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Prediction model for renal outcomes in Latin American Mestizo patients with pure proliferative lupus nephritis

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ABSTRACT

Objective Lupus nephritis (LN) is associated with a poorer prognosis in Latin American populations. However, the contributing risk factors contributing to this remain to be fully elucidated. This study aimed to develop a prognostic model for poor renal outcomes in patients of mestizo descent.

Methods We conducted a multicentre, retrospective analysis including 290 adult mestizo patients with incident, biopsy-proven pure proliferative LN (International Society of Nephrology/Renal Pathology Society (ISN/RPS) class III or IV) from nine Chilean hospitals. Clinical, biological and histological variables were assessed. The primary outcome was a composite of stage IV/V chronic kidney disease, dialysis or death. Predictive variables were selected using multivariable Cox regression, and prognostic scores were derived accordingly. Internal validation was performed via bootstrapping. External validation included 93 Mexican patients, with model performance assessed using Harrel's concordance index.

Results Two baseline factors were independently associated with poor renal outcome: estimated glomerular filtration rate <30 mL/min/m^2 (HR 3.82, 95% CI 2.15 to 6.78; p<0.001) and histological chronicity index >2 (HR 2.01, 95% CI 1.18 to 3.43; p=0.01). Patients were stratified into three risk categories according to the presence of none (low risk), one (intermediate risk) or both (high risk) of these factors. The likelihood of the primary outcome increased progressively across these groups: high versus intermediate risk (HR 3.22, 95% CI 1.64 to 6.34; p=0.001), and intermediate versus low risk group (HR 2.41, 95% CI 1.35 to 4.30; p=0.003). The three-tier model was replicated in the validation cohort with a concordance index of 79% (95% CI 71% to 87%; p<0.001) between predicted and observed results.

Conclusions Based on two readily available features at the time of diagnosis, the proposed model effectively stratifies Latin American mestizo patients with pure proliferative LN (ISN/RPS class III or IV) into three risk categories for poor renal outcome. This tool may support improved risk-based management in this high-risk population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Lupus nephritis (LN) is a serious complication of SLE, particularly prevalent and severe in Latin American populations of mestizo descent. While poor renal function at LN diagnosis and certain histopathological features have been recognised as predictors of progression to end-stage renal disease, specific risk factors and validated prognostic models tailored to the mestizo population are lacking, limiting clinicians' ability to stratify risk and personalise management in this group.

WHAT THIS STUDY ADDS

⇒ This study introduces and externally validates a simple, bedside-applicable clinical prediction model—the Score Mestizo—based on estimated glomerular filtration rate and the histological chronicity index at diagnosis of LN, which stratifies Latin American mestizo patients with proliferative LN (International Society of Nephrology/Renal Pathology Society class III or IV) into three distinct risk categories for adverse renal outcomes. The model's reproducibility and discrimination were confirmed in both Chilean and Mexican cohorts, providing the first robust, population-specific tool for early risk assessment in this under-represented group.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Implementation of the Score Mestizo could improve the management of LN in Latin American mestizo patients by enabling clinicians to identify high-risk individuals at diagnosis and tailor immunosuppression and monitoring intensity accordingly. The model's use may also facilitate more precise patient selection and stratification in future clinical trials, and inform policy and guideline development to address disparities in LN outcomes among Latin American populations.

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INTRODUCTION

SLE is a chronic, multisystem autoimmune disease, primarily affecting women of childbearing age. Renal involvement, known as lupus nephritis (LN), occurs in about 50% of patients during the course of the disease.[1] The presence of LN increases both morbidity and mortality in patients with SLE, highlighting the importance of early diagnosis and treatment to prevent irreversible organ damage.[2] Unfortunately, no single reliable biomarker currently exists to predict which patients will progress to end-stage renal disease (ESRD).[3] Therefore, identifying specific prognostic factors—whether clinical, histological or immunological—is essential for each population group.

LN shows geographical variability in both incidence and prognosis. Afro-descendant and Latin American patients have higher rates of LN and worse renal outcomes compared with Caucasians, who more often present with less severe class IV disease and better long-term prognosis.[4 5] However, the specific risk factors underlying the worse prognosis of Latin American patients with LN remain poorly defined. A key limitation in evaluating this population is that demographic studies involving Latin American populations often group several ethnic subgroups under the same umbrella, treating them as a single, homogeneous ethnic group. These subgroups include not only mestizos—the predominant group in Latin America—but also Afro-Latin Americans, Caucasian-Latin Americans and others. Additionally, they are often collectively referred to as 'Hispanics', a term derived from the language spoken rather than their ethnic origin.[6–8] This oversimplification creates confusion and hinders the identification of specific characteristics unique to each ethnic subgroup, which may vary significantly across Latin American countries.

These differences within the Latin American population can be intuited in the GLADEL cohort, a multinational study of patients with SLE, which included a high proportion of mestizo, Caucasian-Latin American and Afro-Latin American patients. In this cohort, mestizo and Afro-Latin American patients had a higher incidence of renal involvement compared with Caucasian-Latin Americans (those of European ancestry).[7] Genetic studies support these findings, showing that a higher percentage of genes of European ancestry provide protection against LN, while Amerindian and African ancestry increases the risk.[9] Additionally, patients with Amerindian or African ancestry tend to develop the disease at a younger age, suggesting a predisposition to present with more severe disease manifestations.[10 11]

Patients at high risk of ESRD are generally identified through different concomitant poor prognostic factors, whether clinical, histological or immunological. In subanalyses of the Euro-Lupus Nephritis Trial and the MAINTAIN trial (azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis), both predominantly composed of Caucasian patients, achieving proteinuria levels below 0.7–0.8 g/day at 12 months after treatment initiation was a strong predictor of favourable long-term renal outcomes.[12 13] Similar findings were reported in a subanalysis of the GLADEL cohort.[14] However, data on clinical and histological predictors of poor renal prognosis at presentation remain limited for the mestizo ethnic subgroup within Latin American patients. Indeed, despite therapeutic advances, 22% of patients with LN develop ESRD 15 years after diagnosis, rising to 44% among those with class IV LN.[15]

This study aimed to develop a clinical prediction model to estimate the risk of poor renal outcomes in Latin American mestizo patients, based on clinical and histological features assessed at the time of diagnosis of pure proliferative LN (International Society of Nephrology/Renal Pathology Society (ISN/RPS) class III or IV). The model was developed on data from a cohort of Chilean patients and externally validated in an independent cohort of Mexican patients.

MATERIALS AND METHODS

This retrospective study included 290 adult (≥18 years old) mestizo patients with a diagnosis of SLE, according to the 1982 revised American College of Rheumatology SLE classification criteria, and biopsy-proven incident (first flare) pure proliferative LN, classified as class III or IV, based on the 2003 ISN/RPS classification. To minimise confounding factors related to the degree of proteinuria, patients with membranous (class V) or mixed LN were excluded. These patients were jointly followed in nine Chilean Nephrology Departments from January 1999 to December 2023. External validation was performed in an independent cohort of 93 patients with LN diagnosed and managed in several Mexican hospitals between 2007 and 2023. All included patients underwent an initial renal biopsy at the onset of LN. Induction and maintenance treatment regimens were based on the European Alliance of Associations for Rheumatology/Kidney Disease Improving Global Outcomes (KDIGO) recommendations. The study was approved by the Clinical Research Ethics Committee of the Metropolitan Health Service of Eastern Santiago, Chile and the 'UMAE Hospital de Especialidades Dr. Bernardo Sepúlveda G', Mexico. Study registration at any clinical research database was not deemed necessary because of the retrospective methodology.

Clinical and laboratory variables

Mestizo ethnicity was assigned as self-reported by the patient in medical records. The following variables were retrieved from patients' medical records: demographic data (gender, ethnicity, age at SLE diagnosis and age at onset of renal involvement), smoking status and clinical variables related to LN, including arterial hypertension and renal function parameters. Renal function was assessed through serum creatinine and estimated glomerular filtration rate (eGFR), calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration

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(CKD-EPI) equation,[16] as well as 24 hours urine protein excretion (g/24 hours), haematuria (≥5 red blood cells/field) and the presence of urinary casts. Immunological parameters included serum anti-double-stranded DNA antibody levels, complement components 3 and 4 serum levels and anti-phospholipid (aPL) antibodies, namely lupus anticoagulant and IgG/IgM isotypes of anticardiolipin and anti-β2-glycoprotein I antibodies. Data on induction and maintenance treatment were also collected.

Renal pathology evaluation

Baseline kidney biopsies were evaluated by experienced nephropathologists, using light microscopy and immunofluorescence and classified according to the 2003 ISN/RPS classification of LN.[17] Biopsy samples were processed using H&E, periodic acid–Schiff, Masson's trichome and methenamine-silver staining; immunofluorescence reports scored intensity on a 0–3+scale. Renal activity and chronic damage were determined using the National Institutes of Health (NIH) activity index (AI) and chronicity index, respectively.[18] Interstitial fibrosis (IF) and tubular atrophy (TA) are defined as the IFTA score (absence of IFTA lesions in renal biopsy=0, <25%=1, 25–50%=2, >50%=3).[19] Findings of thrombotic microangiopathy in the context of aPL antibodies were also considered.

Definition of renal response and flare

We used the definitions of complete renal response, partial renal response and renal flare proposed by the kidney disease: Improving Global Outcomes guidelines 2024 Clinical Practice Guideline for the Management of LN.[20] Follow-up was defined as the time from the first kidney biopsy until the last outpatient appointment. Advanced CKD and ESRD according to the definition of the kidney disease: Improving Global Outcomes guidelines[21] or the need for dialysis and/or renal transplant and death were also recorded.

Data evaluated and outcomes

Initial variables and cut-off values investigated for prognostic assessment were selected based on clinical meaningfulness or having demonstrated prognostic value in previous studies. Among those reported in online supplemental table 1, variables were further selected for multivariable evaluation on the basis of (1) having a p<0.05 Bonferroni-adjusted association with the outcome, (2) being available in a majority of patients and (3) not being correlated with other selected variables (eg, eGFR and serum creatinine). In some cases, we selected the median value of the variable distribution (eg, activity and chronicity indexes) when no clinically meaningful cut-off was available.

The primary outcome was a composite of CKD stage IV/V (eGFR <30 mL/min/m^2) with or without dialysis, or death from any cause, whichever occurred first. The secondary outcome was the achievement of remission 1 year after diagnosis, as defined by 24-hour proteinuria <0.5 g and stable renal function (CKD stage improved, unchanged or eGFR worsened no more than one stage).

Statistical methods

Categorical variables were expressed as frequency and percentages and compared by the χ^2 test. Continuous variables were summarised by the median and IQR and statistically compared by the Mann-Whitney U-test. Survival and other time-to-event curves were drawn using the method of Kaplan and Meier. Prognostic factors were investigated by univariable and multivariable Cox regression and expressed as HR with the corresponding 95% CI. All Cox models were tested for the proportional hazards assumption by graphical methods and the Grambsch-Therneau test.[22] Statistical significance levels at the univariable exploratory screening were Bonferroni-adjusted to avoid spurious associations emerging by chance. All the statistical tests were performed with Stata, V.17 (www.stata.com).

We first conducted a univariable screening of all the variables listed above to investigate initial factors predictive of poor renal outcome. Those who achieved a Bonferroni-adjusted significant association were further investigated in multivariable regression models, guided by clinical relevance, the pattern of correlations among variables and model's simplicity. The balance between the model's complexity (number of covariates) and prediction capability was evaluated by means of the Akaike's information criteria and the likelihood ratio test.[23]

The replicability of the prognostic scoring models in the development cohort was tested by bootstrap resampling. One thousand samples, the same size as the original series, were built through random extraction with repositioning so that, in each sample, a given patient may either not be represented at all or represented once, twice or more times. The parameters assessed by resampling were the HRs of the prognostic factors identified at the Cox regression and the risk categories derived from combining such prognostic factors. Bootstrap resampling allows verifying that the prognostic factors identified by the Cox model and the derived prognostic categories were not critically dependent on the particular composition of the development cohort.

External validation was conducted in a cohort of pure proliferative patients with LN (ISN/RPS class III or IV) diagnosed and managed in several Mexican hospitals, and consisted of replicating the prognostic categories and their association with the main study outcome. Discrimination power in this validation cohort was measured through Harrell's concordance index and compared with values obtained in the development cohort. Harrell's C-index is the standard statistic for quantifying discrimination in right-censored time-to-event data and can be interpreted as equivalent to the area under the receiver operating characteristic curve.[24]

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RESULTS

The development cohort consisted of 290 patients of mestizo descent who were diagnosed with incident (first flare), pure proliferative LN (ISN/RPS class III or IV) in several Chilean hospitals between 1999 and 2023 and who met the inclusion criteria. The median age at the time of LN diagnosis was 28 years (IQR: 22–36), and 258 (89.0%) were females. Table 1 summarises the main features at diagnosis of LN.

Main outcome

After a median follow-up of 5.5 years (IQR: 2.1–10.0) from the diagnosis of LN, 89 (30.7%) patients achieved the main outcome (advanced CKD or death). The projected median time-to-outcome for the whole development cohort was 17.2 years (IQR: 12.1–27.4; figure 1) and was not significantly different between histological classes III and IV (16.4 years, 95% CI 11.3 to not reached and 18.8 years, 95% CI 10.9 to 30.7, respectively; p=0.51).

Factors predicting a poor renal outcome

Results of the exploratory univariable association between the presenting features and poor renal outcome are summarised in online supplemental table S1. Based on these results, variables selected for further multivariable analysis included haemoglobin <10 g/dL, serum creatinine >1.3 mg/dL, eGFR <30 mL/min/m^2, histological AI >10 and histological chronicity index >2. Because of the strong correlation between serum creatinine and eGFR (since the latter is inferred, among others, from the former) (Spearman's rho=0.90, p<0.001), we selected the eGFR as more appropriate since it considers also the age and sex (according to the CKD-EPI formula). After parsimonious backward elimination and reintroduction of candidate variables, the final prognostic model included two risk factors: eGFR at diagnosis <30 mL/min/m^2 (HR 3.82, 95% CI 2.15 to 6.78; p<0.001) and histological chronicity index >2 (HR 2.01, 95% CI 1.18 to 3.43; p=0.01).

eGFR and chronicity index were significantly correlated to each other (Spearman's rho=0.3730, p<0.001), so the question arose as to whether the histological chronicity index added significant information to a model based only on eGFR. We found that both the likelihood ratio test and the Akaike's information criteria supported keeping the histological chronicity index in the model (online supplemental table S2). Therefore, and for the sake of simplicity, we ascribed one point to each of eGFR <30 mL/min/m^2 and chronicity index >2. Three prognostic groups with significantly different probabilities of poor renal outcome emerged according to whether patients had none, one or two risk factors (table 2 and figure 2). Patients with one risk factor—intermediate risk—were 2.41 times more likely to experience the main outcome earlier compared with those with no risk factors—low risk—(HR 2.41, 95% CI 1.35 to 4.30; p=0.003). Similarly, patients with two risk factors—high risk—were 3.22 times more likely to experience the main outcome earlier compared with

Table 1 Clinical and histological features at presentation in 290 mestizo patients with pure proliferative lupus nephritis (ISN/RPS class III or IV) in several Chilean hospitals (development cohort)*

Age, years†	28 (22–36)
Age >50 years (late onset)	20 (6.9%)
Sex, female	258 (89.0%)
Years from diagnosis of lupus†	7 (0.2–60)
History of arterial hypertension	98 (40.2%)
Serum creatinine, mg/dL†	1 (0.7–1.6)
>1.3 mg/dL	93 (32.1%)
eGFR†, mL/min/m2	78 (48–115)
Renal function stage	
G1	124 (43%)
G2	65 (22%)
G3a	32 (11%)
G3b	33 (11%)
G4	22 (8%)
G5	14 (5%)
Serum albumin (g/dL)†	3 (2.4–3.6)
<3 g/dL	118 (48.4%)
Haemoglobin (g/L)†	108 (92–124)
<10 g/dL	86 (35.5%)
ANA	254 (93.4%)
Anti-DNA	204 (80.6%)
Low complement	245 (90.7%)
Anti-SM	45 (48.9%)
ANCA	12 (8.1%)
P-ANCA	3 (3.4%)
C-ANCA	1 (1.2%)
MPO	1 (1.4%)
PR3	3 (3.4%)
Proteinuria, g/24 hours†	2.6 (1.2–4.8)
>1 g/24 hours	217 (79.2%)
>3 g/24 hours	111 (40.5%)
Haematuria	243 (84.4%)
Histology	
Activity index†	11 (8–14)
Chronicity index†	2 (0–3)
Glomerulosclerosis	44 (26.0%)
IFTA†	10 (5–20)
Treatment induction	
Without	25 (7.8%)
Cyclophosphamide	224 (70.2%)
Mycophenolate	63 (19.7%)
Other	7 (2.2%)
Treatment maintenance	

Continued

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Table 1 Continued

Mycophenolate	208 (73.2%)
Azathioprine	72 (25.3%)
Other	4 (1.4%)
Any antimalarial drug	277 (87.9%)
ACE inhibitor or ARB	290 (92%)

*Some variables were missing in some patients.
†Median (IQR).
ANCA, antineutrophil cytoplasmic antibody; Anti-SM, anti-Smith; ARB, angiotensin II receptor blockers; C-ANCA, cytoplasmic ANCA; eGFR, estimated glomerular filtration rate; IFTA, Interstitial fibrosis and tubular atrophy; ISN/RPS, International Society of Nephrology/Renal Pathology Society; MPO, myeloperoxidase; P-ANCA, perinuclear ANCA; PR3, proteinase 3.

those in the intermediate risk category (HR 3.22, 95% CI 1.64 to 6.34; p=0.001), and 7.53 more likely compared with the low-risk group (HR 7.53, 95% CI 3.89 to 14.76; p<0.001).

Internal validation

The prognostic model was internally validated by bootstrapping the HRs of each prognostic group as compared with its immediately inferior risk category and counting the proportion of bootstrap samples with HRs >1.00 (online supplemental table S3). The bootstrapped HR was >1.00 in 100% of samples for intermediate versus low-risk categories and 97% for high versus intermediate-risk categories. These results mean that the model's discriminating capacity is not critically dependent on a particular composition of the development series because it can significantly distinguish the three prognostic categories from each other in nearly all the bootstrapped samples.

External validation

External validation was performed on a test cohort of 93 mestizo patients diagnosed with pure proliferative LN (ISN/RPS class III or IV) in several Mexican hospitals from 2007 to 2023. The median age of this cohort was 30 years (IQR: 22–38), and 79 (85.0%) patients were females. Online supplemental table S4 summarises the main clinical and histological features at diagnosis of LN.

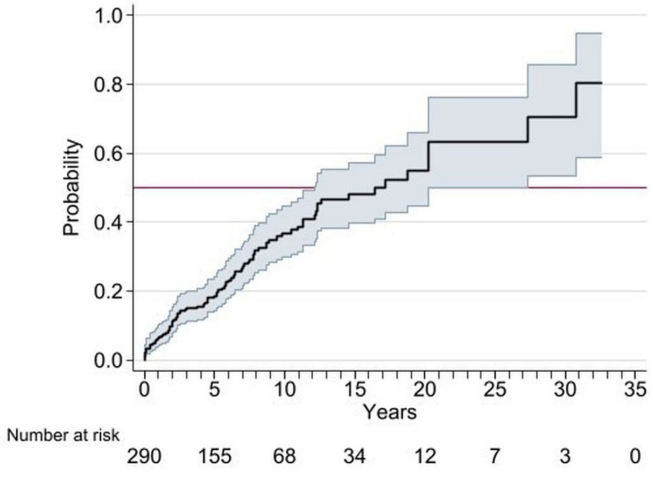

Figure 1 Time to poor renal outcome (end stage renal disease or death from any cause) in 290 mestizo patients diagnosed with pure proliferative lupus nephritis.

After a median follow-up of 6.6 years (IQR: 4.4–8.2), 26 patients (27.9%) had progressed to the composite endpoint (online supplemental figure S1). Table 3 and figure 3 show the results of applying the prognostic models to the validation series. As summarised in online supplemental table S5, Harrell's index for concordance between outcome predicted by the model and those actually observed was over 79% (95% CI 71% to 87%) in the validation series and significantly greater than the 50% that would be obtained by mere chance (p<0.001). According to the R2 statistic, the prognostic model could explain 63% of the outcome variation observed in the validation series.

Prognostic value of renal function at 1 year from diagnosis

We evaluated the prognostic significance of achieving a remission at 1 year after diagnosis (24 hours proteinuria <0.5 g and improved or stable eGFR) in 215 patients from the Chilean cohort with information on both parameters. Among the 70 patients not evaluable for 1-year remission, 30 had a shorter follow-up (14 had already achieved the outcome) and 40 had no information on proteinuria or eGFR just at this landmark. A remission was achieved or had been maintained from diagnosis in 127 of 215 (59.1%) evaluable patients 1 year after diagnosis, and it was associated with a better prognosis for the remaining follow-up, as compared with non-remitting patients (HR: 0.33, 95% CI 0.18 to 0.60; p<0.001 for the remaining time-to-outcome).

We then investigated whether achieving a 1-year remission modulated the prognostic effect of the initial risk categories in 161 patients with information on the former variable. 1-year remission decreased the probability of poor renal outcome associated with the intermediate-risk and high-risk categories (HR: 0.26, 95% CI 0.14 to 0.50; p<0.001, adjusted for the risk category) but had no significant effect in patients who had been classified as low-risk at diagnosis (HR: 1.01, 95% CI 0.32 to 3.19; p=0.98).

The probability of having achieved (or maintained) a remission at 1 year after diagnosis of proliferative LN (ISN/RPS class III or IV) was higher for patients initially classified in the low-risk group (77 of 106, 72.6%) than for those in the intermediate (17 of 44, 38.6%) or high-risk groups (4 of 11, 36.4%).

DISCUSSION

Accurate early prediction of long-term renal outcomes remains an unmet need in the management of LN, especially among Latin American mestizo patients. Although this population has been included in previous studies, detailed analyses focused specifically on biopsy-proven LN in mestizo individuals remain limited. Notably, in the

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Table 2 Prognostic categories for poor renal outcome in mestizo patients diagnosed with pure proliferative lupus nephritis (ISN/RPS class III or IV) in several Chilean hospitals (development cohort)*

Risk category	Nr. patients	Nr. of risk factors†	HR (95% CI)‡	P value
Low	141 (64.0%)	None	—	—
Intermediate	61 (27.8%)	One	2.41 (1.35 to 4.30)	0.003
High	18 (8.2%)	Two	3.22 (1.64 to 6.34)	0.001

*Model developed in 220 patients who had all the required variables.
†eGFR <30 mL/min/m^2 and chronicity index >2 in the renal biopsy.
‡HRs were calculated over the immediately inferior risk category.
eGFR, estimated glomerular filtration rate; ISN/RPS, International Society of Nephrology/Renal Pathology Society.

GLADEL cohort from Latin America,[14] fewer than 50% of participants were of mestizo descent. Furthermore, unlike our cohort, not all patients in the GLADEL series had biopsy-proven LN, precluding the assessment of histopathological features as prognostic factors. Additionally, the GLADEL cohort included patients with mixed and non-proliferative lesions, which are associated with distinct prognostic outcomes.

In this retrospective study, we analysed the prognostic value of clinical, laboratory and histopathological variables at the time of diagnosis of pure proliferative LN (ISN/RPS class III or IV) in a Latin American mestizo population. Based on these variables, we developed a predictive model for long-term renal outcome, with the primary endpoint defined as a composite of CKD stage IV/V (eGFR <30 mL/min/m^2), with or without dialysis, or death from any cause, whichever occurred first. Given that patients with proliferative LN have worse outcomes than those with non-proliferative LN[25] and receive significantly different immunosuppressive treatments, the model was specifically developed for patients with pure proliferative lesions (ISN/RPS class III or IV). Patients with mixed lesions (proliferative and membranous) were excluded from the analysis to avoid the confounding effect on proteinuria potentially caused by lesions in the glomerular basement membrane. After taking into account these considerations, our study identified eGFR <30 mL/min/m^2 and chronicity index higher than 2 in the renal biopsy as the only presenting factors independently associated with a higher risk of poor renal outcome.

Poor renal function at the time of LN diagnosis had long been recognised as a predictor of progression to ESRD.[26–29] In contrast, the prognostic value of histopathological findings is less consistently established. In 1983, Austin *et al* developed a histopathological index of acute and chronic lesions.[18] They demonstrated that an AI >10 and a chronicity index >2 were inversely correlated with renal survival.[18 30] Since then, many studies have evaluated the histological correlation with renal prognosis. For instance, Rijnink *et al*[31] evaluated 105 patients with biopsy-proven LN and found that fibrous crescents (HR 1.09; 95% CI, 1.02 to 1.17) and IF/TA ≥25% (HR, 3.89; 95% CI, 1.25 to 12.14) were significantly associated with ESRD, reinforcing the long-standing relevance of the chronicity index. Among AI components, only fibrinoid necrosis (HR 1.08; 95% CI, 1.02 to 1.13) showed a significant association with ESRD. In our study, a high AI (>10) did not retain prognostic significance after adjustment for other covariates, whereas a chronicity index >2 remained independently associated with an increased risk of ESRD in the multivariable analysis. Nevertheless, we acknowledge that the prognostic value of chronicity index >2 may

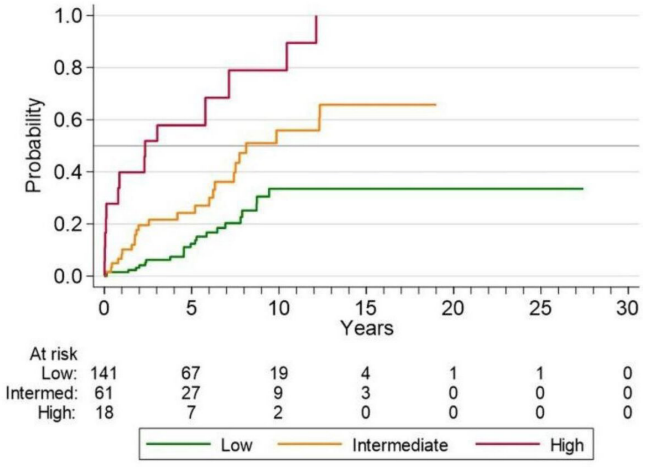

Figure 2 Time to poor renal outcome (end stage renal disease or death from any cause) according to risk categories in mestizo patients diagnosed with pure proliferative lupus nephritis.

Table 3 Prognostic categories for poor renal outcome in mestizo patients diagnosed with pure proliferative lupus nephritis (ISN/RPS class III or IV) in several Mexican hospitals (validation cohort)

Risk category	Nr. patients	Nr. of risk factors*	HR (95% CI)†
Low	43 (46.2%)	None	—
Intermediate	42 (45.2%)	One	10.2 (2.3 to 44.1)
High	18 (8.6%)	Two	6.4 (2.4 to 16.6)

*eGFR <30 mL/min/m2 or and chronicity index >2 in the renal biopsy.
†HRs were calculated over the immediately inferior risk category.
eGFR, estimated glomerular filtration rate; ISN/RPS, International Society of Nephrology/Renal Pathology Society.

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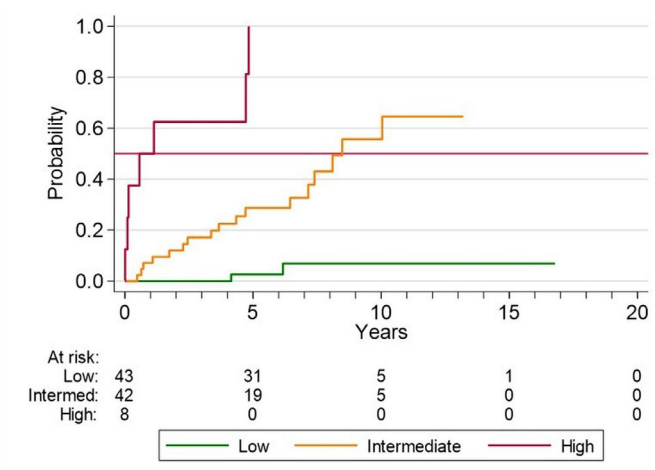

Figure 3 Time to poor renal outcome (end stage renal disease or death from any cause) according to risk categories in 93 Mestizo patients diagnosed with pure proliferative lupus nephritis in several Mexican hospitals (validation cohort).

vary depending on which components contribute to the score, and this should be interpreted with caution.

That caveat in mind, our study supports the prognostic utility of the NIH chronicity index, assessed at the time of the initial renal biopsy, in predicting long-term renal outcomes in Latin American mestizo patients with pure proliferative LN (ISN/RPS class III or IV). Nevertheless, its prognostic value in other populations remains debated, with conflicting findings reported in the literature.[32 33] Notably, a broader consensus has emerged around the prognostic significance of IFTA—which are included in two of the four components of the chronicity index—as independent predictors of adverse renal prognosis.[34 35] It is more difficult to draw conclusions about the impact of the AI in the initial biopsy on the long-term renal prognosis. Although it affects the choice of treatment in real clinical practice, our study, as well as several previous works,[36 37] does not corroborate the impact on the prognosis published by Austin.

The prognostic model proposed in our study is based on two readily available features at the time of LN diagnosis: eGFR and the histological chronicity index, which facilitates its applicability at the patient's bedside. By combining these two factors, we were able to stratify patients into three prognostic categories with significantly different and non-overlapping risks of poor renal outcomes. In addition, external validation in an independent cohort yielded both a clear-cut reproducibility of the prognostic classification and a significant degree of concordance, which anticipates good generalisability to other groups of mestizo patients with pure proliferative LN (ISN/RPS class III or IV).

The contribution of the initial renal biopsy, otherwise essential to diagnose LN, is noteworthy in providing relevant prognostic information. In our study, the extent of glomerular versus tubulointerstitial fibrosis was particularly valuable in refining the prognostic significance of renal function as measured by eGFR. Although the current classification system mainly focuses on glomerular lesions, the prognostic relevance of tubulointerstitial damage in both short- and long-term outcomes has been consistently highlighted in the literature.[19 38–40] These findings further support the inclusion of the tubulointerstitial compartment among emerging prognostic markers and outcome measures in LN.[1]

Renal fibrosis is commonly assessed using semiquantitative scoring systems, and several such scores have been proposed for a variety of renal diseases over the last decade, in addition to the chronicity index for LN.[41] However, these scores have limited reproducibility due to interobserver variability and sampling bias.[42 43] Advances in digital pathology and AI-based image analysis now allow more precise fibrosis quantification, potentially improving our understanding of its role in LN progression and prognosis.[44–49]

The primary goal of LN treatment is to achieve complete renal remission within 6–12 months of initiating induction treatment.[20] The importance of reaching remission during this period lies in previous observations on the poor prognosis of persistent proteinuria 1 year after diagnosis.[12–14] In our study, achieving remission at 1 year significantly improved outcomes among patients initially classified as intermediate-risk or high-risk, thereby emphasising the importance of attaining an early remission even in poor prognosis patients.

The main limitation of this study lies in the retrospective design, which led to the absence or incomplete recording of some potentially relevant variables. In addition, the study was developed and validated by using data from Chilean and Mexican patients; thus, its applicability to mestizo populations from other Latin American regions cannot be taken for granted, given the diverse genetic backgrounds across geographical areas within the mestizo population. Although KDIGO 2024 definitions were adopted for the present analysis, it is important to acknowledge that clinical decisions during the period of patient inclusion (1999–2023) were guided by earlier protocols and consensus documents available at that time. Regional guidelines, such as the GLADEL recommendations,[50] the Mexican national consensus[51] and the Chilean LN guidelines,[52] played a significant role in shaping treatment strategies across Latin America. This temporal gap between patient management and the analytical framework applied here represents both a limitation and an opportunity to harmonise long-term outcomes under current international standards. Although most patients received cyclophosphamide for induction and mycophenolate for maintenance, treatment-related variables were not included in the model and we acknowledge this as a relevant limitation. Nevertheless, the model demonstrated consistent performance across these two geographically and genetically distinct subpopulations,[53] which cast further support for its external validity. Finally, the model is based on only two variables—eGFR and chronicity index—which do not fully reflect the complexity

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and multifactorial nature of LN. This simplified approach was chosen to enhance clinical applicability and facilitate its use in routine practice.

Nevertheless, it is important to recognise that unmeasured confounding variables such as treatment adherence, time to treatment initiation, socioeconomic status and access to specialised care may also influence renal outcomes but were not captured in our study. Future validation studies that systematically incorporate these dimensions could further refine the predictive capacity of the score and strengthen its generalisability across different healthcare settings.

In conclusion, our clinical predictive model for pure proliferative LN (ISN/RPS class III or IV) identified three prognostic categories with clearly distinct risks of progression to ESRD among Latin American mestizo patients. This tool may contribute to improved risk stratification and management of LN in a population of patients in whom LN is particularly prevalent and severe and who lack appropriate clinical studies.

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