## Original research

# Clinical and Histologic Characteristics of Renal Parenchymal Diseases in a Renal Biopsy Sample since 2002 to 2017 in Caldas – Colombia

## Características clínicas e histológicas de las enfermedades parenquimatosas renales en una muestra de biopsias renales obtenidas entre el año 2002 y el 2017 en el departamento de Caldas, Colombia

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**Abstract**

**Background:** Renal syndromes are clinical and laboratory manifestations that indicate functional and morphological alterations. Renal biopsy is essential in the diagnosis of kidney parenchymal diseases and provides valuable information in incidence, distribution and possible control of the disease.

**Objective:** To describe the clinical and histological characteristics of renal parenchymal diseases in a sample of renal biopsies.

**Methods:** We included 269 patients older than 14 years who underwent renal biopsy by any method. They were classified by indication of biopsy and by type of primary or secondary kidney injury.

**Results:** The average age was 57.04 (SD ± 17.17 years). The median creatinine was 1.51 mg / dL (IQR=1.22 – 2.01) and the GFR for CKDEPI was 42.7 mil/minute (IQR=30.6 – 56.5). The most frequent renal biopsy indications were unexplained chronic kidney disease (46.8 %), non-nephrotic proteinuria (20.1 %), nephritic syndrome (8.2 %), acute kidney injury (7.1 %), glomerular hematuria with change in the pattern (7.1 %), nephrotic syndrome (6.7 %) and unexplained low glomerular filtration for age (4.1 %). The most frequent findings were IgA nephropathy (20.9 %), hypertensive nephropathy (19 %), focal and segmental glomerulosclerosis (11.6 %), tubulointerstitial nephritis (9.7 %), diabetic glomerulopathy (8.6 %), membranoproliferative glomerulonephritis (3.7 %), extracapillary proliferative glomerulonephritis (3.4 %).

**Conclusions:** IgA nephropathy and focal segmental glomerulosclerosis are the main primary glomerulopathies. Hypertensive nephropathy and tubulointerstitial nephritis are the main secondary etiologies.

**Key words:** Kidney diseases, glomerulonephritis, IGA, epidemiology, proteinuria, hematuria.

**Resumen**

**Antecedentes:** los síndromes renales son manifestaciones clínicas y de laboratorio que indican alteraciones funcionales y morfológicas. La biopsia renal es fundamental en el diagnóstico de enfermedades renales parenquimales y aporta información valiosa sobre la incidencia, distribución y posible control de la enfermedad.

**Objetivo:** describir las características clínicas e histológicas de las enfermedades del parénquima renal en una muestra de biopsias renales.

**Métodos:** se incluyeron 269 pacientes mayores de 14 años, a quienes se les realizó biopsia renal por cualquier método. Se clasificaron por indicación de biopsia y por tipo de lesión renal primaria o secundaria.

**Resultados:** el promedio de edad fue de 57,04 (DE ± 17,17 años). La mediana de creatinina fue 1,51 mg/dl (RIC=1,22 - 2,01); y la de TFG por CKD-EPI, de 42,7 mil/minuto (RIC= 30,6 - 56,5). Las indicaciones de biopsia renal más frecuentes fueron enfermedad renal crónica sin causa clara (46,8 %), proteinuria no nefrótica (20,1 %), síndrome nefrítico (8,2 %), lesión renal aguda (7,1 %), hematuria glomerular con cambio en el patrón (7,1 %), síndrome nefrótico (6,7 %) y tasa de filtración glomerular estimada baja para la edad sin causa clara (4,1 %). Los hallazgos encontrados fueron: nefropatía por IgA (20,9 %), nefropatía hipertensiva (19 %), glomeruloesclerosis focal y segmentaria (11,6 %), nefritis tubulointersticial (9,7 %), glomerulopatía diabética (8,6 %), glomerulonefritis membranoproliferativa (3,7 %) y glomerulonefritis proliferativa extracapilar (3,4 %).

**Conclusiones:** la nefropatía por IgA y la glomeruloesclerosis focal y segmentaria son las principales glomerulopatías primarias. La nefropatía hipertensiva y la nefritis tubulointersticial son las principales etiologías secundarias.

**Palabras clave:** enfermedades renales, glomerulonefritis por IGA, epidemiología, proteinuria, hematuria.

## Introduction

Renal syndromes are clinical and laboratory manifestations that indicate alterations in renal functional and morphological integrity. To properly achieve the diagnosis of renal lesions, the second step after the syndromic approach is to proceed with a renal biopsy to make a histological diagnosis.[1] The definitive diagnosis by biopsy of the pathology that affects a patient differs from the clinical diagnosis in up to a third of cases.[2] Therefore, the renal biopsy is key in the final diagnosis of renal diseases[3] and guides on the pathogenic mechanism and, probably, the etiology. [1]

Up to 70% of the causes of chronic kidney disease are associated with arterial hypertension and diabetes mellitus. The remaining percentage includes other intrinsic renal diseases that typically involve the glomerular or tubulointerstitial compartments and that can be potentially reversible. The identification of treatable lesions requires a renal biopsy.[4] Therefore, the histopathological result alters the medical management in about 40 % of all patients (reversible diseases).[5]

Epidemiological studies based on renal biopsy are the best way to evaluate renal diseases.[3] The latter, when they are confirmed by biopsy, provide valuable information on the incidence, distribution and possible control of the disease with a targeted and effective treatment.

However, the global epidemiology is variable in histopathology, even among regions, due to racial and socioeconomic differences.[6] In Latin America and Colombia there are only few studies on renal diseases that clarify the epidemiological profile of the region.

## Materials and methods

We reviewed a total of 365 histology reports of patients who underwent renal biopsy, treated by the researchers in the outpatient program of the RTS unit in the study or renal parenchymal diseases from 2002 until 2017 in the city of Manizales, Caldas, Colombia.

We included patients older than 14 years, who underwent renal biopsy by any method, in which light microscopy, immunofluorescence and electron microscopy were used in the sample processing. The biopsy reports of transplanted patients, lupus nephropathy, study of renal masses or cysts, samples with 6 or less glomeruli or report with insufficient material by the pathologist, repeated reports or insufficient or not available clinical history were excluded.

The population sample was taken by convenience, according to the total number of biopsies obtained. The respective clinical histories of the patients were identified to extract the data related to sex, age, origin, values of serum creatinine, proteinuria by 24-hour collection or by urinalysis, urinary sediment findings and reports of renal imaging studies (ultrasound, tomography or magnetic resonance) performed before the renal biopsy. The glomerular filtration rate (GFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula,[7] and the expected glomerular filtration rate for the age was determined.[1]

According to the clinical and laboratory data indicated by the renal biopsy, the patients were classified into 7 renal syndromes: 1) nephrotic syndrome (proteinuria greater than 3.5 g/24 hours/ 1.73 $m^2$ of body surface area),[1,8] 2) non-nephrotic proteinuria (proteinuria between 0.3 and 3.49 g/24 hours/1.73 $m^2$ of body surface area), [1,8] 3) nephritic syndrome (hematuria of more than 3 red blood cells per high power field in urinary sediment in 2 samples separated by 1 week, uncontrolled hypertension, oliguria, edema, and reduced GFR), [1,8] 4) acute kidney injury (AKI) without improvement at 8 weeks, and with normal renal ultrasound[1,8] (reduction in GFR due to 1 to 1.5-fold increase in baseline creatinine or reduction in urine output —less than 0.5 cc/Kg/ hour—), 5) glomerular hematuria with change in the pattern (hematuria of more than 3 crenated blood red cells in sediment of urine test plus appearance of proteinuria greater than 300 mg/24 hours and/or, increase in nitrogen compounds and/or, arterial hypertension),[1,8] 6) chronic kidney disease (CKD) with no clear cause (GFR lower than 60 ml/min/

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1.73 m$^2$ or elevation of baseline creatinine greater than 1.5-fold for more than 3 months), [1,8] accompanied by renal ultrasound showing kidneys of normal appearance; and finally, 7) low glomerular filtration rate with no clear cause, and lower than expected for the age or lower than 60 ml/min/1.73 m$^2$ or elevation of baseline creatinine greater than 1.5-fold for less than 3 months). [1] According to the biopsy report, patients were classified by type of kidney parenchymal disease and by primary and secondary etiology.

The collection of the information was done through a database designed in Google Docs, which was filled out by the researchers and processed using the SPSS 15.0 statistical program.

For the statistical analysis, relative and absolute frequency values were used with the qualitative variables. With the quantitative variables, the normal or abnormal distribution type was determined and measures of central tendency and dispersion were used, respectively (mean and standard deviation -SD-, or median and interquartile range -IQR-).

The project was approved by the teaching committee of the University of Caldas and by the research committee of RTS Colombia.

## Results

365 reports of renal biopsy were reviewed. 350 met the inclusion criteria. 37 repeated reports, 30 with insufficient or not available clinical history, 13 with insufficient sample or with less than 6 glomeruli and 1 of transplanted patient were excluded. The final sample to analyze was of 269 histological reports.

The average age was 57.04 years (SD ± 17.17). 38.28 % (103) of patients were over 65 years old. 53.5 % (144) were men. 69.14 % (186) came from Manizales, 5.95 % (16) from Chinchiná, 4.09 % (11) from Villamaría, 3.72 % (10) from municipalities outside Caldas, 2.6 % (7) from Riosucio and Aranzazu, 1.86 % (5) from Neira y 10.04 % from other municipalities.

Of the total of patients, the median creatinine was 1.51 mg/dl (IQR=1.22 – 2.01). The median eGFR by CKD-EPI was 42.7 ml/min (IQR =30.6 – 56.5) and the median proteinuria was 246 mg in 24 hours (IQR =100 - 1025). The median number of glomeruli in light microscopy was 18 (IQR =12 - 29); in immunofluorescence, 3 (IQR =2-5); and in the electron microscopy, 2 (IQR =1 - 2).

Figure 1. shows the order of frequency of the seven renal syndromes for indication of renal biopsy in the total of patients and in those older than 65 years.

The most frequent histological findings were: immunoglobulin A nephropathy (IgAN) (20.9 %, 56 patients), hypertensive nephropathy (19 %, 51), focal and segmental glomerulosclerosis (FSGS) (11.6 %, 31), normal biopsy (10.8 %, 29), tubulointerstitial nephritis (TIN) (9.7 %, 26), diabetic glomerulopathy (8.6 %, 23), membranoproliferative glomerulonephritis (MPGN) (3.7 %, 10), extracapillary proliferative glomerulonephritis (EPGN) (3.4 %, 9), chronic glomerulonephritis (3 %, 8), membranous glomerulonephritis (MGN) (2.6 %, 7), amyloidosis (2.2 %, 6), hereditary diseases (1.5 %, 4), minimal change disease (MCD) (1.1 %, 3); and other causes (1.8 %, 5), including immunoglobulin M nephropathy, mesangioproliferative glomerulonephritis and fibrillary glomerulopathy.

In patients older than 65 years, the most frequent findings were hypertensive nephropathy (33 %, 34), TIN (17.5 %, 18), diabetic glomerulopathy (10.7 %, 11), IgAN (8.7 %, 9), normal biopsy (6.8 %, 7), FSGS (6.8 %, 7), EPGN (3.9 %, 4), MGN (2.9 %, 3), MPGN (2.9 %, 3), chronic glomerulonephritis (2.9 %, 3), amyloidosis (2.9 %, 3) and other causes (0.97 %, 1).

The diagnoses and their main forms of presentation, according to the renal syndrome, in the total sample and in patients older than 65 years, are presented in Figures 2 and 3, respectively.

Of the total of patients with IgAN, only 5.3% (3) were considered due to secondary causes: 1 case associated with unspecified autoimmune disease, 1 case associated with Sjögren's syndrome and 1 case associated with liver cirrhosis.

Hypertensive nephropathy was the main cause of CKD with no clear cause (35.7%) and in patients
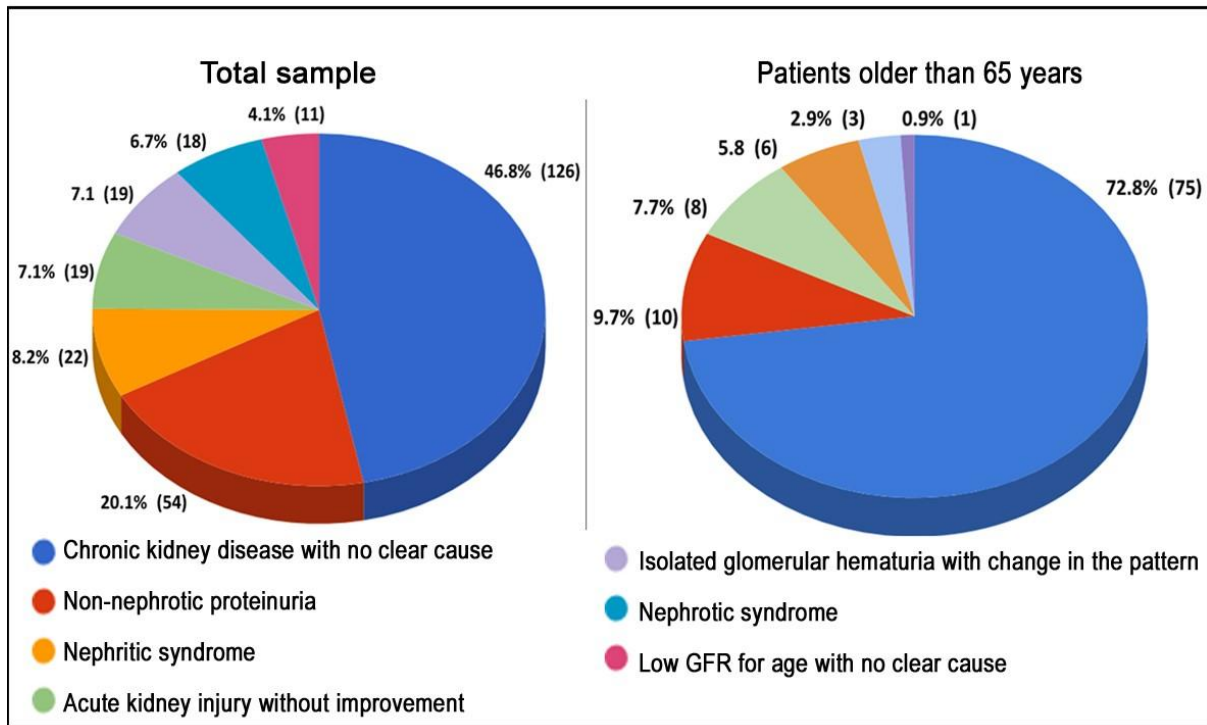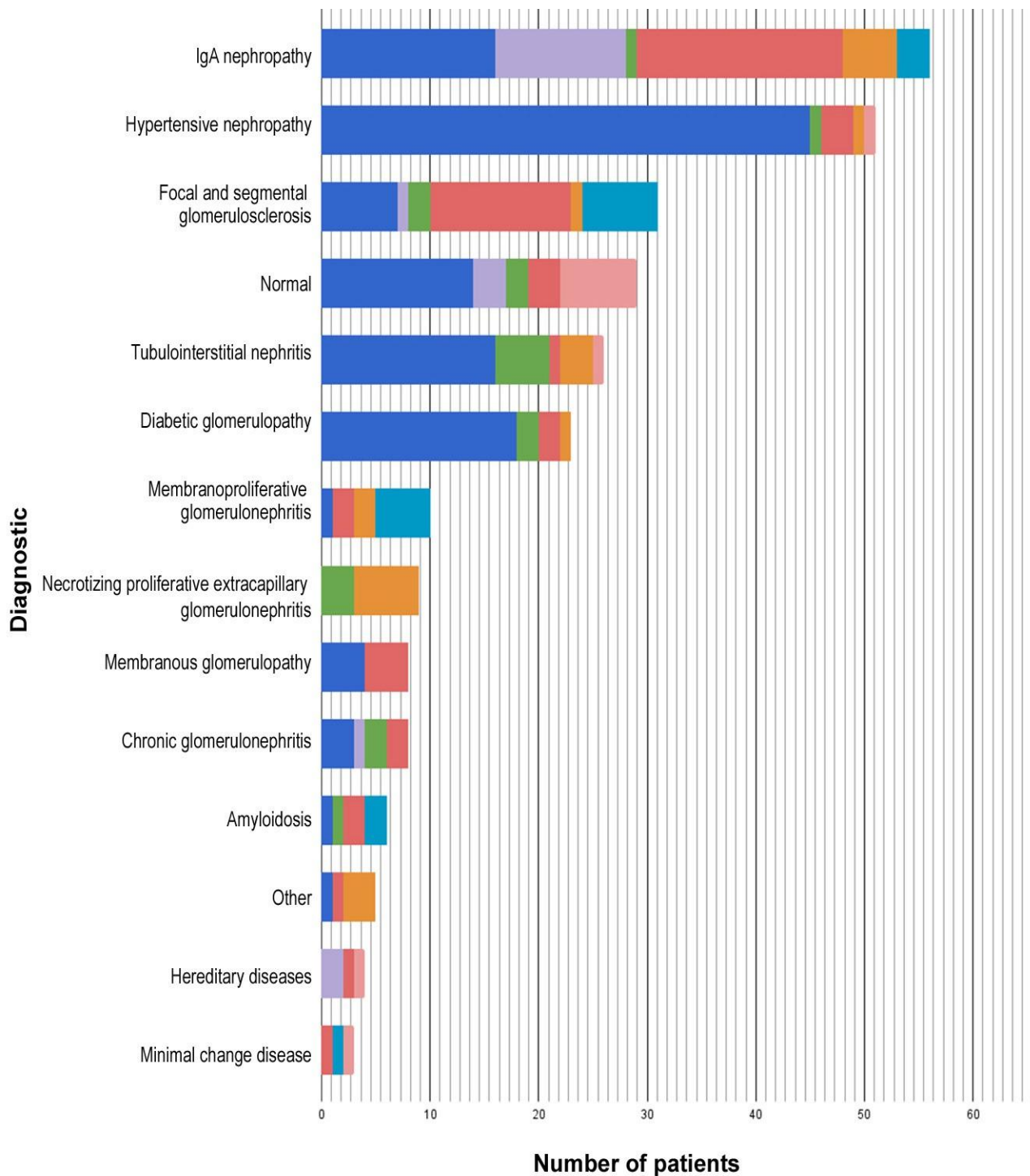
**Figure 1.** Frequency of renal syndromes/indications for renal biopsy in the totality of patients and in patients older than 65 years.

older than 65 years it was the leading cause of kidney disease. Among the identified secondary causes of FSGS were found 8 miscellaneous (5 cases due to hypertensive nephrosclerosis, and 3 due to functional and structural adaptations), 4 hemodynamic (obesity), 2 due to drugs, 1 inflammatory (lung-kidney syndrome) and 1 due to virus (HIV). Of all the ca-

ses of patients with nephrotic syndrome, FSGS was the main cause (38.8 %, 7); and of all cases of non-nephrotic proteinuria, it was the second cause (24 %, 13), after IgAN. TIN was the main cause of AKI in 29.3 % (5). In patients older than 65 years, it ranked second among nephropathies. The main causes of TIN are described in Table 1.

**Table 1.** Causes of tubulointerstitial nephritis.

| Causes of tubulointerstitial nephritis | Number of patients |
|---|---|
| Analgesic agents | 10 |
| Atherosclerotic ischemic renal disease | 4 |
| Urinary infection | 3 |
| Hiperuricemia | 2 |
| No clear cause | 2 |
| Aminoglycosides | 2 |
| Obstructive uropathy | 1 |
| Sjögren's syndrome | 1 |
| Phenytoin | 1 |
| **Total sum** | **26** |

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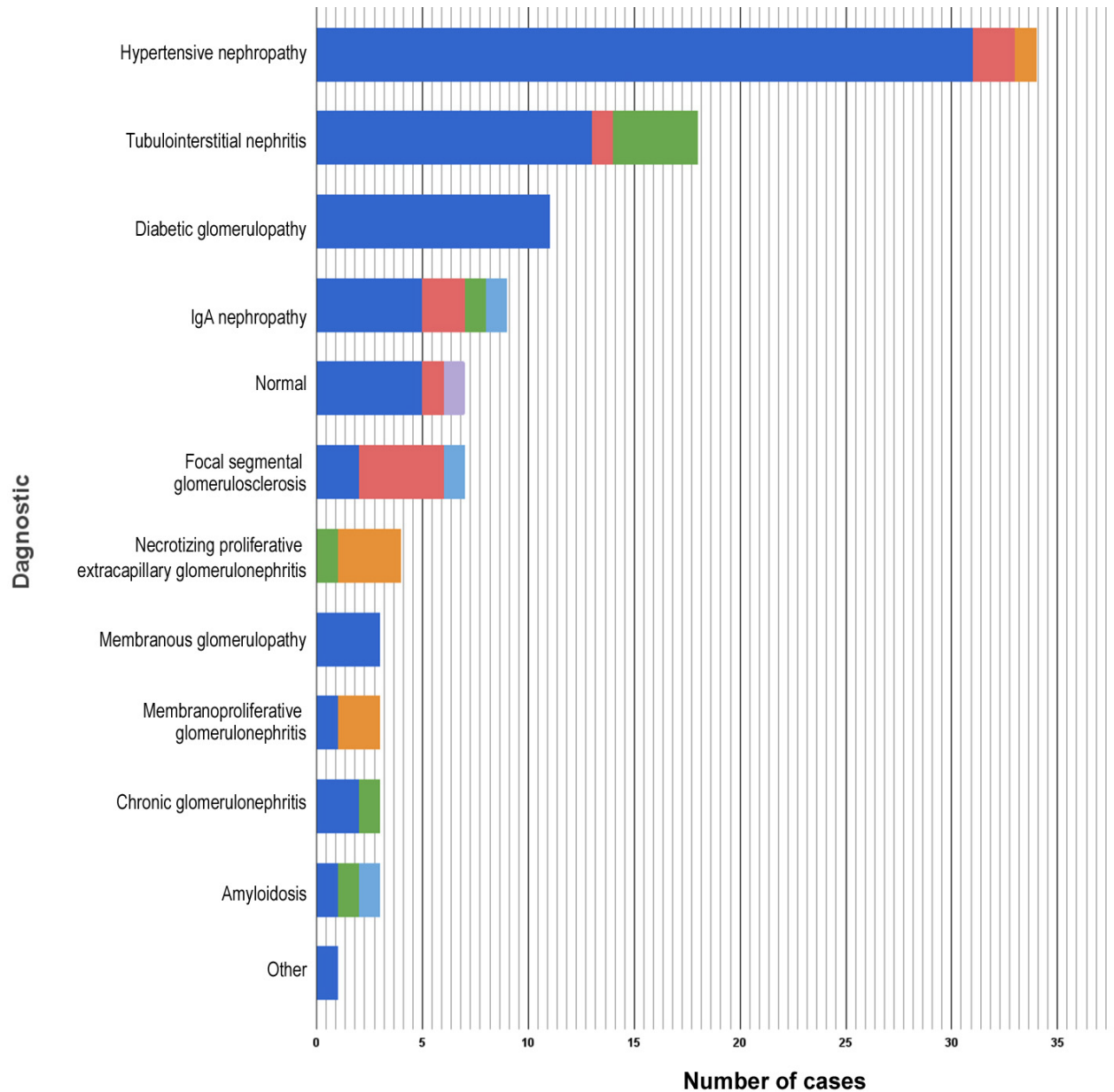
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**Figure 2.** Renal syndrome according to the diagnosis of renal disease in all patients.

Diabetic glomerulopathy was the second cause in patients with CKD with no clear cause (14.2 %, 18).

There were 3 cases of MPGN of secondary etiology, 2 cases associated with autoimmune disease (cryoglobulinemia and Sjögren's

**Figura 3.** Síndrome renal según el diagnóstico de enfermedad renal en pacientes mayores de 65 años.

syndrome) and 1 case associated with neoplastic process. EPGN was the main cause of nephritic syndrome (27.2 %). Of the 9 cases, 7 had pauci-immune causes, 1 due to immunocomplexes and 1 with no data. Of the GMNM, 7 cases corresponded to primary etiologies and 1 to a secondary cause related to autoimmunity. Of the 6 cases of amyloidosis, 4 corresponded to amyloidosis type AL (2 due to multiple myeloma) and two cases to primary forms (AA and another not determined). The 4 cases of hereditary diseases corresponded to thin basement membrane disease. In the category of other glomerular diseases, there were 2 cases of IgM nephropathy, 2 cases of mesangioproliferative GMN and 1 case of fibrillary glomerulopathy. The medians of creatinine, GFR and 24-hour proteinuria for each histological finding are described in Table 2.

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**Table 2.** Median of creatinine eGFR, TFGe CKD-EPI and proteinuria according to the histological finding.

| Histological finding | Median of creatinine (mg/dl) | Median of TFGe CKD-EPI (ml/min) | Median of proteinuria (mg/24 hours) |
|---|---|---|---|
| Hypertensive nephropathy | 1.63 | 38.3 | 150 |
| IgA nephropathy | 1.39 | 52.6 | 324 |
| Normal | 1.29 | 58.3 | 66 |
| Tubulointerstitial nephritis | 1.72 | 34.8 | 367 |
| Diabetic glomerulopathy | 1.6 | 34.6 | 207 |
| Focal and segmental glomerulopathy | 1.5 | 41.3 | 688 |
| Necrotizing proliferative extracapillary glomerulonephritis | 3.86 | 13 | 3126 |
| Chronic glomerulonephritis | 1.67 | 39.5 | 366 |
| Membranous glomerulopathy | 2.21 | 32.6 | 286 |
| Membranoproliferative glomerulonephritis | 3.79 | 14.2 | 958 |
| Amyloidosis | 3.38 | 16.5 | 1160 |
| Minimal change disease | 1.14 | 53.7 | Without value |

## Discussion

The renal syndromes indicate alterations in the renal functional and morphological integrity that are confirmed in the histological diagnosis with biopsy.[1] In addition to identifying potentially treatable lesions,[5] the renal biopsy provides information to establish the epidemiology of renal parenchymal diseases.[3]

Although IgAN has been the most prevalent glomerulopathy described worldwide, MGN and FSGS are the most common in other countries.[9] This variation depends on the predominant ethnic group in the population: in Asians, IgAN is more frequent;[10] while in African-Americans it is the FSGS.[11]

In the study of Sim et al.[9] in North America, the most common glomerulopathy was the FSGS (38.9 %), followed by MGN (12.7 %). In the African-American population, the most frequent disease was FSGS (49.8 %). The distribution in non-Hispanic Whites was similar, since FSGS prevailed (35.9 %), followed by the MGN (14.5 %) and MCD (11.9 %). In the Asian patients, the FSGS (41.5 %) and IgAN (23.5 %) were the most frequent. Finally, FSGS (36 %) and MGN (12.5 %) were the most recurrent in Hispanics.

In patients older than 60 years, Bomback et al.[4] describe the nephrotic syndrome as the most frequent indication for biopsy, and the MGN is the most common finding (32.1 %). Amyloidosis is the second cause, followed by MCD. In very elderly patients or older than 80 years, the most frequent diagnoses are variable in the literature. The described causes include MGN, pauci-immune glomerulonephritis and benign nephrosclerosis.[12]

In Argentina, Arenas et al.[13] reported renal failure with alterations in the urinary sediment (azotemia plus proteinuria and hematuria), followed by nephrotic syndrome and isolated proteinuria as the main indications for biopsy. The main diagnoses were lupus GN and mesangial proliferative GN without deposition of IgA.

In Lima, Peru, Hurtado et al.[14] described as the most common glomerular disease, the secondary to SLE, followed by MGN and FSGS. IgAN was infrequent. In Brazil, Cruz et al.[15] reported that the FSGS was the most frequent finding, followed by MGM. IgAN, MCD and MGN had a low frequency.

In Colombia, the study conducted by Mejía et al.[16] in Medellin, Antioquia, has the largest sample

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collected so far, with 383 biopsies. The most frequent indications for renal biopsy were nephrotic syndrome (42 %), glomerulonephritis (28.2 %) and isolated hematuria (19.8 %). The most frequent glomerulopathies were MCD (30 %), FSGS (21.1 %) and diffuse endocapillary proliferative glomerulonephritis (10.4 %). The main secondary pathology was lupus. The FSGS appeared mainly as nephrotic syndrome (69.2 %), as well as in MGN (74.3 %). However, in this report the sample was studied by immunofluorescence (IF) only in some cases, and none by electron microscopy (EM).

The study by Gómez-Jiménez et al.,[17] conducted in Medellin, Antioquia, reports the biopsies of 11 pregnant patients. There were 4 cases of lupus nephritis, 2 patients with RPGN due to extracapillary GN and granulomatous polyangiitis and 3 with nephrotic syndrome due to FSGS.

The study of Serna-Flórez et al.[18] in Armenia, Quindío, included 168 patients. The main primary glomerulopathies were FSGS (17.58 %), IgAN (17.58 %), MGN (14.29 %) and minimal change disease (13.19 %). In patients older than 60 years, the main was FSGS (37.5 %). The secondary glomerulopathies (14.95 %) were mainly represented by lupus nephropathy (81.25 %). In the study is not specified if the total of biopsies were submitted to study by IF and EM.

The study of Coronado et al.[19] in Ibague, Tolima, included 181 patients. The indications for biopsy, in their order, were nephrotic syndrome (35.51 %), followed by renal failure (32.7 %). All biopsies were analyzed by immunohistochemistry, and 97.24 % by electron microscopy. The diagnoses of glomerulopathy were, in their order lupus GN (27.6 %), MGN (18.2 %), FSGS (14.9 %), chronic nephropathy (6 %), IgAN (5.5 %) and MCD (4.9 %).

Our study is the fifth in Colombia that describes the findings of a series of renal biopsies. Unlike the report of Mejía et al.,[16] only the samples that were submitted to studies with light microscopy, IF and EM were selected. This work also differs from the study of Coronado et al.,[19] in which patients with lupus nephritis were excluded. It is the first that

differentiates primary and secondary renal diseases and reports them separately for the group of patients older than 65 years.

The average age was higher, compared with that reported in other national[16,17,18,19] and international studies.[13,14,15] The median creatinine was higher and the GFR lower, compared with the Colombian studies of Serna-Flórez et al.[11] and Coronado et al.[12]

In this study, the CKD with no clear cause was the main indication for biopsy. The advanced age of the population and the non-inclusion of patients with lupus nephropathy would explain this finding. Non-nephrotic proteinuria ranked second as an indication for biopsy and remained, although to a lesser extent, in those patients older than 65 years. The nephrotic syndrome occupied a less frequent role (sixth cause in the general population and fifth in those patients older than 65 years).

The nephritic syndrome occupied the third place as a form of clinical presentation. On the contrary, AKI is the third cause in patients over 65 years (7.8 %). There was only one case of glomerular hematuria with change in the pattern in individuals older than 65 years.

In this case series, IgAN was the most frequent histological finding, similar to the majority of populations in the world,[9,20] but different from previous Latin American studies.[13-19] Usually, the most frequent clinical presentation in young people is hematuria, and abnormal sediment in the elderly.[21]

In this study, non-nephrotic proteinuria, CKD with no clear cause in a similar proportion and glomerular hematuria with change in the pattern were the main forms of clinical presentation.

The diagnosis of hypertensive nephrosclerosis increases with age.[22] However, the diagnosis is usually made clinically due to the rejection to perform a renal biopsy in this population.[23] In this study, it was de second histological finding in the whole sample and the main in patients older than 65 years.

In the adults with proteinuria who underwent renal biopsy, the FSGS accounts for 35 % of cases.[24]

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In this study, in the patients with nephrotic syndrome, FSGS was the main finding (38.8 %) and non-nephrotic proteinuria occurred in 24 % of cases. Unlike the previous studies in Colombia[16-19] and those in Latin America[13-15] which report frequencies of up to 5 %, in this study 9.7 % were histological findings. In patients older than 65 years it was more frequent (17.5 %).

As described in the literature,[25] the main cause of TIN in this study were the analgesics associated with the management of joint diseases (38.8 %). The renal and atherosclerotic renal disease, more common in elderly people, occupied the second place (15.3 %).

In diabetes mellitus, the biopsy is not routinely indicated in all cases, especially in patients with a history and progression typical of the disease (progression in the decrease in GFR and persistent albuminuria). The indication is in case of suspicion or another kidney disease or if there are atypical characteristics present.[26,27] The group of patients of this study represents the atypical presentation which is manifested mainly as CKD with no clear cause and as the only manifestation in those older than 65 years.

This study had the second largest sample in Colombia, the definitions of the renal syndromes are similar to those of previous studies and only biopsies with the three studies (light microscopy, immunofluorescence and electron microscopy) were included.

However, associations cannot be made, since it is a descriptive case series study. Therefore, further studies are required in Colombia. In addition, patients with lupus nephropathy, which plays and important role as a cause of secondary nephropathy, were not included. Finally, the type of study increases the risk of bias and, being a convenience sample, it is not possible to generalize to the Caldense population and, therefore, to the population of Caldas, and therefore, to the Colombian population.

Studies that allow to evaluate associations between renal indications and different glomerulopathies are required. The current results and those of the previous studies at national level are the available tools to have a pretest probability when there is a patient with a renal syndrome and the suspicion of renal parenchymal disease.

# Conflict of interest

The authors declare that they do not have any current or potential conflict of interest.

# Ethical responsibilities

### Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

### Data confidentiality

The authors declare that they have followed the protocols of their workplace on the publication of patient data.

### Right to privacy and informed consent

The authors declare that patient data do not appear in this article

# Contribution of the authors

It is stated that the authors had participated in the design, implementation and interpretation of the results.

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