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REPORT OF THE CROATIAN REGISTRY OF NATIVE KIDNEY BIOPSIES FOR YEAR 2019

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SUMMARY – *Background:* This report describes data collected by the Croatian Registry of Renal Biopsies (CRRB) for the year 2019. *Patients and methods:* nine centers (82%) provided data for 255 native kidney biopsies. We assessed the anthropometric data, data on serum creatinine concentration (sCr), 24 h proteinuria, haematuria, serum albumin level, arterial hypertension, histological diagnosis, and complications after renal biopsy. *Results:* examined group consisted of 58% males, median age 58 y (18-80 y) and 42% women, median age 57 y (20-86 y). Males had a more impaired renal function at the time of renal biopsy, nephrotic syndrome, and hypertension. The most prevalent clinical presentation were urinary abnormalities (34.9%). Among all biopsy cases, primary glomerular diseases were

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the most often found histology group (41.5%), and IgA nephropathy was the most frequent diagnosis(47.1%). Among secondary glomerular diseases, pauci-immune glomerulonephritis (PIGN) was most often found (30.9%). The highest proteinuria was observed in minimal change disease and diabetic nephropathy (DN). The highest sCR values were found in membranoproliferative glomerulonephritis (MPGN) and necrotizing vasculitis. Patients with MPGN and DN had the highest blood pressure levels. *Conclusion:* CRRB provides important data on the epidemiology of biopsy-proven kidney diseases from the whole territory of Croatia

Key words: *registry, renal biopsy, glomerular disease, epidemiology*

Introduction

One of the key features for the development of quality clinical, epidemiologic research has been identified in the development of databases or registries for the collection of epidemiologic data related to specific disease[1]. Glomerulonephritis (GN) is a relatively rare disease, and most nephrology centers see only a limited number of patients with each type of GN every year.

Current epidemiological data of renal disease in Europe are available from large national renal biopsy registries[2-5]. Incidence and prevalence of glomerular diseases vary according to geographical location, gender, age, and race. Therefore, establishing a national registry is of utmost importance, giving us the opportunity to learn more about the epidemiology of glomerular diseases in our country.

Until recently, the epidemiological data on the incidence of kidney disease in the Croatian population were mostly based on reports of Croatian Institut of Public Health or Renal Replacement Registry of Croatian Society of Nephrology, Dialysis and Transplantation (CSNDT) and data providing histopathology results of kidney biopsy were sporadically reported as single-center reports[6].

The nationwide Croatian Registry of Renal Biopsies (CRRB) was founded in 2019 after the initiative of CSNDT and included nine nephrology centers that reported clinical, laboratory and histopathological data of adult patients who underwent native kidney biopsy for the first time on a national level.

The aim of this study was to report on the relative frequency of nephropathies according to gender, age, clinical presentation, and renal function at the time of renal biopsy based on the histologic diagnosis.

Patients and methods

Renal biopsy records were collected during the period from January 1st till December 31st, 2019. Nine renal centers out of eleven (82%) have participated. Using a simple questionnaire, the following data were collected at the time of renal biopsy: age, gender, anthropometric data, serum creatinine concentration (sCr), eGFR according to CKD EPI formula, 24-h proteinuria (UP), the presence of microscopic or macroscopic hematuria (H), blood pressure (BP) values and the presence of arterial hypertension defined as blood pressure >140/90 mmHg or treatment with antihypertensive drugs, clinical and histological diagnosis, clinical complications after renal biopsy (clinically symptomatic subcapsular or perirenal hematoma, gross hematuria and need for blood transfusion).

The following clinical syndromes were assessed at the time of renal biopsy: nephrotic syndrome proteinuria >3.5 g/24 h, hyperlipidemia, edema); urinary abnormalities: persistent lowgrade proteinuria (<3.5 g/24 h) with or without microhaematuria; nephritic syndrome (a combination of hematuria, hypertension and acute reduction of renal function, sCr > 110 μmol/l); rapidly progressive GN (progressive decline in renal function, hematuria, hypertension), advanced renal insufficiency(sCr >200 μmol/l with or without hematuria and proteinuria). We retrospectively analyzed the distribution of renal diseases according to clinical syndromes, and therefore more than one clinical syndrome could be found in some patients. The indications for renal biopsy varied among centers according to local practice. Histological evaluation by light microscopy and immunofluorescence was performed routinely in all patients combined with electron microscopy in a substantial number of cases. Histological diagnosis were mainly based on WHO recommendations modified by others as follows: (1) Primary GN: minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MGN), IgA nephropathy (IgAN), C3 membranoproliferative GN (C3MPGN), (2) Secondary GN: systemic lupus erythematosus (SLE), Henoch–Schonlein

purpura (HSP), pauci-immune GN (PIGN; Goodpasture's syndrome (GPS); renal amyloidosis (AM), light-chain deposit disease (LCDD), myeloma cast nephropathy (MCN) essential mixed cryoglobulinemia; GN associated with infectious diseases (non-streptococcal GN, endocarditis, shunt GN and others); diabetic nephropathy (DN); hereditary nephropathies, i.e., Alport syndrome (AS), Fabry disease, thin basement membrane glomerulopathy (TBMN)[3]. Acute and chronic tubulointerstitial nephritis (TIN) and acute tubular injury (ATI)[4]. Vascular diseases including benign and malignant nephroangiosclerosis (NAS), hemolytic–uraemic syndrome and thrombotic thrombocytopenic purpura (HUS/TTP), renal scleroderma, and cortical necrosis[5]. Others, including end-stage renal disease (ESRD) of undetermined cause, unclassified nephropathies[2,4,7,8]. Ultrasound needle guidance was used most commonly except in 5 cases (1.9%) where CT guidance was performed.

Statistical analysis

Parameters are expressed as percentages or mean values ± standard deviation. A Chi-square test or Fisher exact test was used for categorical data according to simple size. A two-tailed t-test was used for continuous variables. $P<0.05$ was considered statistically significant. Statistical analyses were performed using STATISTICA, vers.8 (StatSoft, Inc).

Results

During the observed period of one year, data for 255 native kidney biopsies were recorded. Examined group consisted of 58% males median age 58 years (range 18-80 years), and 42% females, median age 57 years (range 20-86 years). Characteristics of renal biopsy cases according to gender are shown in Table 1.

Males presented more often (72.2%) with renal impairment and with higher sCr in the time of renal biopsy (235 ±186 *vs.* 168±162 μmol/l, p=0.002). There was no significant difference between proteinuria (3.69± vs. 2.94 g/dU) and blood pressure values (140/83 vs. 138/82 mmHg) compared to females. Clinical syndromes recorded at the time of renal biopsy are shown in figure 1.

The most prevalent diagnosis in UA was IgA nephropathy (29.1%), FSGS (14.5%), and nephroangiosclerosis (12.5%); in the nephrotic syndrome group, MN was most often diagnosed (25.8%), then DN (17.2%) and FSGS (15.5%); nephritic syndrome was a presentation of IgA nephropathy in 31% of cases, SLE nephritis in 13.7% and MPGN 10.3%. Patients with RPGN were the oldest, the average age was 63 years old, and the highest percentage of males (76%) were found. The most prevalent diagnosis in that group was PIGN (64%). In the group with advanced renal insufficiency with or without hematuria and proteinuria most prevalent diagnosis was nephroangiosclerosis (21.9%) and DN (17.1%). The youngest patients were found in the UA group (50 years). 11.7% of patients had the overlap of two or more clinical syndromes.

Table 1. Characteristics of renal biopsy cases in the whole group and according to gender

	Whole group (n=255) %	Males (n=148) %	Females (n=107) %
Age group (years)			
18-30	7.8	8.1	7.4
31-65	59.6	59.4	59.8
>65	29.4	32.4	32.8
Serum creatinine (μmol/l)			
≤ 110	37.6	27.7	51.4
110-500	54.5	63.5	42.0
>500	7.8	8.7	6.5
Proteinuria (g/dU)			
< 3,5	69.5	70.2	68.2
≥ 3,5	30.5	29.7	31.7
Arterial hypertension (>140/90 mmHg)	47.0	50.6	42.0

Among all biopsy cases, primary glomerular diseases were the most often found histology group (41.5%), then secondary glomerular diseases (32.9%), vascular diseases (10.9%), and tubulointerstitial nephritis (7.1%). Ten most common renal biopsy diagnoses (more than 10 cases or above 5% during the observed period) in our population are listed in figure 2.

The most frequent diagnosis among primary glomerular diseases was IgA nephropathy (47.1%), FSGS (25.4%), and membranous nephropathy (19.8%). In comparison, among secondary glomerular diseases, PIGN was found in 30.9% of cases, DN in 23.8%, and

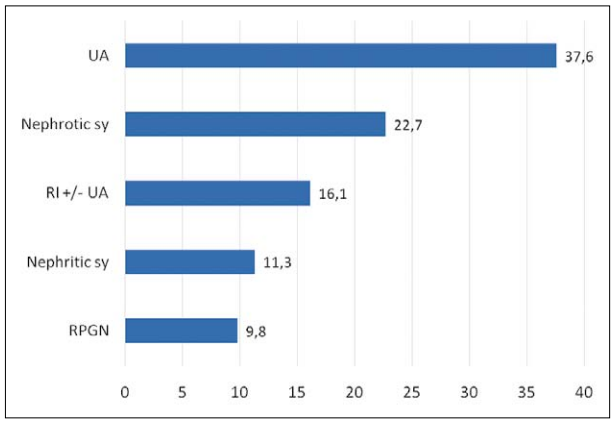

Figure 1. Clinical syndromes recorded at the time of renal biopsy

Legend: UA – urinary abnormalities, RI+/-UA – renal insufficiency with or without hematuria and proteinuria; RPGN – rapidly progressive GN

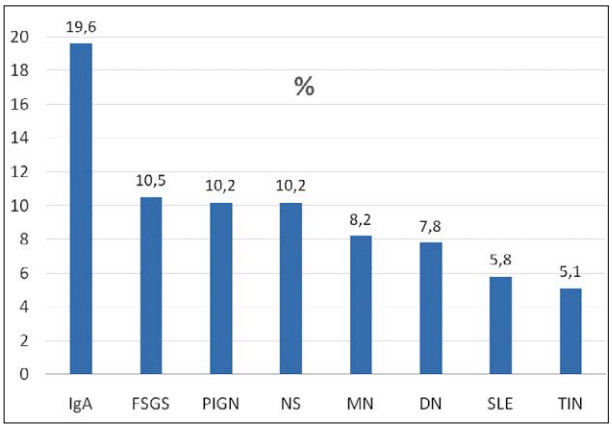

Figure 2. Most common renal biopsy diagnosis in the adult population

Legend: IgA – IgA nephropathy, FSGS – focal segmental glomerulosclerosis, PIGN – pauci-immune glomerulonephritis, NS – nephroangiosclerosis, MN – membranous nephropathy, DN – diabetic nephropathy, SLE – lupus nephritis, TIN- tubulointerstitial nephritis

Table 2. The epidemiology and clinical characteristics of most common renal biopsy diagnosis in the time of renal biopsy

Diagnosis	No of cases	% of CRRB	Mean age	Gender (%male)	Mean sCr (μmol/l)	RI (%)	Mean proteinuria (g/dU)	NS (%)	Hypertension (%)
Primary GN	106	41.5	53	62.2	137	50.9	3.84	37.7	47.1
IgA	50	19.6	51	66.0	160	62.0	2.71	18.0	40.0
FSGS	27	10.5	54	62.9	116	44.4	3.37	46.7	40.7
MN	21	8.2	55	57.1	104	28.5	6.49	66.7	57.1
Secondary GN	84	32.9	58	50.0	255	76.1	3.81	38.1	47.6
PIGN	26	10.2	64	69.2	362	96.1	3.16	23.1	50.0
DN	20	7.8	58	45.0	198	85.0	5.06	65.0	60.0
SLE	15	5.8	43	20.0	159	60.0	3.67	33.3	53.3
Tubulointerstitial nephritis	13	5.1	67	55.5	441	100	1.31	7.6	40,7
Vascular diseases	31	12.1	52	64.5	205	74.1	2.29	12.9	58.1
NS	26	10.2	56	61.5	165	73.0	1.81	11.5	57.6

Legend: IgA – IgA nephropathy, FSGS – focal segmental glomerulosclerosis, MN – membranous nephropathy, PIGN – pauci-immune glomerulonephritis, DN – diabetic nephropathy, SLE – lupus nephritis, TIN- tubulointerstitial nephritis, NS – nephroangiosclerosis; RI – renal insufficiency; NS – nephrotic syndrome

lupus nephritis in 17.8%. Nephroangiosclerosis were found in 92.8% of cases among vascular causes. The epidemiology and clinical characteristics of selected glomerulopathies and TIN at the time of renal biopsy are shown in table 2.

Among primary GN highest proteinuria was found in MCD (11.1 ± 6.3 g/dU), MN (6.4+4.1 g/dU) and MPGN (3.9±1.4 g/dU). DN manifested with the highest proteinuria between secondary forms of GN. The highest levels of serum creatinine were found in patients with MPGN (183.1+123.6 μmol/l) in primary forms of PG, in secondary GN in PIGN (362.2+314.3 μmol/l) and in TIN (441.7 +181.9 μmol/l). The highest blood pressure values were observed in MPGN (154/92 mmHg) and DN (152/85 mmHg).

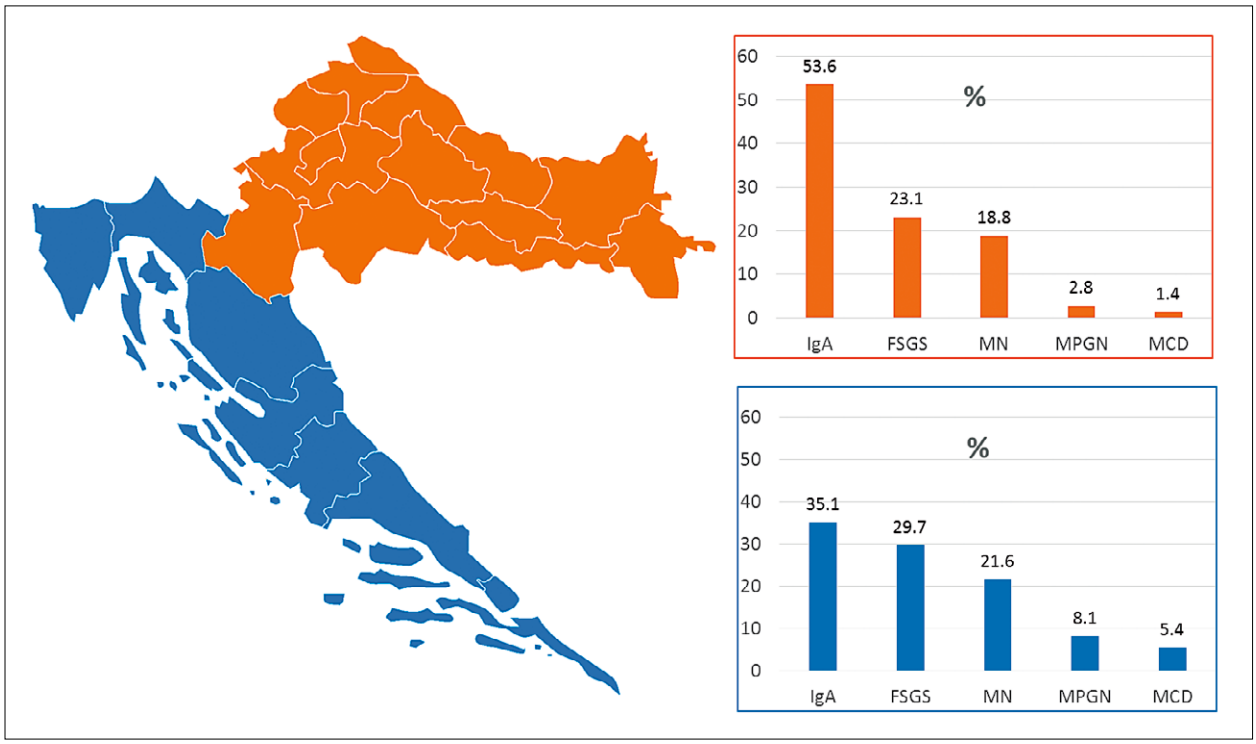

Figure 3. Geographical distribution of primary glomerular diseases between the continental and Mediterranean part of Croatia

Legend: IgA – IgA nephropathy, FSGS – focal segmental glomerulosclerosis, MN – membranous nephropathy MPG – membranoproliferative GN, MCD – minimal change disease

We analyzed the geographical distribution of primary glomerular diseases in Croatia according to continental and Mediterranean parts (figure 3). There were no significant differences in the frequency of subtypes of primary glomerular diseases. Although not statistically significant, the comparison of particular subtypes revealed the higher creatinine levels in IgA nephropathy in the Mediterranean region compared to IgA nephropathy in the continental part of Croatia (143.3±181.1 *vs.* 209.3±182.8 μmol/l p=0.073). Similar observation was found for FSGS (100.6±56.9 *vs* 139.2±56.6 p=0.09). Higher proteinuria levels were found in MN diagnosed in the Mediterranean part of the country (5.62±4.5 *vs.* 7.81±3.4 p=0.263). Further analysis of four geographical regions (central Croatia, west Croatia, Slavonia and Baranja, and Dalmatia) showed similar results regarding the frequency of primary glomerular disease subtypes.

In our group, we found almost 30% of patients older than 65 years. Average sCr was 264.4 μmol/l, proteinuria 3.46 g/dU, blood pressure 143/81 mmHg. Secondary GN was the most prevalent (37.3%) form of the disease, then primary GN (30.6%) and TIN (13.3%). PIGN was found in 17.3% of cases, MN and nephroangiosclerosis in 12%.

Patients younger than 65 years had average sCr 183 μmol/l, proteinuria 3.34 g/dU, blood pressure 137/83 mmHg. Primary GN was most often found (45%), and IgA nephropathy was the most prevalent diagnosis (23%), then FSGS (11%), MN, and nephroangiosclerosis (9.5%).

The frequency of serious complications (symptomatic hematoma, gross haematuria, need for blood transfusion) was observed in 14 cases (5.8%). Forty-two of them had renal impairment, and 71% had hypertension.

Discussion

This study provides information about demographics, clinical presentation, and frequency of renal disease diagnosed by renal biopsy in the year 2019, covering population on the national level.

Male gender was associated most frequently with most diagnostic categories (table 2), except SLE nephritis being more frequent among females. Clinical presentation was more severe in the male population. Males had significantly higher SCr values at the time of renal biopsy than females and were more hypertensive (table 1). Other authors report similar observations[3,4,5].

The most prevalent indication for renal biopsy was urinary abnormalities (37%) and nephrotic syndrome (23%). Similar indications were found in the Italian registry, while in other registries, slightly different results were found, the nephrotic syndrome was the leading indication (up to 53%) and then urinary abnormalities (up to 38%)[2,3,4,9].

In the group of patients presented with UA and nephritic syndrome, the most prevalent diagnosis was IgA nephropathy, and in the group with advanced renal insufficiency, PIGN was most often found, which is similar to others (2,4). In the nephrotic syndrome group, MN was most often diagnosed, which is similar to the Italian registry, while in the Czech and Polish registries, MCD was the leading diagnose[2-4].

Our report showed that primary and secondary GN were most often found in our patients who underwent renal biopsy and comprised almost 75% of patients. IgA nephropathy was the most prevalent form of primary GN occurring in around 20% of patients, which is the same as findings of Czech and Polish registry[2,4]. PIGN was the most prevalent diagnosis found in the group of secondary GN. The most common diagnosis found in our population besides IgA nephropathy and PIGN were FSGS and nephroangiosclerosis, which is similar to the finding of Czech registry[2]. The distribution pattern of primary GN diagnosis also corresponded to other European series[10].

Among those with nephrotic proteinuria highest values were observed in patients with MCD and MN. If we compare results for primary GN, similar results were found in Czech, Polish, Italian and French registry[2-4,11]. Among patients with secondary GN and nephrotic proteinuria, DN was the most frequent diagnosis (65%).

The highest sCr values at presentation were observed in patients with TIN and PIGN being almost all diagnosed with renal insufficiency (almost 100%) at the time of renal biopsy, which is in accordance with others (4). Renal insufficiency among primary GN s was highest in patients with MPGN and IgAN.

The overall prevalence of hypertension in our group was 47%. According to subgroup analysis, the highest frequency of hypertension was found in patients with DN (60%), and among patients with primary GN, hypertension was most often found in MN (57%). Similar findings but even higher values were found in other registries, up to 71% in MN and 91% in patients with DN[2,4].

Different pathology was observed in patients > 65 years. We found secondary GN more often than primary GN, which is similar to others. We found PIGN as the most prevalent diagnosis, followed by MN and nephroangiosclerosis. This result is slightly different compared to others where MN, DN, and amyloidosis or nephroangiosclerosis are the most prevalent findings in the older population[2-5].

The geographical distribution of primary glomerular diseases according to continental and Mediterranean parts (figure 3) was similar when we analyze the frequency of subtypes of primary glomerular diseases. However, a lower incidence of IgAN and higher incidence of FSGS and MN were found in the Mediterranean part. However, when we compare particular subtypes, we found, although not statistically significant, worse clinical presentation, lower renal function in IgA nephropathy and FSGS, and higher proteinuria in MN in the Mediterranean region compared to the continental part of Croatia. Whether this has some meaning is yet to be determined by follow-up of these patients and on a larger study sample.

In conclusion, the results of CRRB, which include renal biopsies of the native kidneys performed in almost all Croatian renal biopsy centers, represent an important contribution to the epidemiology of renal diseases in Croatia. Our results showed that the epidemiology of renal disease, mainly primary and secondary GN are similar to the results of surrounding countries in the region. We believe that the availability of these data will be a valuable source to nephrologists to stimulate further research and encourage work on the national biopsy register.

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Sažetak

IZVJEŠTAJ HRVATSKOG REGISTRA BIOPSIJA NATIVNIH BUBREGA ZA 2019. GODINU

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Uvod: izvještaj opisuje podatke Hrvatskog registra biopsija nativnih bubrega za 2019.godinu. *Ispitanici i metode:* poslani su podaci za 255 biopsija nativnih bubrega. Evidentirana je dob, spol, antropometrijski podaci, serumski kreatinin, 24h proteinurija, eGFR, prisutnost eritrociturije, arterijski tlak, klinička prezentacija, histološka slika i komplikacije biopsije bubrega. *Rezultati:* ispitivanu grupu činilo je 58% muškaraca, medijan dobi 58 g (18-80 g) i 42% žena, medijan dobi 57 g(20-86 g). Muškarci su se češće prezentirali azotemijom u času biopsije (67,5 %), nefrotskim sindromom (55,7 %) i hipertenzijom (62,5 %). Najčešće klinička prezentacija zbog koje je učinjena biopsija bubrega bio je sindrom eritrociturije i proteinurije (34,9 %). Najčešća skupina bubrežnih bolesti su bile primarne glomerulopatije (41,5 %). Među primarnim glomerularnim bolestima najučestalija je IgA nefropatija (IgAN)(47,1 %), a među sekundarnim glomerulonefritisima pauci imuni glomerulonefritis (PIGN) (30,9 %). Najvišom proteinurijom manifestirali su se od primarnih glomerularnih bolesti bolest minimalnih promjena a od sekundarnih formi dijabetička nefropatija (DN). Najvišim vrijednostima kreatinina u času biopsije manifestirali su se MPGN i PIGN. Hipertenzija je bila najviša kod MPGN i DN. Učestalost ozbiljnih komplikacija zabilježena je u 14 bolesnika (5,8 %). *Zaključak:* rezultati ukazuju na važne epidemiološke podatke prikupljene iz reprezentativnog broja nefroloških centara s cijelog teritorija Republike Hrvatske.

Ključne riječi: *registar, biopsija bubrega, glomerularne bolesti, epidemiologija*