast phase microscopy was not routinely available, therefore the value of non-standardized visual characterization of hematuria is debated, as highly operator-dependent [16].

The mean number of glomeruli over the studied decade was within the definition of an optimal fragment for OM in 81.4% of patients. Nonetheless, when in 2016 a direct extemporaneous control through visual inspection of the biopsy fragment on light microscopy x10 magnification was implemented (see methods), this led to a significant improvement in the quality of the biopsy fragment for OM with an increase (65% from 2015 to 2017) of the number of glomeruli available for OM, continuing to improve thereafter. Immunofluorescence was available in most patients (86.3%), under the current standard of care [17]. In our center, biopsy fragment for EM was harvested in 77% of biopsies, and a full work-up was performed in 35% when it was deemed to improve diagnosis (see methods) this is to be compared to the low use in some of the regional registries (0–5%) [1,2,11] but much higher in developed countries, varying from 38% in an older Italian registry [18] to “routine”, including the data reported from “Carol Davila” University of Medicine and Pharmacy [3].

When the histologic pattern was examined, a surprisingly high prevalence of mesangial expansion was listed as the predominant pattern. This may reflect a conglomerate of diseases like diabetes monoclonal gammopathy of renal significance or IgAN (27 patients with IgAN listed as a predominant mesangial expansion).

Regarding different types of renal disease, we observed the highest prevalence of MN (14.8%) in agreement with the recently published paper from “Carol Davila” University of Medicine and Pharmacy (16%), and with some of the available biopsy registries [11,14] around 13% in Europe overall [6]. However, other registries report a lower prevalence of MN: under 10% in the Spanish registry [12], and 5.5% in Flanders [15]. The likely explanation is the increasingly widespread availability of APLA2 testing, and thus decrease in indications for biopsy. Noteworthy, the Flemish registry reflects the most recent period (2019–2022), and in the Spanish registry, frequency decreased over time from 13% to 8%. A similar trend was also observed in our study (Figure 5).

The other prevalent nephrotic syndrome in adult patients was almost equally represented by MCD, and FSGS.

FSGS had a prevalence of 11.4% comparable to that reported in other registries with similar ethnic backgrounds – 11.3% in white patients in Europe [6], our population being entirely Caucasian.

Regarding nephritic syndrome, the highest incidence was noted for IgA nephropathy, 13.9% lower than other data reported from Romania –

20% [3], and from other European countries (20–36%) [6,14,19,20]. Nevertheless, in other registries figures are closer to ours: the Spanish registry reports 14.6%, and the Flemish registry 17.3% [12,15]. IgAN patients presented at 41.62 years, comparable to some European registries [3,21] somewhat lower than in reports from the USA – 47.7 years [22] but higher than in reports from northern Europe [23]. There was a tendency to increase over time. This phenomenon was also observed in the RaDaR report, and in the Spanish registry [12,21]. We confirm male predominance and report on a mean eGFR at presentation of 61.25 (39,43;111,04) ml/min/1.73 higher than that described in other registries [21].

Regarding membranoproliferative GN we observed a prevalence of 7.2%, similar to the report from biopsy center in Romania (5%) [3] but much lower than in another study from the eastern part of Romania (24.4%) [2]. Decreasing prevalence of MPGN is a generally observed tendency, accounting for 3.7 % in Europe [6], and even 0.7% in the more recent Flemish biopsy registry which describes data from 2019–2022.

Diabetic nephropathy accounts for a minority of patients who underwent kidney biopsy (3.3%) but an important increase during the last year of observation was noted (8.9%), which is in line with other reports where DN represents 7.5% – 10% of patients [3,15]. This trend persists in 2024 (11.53% – unpublished data). Also, the comorbidity of diabetes was reported in 10.43% overall in our cohort but 14.28% in 2023, and 20.37% in 2024. The escalating frequency of diabetic nephropathy was also reported in other registries [24]. The relative abrupt increase most likely reflects a shift in perspective towards repositioning indication of kidney biopsy in diabetic patients, and/or increased awareness, and referral.

There is a considerable overlap in the literature regarding the terms of primary, and secondary glomerular disease. As do most of the published reports, we also used the terms primary for unknown etiology, and secondary for glomerular disease with identifiable cause.

As per total kidney biopsies 57% were considered primary, and 43% secondary (see Figure 6). Other registries also report a wide variation in these numbers, presumably influenced by the definitions used [1,3,12]. Regarding FSGS we observe that the majority of patients are described as idiopathic, which disagrees with current knowledge on secondary, and/or genetic forms of FSGS. The likely explanation is the fact that EM for the evaluation of the extent of foot process effacement was available only since 2021, and genetic testing is not reimbursed in Romania, hence many secondary, and genetic forms might have been missed. For MN, 3.8% were secondary forms. However, APLA2 receptor positivity is performed in Romania only in approximately half of the reported timeframe, and it was available in our hospital only since 2023. Consequently, meaningful data on the number of PLA2-positive MN that underwent biopsy could not be retrieved. For MCD disease, as expected, the majority were primary forms. IgA nephropathies were also mainly primary with only 6.5% secondary forms, which is lower than previously reported in a cohort from Romania [21,22,23,25].

The percentage of TIN was low (3.8%), in line with most data in registries from different regions over the globe [6], however, registry data from Flanders, and Finland report several times higher figures, probably explained by a higher biopsy rate for this diagnosis [9,15].

CONCLUSIONS

Data from biopsy rates in different countries are difficult to compare for several reasons: firstly, prevalence is mainly being reported, and conclusions about incidence are sometimes difficult if addressability for kidney biopsy is unclear. Secondly, figures are frequently presented as percentages of variously defined subgroups. Additionally, different age groups, and different periods are compared, which makes matching data challenging. Although reported from one region in Romania, our study adds data for the completion of the kidney biopsy map in our region.

Scop: Furnizarea de date epidemiologice privind biopsia renală din România.

Metode: Studiu retrospectiv observațional al datelor de biopsie renală la pacienții adulți dintr-un centru de referință din nord-vestul României, raportat pentru perioada 2014–2023.

Rezultate: Au fost efectuate 556 de biopsii, corespunzând unei incidențe de 12 biopsii per milion de locuitori/an, cu o creștere a numărului de biopsii de peste 50% în

ultimul an raportat. Probă de țesut optimă pentru microscopia optică a fost disponibilă la 81,4%, imuno fluorescența a fost efectuată la 86,3% și microscopia electronică la 35,2% dintre pacienți. Vârsta medie la biopsie a fost de 47,12 ani, iar 53,8% au fost bărbați. Indicațiile pentru biopsia renală au fost sindromul nefrotic la 63,1% dintre pacienți, nefritic la 25,9% dintre pacienți, anomalii urinare asimptomatice la 2,9%, insuficiență renală acută/insuficiență renală rapid progresivă la 3,6% și boala renală cronică la 1,4%. Cele mai frecvente categorii de diagnostic au fost nefrita membranoasă (14,7%), nefropatia IgA (13,9%), glomeruloscleroza segmentară focală (11,1%), glomerulopatia cu modificări minime (12,2%), nefrita lupică (10,9%), vasculită (7,6%) și glomerulonefrita membranoproliferativă (8%).

Pe parcursul perioadei studiate vârsta la diagnostic a crescut pentru nefropatia IgA și a scăzut pentru nefrita membranoasă.

Concluzii: Studiul nostru adaugă date pentru completarea hărții biopsiei renale în regiunea noastră.

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List of abbreviations, and acronyms:

CKD – chronic kidney disease
OM – optic microscopy
IF – immunofluorescence
EM – electron microscopy
APLA2 – anti phospholipase A2
ANCA – anti-neutrophil cytoplasmic antibody
MN – membranous nephritis
LN – lupus nephritis
FSGS – focal segmental glomerulosclerosis
eGFR – estimated glomerular filtration rate
AUA – asymptomatic urinary abnormalities
AKI – acute kidney injury
RPRF – rapid progressive renal failure
MCD – minimal change disease
MPGN – membranoproliferative glomerulonephritis
IgAN – IgA Nephropathy
MGRS – monoclonal gammopathy of renal significance
DN – diabetic nephropathy
GBM – glomerular base membrane
ATN – acute tubular necrosis
TIN – tubulointerstitial nephritis

Acknowledgements: This research received funding from Iuliu Hațieganu University of Medicine and Pharmacy, Cluj-Napoca under internal grant agreements PCD 771/4/2023 and 771/41/2023.

Declaration of interest: The authors declare that there are not conflicts of interest.

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