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ORIGINAL ARTICLE

# Changing trends in presentation and indications of biopsy in lupus nephritis: data from the Spanish Registry of Glomerulonephritis

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## ABSTRACT

**Background.** With the ageing population and changes in the indications of diagnostic and protocol biopsies in systemic lupus erythematosus in recent years, an impact on the incidence and presentation of lupus nephritis (LN) is expected. The aim of this study was to analyse the epidemiological changes regarding clinical and histological presentation of LN in kidney biopsies performed from 1994 to 2019 included in the Spanish Registry of Glomerulonephritis.

**Methods.** We analysed data from 28 791 kidney biopsies from 130 Spanish hospitals comparing demographic, clinical and histological data. We divided the cohort according to the age of onset of LN into pediatric onset (<18 years), adult onset (18–50 years) and late onset (>50 years).

**Results.** The incidence of LN has decreased from 9.6% of all kidney biopsies in the period 1994–2013 to 7% in the last quarter of the observation period (2014–2019) ($P < 0.001$), despite an increase in the proportion of patients with LN that underwent repeat biopsies (16.6–24%; $P < 0.001$). The age of onset of LN has increased from $32 \pm 14$ to $38 \pm 14$ years ($P < 0.001$), with an increase in the proportion of late-onset LN (from 13% to 22% of incident LN; $P < 0.001$). There were no differences in the distribution of histological features at presentation over the study period. Patients with late-onset LN showed fewer gender differences, had lower GFR and presented with less-proliferative forms of LN compared with early-onset LN.

**Conclusions.** The frequency of biopsy-proven LN has been decreasing in recent years, despite an increasing number of repeat biopsies. Late-onset LN is increasing, presenting with worse kidney function but fewer proliferative lesions compared with younger-onset LN.

**Keywords:** age, epidemiology, glomerulonephritis, late-onset lupus nephritis, systemic lupus erythematosus

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## INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease associated with a wide spectrum of clinical and immunological manifestations, with lupus nephritis (LN) being one of the most frequent manifestations that entails an increased morbidity and mortality [1]. The presence of proteinuria, hematuria or a decline in kidney function in a patient with SLE indicates the onset of renal involvement, which should be confirmed with a kidney biopsy. The poor correlation between the clinical manifestations and renal involvement of lupus is recognized, and for this reason renal biopsy has always been considered a basic element for the diagnosis and follow-up of patients with LN. Over time, different classifications have been proposed [2] with the intention of not only establishing the diagnosis of renal involvement in SLE, but also providing information on activity and chronicity that aids in guiding the therapeutic strategy and predicting prognosis.

Epidemiological studies worldwide have revealed considerable variations in the incidence and prevalence of SLE, probably reflecting differences in the risk of SLE development related to ethnic and genetic factors and differences in methodology [3]. Few studies exist on the epidemiology of LN [4–7].

Three major guidelines for the management of LN, the American College of Rheumatology (ACR) guideline [8], the Kidney Disease: Improving Global Outcomes (KDIGO) guideline [9] and the Joint European League Against Rheumatism/European Renal Association–European Dialysis and Transplantation Association (EULAR/ERA-EDTA) guideline [10], base their recommendations on the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification system. However, the current approach to the management of LN is based on steroids and other non-specific immunosuppressive drugs, and the histological findings in renal biopsy do not usually modify the preselected treatment in most cases. For this reason, scepticism about the currently used classification has grown in the last decade [11–14].

LN can present in many different ways, with various subtleties depending on age. In 15% of all patients with SLE, the diagnosis is made before 18 years of age [15]. Late-onset SLE represents a specific subtype of the disease, typically defined as SLE appearing after 50 years of age. Late-onset SLE affects 12–18% of the SLE population [16]. The clinical course of SLE is thought to be more benign in the late-onset form than in the early-onset form, and previous studies have shown greater immunological activity and a more aggressive course of LN in younger populations than when it appears later in life [17, 18].

The objective of this study was to describe the changes in the indications for renal biopsy in SLE, the epidemiological changes regarding the age of onset of LN and its histological types over a period of 26 years (1994–2019).

## MATERIALS AND METHODS

The Spanish Registry of Glomerulonephritis began collecting data on patients undergoing a native kidney biopsy in 1994 and is still ongoing. It records clinical and histological data from kidney biopsies performed in 130 Spanish hospitals. It includes 28 791 native kidney biopsies (26 593 first biopsies and 2198 repeat biopsies) collected over a span of 26 years until 2019.

In this study we analysed patients with a diagnosis of LN from the kidney biopsy. We studied the frequency of LN and repeat biopsies for these patients throughout the study period. To study the effect of age on clinical and histological features, we excluded repeat biopsies and patients without age records. Patients were divided into three groups according to the age at the time of biopsy: pediatric-onset LN (<18 years), adult-onset LN (18–50 years) and late-onset LN (>50 years).

Given that the registry includes information over a long period of time (26 years), in order to detect changes in trends in clinical and histological presentations, we arbitrarily divided our analysis into four time periods: 1994–2000, 2001–2007, 2008–2013 and 2014–2019.

The demographic, clinical and histological data were obtained from the registry and included date of birth, sex, date of biopsy, serum creatinine (mg/dL), estimated glomerular filtration rate (eGFR), proteinuria (g/24 h), hypertension and urinary sediment and histological analysis (optical microscopy and immunofluorescence, with or without electron microscopy). The clinical syndrome at presentation was recorded using the following definitions: acute kidney injury (AKI): defined according to the KDIGO guidelines as an increase in serum creatinine ≥1.5 times baseline; nephrotic syndrome: proteinuria ≥3.5 g/day along with hypoalbuminemia (<2.5 g/dL), hyperlipidemia and oedema; nephritic syndrome: oliguric AKI with hypertension, haematuria with or without oedema; asymptomatic urinary abnormalities: proteinuria and/or haematuria, with normal glomerular filtration rate (GFR) and without clinical symptoms; arterial hypertension: blood pressure ≥140/90 mmHg or use of antihypertensive medications regardless of blood pressure; and chronic kidney disease (CKD): eGFR <60 mL/min for >3 months.

### Statistical analysis

The statistical analysis was performed using SPSS version 16.0 (IBM, Armonk, NY, USA). The normal distribution of samples was determined by using the Kolmogorov–Smirnov test. Values are expressed as mean ± standard deviation (SD) when the distribution is normal or as median [interquartile range (IQR)] when they do not follow a normal distribution. Qualitative variables were compared by using either a chi-squared test or Fisher's exact test. Quantitative data were compared using independent samples *t*-tests when normally distributed or Mann–Whitney tests for non-parametric variables. P-values <0.05 were considered statistically significant.

## RESULTS

The Spanish Registry of Glomerulonephritis has reported 28 791 kidney biopsies between 1994 and 2019, with a diagnosis of LN in 2580 biopsies (9%); 2052 biopsies (7.1%) were first biopsies and 528 (1.8%) were repeat biopsies. Most patients presented with LN with the classic adult-onset [$n = 1556$ (75.5%)], while 329 patients (16%) had a later onset of disease and 175 patients (8.5%) presented LN at a pediatric age (Figure 1).

The incidence of LN gradually decreased from 104 patients/year to 86 patients/year over the study period, and the frequency of diagnosis of LN within the total number of kidney biopsies significantly decreased in the period 2014–2019 (7% of total biopsies) compared with the previous years (9.6% from 1994 to 2013) ($P = 0.0001$). This decline in incidence was mainly due to a reduction in first kidney biopsies (31%) ($P = 0.0001$), while the number of repeat kidney biopsies remained stable with respect to the total number of biopsies (Figure 2).

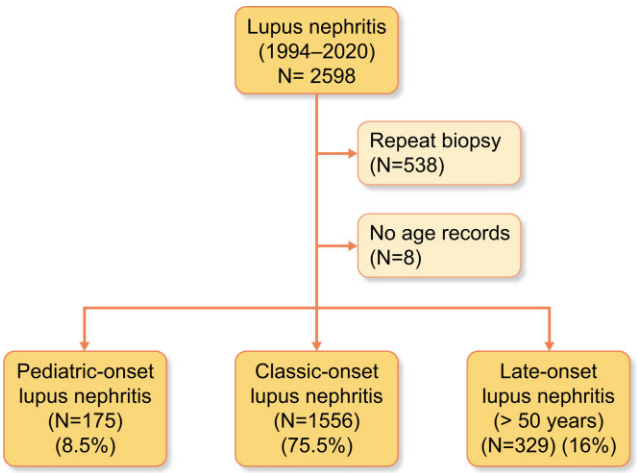


FIGURE 1: Flow chart of the study population.

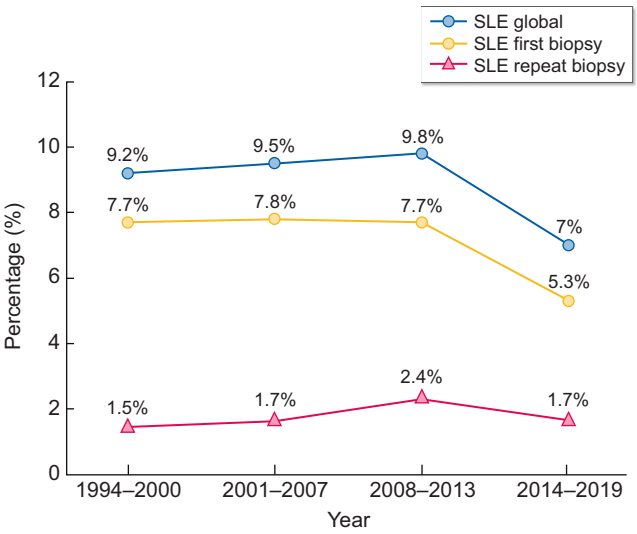


FIGURE 2: Prevalence of patients with LN out of the total number of biopsies throughout the study period.

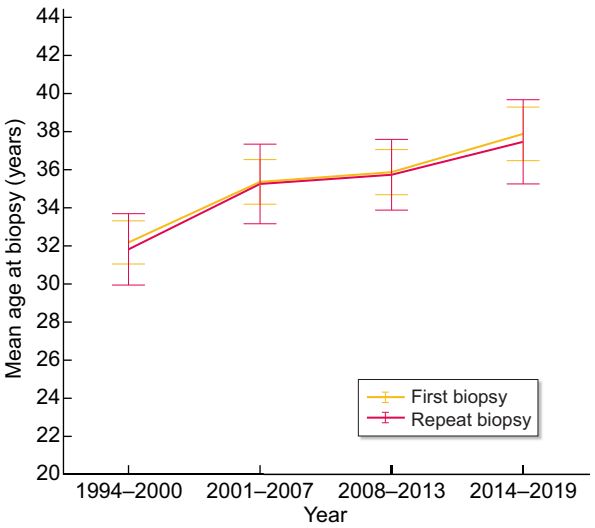


FIGURE 3: Changes in mean age at the time of biopsy over the study period (comparing first biopsies to repeat biopsies).

## Changes in clinical presentation over time

Patients' characteristics at the time of biopsy have changed over time, as can be observed in Table 1. Kidney function tends to be more preserved and with less proteinuria over the last decade compared with previous years. The GFR at the time of biopsy has gradually increased from 74 to 80 mL/min/1.73 $m^2$ and proteinuria has decreased from 3.0 to 2.0 g/day. The presence of nephrotic syndrome as the indication for kidney biopsy has decreased from 42.6% of patients in 1994–2000 to 30.5% in 2014–2019 (P = 0.001), with non-nephrotic proteinuria remaining the most frequent indication for biopsy throughout all time periods.

The age of patients with SLE at the time of diagnosis of LN has progressively increased (Figure 3). In the period 1994–2000, 12.8% of patients were >50 years of age, which rose to 15.4% in 2001–2007 and 14.7% in 2008–2013 and increased to 21% in 2014–2019.

**Table 1. Changes in clinical characteristics over time in patients with LN**

| Characteristics | 1994–2000 | 2001–2007 | 2008–2013 | 2014–2019 | P-value |
|---|---|---|---|---|---|
| Kidney biopsies (*n*) | 7896 | 7052 | 6396 | 7447 | |
| Lupus nephritis, *n* (%) | 728 (9.2) | 707 (10) | 624 (9.8) | 521 (7.0) | <0.001 |
| Age (years), mean ± SD | 32.1 ± 13.6 | 35.3 ± 13.9 | 35.8 ± 12.7 | 37.8 ± 13.8 | <0.001 |
| Female:male ratio | 4.2:1 | 4.5:1 | 4.5:1 | 4:1 | 0.809 |
| Hypertension, *n* (%) | 261 (35.9) | 277 (39.2) | 242 (38.8) | 208 (39.9) | 0.437 |
| Serum creatinine (mg/dL), median (IQR) | 1 (0.8–1.5) | 1 (0.8–1.4) | 0.9 (0.7–1.3) | 0.9 (0.7–1.2) | <0.001 |
| eGFR (mL/min/1.73 $m^2$)[a], mean ± SD | 74.4 ± 34.5 | 78.7 ± 35.4 | 78.8 ± 36.5 | 80.5 ± 36.7 | 0.056 |
| Proteinuria (g/day), median (IQR) | 3 (1.7–5.2) | 3 (1.5–5) | 2 (1–4) | 2 (1–4.1) | <0.001 |
| eGFR <60 mL/min/1.73 $m^2$, *n* (%) | 158 (32.8) | 160 (30.2) | 161 (30.7) | 151 (29.9) | 0.752 |
| Kidney biopsy indication, *n* (%) | | | | | |
| Non-nephrotic proteinuria | 283 (41.3) | 229 (33.3) | 273 (44.1) | 241 (46.3) | 0.001 |
| Nephrotic syndrome | 292 (42.6) | 299 (43.5) | 212 (34.2) | 159 (30.5) | <0.001 |
| Nephritic syndrome | 43 (6.3) | 67 (9.7) | 62 (10) | 66 (12.7) | <0.001 |
| CKD | 24 (3.5) | 35 (5.1) | 30 (4.8) | 19 (3.6) | 0.3 |
| AKI | 35 (5.1) | 50 (7.3) | 33 (5.3) | 34 (6.5) | 0.25 |
| Others | 51 (7) | 27 (3.8) | 14 (2.2) | 2 (0.4) | 0.001 |

[a]Calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.

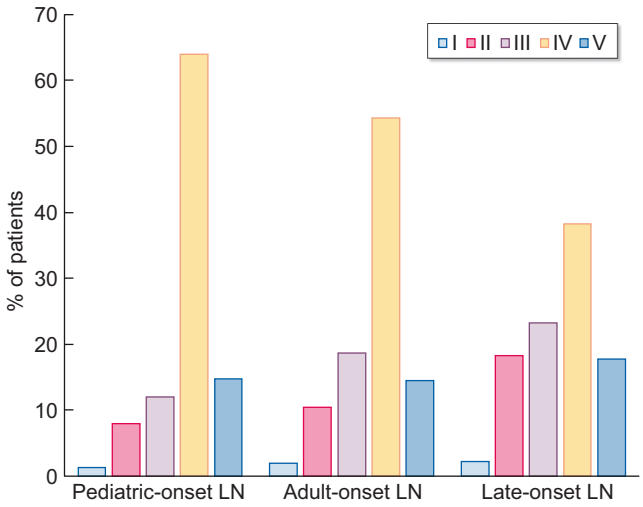


**FIGURE 4:** Distribution of ISN/RPS LN histological classes at presentation according to age of onset.

## Differences according to age of presentation

Table 2 shows the comparison in clinical characteristics according to the age at the time of diagnosis of LN. The GFR of patients >50 years of age was 61.5 mL/min/1.73 $m^2$, which was significantly lower than the eGFR of adult patients diagnosed with LN at an age of <50 years and pediatric patients (81 and 94 mL/min, respectively; P = 0.001). The proportion of patients presenting with hypertension was higher in older patients (58.7% versus 31%; P < 0.001). There were no differences in proteinuria. Regarding the indication for biopsy, AKI (10.9% versus 4.9%; P < 0.001) and progressive CKD (6.1 versus 2.9%; P < 0.001) were more frequent in older patients than in adult younger patients. There were no differences in other forms of clinical presentations. The most frequent presentation was still non-nephrotic proteinuria (40.1% in late-onset LN versus 41.5% in adult-onset LN and 44.2% in pediatric LN) followed by nephrotic syndrome (32.2%, 36.1% and 40%, respectively; P = 0.20) in all age groups. Gender differences were significantly lower in late-onset LN, with a female:male ratio of 2.7:1 compared with pediatric onset (3.4:1) and classic adult-onset LN (4.9:1) (P = 0.009).

The number of patients diagnosed with LN >65 years of age was small ($n$ = 85). In these patients, the trends observed were similar to those for patients between 50 and 65 years old, showing a reduction in gender differences (2.2:1), lower eGFR at presentation (41 mL/min/1.73 $m^2$) and an increased proportion of patients presenting with AKI (23% in >65 years compared with 10% in 50–65 years and 5% in <50 years; P < 0.01).

## Histological classes

Most patients presented with proliferative classes of LN. The most frequent histological class was class IV (52%), followed by class III (19%). Only 16% of patients presented class V, while a minority presented class II (12%) or class I (2%). Diagnosis was achieved after a histological analysis with optical microscopy and immunofluorescence, with a minority of patients [417 (16%)] in which electron microscopy was performed. This distribution of histological lesions at presentation did not change over time and was similar to that found at repeat biopsies. However, differences in the distribution of histological classes were observed according to age. In pediatric LN, 61% presented with class IV LN, which decreased to 57% of patients between 18 and 30 years and 51% between 30 and 50 years, whereas only 31% of patients >50 years of age presented with class IV. This decrease was compensated for between classes II and III, with a stable frequency of class I and V throughout all age groups (Figure 4).

## Repeat biopsies

Repeat biopsies accounted for 20.5% of kidney biopsies with a diagnosis of LN. A slight trend towards an increase in the indication of repeat biopsies was observed throughout the study period, increasing from 16.6% in 1994–2000 to 24% in 2014–2019 (P < 0.001). Unlike first biopsies, the most frequent indication for repeat biopsies through all time periods was the onset of nephrotic syndrome (43% versus 36%; P < 0.001).

# DISCUSSION

This study reveals that the frequency of LN among all kidney biopsies has decreased in recent years, whereas the age of presentation is increasing. It is arguable whether this represents a real decrease in the frequency of renal manifestations of SLE or

**Table 2. Clinical characteristics according to the age at diagnosis**

| Characteristics | <18 years (pediatric onset) ($n$ = 175) | 18–50 years (adult onset) ($n$ = 1556) | >50 years (late onset) ($n$ = 329) | P-value |
|---|---|---|---|---|
| Age (years), mean ± SD | 14.4 ± 2.7 | 32.2 ± 8.3 | 59.4 ± 8.0 | <0.001 |
| Female:male ratio | 3.4:1 | 4.7:1 | 2.9:1 | 0.009 |
| Hypertension, $n$ (%) | 54 (30.9) | 495 (31.8) | 193 (58.7) | <0.001 |
| Serum creatinine (mg/dL), median (IQR) | 0.8 (0.67–1) | 0.9 (0.71–1.24) | 1.1 (0.86–1.7) | <0.001 |
| eGFR (mL/min/1.73 $m^2$)[a], mean ± SD | 94 ± 40.6 | 82.7 ± 34.3 | 61.5 ± 33.4 | <0.001 |
| eGFR <60 mL/min/1.73 $m^2$, $n$ (%) | 41 (20) | 427 (28.1) | 168 (51.1) | <0.001 |
| Proteinuria (g/24 h), median (IQR) | 3.4 (2.1–4.9) | 2.6 (1.2–4.7) | 2.4 (1.1–4.6) | 0.60 |
| Kidney biopsy indication, $n$ (%) | | | | |
| Non-nephrotic proteinuria | 78 (44.6) | 646 (41.5) | 132 (40.1) | <0.001 |
| Nephrotic syndrome | 70 (40) | 561 (36.1) | 106 (32.2) | 0.20 |
| Nephritic syndrome | 17 (9.7) | 150 (9.6) | 28 (8.5) | 0.81 |
| CKD | 2 (1.1) | 45 (2.9) | 20 (6.1) | <0.001 |
| AKI | 8 (3.7) | 74 (4.9) | 36 (10.9) | <0.001 |
| Other | 0 | 80 (5.1) | 7 (2.1) | 0.60 |

[a]Calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.

if it is due to a decreased tendency to biopsy patients with suspected LN. A population-based cohort study of SLE in Norway also showed a decreased incidence of LN between 1978 and 2006, and it was associated to an increased use of antihypertensive drugs, suggesting that the use of early nephroprotective measures could be behind this recent decrease in the incidence of renal manifestations [4].

Although clinical guidelines base their therapeutic algorithms according to the histological subclass, there is consensus in recognizing that the histological information offered by the renal biopsy at the time of diagnosis should be more ambitious, so that the biopsy could provide data that would offer real therapeutic and prognostic implications. Currently there is sufficient evidence that indicates that classes I and II have better outcomes compared with classes III, IV and V. However, few studies have described differences in the outcomes of classes III and IV with class V, which constitute the majority of LN cases. In a Dutch study that included 105 patients with LN (91% with class III or IV) between 1987 and 2011 and followed for a median of 9.9 years, the ISN/RPS classification was poorly associated with clinically relevant outcomes [19].

Some authors have stated the need to expand the aspects to be considered in a renal biopsy for SLE patients [20]. It has been considered that the ISN/RPS classification of LN might be too glomerulocentric and concentrated only on the evaluation of endocapillary (compared with extracapillary) proliferation, missing other important elements such as podocyte lesions, the presence of crescents, thrombotic microangiopathy or interstitial fibrosis that are well-known predictors of outcome in most CKDs. Moreover, different studies have shown that a detailed analysis of infiltrating cell populations (e.g. CD163) could also provide useful information to predict prognosis [21].

There is a broader and growing consensus on the need to perform repeat kidney biopsies in patients with LN, and it has even been proposed to establish the performance of protocol biopsies for these patients [22]. In our study, we observed a slight increase in the indication of repeat biopsies, although most of these biopsies were indicated due to suspected relapses. The most frequent cause for rebiopsy was the onset of nephrotic syndrome, which was more frequent in repeat biopsies than in first biopsies.

On the other hand, the importance of renal biopsy in deciding the duration of maintenance treatment has been emphasized in recent years. A cohort of 76 patients with classes III and IV LN who underwent a second renal biopsy after receiving at least 42 months of immunosuppressive treatment without clinical activity data for the last year, with the intention of discontinuing immunosuppression, showed that the outcome of these patients was remarkably favourable, with a reduction in relapses of 9.2%, with a median follow-up of 96 months. This study highlighted the poor correlation between clinical data and histological activity; 30% of the patients with remission of proteinuria had data of histological activity and half of the patients with persistent proteinuria had histological remission [23].

Although SLE is a disease that typically affects the young population, and renal involvement is more frequent in the early-onset forms [24], our study shows that the mean age at diagnosis of LN is increasing; 20% of the cases were diagnosed in those >50 years of age, with varied clinical presentations and less severe histological forms but with a greater compromise of renal function, which suggests that these patients would probably benefit from a differentiated therapeutic approach than those with a standard younger onset of the disease.

Previous retrospective studies have shown that early-onset SLE has a worse outcome than late-onset SLE, with a poor course and higher mortality [24–27]. However, late-onset LN has been rarely described in the literature, with an incidence of <2% of total SLE patients in small case series [28]. In our study, patients with late-onset LN had lower eGFR at presentation and histological class IV was less frequent in older patients compared with other age groups. These results agree with the few studies that have compared early with late onset [29–31]. The studies that have analysed differences in indices across age groups reported lower activity and chronicity scores in late-onset LN [29, 30]. We could not confirm these differences in this study since the registry did not include activity and chronicity indices in kidney biopsies. These differences reaffirm the necessity of performing kidney biopsies to pursue an individualized treatment approach for LN patients, avoiding unnecessary immunosuppressive treatment and optimizing therapy to target delay in the progression of CKD.

Our study has some limitations. The data obtained come from a national registry of kidney biopsies that lacks more specific clinical and histological information, as well as information regarding treatments received and outcomes. The incidence and severity of LN are affected by ethnicity; however, we could not determine its effect on our cohort since data regarding race are not recorded in the registry, although we can assume that the majority of patients included in our population are of white race. Nevertheless, this study provides a large number of kidney biopsies sufficient to draw valid conclusions regarding the epidemiological trends in LN in Spain.

In conclusion, the frequency of LN diagnosed by a kidney biopsy has decreased in recent years. On the other hand, the incidence of late-onset LN is increasing, with different clinical and histological presentations compared with a standard younger-onset LN. Therefore we suggest considering a more personalized approach in the management of late-onset LN. A thorough review of the histological aspects that provide prognostic implications is required to help guide therapeutic decisions and thereby improve outcomes in LN.

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## AUTHORS' CONTRIBUTIONS

A.S. and G.F.J. were responsible for the research idea and study design, statistical analysis, draft preparation and editing. G.F.J. was responsible for supervision and mentorship. E.L.T. and J.E.S.A were responsible for validation. A.S. was responsible for the formal analysis. J.E.S.A. and G.F.J. were responsible for resources. A.S. was responsible for data curation. All authors were responsible for reviewing the manuscript.

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## CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest to disclose.

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