ORIGINAL ARTICLE

EPIDEMIOLOGY OF BIOPSY CONFIRMED GLOMERULONEPHRITIS IN THE REPUBLIC OF MOLDOVA: PILOT STUDY

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Abstract: ***Introduction:*** *Renal biopsy is an important tool for the diagnosis of renal pathologies and for the choice of subsequent treatment tactics.* ***Objectives:*** *To report the epidemiology of glomerulonephritis in the Republic of Moldova, based on histological diagnosis, and set up the premises for the creation of the National Renal Biopsy Registry.* ***Material and methods:*** *The histological results of percutaneous renal ultrasound-guided biopsies, performed from March 30 to February 19, 2023, were evaluated in the* Timofei Moșneaga *Republican Clinical Hospital, Chisinau. Demographic characteristics, paraclinical parameters (serum creatinine, serum urea, glomerular filtration rate, nictemeral protein), and histological results were analyzed.* ***Results:*** *The outcomes of kidney biopsies performed on fifty-three patients were examined. The prevalence of renal pathologies in young and mature adults was observed, with the average age being 46.2 years. Most of the examined patients were men (71.70%). The main indication for performing renal biopsy was nephrotic syndrome, present in 64.15% of patients. The most common types of primary glomerulonephritis were membranous glomerulonephritis (50% of cases) and membranoproliferative glomerulonephritis (20% of cases). The most frequent types of secondary glomerulonephritis were lupus nephropathy (40%) and renal amyloidosis (30%).* ***Conclusions:*** *This study provides the first image of the current spectrum of glomerular kidney disease in the Republic of Moldova. It also serves as the basis for the development of the National Renal Biopsy Registry, which can serve as a useful resource for health policy development.*

Keywords: renal biopsy, glomerulonephritis, nephrotic syndrome.

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Abbreviations: AGN – Acute glomerulonephritis; CR – Chronic rejection; DN- Diabetic nephropathy; ERA-EDTA- European Renal Association-European Dialysis and Transplant Association; FSGS – Focal segmental glomerulosclerosis; LN – Lupus nephritis; MCGN – Minimal change glomerulonephritis; MGN – Membranous glomerulonephritis; MPGN – Membranoproliferative glomerulonephritis; PICGN- Pauci-immune crescentic glomerulonephritis; PIGN – Post-Infectious Glomerulonephritis; RA – Renal amyloidosis; RPGN – Rapidly progressive glomerulonephritis; SLE- Systemic lupus erythematosus

Introduction

Renal biopsy is an essential diagnostic tool and the gold standard for renal diseases [1]. The first surgical biopsy of the kidney was performed by Dr. George Edelbohls as part of a technique to remove the renal capsule in patients with Bright's disease. Percutaneous renal biopsy was first performed by chance when kidney tissue was accidentally obtained during liver biopsy. The first needle aspiration biopsy of the kidney was performed by Nils Alwall in 1944 using X-rays and retrograde pyelography [2]. Since the 1980s, percutaneous biopsy has been performed under ultrasound guidance using automated biopsy needles [3].

Important achievements in the physiological and pathophysiological mechanisms of the kidney can be attributed to advances in microscopy. Much of what we know about the architecture of the kidney is based on fundamental descriptions obtained by light microscopy and later provided by electron microscopy. With the recent technical innovation of super-resolution microscopy and advances in molecular imaging techniques, researchers can now visualize individual biomolecules directly in tissues and determine how they interact at the cellular and subcellular level [4].

Despite the clinical benefits, the procedure is not without risks. The major risks associated with kidney biopsies relate to bleeding and its sequelae. Major bleeding is associated with significant pain, hemodynamic instability, and urinary obstruction and may require blood transfusions or interventions or even lead to death [5]. However, the literature indicates that renal biopsy is a relatively safe procedure, with 1.6% of cases requiring a blood transfusion after biopsy and 0.3% requiring angiographic or surgical intervention (nephrectomy) [6]. The estimated frequency of death as a complication of the procedure is <0.1% [6,7].

The correct interpretation of renal biopsies is the result of the summation of several variables, such as the variety of clinical presentations, complexity of histological patterns, numerous additional clinical data, and laboratory values. Therefore, a defined set of data from patients with certain medical characteristics is systematically collected by medical registries and stored in a central database to better understand the pathogenesis of renal disease and to optimize treatment methods. There are several clinical registries of renal pathologies, of which The United States Renal Data System and the ERA-EDTA registry are probably the best known [8,9]. Compared to these clinical registries, little is known about the number, size, and geographical distribution of specific renal biopsy registries in other regions.

Sixteen regional or national renal biopsy registries were identified in Europe, Asia, North America and South America, of which 11 were over 10 years old. Most registries were located in either Europe (10/16) or Asia (4/16). The geographical distribution of renal biopsy registries is shown in Figure 1. In contrast to the large number of registries in Europe, there are large geographical areas without a single renal biopsy registry [10].

Romania is among the Eastern European countries that collect and systematize data on the spectrum of renal pathologies confirmed by renal biopsy, which is necessary for the formation of the Romanian Renal Biopsy Registry. Most of the data are obtained from the nephrology clinic of the "Dr. C.I. Parhon" Hospital in Iasi [11-13].

The aim of this paper is to create a picture of the current spectrum of glomerular renal pathologies in the Republic of Moldova by reporting the results of histological examination from a sample and to provide a basis for the National Kidney Biopsy Registry, which can serve as a useful resource for health policy decision-making.

Materials and methods

The histological results of renal biopsies from March 30, 2020, to February 19, 2023, performed in the *Timofei Moşneaga Republican* Clinical Hospital, Chisinau, were retrospectively evaluated. The data were collected from a single medical institution in the country since the performance of renal biopsy and subsequent histological examination (including immunohistochemistry) is possible only in this center.

This work was carried out on the basis of a retrospective study; patients' medical records

were analyzed with the consent of the Ethics Committee of the *Timofei Moșneaga* Republican Clinical Hospital.

Percutaneous renal biopsy was performed under ultrasonographic guidance, using the UROMED "CORAZOR®" device, biopsy puncture cannula (UROMED CORAZOR® 3K|TROKAR) size 18G or 16G.

Morphopathologists evaluated renal tissue. The biopsy specimen was fixed in formalin for a light microscopic examination. Renal tissue sections were prepared using different staining methods such as hematoxylin-eosin, Congo Red, Masson's trichrome, PAS (Periodic Acid Schiff) reaction, and Jones silver reaction. Immunohistochemical analysis was performed on only 10 patients (18.9%) on the Ventana BenchMark GX Automated Staining System, evaluating IgA, IgM, IgG, Kappa and Lambda.

Morphological variants have been classified as follows [13,14]:

1. Primary glomerulonephritis: membranoproliferative glomerulonephritis (MPGN), Membranous glomerulonephritis (MGN), rapidly progressive glomerulonephritis (RPGN), Minimal change glomerulonephritis (MCGN), acute intracapillary glomerulonephritis (AGN).
2. Secondary glomerulonephritis: renal amyloidosis (RA), post-infectious glomerulonephritis (PIGN), pauci-immune crescentic glomerulonephritis (PICGN), diabetic nephropathy (DN), lupus nephritis (LN), chronic transplant rejection (CR).
3. Vascular nephropathies: focal segmental glomerulosclerosis (FSGS).
4. Tubulo-interstitial nephropathies: chronic tubulo-interstitial nephritis.

Each case was examined for the following clinical parameters: serum creatinine, serum urea, glomerular filtration rate, urine protein/24 h, and histological result.

Indications for renal biopsy puncture were: nephrotic syndrome, nephritic syndrome, acute kidney injury, and proteinuria in patients with systemic lupus erythematosus (SLE). Criteria for the diagnosis of nephrotic syndrome: proteinuria > 3.5 g/24 h, hypoproteinemia, hypoalbuminemia, hyperlipemia, oedema. Nephritic syndrome implies the presence in the patient of proteinuria < 3.5 g/24 h, haematuria, hypertension. Acute renal injury implies rapid

alteration of renal function, through a decrease in glomerular filtration rate. The presence of proteinuria in patients with SLE confirms renal damage and the exact morphological variant needs to be determined.

Data was stored in an Excel database; absolute and percentage values were used.

Results

Between 30/03/2020-19/02/2023, 53 percutaneous renal biopsies were performed. The majority of examined patients were from the central part of the country (n=26, 49.06%), followed by the north of the country (n=15, 28.30%) and the south of the country (n=11, 20.75%), as shown in Figure 2.

The data show that renal pathology affects all age groups, from 19 years to 72 years, with a mean age of 46.2 years. The distribution by age group is shown in Figure 3, so that the predominance of renal pathology in young and mature, employable adults is observed. The majority of patients examined were male (n= 38, 71.70%), which is in line with the worldwide trend of glomerular pathologies [6].

The clinical presentation depending on age and sex is shown in Table 1 and Table 2. The main indication for renal biopsy puncture was nephrotic syndrome, present in 64.15% of patients, 79.41% of whom were male.

The frequency of the main histological diagnosis established is shown in Table 3. Primary glomerulonephritis was the most common diagnosis in our center (45.28%), followed by secondary (37.74%), vascular nephropathy (10.71%) and tubulointerstitial nephropathy (5.66%). The most common type of primary glomerulonephritis was MGN (50%), followed by MPGN (20%), MCGN (15%), IgA nephropathy, AGN and RPGN, which were equally detected (5%) (Figure 4). Morphological variants of secondary glomerulonephritis are shown in Figure 5, lupus nephropathy (40%) and renal amyloidosis (30%) prevail.

Only 3 (5.66%) of the 53 patients who underwent biopsies experienced complications, which included perirenal hematoma. Of these three patients with complications, only one patient with severe hypoproteinemia required intravenous administration of a 5% aminocaproic acid solution (100 ml).

Discussion

This study details the prevalence of renal diseases detected by renal biopsy over a relatively short period of time but represents the

first in-depth analysis of histological data from the Republic of Moldova.

Important findings of this regional database are: (A) the main indication for renal biopsy puncture was nephrotic syndrome; (B) the majority of patients examined were adults of reproductive age, fit for work; (C) male sex was dominant; (D) the frequently described histological variant was membranous and membranoproliferative glomerulonephritis.

A similar picture is described in the neighboring country, Romania. The last published study on the epidemiology of histologically confirmed glomerulonephritis summarizes data collected over 25 years from a center in the north-eastern part of Romania [13].

Our study has several limitations, such as a retrospective analysis of patients from a single center. The socio-economic situation in the country could explain the lower addressability to health care providers, at least in the case of an initial, asymptomatic disease. Correlated with a conservative approach, this led to a lower frequency of biopsies, with a relatively small number of patients included in our study. Immunohistochemistry was performed in only 10 patients (18.87%).

Although the volume of data obtained in our center is incomparable to that in Romania, it is certain that the same trends exist. Therefore, we will continue our research to create an overview of the spectrum of renal pathologies in the Republic of Moldova.

Conclusions

Nephrotic syndrome was the reason for a renal biopsy in more than half of the cases examined in our center. Membranous and membranoproliferative glomerulonephritis are the most common forms of primary glomerulonephritis, and lupus nephritis is the most common variant of secondary glomerulonephritis. The data presented here create an overview of the spectrum of renal pathologies in the Republic of Moldova and contribute to the epidemiology of renal diseases in Europe.

Author Contributions:

P.B., A.N., R.P., B.G.; A.G., E.M. and E.C conceived the original draft preparation. P.B., A.N., R.P., B.G.; A.G., E.M. and E.C were responsible for conception and design of the review. P.B., A.N., R.P., B.G.; A.G., E.M. and E.C were responsible for the data acquisition. L.B.G. was responsible for the collection and assembly of the article/published data, and their inclusion and interpretation in this review. P.B., A.N., R.P., B.G.; A.G., E.M. and E.C contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article".

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Figure 1. Geographical distribution of renal biopsy registries [10].

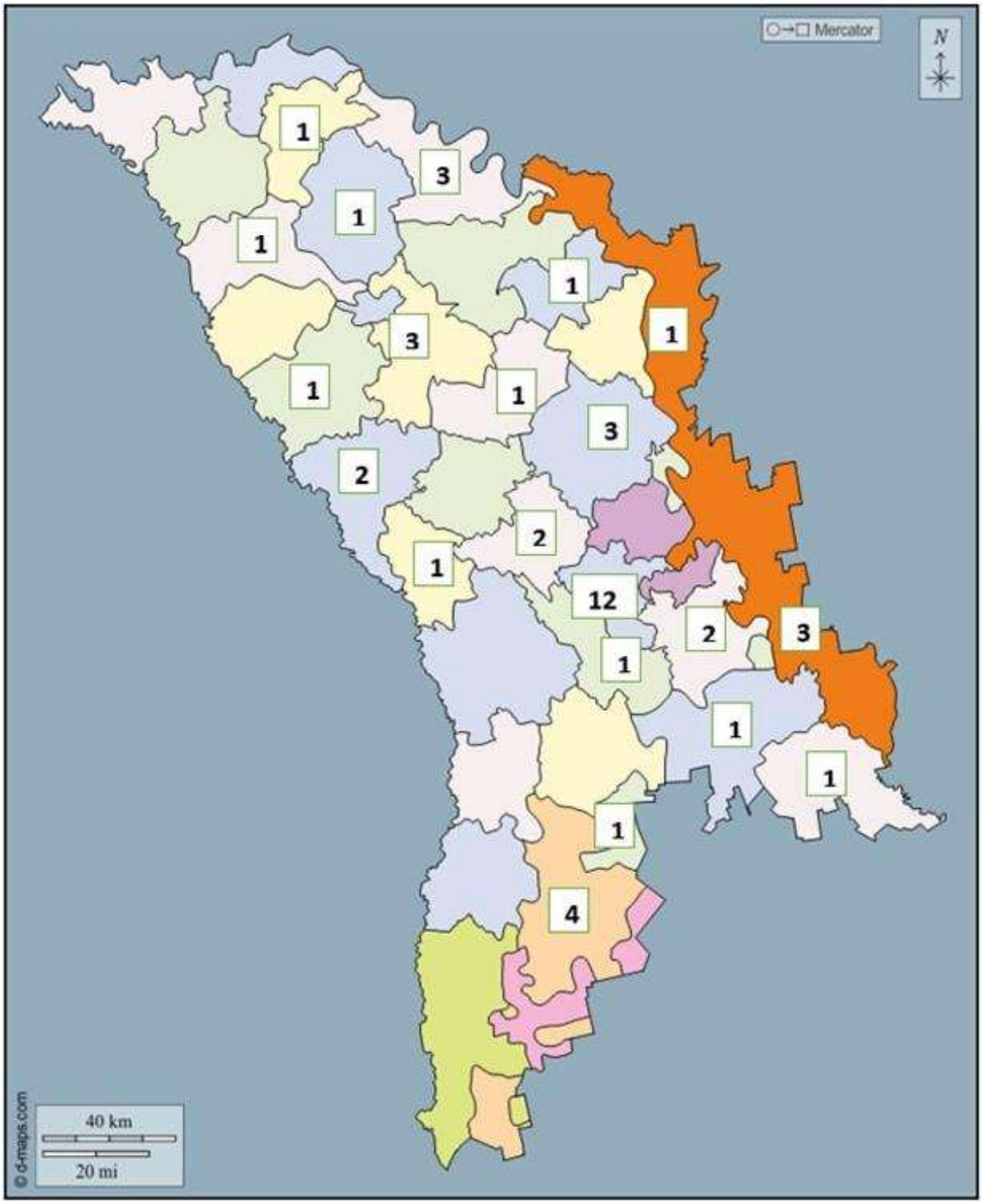

Figure 2. Distribution by geographical area

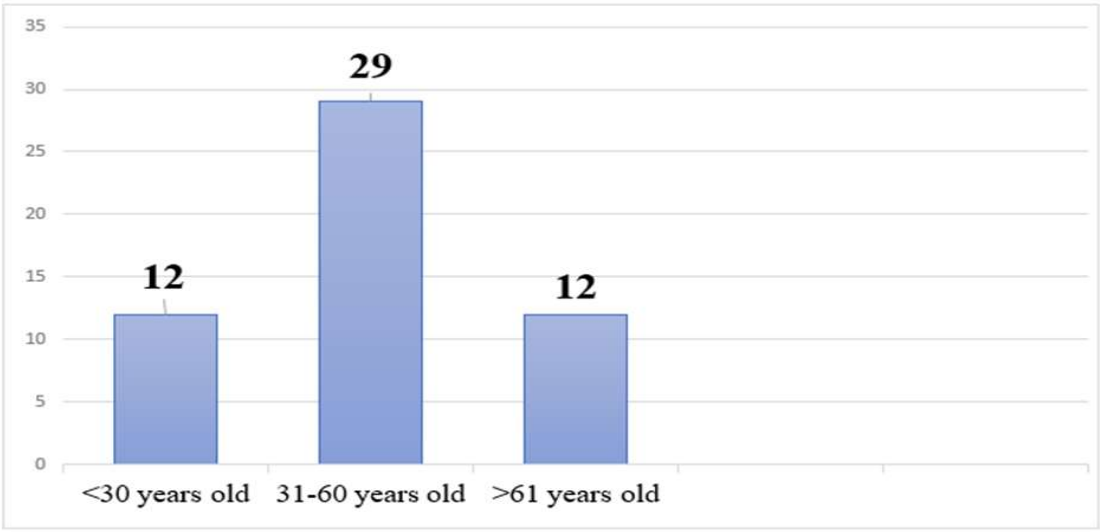

Figure 3. Distribution by age group

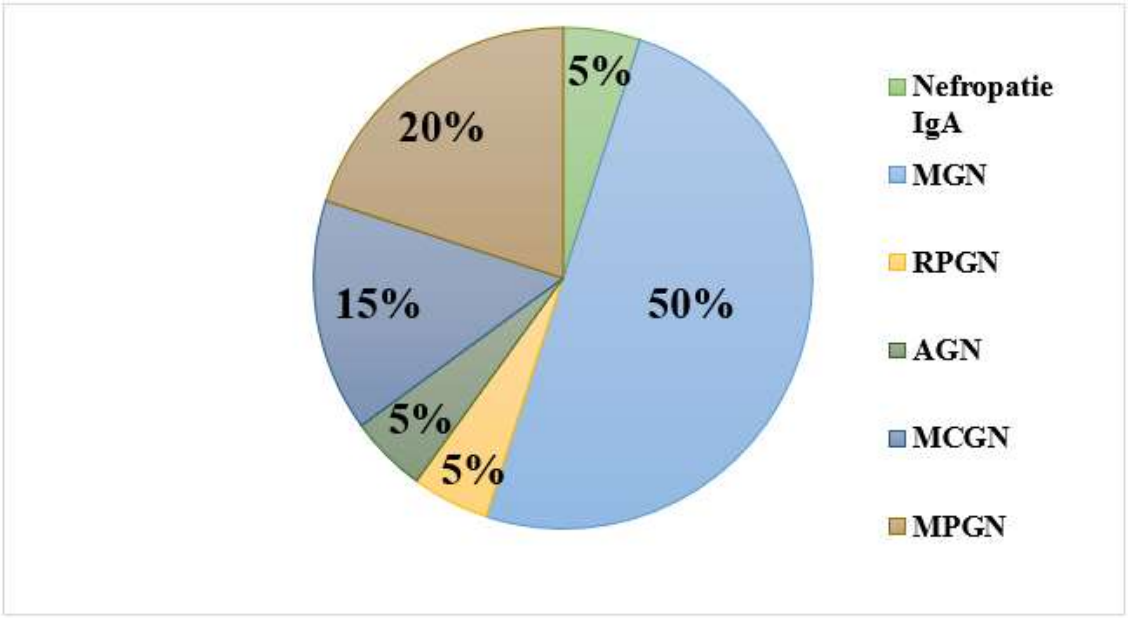

Figure 4. Primary glomerulonephritis.

AGN- Acute intracapillary glomerulonephritis, MCGN- Minimal lesion glomerulonephritis, MGN-Membranous glomerulonephritis, MPGN-Membranoproliferative glomerulonephritis, RPGN-Rapidly progressive glomerulonephritis.

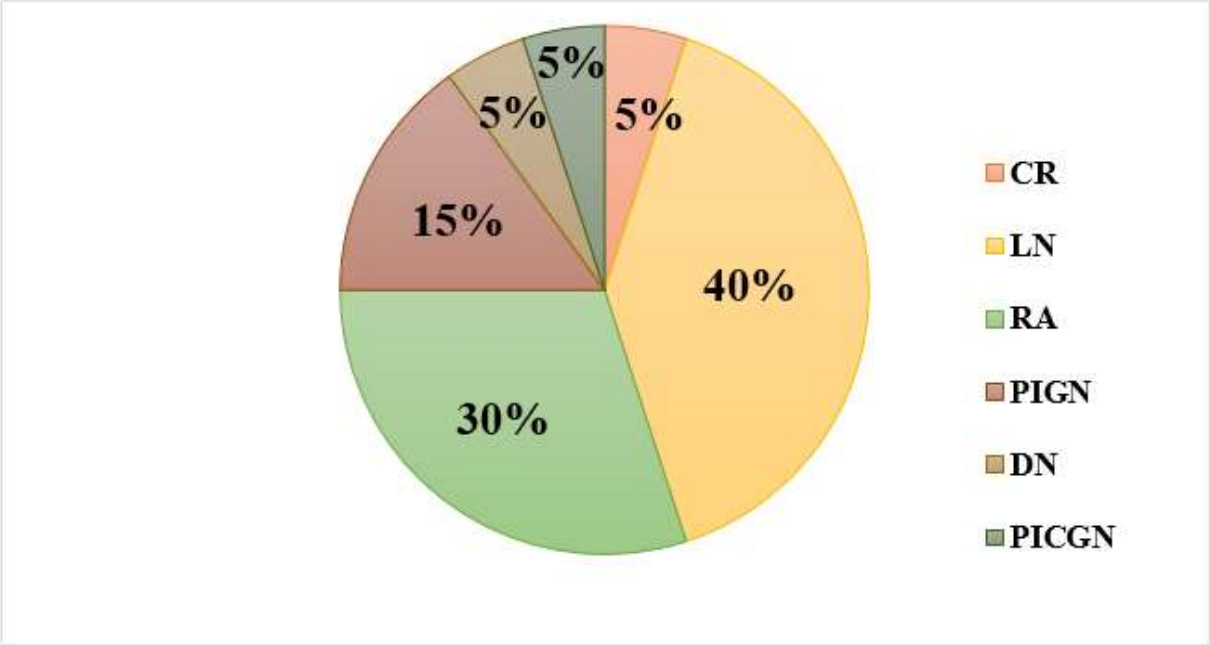

Figure 5. Secondary glomerulonephritis

CR- Chronic rejection, LN- Lupus nephritis, RA- Renal amyloidosis, PIGN- Post infectious glomerulonephritis, DN- Diabetic nephropathy, PICGN- Pauci-immune glomerulonephritis.

Table 1. Age-dependent clinical presentation

Indication	**Total number n (%)**	**Age group**		
		< 30 de ani n (%)	31-60 de ani n (%)	> 61 de ani n (%)
Nephrotic syndrome	34 (64.15)	6 (17.65)	19 (55.88)	9 (26.47)
Nephritic syndrome	10 (18.87)	2 (20)	5 (50)	3 (30)
Acute kidney injury	2 (3.77)	2 (100)	-	-
SLE	7 (13.21)	2 (28.57)	5 (71.43)	-
Total number	53 (100)	12	29	12

SLE-Systemic lupus erythematosus

Table 2. Clinical presentation depending on gender

Indication	**Total number n (%)**	**Gender**	
		Male, n (%)	Female, n (%)
Nephrotic syndrome	34 (64.15)	27 (79.41)	7 (20.59)
Nephritic syndrome	10 (18.87)	7 (70)	3 (30)
Acute kidney injury	2 (3.77)	2 (100)	-
SLE	7 (13.21)	2 (28.57)	5 (71.43)

SLE-Systemic lupus erythematosus

Table 3. Histological diagnosis

Histological diagnosis	**Total number n (%)**
Primary glomerulonephritis	24 (45.28)
Secondary glomerulonephritis	20 (37.74)
Vascular nephropathies	6 (11.32)
Tubulointerstitial nephropathies	3 (5.66)

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