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Programvezető: Dr. Zsembery Ákos, egyetemi docens

Témavezető: Dr. Ledó Nóra, egyetemi adjunktus

RENAL BIOPSY DATABASES IN ADVANCING CLINICAL RESEARCH: CARDIOVASCULAR RISK ASSESSMENT IN LUPUS NEPHRITIS

PhD thesis

Adél Thomas-Molnár

Theoretical and Translational Medicine Division

Semmelweis University Doctoral College

Supervisor: Nóra Ledó, MD, PhD

Official reviewers: Csilla Markóth, MD, PhD

Miklós Kempler, MD, PhD

Head of the Complex Examination Committee: György Reusz, MD, DSc

Members of the Complex Examination Committee: Orsolya Kiss, MD, PhD

Ákos Jobbágy, DSc

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List of Abbreviations

AA	amyloid A
AAV	ANCA-associated vasculitis
ACE-I	angiotensin-converting-enzyme inhibitor
ACR	American College of Rheumatology
ANCA	anti-neutrophil cytoplasmic antibody
anti-dsDNA	anti-double-stranded deoxyribonucleic acid
anti-GBM	anti-glomerular basement membrane
anti-PLA2R	anti-phospholipase A2 receptor
APS	antiphospholipid syndrome
ARB	angiotensin receptor blocker
ASCVD	atherosclerotic cardiovascular disease
AUC	area under the curve
BMI	body mass index
C1q	complement 1q
C3c	complement 3c
C4c	complement 4c
CANDE	Cardiovascular risk – based on Age, Neutrophil count, and Diastolic blood pressure Estimation Score
COVID-19	coronavirus disease 2019
CV	cardiovascular
DBP	diastolic blood pressure
DM	diabetes mellitus
EGPA	eosinophilic granulomatosis with polyangiitis
ERA – EDTA	European Renal Association – European Dialysis and Transplant Association
EULAR	European League Against Rheumatism
FHN	familial or hereditary nephropathies
FSGS	focal segmental glomerulosclerosis

GD	glomerular diseases
GPA	granulomatosis with polyangiitis
HIV	human immunodeficiency virus
HT/RV	hypertension/renal vascular diseases
IBM	International Business Machines Corporation
IgA	immunoglobulin A
IgAN	immunoglobulin A nephropathy
IgG	immunoglobulin G
IgM	immunoglobulin M
ISU	immunosuppressive
LDG	low-density granulocyte
LDL	low-density lipoprotein
LN	lupus nephritis
MACE	major adverse cardiovascular event
MCD	minimal change disease
MISC	miscellaneous
MN	membranous nephropathy
MPA	microscopic polyangiitis
MPGN	membranoproliferative glomerulonephritis
NET	neutrophil extracellular trap
NHANES III	National Health and Nutrition Examination Survey III
OR	odd ratio
OSD	kidney diseases related to other systemic diseases
PP	pulse pressure
QRISK3	Quantitative Risk Assessment for Individuals version 3.
ROC	receiver operating characteristics
SBP	systolic blood pressure
SLE	systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
TID	tubulointerstitial diseases

1. Introduction

1.1. The significance of kidney biopsy registries and databases

The precise documentation of renal biopsy results and the establishment of structured databases are important for multiple reasons.

These databases provide valuable demographic data, including age, sex, geographical distribution, and long-term trends in disease presentation and outcomes. They facilitate the monitoring of temporal changes in disease prevalence and characteristics. Beyond demographic analysis, understanding the incidence and distribution of kidney diseases enables more effective public health planning and optimal allocation of healthcare resources. Identifying high-risk populations vulnerable to specific renal conditions facilitates the development of targeted prevention strategies and more effective therapeutic protocols. Importantly, large-scale renal biopsy databases contribute to improving disease classifications and staging systems. By capturing the pathological heterogeneity on a broader population level, they also help create more detailed clinical guidelines (1).

In addition to their epidemiological value, comprehensive and reliable registries serve as indispensable tools for clinical research. They provide rapid access to patients who meet specific criteria, significantly improving study efficiency by reducing recruitment time, lowering costs, and enhancing the precision of targeted clinical trials. High-quality biopsy-derived data allow for refined patient stratification based on histological subtypes, disease activity, chronicity indices, and biomarker profiles. This precision strengthens the validity and reproducibility of study outcomes and ensures more efficient allocation of research resources. Furthermore, longitudinal follow-up of patients within registries enables the study of disease progression, response to therapy, and long-term outcomes.

Ultimately, well-curated renal biopsy databases play a critical role in deepening our understanding of kidney disease pathophysiology and driving innovation in diagnostics, prognostics and therapeutic interventions.

Given these advantages, disease-specific analysis using biopsy databases offers unique opportunities to address important clinical questions, particularly in conditions like lupus nephritis, where conventional epidemiological datasets are often insufficient to capture the complexity of the disease.

Lupus nephritis is a well-characterized clinic-pathological entity, affecting 30–50% of systemic lupus erythematosus (SLE) patients and contributing to both morbidity and mortality. Cardiovascular morbidity remains one of the leading causes of mortality among lupus patients, yet accurate prediction remains challenging. In SLE, cardiovascular complications occur more frequently and with greater severity compared to non-SLE populations, with renal involvement further amplifying this risk (2). Notably, this elevated cardiovascular risk persists even after the elimination of traditional risk factors, suggesting a role for chronic inflammation and immunosuppressive therapy-related side effects (3). Even after adjusting for conventional risk factors, SLE patients – particularly those with lupus nephritis – exhibit a disproportionately higher risk of cardiovascular complications, underscoring the urgent need for a deeper investigation into disease-specific mechanisms and predictors (4).

In this context, a well-structured kidney-biopsy database becomes an invaluable research tool. It facilitates the systematic identification of SLE patients and allows for integration of histopathological, clinical, and laboratory data. Such comprehensive datasets are critical for examining cardiovascular risk factors beyond traditional models and for identifying novel predictors based on renal pathology. By enabling stratification based on detailed renal histology-associated clinical variables, the database helps to uncover previously unrecognized patterns of cardiovascular risk in lupus nephritis. This comprehensive information allows for identifying and analyzing risk factors specific to the cardiovascular risk associated with lupus nephritis, ultimately leading to a better understanding of the disease and more comprehensive management.

2. Objectives

My PhD research has two main objectives.

First, to establish a comprehensive kidney biopsy database by collecting demographic and histopathological data. Through this effort, we aimed to analyze biopsy trends over time, assess the distribution of various kidney diseases by age, sex, and monitor shifts in histopathological patterns related to changing epidemiologic factors. This database serves as a resource not only for epidemiologic analysis but also for clinical research for the second part of the study.

The second objective focuses specifically on patients with lupus nephritis. We aimed to identify and evaluate clinical, laboratory, and histopathological risk factors associated with cardiovascular events in this population. By analyzing a wide range of parameters available at the time of kidney biopsy, our goal is to pinpoint key predictive variables. Based on these findings, we intended to develop a new cardiovascular risk prediction model, which can be calculated at the time of the kidney biopsy. This tool would help clinicians identify high-risk individuals early and guide preventive cardiovascular care in lupus nephritis patients more effectively.

3. Methods

The study was divided into two main sections, and the methodology will be outlined in alignment with this structure.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Regional and Institutional Committee of Science and Research Ethics of Semmelweis University, Budapest, Hungary (SE RKEB 225/2018). All analyses were carried out following relevant guidelines and regulations, with informed consent obtained from all subjects and/or their legal guardians for further analyses at the time of the biopsies.

3.1. Establishment of the renal biopsy database

The first part of the research aimed to establish a renal biopsy database. Renal biopsy reports were initially documented on paper, then in electronic medical records (Medsol); therefore, we needed to manually transfer and digitize the data to create a structured electronic database (Microsoft Excel version 2016). We conducted a retrospective analysis of biopsy specimens processed at the Department of Pathology, Forensic, and Insurance Medicine, Semmelweis University, between January 2005 and December 2020. The samples were sourced from 28 different secondary and tertiary nephrology departments in Northern and Central Hungary, spanning four counties, including the capital, Budapest. These centers included both adult and pediatric care facilities.

All samples, including those with sampling errors (e.g., adipose tissue), were included in our analysis. We recorded patients' age, sex, primary, secondary, and tertiary diagnoses (if multiple histological features were present), and the institution where the biopsy was performed. Repeated kidney biopsies were also noted.

3.1.1. Demographics

Population data was sourced from the Hungarian Central Statistical Office to compare the average Hungarian population to our dataset.

3.1.2. Histological assessment

As per the pathological protocol, all specimens were stained using standardized techniques and evaluated systematically under light microscopy, immunofluorescence, and electron microscopy. Kidney tissue sections embedded in paraffin were routinely stained with hematoxylin and eosin, periodic-acid Schiff, Masson's trichrome, Congo red, and Jones' methenamine silver stains. For immunofluorescence, specimens were labeled with fluorescent dye-conjugated antibodies against IgG, IgA, IgM, C3c, C4c, C1q, fibrin, kappa, and lambda chain. For cases suspected of Alport syndrome, staining for collagen IV alpha 5 chain was also performed. From 2006 to 2019, two experienced nephropathologists independently assessed the specimens. In 2020, another nephropathologist joined the assessment team. Clinical information provided by the attending clinicians was used to support the evaluation in most cases.

3.1.3. Diagnoses

Over the 15 years, various coding systems were used to describe the diagnoses. To create a unified database, terminology was used as defined by the European Renal Association – European Dialysis and Transplant Association (ERA – EDTA) coding system (5). Based on this classification, we categorized the diagnoses into seven major renal diagnostic groups: glomerular diseases, tubulointerstitial diseases, diabetes mellitus, hypertension, other systemic diseases, familial nephropathies, and miscellaneous renal disorders. Transplant kidney biopsies were excluded from the analysis.

For improved comparability with previous studies, patients were grouped by age and sex. Individuals aged 18 years or younger were classified as children, those between 19 and 65 years as adults, and those aged 66 years or older as elderly.

3.1.4. Statistical analysis

We employed Chi-square and Fisher's exact tests to analyze categorical variables, while Kruskal-Wallis test was applied for continuous variables, guided by the outcomes of the Shapiro-Wilk normality test. Logistic regression analysis was also performed for binary

dependent variables. Two-tailed p-values below 0.05 were regarded as statistically significant.

3.2. Cardiovascular risk factors of lupus nephritis

The second part of the study was carried out by using the database.

The study cohort included Caucasian individuals aged 18 years and older who underwent renal biopsy between 2005 and 2020 at a tertiary-care hospital in the Department of Internal Medicine and Oncology, Semmelweis University. SLE diagnoses were made using the 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) criteria for cases after 2019, the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria for cases between 2012 and 2019, and the 1997 American College of Rheumatology (ACR) criteria for cases from 1997 to 2012 (6-8).

Comprehensive clinical data were retrospectively collected from the Medsol system, which included physical examination findings, blood pressure measurements, laboratory parameters, medication regimens, age, time since lupus diagnosis, comorbidities, cardiovascular disease history, echocardiographic and electrocardiographic values, and smoking status. To ensure the accuracy and reliability of the calculations, only variables with at least 75% data completeness were incorporated into the analysis.

Immune serology tests were conducted up to three months prior to the biopsy, while standard laboratory parameters were assessed at the time of the biopsy. Immunosuppressive therapy was monitored both at the time of the biopsy and throughout the remission induction and maintenance phases. Cardiovascular medication usage was recorded concurrently with the biopsy. Blood pressure was measured using various automatic monitors during the hospital admission for the biopsy, and smoking status was self-reported.

Major adverse cardiovascular events (MACE) were defined as a composite of nonfatal myocardial infarction, hospitalization due to heart failure, coronary revascularization, stroke, and cardiovascular death. MACE occurrences were evaluated from the time of lupus diagnosis and from the time of biopsy.

3.2.1. Statistical analysis

Data were anonymized and stored in an Excel (Microsoft, version 2016) file. Statistical analysis was performed using IBM SPSS Statistics version 28 software, with figures generated using GraphPad Prism 9.0.0 and IBM SPSS Statistics.

To compare variables based on MACE status, we used Chi-square or Fisher's exact tests for categorical variables, depending on sample size and expected frequencies, and Mann-Whitney U-tests for continuous variables – based on the Shapiro-Wilk normality test. To identify independent predictors of MACE, we conducted multiple logistic regression analysis. First, individual logistic regression models were created for each predictor that showed significant differences in univariate analysis, with MACE as the dependent variable. Due to the relatively small sample size, predictors included in the final model were selected based on their performance in univariate analysis and the availability of sufficient data points. The final multivariate logistic regression model included all selected independent variables. Non-significant predictors were systematically removed using a stepwise elimination process to refine the model. To evaluate the model's predictive accuracy, a Receiver Operating Characteristic (ROC) curve was plotted for the final model, and the area under the curve (AUC) was calculated to assess its discriminatory power. Based on the final logistic regression model, we developed a risk score to predict cardiovascular events in lupus nephritis patients. This score was derived by using a previously established method, assigning weights to predictors based on their regression coefficient (9). Two-tailed p-values <0.05 were considered statistically significant.

4. Results

4.1. Kidney-biopsy-based demographic analyses

4.1.1. Demographics

Analysis was carried out between 2006 and 2020. 2140 native kidney biopsies and 111 transplant biopsies were examined, with transplant biopsies being excluded from the analysis. This resulted in 2296 diagnoses from native biopsies.

The average population of Hungary between 2006 and 2020 was 9916101, while the average population of the catchment area during this period was 3932556, representing 39.7% of Hungary's total population.

The average population density in these areas during this time was 107 inhabitants per km², which is 1.2 times higher than the national average and 3.19 times greater than the European average for the same period (10, 11). The male-to-female ratio was nearly equal at 49.8% to 50.2%, with a mean age of 44.2 ± 21.9 years. Patient ages ranged from 4 months to 90 years, with a median age of 46 years, indicating a slightly skewed age distribution. Among the biopsies, 18.3% were from children, 61.3% from adults, and 20.4% from elderly individuals.

Over the final six years of the study period (2015–2020), the median age showed a significant increase ($p < 0.0001$), accompanied by a rise in the proportion of patients aged 18 years or older ($p < 0.0001$) (Table 1).

Table 1. Demographics of the renal biopsy database

The age of the patients is presented as mean ± standard deviation (median; 25-75 percentile); the sex and the age group are presented as the patient number with the percentage (%). P-values show the result of the statistical analysis of the difference between the 3-year intervals. Kruskal-Wallis test (age) or Chi-square test were used (sex, age groups), accordingly.

NS non-significant, m male, f female, y year, pmp per million person-years (12).

Category	All	2006 - 2008	2009 - 2011	2012 -2014	2015 - 2017	2018 - 2020	*p*
Age (years)	44.2 ± 21.9 (46; 27-63)	37.8 ± 22.7 (37; 16.25-57)	37.5 ±23.2 (38; 16-58)	38.7 ± 22.4 (40; 17-59)	47.5 ± 20.5 (49; 33-65)	49.0 ± 19.9 (51; 35-65)	< ***0.0001***
Sex (m/f)	1065 (49.8)/ 1075 (50.2)	144 (49.0)/ 150 (51.0)	145 (49.2)/ 150 (50.8)	146 (53.9)/ 125 (46.1)	304 (49.0)/ 316 (51.0)	326 (49.4)/ 334(50.6)	NS
Children	391 (18.3)	81 (27.6)	92 (31.2)	74 (27.3)	73 (11.8)	71 (10.8)	< ***0.0001***
Adult	1312 (61.3)	172 (58.5)	161 (54.6)	154 (56.8)	400 (64.5)	425 (64.4)	< ***0.0001***
Elderly	437 (20.4)	41 (13.9)	42 (14.2)	43 (15.9)	147 (23.7)	164 (24.8)	< ***0.0001***
Biopsy rate (pmp)	36.3	24.5	24.2	22.3	55.2	57.9	

Throughout the 15-year period, the sex distribution remained stable, while the overall biopsy rate increased between 2015 and 2020. The average biopsy rate across the study period was 36.3 per one million person-years. Sex-specific analyses revealed average biopsy rates of 38.2 per one million person-years for males and 34.6 per one million person-years for females.

4.1.2. Frequency of the main disease groups

Among all kidney biopsies analyzed, glomerular diseases (GD) were the most prevalent diagnosis, accounting for 65.3% of cases. Tubulointerstitial diseases (TID) followed at 8.4%, while diabetes mellitus-related nephropathy (DM) comprised 6.1% of diagnoses. Other categories included other systemic diseases (OSD) at 4.7%, renal vascular diseases (HT/RV) at 4.6%, familial or hereditary nephropathies (FHN) at 2.9%, and miscellaneous diagnoses (MISC) at 7.9% (Table 2, Figure 1A.).

Table 2. Frequency of the main renal diagnostic categories between 2006-2020 Frequencies of the main renal diagnostic categories between 2006-2020. They are presented as absolute numbers and percentages (%). P-values show the result of the statistical analysis of the difference between the 3-year intervals. P*-values demonstrate the difference between the last 3 years (2018-2020) and the first 12 years (2006-2017). Chi-square test was used. GD glomerular diseases, TID tubulointerstitial diseases, DM diabetes mellitus, HT/RV hypertension/renal vascular disease, OSD other systemic disease affecting the kidney, FHN familial/hereditary nephropathies, MISC miscellaneous diseases, NS non-significant (12).

Category	All n = 2296	2006 - 2008 n = 331	2009 - 2011 n = 327	2012 - 2014 n = 288	2015 - 2017 n = 678	2018 - 2020 n = 672	*p*	*p**
GD	1499 (65.3)	205 (61.9)	204 (62.4)	189 (65.6)	445 (65.6)	456 (67.9)	NS	NS
TID	192 (8.4)	44 (13.3)	33 (10.1)	25 (8.7)	51 (7.5)	39 (5.8)	***0.001***	***0.007***
DM	141 (6.1)	15 (4.5)	17 (5.2)	18 (6.3)	44 (6.5)	47 (7.0)	NS	NS
HT/RV	106 (4.6)	17 (5.1)	16 (4.9)	5 (1.7)	48 (7.1)	20 (3.0)	***0.001***	***0.009***
OSD	109 (4.7)	5 (1.5)	16 (4.9)	17 (5.9)	31 (4.6)	40 (6.0)	NS	NS
FHN	67 (2.9)	18 (5.4)	15 (4.6)	14 (4.9)	8 (1.2)	12 (1.8)	***<0.0001***	***0.02***
MISC	182 (7.9)	27 (8.2)	26 (8.0)	20 (6.9)	51 (7.5)	58 (8.6)	NS	NS

Figure 1. Frequencies of the main diagnostic categories and glomerular diseases (12)

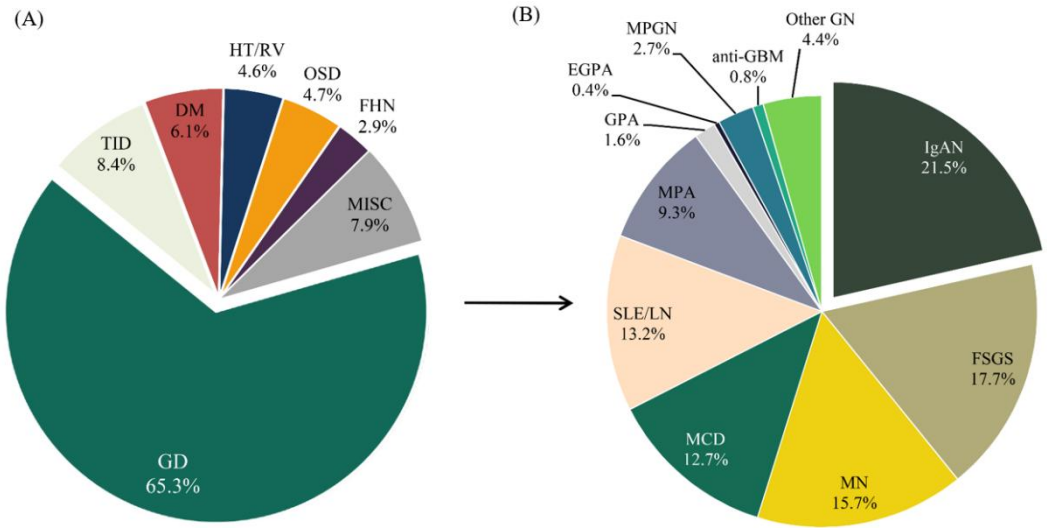

Figure 1. **(A)** Frequencies of the main groups throughout 15 years. GD glomerular diseases, TID tubulointerstitial diseases, DM diabetes mellitus, HT/RV hypertension/renal vascular disease, OSD other systemic disease affecting the kidney, FHN familial/hereditary nephropathies, MISC miscellaneous diseases. **(B)** Frequencies of glomerular diseases throughout the 15 years. IgAN IgA nephropathy – histologically proven and Henoch-Schönlein purpura/nephritis, FSGS focal segmental glomerulosclerosis, MN membranous nephropathy (primary and secondary), MCD minimal change disease, SLE/LN systemic lupus erythematosus/lupus nephritis, MPA microscopic polyangiitis, GPA granulomatosis with polyangiitis, EGPA eosinophilic granulomatosis with polyangiitis, MPGN membranoproliferative glomerulonephritis, Other GN other glomerulonephritis (12).

4.1.3. Detailed analysis of the main disease groups

The glomerular diseases group encompassed a diverse range of etiologies, analyzed individually and detailed later in the thesis (Figure 1B). Tubulointerstitial diseases (n = 192) were primarily composed of drug-induced tubulointerstitial nephritis (n = 176, 91.7%), with smaller contributions from autoimmune mechanisms (n = 7, 3.6%), calcium deposition diseases (n = 4, 2.1%), uric acid deposition diseases (n = 2, 1%), and HIV (human immunodeficiency virus) - associated nephropathy (n = 3, 1.6%). The other systemic diseases (n = 109) included amyloidosis (n = 90, 82.6%) and thrombotic microangiopathy (n = 19, 17.4%). Familial/hereditary nephropathies (n = 67) comprised thin basement membrane disease (n = 46, 68.7%), Alport syndrome (n = 13, 19.4%), primary hyperoxaluria (n = 4, 6%), nephronophthisis (n = 2, 3%) and genetically confirmed congenital thrombotic microangiopathy (n = 2, 3%). The miscellaneous group (n = 182) included chronic kidney

failure of unknown etiology (n = 48, 26,4%), acute kidney injury (n = 32, 17.6%), acute pyelonephritis (n = 5, 2.7%), tumors (n = 5, 2.7%), oligomeganephronia (n = 1, 0.5%), *sine morbo* diagnoses (n = 8, 4.4%), and specimens with no diagnosis due to technical problems (n = 83, 45.6%).

4.1.4. Three-year trends in the main diagnostic categories

To evaluate temporal changes in diagnostic patterns, we analyzed trends in three-year intervals. Glomerular diseases consistently remained the most prevalent diagnostic category throughout the study period, with their proportion of total diagnoses remaining unchanged. However, tubulointerstitial diseases exhibited a significant decline in prevalence during the final three years (2018–2020) (p=0.007). Similar decreases were observed for familial/hereditary nephropathies (p = 0.02) and renal vascular diseases (p = 0.009).

The reduction in FHN diagnoses was largely attributed to the increasing age of the patient cohort over time, whereas the decline in HT/RV diagnoses appeared independent of patient age (based on the results of multivariate logistic regression tests). Despite a noticeable rise in the frequency of diabetes mellitus-related diagnoses, this trend did not achieve statistical significance (p = 0.745).

4.1.5. Analysis of female/male differences across main diagnostic categories

Sex was a significant factor influencing the distribution of diagnoses (p = 0.0004). While glomerular diseases showed an equal distribution between sexes, there were notably more males diagnosed with DM (p = 0.025), females were significantly more prevalent in the OSD group (p = 0.002) and the FHN group (p = 0.038) (Table 3, Figure 2A).

Table 3. Percentages of the main diagnostic categories according to sex and age (12)

The table shows the fraction of total of the main diagnoses according to sex and age. They are presented as percentages (%). P-values show the result of the statistical analysis of the difference between sex and age groups. Chi-square test was used.

GD glomerular diseases, TID tubulointerstitial diseases, DM diabetes mellitus, HT/RV hypertension/renal vascular disease, OSD other systemic disease affecting the kidney, FHN familial/hereditary nephropathies, MISC miscellaneous diseases, NS non-significant, y years (12).

Category	2006-2020						
	Male n = 1161	Female n = 1135	p	≤ 18 y n = 412	19 – 65 y n = 1416	≥ 66 y n = 468	*p*
GD (%)	64.3	66.3	NS	68.4	65.8	60.9	NS
TID (%)	9.3	7.4	NS	10.7	7.8	7.9	NS
DM (%)	7.1	5.1	***0.025***	0.7	7.3	7.3	***<0.0001***
HT/RV (%)	5.3	3.9	NS	1.0	5.4	5.6	***<0.0001***
OSD (%)	3.4	6.2	***0.002***	2.2	4.5	7.7	***0.001***
FHN (%)	2.2	3.7	***0.038***	11.4	1.4	0.0	***<0.0001***
MISC (%)	8.4	7.4	NS	5.6	7.7	10.7	***0.012***

Figure 2. The fraction of total of the main diagnoses according to sex and age groups

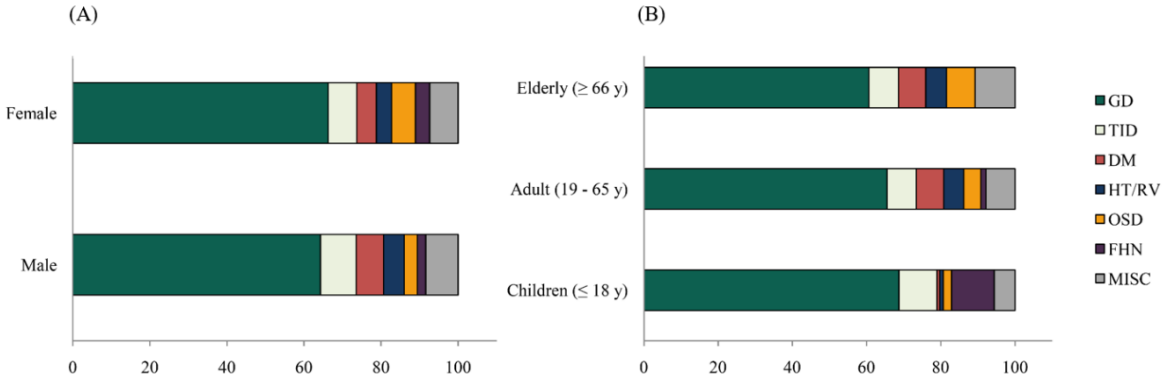

Figure 2. (A) The fraction of total of the main diagnoses according to sex and **(B)** age groups. They are presented percentages (%). GD glomerular diseases, TID tubulointerstitial diseases, DM diabetes mellitus, HT/RV hypertension/renal vascular disease, OSD other systemic disease affecting the kidney, FHN familial/hereditary nephropathies, MISC miscellaneous diseases, y years (12).

4.1.6. Analysis of age-related trends in the main diagnostic categories

The distribution of diagnoses varied significantly across age groups – children, adults, and the elderly ($p < 0.0001$).

Glomerular diseases were the most prevalent category in all age groups, accounting for 60.9–68.4% of cases. Adults and the elderly demonstrated a significantly higher prevalence of diabetes mellitus ($p < 0.0001$), hypertension/renal vascular conditions ($p < 0.0001$), other systemic diseases ($p = 0.001$), and miscellaneous diagnoses ($p = 0.012$). In contrast, familial and hereditary nephropathies were significantly more frequent among children ($p < 0.0001$) (Table 3, Figure 2B).

4.1.7. Female/male distribution across age groups in main diagnostic categories

The female/male distribution within age groups demonstrated distinct patterns over the years. In the adult group, there was a significant female predominance in the category of other systemic diseases ($p = 0.0045$, 3.0% vs. 6.2%). Conversely, in the elderly group, diabetes mellitus exhibited a notable male predominance ($p = 0.0312$, 10.2% vs. 4.8%).

4.1.8. Frequency of glomerular diseases

Given that glomerular diseases represented the majority of specimens, we conducted a detailed analysis of this category.

The IgA nephropathy (IgAN) group included both IgA nephropathy and IgA vasculitis (Henoch-Schönlein purpura). The membranous nephropathy group comprised primary and secondary forms. The "other glomerulonephritis" group included rare entities in the database: IgM nephropathy ($n = 3$), diffuse endocapillary glomerulonephritis ($n = 41$), histologically indeterminate glomerulonephritis ($n = 15$), cryoglobulinemia ($n = 6$), and C1q nephropathy ($n = 1$). The ANCA (anti-neutrophil cytoplasmic antibody) - associated vasculitis group consisted of microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA).

Among glomerular diseases, the most common was IgA nephropathy (IgAN, 21.5%), followed by focal segmental glomerulosclerosis (FSGS, 17.7%), membranous nephropathy (MN, 15.7%), minimal change disease (MCD, 12.7%), systemic lupus erythematosus with

lupus nephritis (SLE/LN, 13.2%), and ANCA-associated vasculitis (11.3%, with MPA accounting for 9.3%). Less frequent diagnoses included the "other glomerulonephritis" group (4.4%), membranoproliferative glomerulonephritis (MPGN, 2.7%), and anti-GBM (anti-glomerular basement) nephropathy (0.8%) (Table 4, Figure 1B).

4.1.9. Three-year trends in glomerular diseases

IgA nephropathy consistently emerged as the most common diagnosis across the entire study period. Over 15 years of observation, a notable decline was identified in biopsy diagnoses of minimal change disease ($p = 0.038$). Focal segmental glomerulosclerosis also showed a decrease in diagnoses during the last three years (2018–2020) ($p = 0.027$) (Table 4). These trends, however, were found to be age-dependent (12).

ANCA-associated vasculitis displayed an increasing frequency over the 15-year period ($p = 0.004$), with microscopic polyangiitis following a similar significant rising trend ($p = 0.012$). However, changes in GPA and EGPA were not significant. The rise in MPA diagnoses was partly attributed to the aging patient population.

Membranoproliferative glomerulonephritis showed a significant increase in diagnoses during the last three years (2018–2020) ($p = 0.021$), a trend that was independent of both age and sex (Table 4) (12).

Table 4. Frequencies of glomerular diseases

The table shows the frequencies of glomerular diseases. They are presented as absolute numbers and percentages (%). P-values show the result of the statistical analysis of the difference between the 3-year intervals. P*-values demonstrate the difference between the last 3 years (2018-2020) and the first 12 years (2006-2017). Chi-square test was used.

IgAN IgA nephropathy – histologically proven and Henoch-Schönlein purpura/nephritis, FSGS focal segmental glomerulosclerosis, MN membranous nephropathy (primary and secondary), MCD minimal change disease, SLE/LN systemic lupus erythematosus/lupus nephritis, MPA microscopic polyangiitis, GPA granulomatosis with polyangiitis, EGPA eosinophilic granulomatosis with polyangiitis, MPGN membranoproliferative glomerulonephritis, Other GN other glomerulonephritis, NS non-significant (12).

	All	2006 - 2008	2009 - 2011	2012 - 2014	2015 - 2017	2018 - 2020	*p*	*p**
Category	n = 1499	n = 205	n = 204	n = 189	n = 445	n = 456		
IgAN	322 (21.5)	48 (23.4)	47 (23.0)	42 (22.2)	84 (18.9)	101 (22.1)	NS	NS
FSGS	265 (17.7)	44 (21.5)	41 (20.1)	38 (20.1)	77 (17.3)	65 (14.3)	NS	***0.027***
MN	235 (15.7)	32 (15.6)	25 (12.3)	26 (13.8)	77 (17.3)	75 (16.4)	NS	NS
MCD	190 (12.7)	30 (14.6)	35 (17.2)	24 (12.7)	60 (13.5)	41 (9.0)	***0.038***	***0.004***
SLE/LN	198 (13.2)	21 (10.2)	25 (12.3)	25 (13.2)	67 (15.1)	60 (13.2)	NS	NS
MPA	140 (9.3)	12 (5.9)	14 (6.9)	16 (8.5)	37 (8.3)	61 (13.4)	***0.012***	***<0.001***
GPA	24 (1.6)	2 (1.0)	5 (2.5)	3 (1.6)	4 (0.9)	10 (2.2)	NS	NS
EGPA	6 (0.4)	-	-	1 (0.5)	2 (0.4)	3 (0.7)	NS	NS
MPGN	41 (2.7)	2 (1.0)	6 (2.9)	4 (2.1)	10 (2.2)	19 (4.2)	NS	***0.021***
anti-GBM	12 (0.8)	2 (1.0)	1 (0.5)	2 (1.1)	3 (0.7)	4 (0.9)	NS	NS
Other GN	66 (4.4)	12 (5.9)	5 (2.5)	8 (4.2)	24 (5.4)	17 (3.7)	NS	NS

Coronavirus pandemic affected the frequencies of kidney biopsies and the histopathologic diagnoses. In 2020, there was a decrease in the number of kidney biopsies compared to the average of the previous three years (2017–2019): 161 biopsies, 43.4 per one million person-years vs. 242.3 biopsies per year, 64.2 per one million person-year between 2017 and 2019. Among the biopsy diagnoses, we found a decrease in membranous nephropathy (10 in 161 (6.2%) in 2020 vs. 86 in 727 (11.8%) between 2017 and 2019, $p = 0.038$), an increase in GPA (6 in 727 (0.8%) between 2017 and 2019 vs. 5 in 161 (3.1%) in 2020, $p = 0.018$).

4.1.10. Analysis of female/male differences across glomerular diseases

Among the diagnoses, IgA nephropathy was the most prevalent in males (30.6%), while lupus nephritis was the most frequent glomerulonephritis in females (21.8%). Subgroup analysis revealed significant sex-specific trends: a male predominance was noted in membranous nephropathy ($p = 0.022$) and IgAN ($p < 0.0001$), while females were significantly more likely to be diagnosed with MPA ($p < 0.0001$) and SLE/LN ($p < 0.0001$). The distribution of minimal change disease, membranoproliferative glomerulonephritis, and anti-GBM nephropathy was balanced between sexes, showing no significant differences (Table 5, Figure 3A).

Table 5. Percentages of the glomerular diseases according to sex and age

The table shows the fraction of total of the glomerular diseases according to sex and age. They are presented as percentages (%). P-values show the result of the statistical analysis of the difference between the sexes or age groups. Chi-square test was used.

IgAN IgA nephropathy – histologically proven and Henoch-Schönlein purpura/nephritis, FSGS focal segmental glomerulosclerosis, MN membranous nephropathy (primary and secondary), MCD minimal change disease, SLE/LN: systemic lupus erythematosus/lupus nephritis, MPA microscopic polyangiitis, GPA granulomatosis with polyangiitis, EGPA eosinophilic granulomatosis with polyangiitis, MPGN membranoproliferative glomerulonephritis, Other GN other glomerulonephritis, NS non-significant, y years (12).

Category	2006-2020						
	Male n = 746	Female n = 753	p	≤ 18 y n =282	19 – 65 y n =932	≥ 66 y n = 285	*p*
IgAN (%)	30.6	12.5	***<0.0001***	30.5	22.3	9.8	***<0.0001***
FSGS (%)	16.8	18.6	NS	25.2	17.3	11.6	***0.001***
MN (%)	18.0	13.4	***0.022***	2.8	14.5	32.3	***<0.0001***
MCD (%)	12.5	12.9	NS	19.9	11.9	8.1	***<0.0001***
SLE/LN (%)	4.6	21.8	***<0.0001***	8.2	18.0	2.5	***<0.0001***
MPA (%)	6.6	12.1	***<0.0001***	3.5	7.4	21.4	***<0.0001***
GPA (%)	2.0	1.2	NS	1.8	1.3	2.5	NS
EGPA (%)	0.3	0.5	NS	-	0.2	1.4	***0.017***
MPGN (%)	2.9	2.5	NS	3.9	2.5	2.5	NS
anti-GBM (%)	0.8	0.8	NS	1.1	0.6	1.1	NS
Other GN (%)	5.1	3.7	NS	3.2	4.0	7.0	NS

Figure 3. The fraction of total of the glomerular diseases according to sex and age groups

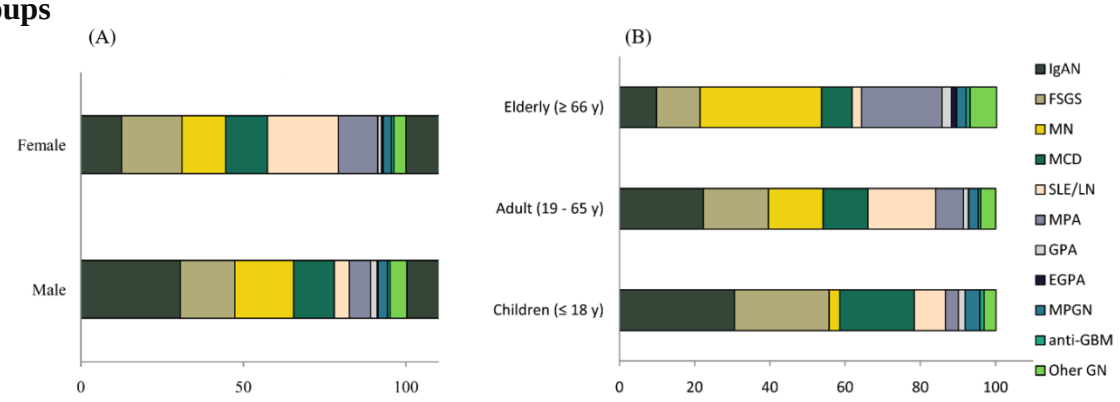

Figure 3. (A) The fraction of total of the glomerular diseases according to gender and **(B)** age groups. They are presented as percentages (%).
IgAN IgA nephropathy – histologically proven and Henoch-Schönlein purpura/nephritis, FSGS focal segmental glomerulosclerosis, MN membranous nephropathy (primary and secondary), MCD minimal change disease, SLE/LN systemic lupus erythematosus/lupus nephritis, MPA microscopic polyangiitis, GPA granulomatosis with polyangiitis, EGPA eosinophilic granulomatosis with polyangiitis, MPGN membranoproliferative glomerulonephritis, Other GN other glomerulonephritis, y years (12).

4.1.11. Analysis of age-related trends across glomerular diseases

IgA nephropathy was the most common glomerulonephritis in children and adults, whereas membranous nephropathy was the leading diagnosis in the elderly group (32.3%).

Within age groups, a significant adult and elderly predominance was observed for MN ($p < 0.0001$), MPA ($p < 0.001$), and EGPA ($p = 0.017$). Conversely, lupus nephritis showed dominance in children and adults ($p < 0.0001$). In pediatric patients, minimal change disease ($p < 0.0001$), focal segmental glomerulosclerosis ($p = 0.001$), and IgAN ($p < 0.0001$) were the most prevalent diagnoses. While membranoproliferative glomerulonephritis was more frequent in children and granulomatosis with polyangiitis occurred more frequently in the elderly, these variations did not reach statistical significance (Table 5, Figure 3B).

4.1.12. Female/male distribution across age groups in glomerular diseases

Further analysis of glomerular diseases by sex across age groups revealed significant findings. IgA nephropathy consistently demonstrated a male predominance in all age groups: children ($p < 0.0001$, 41.4% vs. 19.7%), adults ($p < 0.0001$, 31.6% vs. 12.6%), and the elderly

($p = 0.015$, 14.8% vs. 5.7%). On the other hand, lupus nephritis showed a strong female predominance in all age groups: children ($p < 0.0001$, 1.4% vs. 14.8%), adults ($p < 0.0001$, 6.7% vs. 30.0%), and the elderly ($p = 0.018$, 0% vs. 4.5%). In addition, there was a female predominance in microscopic polyangiitis in the children's group ($p = 0.019$, 0.7% vs. 6.3%). Meanwhile membranous nephropathy was characterized by a male dominance in the adult age group ($p = 0.001$, 35.2% vs. 29.9%).

4.2. Cardiovascular risk factors of lupus nephritis

4.2.1. Demographics

Between 2005 and 2020, 91 adult systemic lupus erythematosus patients underwent kidney biopsies in the Department of Internal Medicine and Oncology. The male-to-female ratio was 14.3% to 85.7%, with a mean age of 37.3 ± 12.3 years. Patients ranged in age from 18 to 74 years. The average follow-up time after biopsy was 62 ± 48 months. Following their lupus diagnosis, 15.38% (14 out of 91) of the patients experienced at least one major adverse cardiovascular event, with 8.79% (8 out of 91) having such events after the renal biopsy. In total, there were 18 MACEs recorded among 14 patients, including three coronary revascularizations, five strokes, six hospitalizations due to heart failure, two acute myocardial infarctions, and two cardiovascular deaths (Table 6). Five patients experienced more than one MACE.

Table 6. Patients' characteristics of the lupus nephritis cohort
Data are presented either as % (number/ all patients) or mean ± standard deviation (median; 25-75 percentile). MACE major adverse cardiovascular event (13).

Parameters	Overall characteristics
Age (years)	37.3±12.3 (36; 28.25-42)
Sex (female)	85.7% (78/91)
Follow-up (months)	62±48 (54.6; 17.4-94.72)
MACE in medical history	15.38% (14/91)
MACE after the kidney biopsy	8.79% (8/91)
Coronary revascularization	3.3% (3/91)
Stroke	5.5% (5/91)
Hospitalization due to heart failure	6.6% (6/91)
Acute myocardial infarction	2.2% (2/91)
Cardiovascular death	2.2% (2/91)

4.2.2. Total major adverse cardiovascular events

Patients who experienced major adverse cardiovascular events were, on average, significantly older than those who did not (45.50 vs. 35.81 years; $p = 0.012$) (Figure 4A). They also had lower diastolic blood pressure (DBP) (78.42 vs. 89.51 mmHg; $p < 0.001$) (Figure 4B), higher leukocyte counts (9.07 vs. 6.99 Giga/liter; $p = 0.026$) (Figure 4C), and higher absolute neutrophil counts (7.30 vs. 5.15 Giga/liter; $p = 0.01$) (Figure 4D, Table 7).

The observed elevations in leukocyte count and absolute neutrophil count were not associated with steroid administration or dosage (r = 0.097, p = 0.375; r = 0.110, p = 0.315).

Figure 4. Risk factors of major adverse cardiovascular events

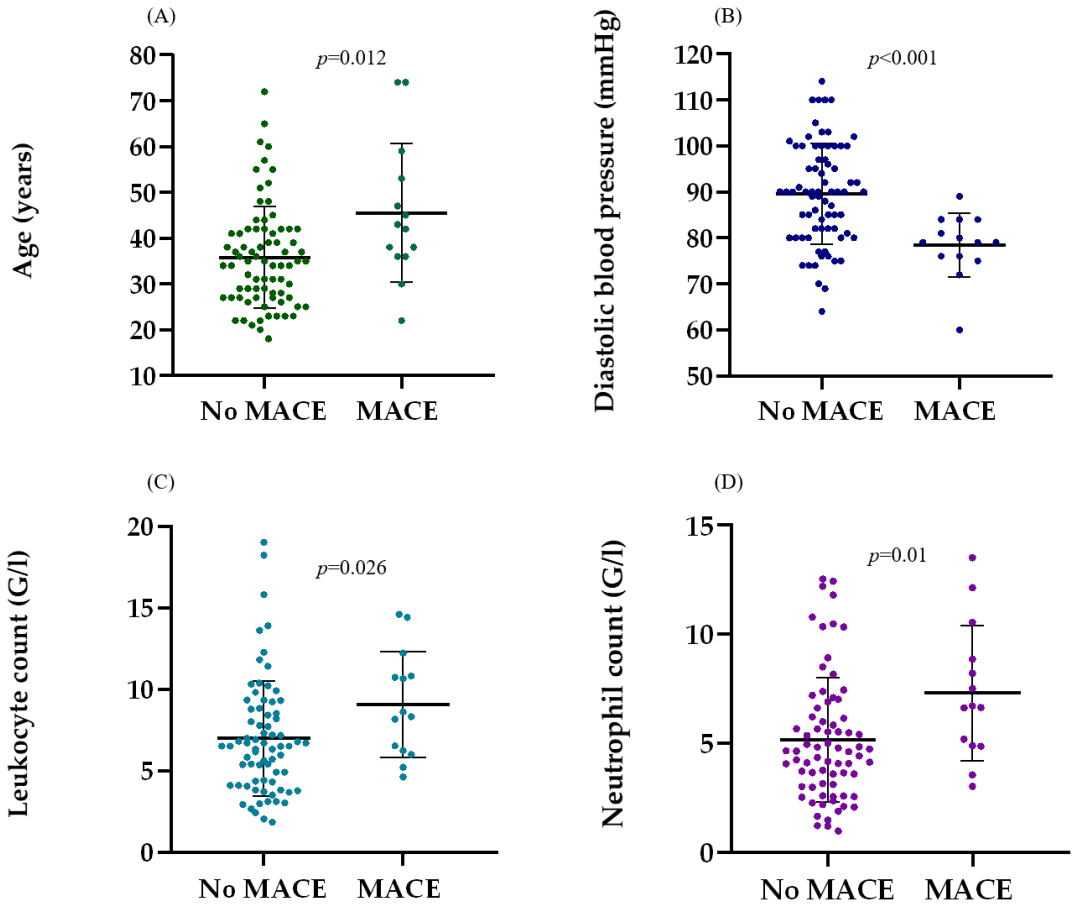

Figure 4. Risk factors of major adverse cardiovascular events. The dot-plots represent the parameters at the time of the kidney biopsy patients who had and had not MACE in medical history. **(A)** Mean (± standard deviation) age of patients with MACE and no MACE was 45.50 ± 15.11 vs. 35.81 ± 11.74 years, p=0.012, respectively. **(B)** Mean (± standard deviation) diastolic blood pressure in patients with MACE and no MACE history was 78.42 ± 6.90 vs. 89.51 ± 10.96 mmHg, p<0.001, respectively. **(C)** Mean (± standard deviation) leukocyte count in patients with MACE and no MACE was 9.07 ± 3.25 vs. 6.99 ± 3.54 G/l, p=0.026, respectively. **(D)** Mean (± standard deviation) neutrophil count in patients with MACE and no MACE was 7.30 ± 3.11 vs. 5.15 ± 2.85 G/L, p=0.01, respectively. Mann-Whitney U-test was used to analyze the differences between the groups. MACE major adverse cardiovascular event, G/l Giga/liter, mmHg Millimeters of Mercury (13).

Table 7. Major adverse cardiovascular events

Data are presented either as % (number/ all patients) or mean ± standard deviation (median) n= number of patients. MACE major adverse cardiovascular event, CRP C-reactive protein, GFR glomerular filtration rate, BUN blood Urea Nitrogen, HPF high-power field, NLR neutrophil-lymphocyte ratio, NPR neutrophil-platelet ratio, PLR platelet-lymphocyte ratio, ANA anti-nuclear antibodies, dsDNA, double-stranded deoxyribonucleic acid, ACE-I/ARB angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, EUROLUPUS glucocorticoids and cyclophosphamide or non-cyclic oral cyclophosphamide, IVIG intravenous immunoglobulin. Chi-square analysis or Mann-Whitney U-test were used to calculate p-values. Only data with at least 75% completeness were included in the table (13).

Variables	MACE in the medical history	No MACE in the medical history	*p*
Age (years)	45.50±15.11 (42.50) n=14	35.81±11.74 (35.00) n=77	***0.012***
Sex (females)	92.9% (13/14)	84.4% (65/77)	0.406
Time from lupus diagnosis to biopsy (years)	8.80±10.12 (5.50) n=14	6.84±6.74 (5.00) n=75	0.640
Clinical and general laboratory parameters			
Systolic blood pressure (mmHg)	132.50±18.73 (127.50) n=14	141.18±19.92 (140.00) n=74	0.069
Diastolic blood pressure (mmHg)	78.42±6.90 (79.00) n=14	89.51±10.96 (90.00) n=74	***<0.001***
Pulse pressure (mmHg)	54.07±19.33 (48.00) n=14	51.66±13.61 (52.00) n=74	0.842
Leukocyte count (G/l)	9.07±3.25 (8.45) n=14	6.99±3.54 (6.50) n=73	***0.026***
Hemoglobin (g/l)	112.21±18.53 (109.00) n=14	108.52±18.97 (106.00) n=73	0.533
Hematocrit (l/l)	0.34±0.07 (0.34) n=14	0.33±0.06 (0.32) n=73	0.595
Neutrophil (%)	79.14±9.3 (81.25) n=14	72.5±12.06 (73.80) n=73	0.058
Neutrophil count (G/l)	7.30±3.11 (6.68) n=14	5.15±2.85 (4.65) n=73	***0.010***
Lymphocyte (%)	15.01±8.26 (14.05) n=14	19.25±10.06 (17.80) n=73	0.146
Lymphocyte count (G/l)	1.29±0.74 (1.26) n=14	1.30±0.98 (1.00) n=73	0.599
Platelet count (G/l)	270.07±100.70 (290.00) n=14	245.63±101.25 =242.00) n=73	0.212
Sodium (mmol/l)	139.92±3.25 (140.00) n=13	139.85±3.62 (140.00) n=71	0.955
Potassium (mmol/l)	4.37±0.58 (4.30) n=13	4.36±0.61 (4.30) n=72	0.536
Calcium (mmol/l)	2.16±0.16 (2.12) n=12	2.15±0.22 (2.15) n=63	0.745
Phosphate (mmol/l)	1.38±0.25 (1.35) n=11	1.28±0.34 (1.27) n=60	0.206
Serum albumin (g/l)	30.65±7.78 (27.80) n=11	31.19±6.91 (30.75) n=62	0.717
CRP (mg/l)	10.86±13.60 (7.85) n=12	7.91±6.91 (3.6) n=62	0.304
GFR (ml/min/1.73 m^2)	90.26±43.37 (96.42) n=13	93.05±41.47 (97.96) n=72	0.807
Creatinine (µmol/l)	116.15±110.79 (87.00) n=13	112.33±89.27 (82.50) n=72	0.831
BUN (mmol/l)	11.98±8.70 (10.30) n=13	10.13±7.45 (7.75) n=72	0.376
Hematuria (erythrocyte/HPF)	123.43±366.56 (5.50) n=14	27.68±50.95 (10.00) n=71	0.648
Leukocyturia (leukocyte/HPF)	14.29±19.41 (11.50) n=14	19.06±46.39 (10.00) n=68	0.951
NLR	7.29±4.99 (5.87) n=14	5.68±4.79 (4.18) n=73	0.101
NPR	0.03±0.02 (0.03) n=14	0.02±0.02 (0.02) n=73	0.111
PLR	288.40±232.37 (177.88) n=14	297.87±315.12 (225.97) n=73	0.881
Auto-antibodies, lupus-specific laboratory parameters			
C3 (g/l)	0.69±0.23 (0.67) n=10	0.62±0.29 (0.59) n=60	0.411
C4 (g/l)	0.08±0.04 (0.07) n=10	0.11±0.11 (0.07) n=60	0.880
ANA positivity	100.0% (13/13)	93.3% (56/60)	0.338
Anti-dsDNA positivity	63.6% (7/11)	90.5% (57/63)	***0.016***
Pericardial effusion	14.3% (2/14)	11.7% (9/77)	0.534

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Variables	MACE in the medical history	No MACE in the medical history	*p*
Comorbidities			
Hypertension	42.9% (6/14)	38.2% (29/76)	0.740
Diabetes mellitus	14.3% (2/14)	2.6% (2/76)	0.113
Deep vein thrombosis	50.0% (7/14)	14.3% (11/77)	***0.002***
Antiphospholipid syndrome	35.7% (5/14)	7.8% (6/77)	***0.011***
Smoking	33.3/ (4/12)	27.0% (17/63	0.729
Medication at the time of the kidney biopsy			
Vitamin D3	21.4% (3/14)	29.9% (23/77)	0.749
Anticoagulant	57.1% (8/14)	19.5% (15/77)	***0.003***
Thrombocyte aggregation inhibitor	21.4% (3/14)	6.5% (5/77)	0.102
Calcium channel blocker	28.6% (4/14)	27.3% (21/77)	0.575
Spironolactone	14.3% (2/14)	2.6% (2/77)	0.110
Furosemide	50.0% (7/14)	32.5% (25/77)	0.206
Thiazide/thiazide-like diuretics	21.4% (3/14)	13.0% (10/77)	0.683
ACE-I/ARB	71.4% (10/14)	44.2% (34/77)	0.060
Statin	28.6% (4/14)	9.1% (7/77)	0.062
Beta blocker	50.0% (7/14)	22.1% (17/77)	***0.029***
Antimalarial medication	7.1% (1/14)	6.8% (5/74)	0.658
Methotrexate	0.0% (0/14)	4.1% (3/74)	0.591
Mycophenolate-mofetil	0.0% (0/14)	4.1% (3/74)	0.591
Azathioprine	7.1% (1/14)	10.8% (8/74)	0.563
Cyclosporin A	0.0% (0/14)	4.1% (3/74)	0.591
Cyclophosphamide	0.0% (0/14)	5.4% (4/74)	0.611
Glucocorticoids	92.9% (13/14)	81.1% (60/74)	0.283
Remission induction therapy			
EUROLUPUS induction	54.5% (6/11)	52.9% (37/70)	0.917
Cyclophosphamide induction	0.0% (0/11)	7.1% (5/70)	0.606
Glucocorticoids induction only	0.0% (0/11)	25.7% (18/70)	0.111
Plasmapheresis upon induction	0.0% (0/11)	4.3% (3/70)	0.642
Glucocorticoids and calcineurin inhibitor induction	0.0% (0/11)	1.4% (1/70)	0.864
Mycophenolate-mofetil	0.0% (0/11)	15.7% (11/70)	0.345
IVIG upon induction	0.0% (0/12)	2.8% (2/72)	0.733
Maintenance therapy			
Methotrexate	10.0% (1/10)	1.4% (1/69)	0.258
Mycophenolate-mofetil	20.0% (2/10)	26.1% (18/69)	0.596
Calcineurin inhibitor maintenance	20.0% (2/10)	8.7% (6/69)	0.591
Antimalarial medication	20.0% (2/10)	21.7% (15/69)	0.873
Azathioprine	30.0% (3/10)	31.9% (22/69)	0.531
Cyclophosphamide	0.0% (0/10)	14.5% (10/69)	0.342
Glucocorticoids	100.0% (10/10)	94.2% (65/69)	0.435

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Variables	MACE in the medical history	No MACE in the medical history	*p*
Remission – relapses			
Complete remission in 1 year	75.0% (6/8)	53.1% (34/64)	0.240
Partial remission in 1 year	12.5% (1/8)	20.3% (13/64)	0.594
No remission in 1 year	12.5% (1/8)	26.6% (17/64)	0.437
Relapse in 3 years	66.7% (6/9)	65.4% (34/52)	0.940
Histopathological data			
Class I	7.1% (1/14)	1.3% (1/77)	0.285
Class II	7.1% (1/14)	5.2% (4/77)	0.575
Class III	14.3% (2/14)	23.4% (18/77)	0.727
Class IV	50.0% (7/14)	55.8% (43/77)	0.774
Class V	28.6% (4/14)	19.5% (15/77)	0.480
Class VI	0.0% (0/14)	2.6% (2/77)	1.000
Overall distribution of the Classes			0.772

Antiphospholipid syndrome (APS) was significantly more common in patients with MACE at the time of kidney biopsy (35.7% vs. 7.8%; p = 0.011). These patients also had a higher incidence of deep vein thrombosis (50.0% vs. 14.3%; p = 0.02), and they were more frequently prescribed anticoagulant therapy (57.1% vs. 19.5%; p = 0.003) (Table 7, Figure 5A-C, respectively). Notably, all patients with APS were receiving anticoagulant therapy, though not all anticoagulated patients had APS.

Figure 5. Distribution of antiphospholipid syndrome, deep vein thrombosis and anticoagulant use

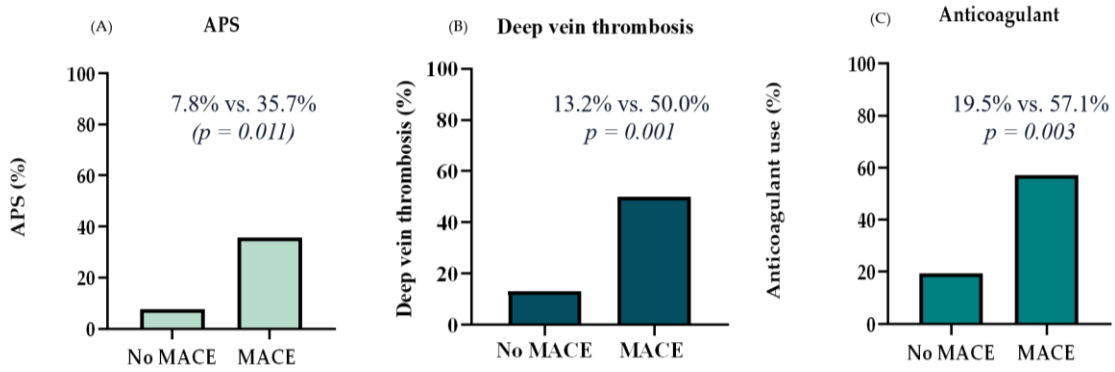

Figure 5. (A) Distribution of antiphospholipid syndrome in patients with MACE and no MACE in medical history. **(B)** Distribution of deep vein thrombosis in patients with MACE and no MACE in the medical history. **(C)** Distribution of anticoagulant use in patients with MACE and no MACE in the medical history. Chi square test was used to analyze the differences between the groups. MACE major adverse cardiovascular event, APS antiphospholipid syndrome (13).

Patients who experienced MACE were more likely to use beta-blockers (50.0% vs. 22.1%; p = 0.029) (Figure 6A) at the time of renal biopsy. However, the use of antihypertensive and diuretic medications did not demonstrate a significant association with MACE risk. Nevertheless, beta-blocker use was associated with older age (p=0.033) (Figure 6B).

Figure 6. Distribution of antiphospholipid syndrome, deep vein thrombosis and anticoagulant use

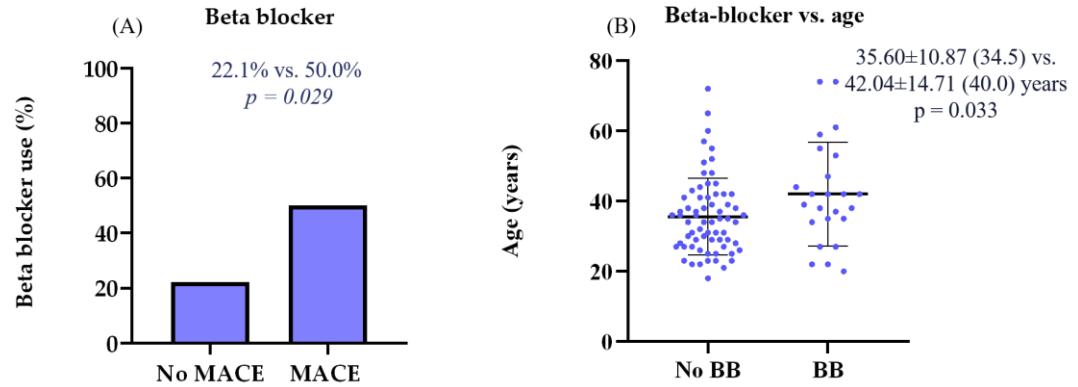

Figure 6. (A) Distribution of beta blocker use in patients with MACE and no MACE in medical history. **(B)** Age of beta-blocker users/non-users. Mean ± standard deviation (median) age of patients with beta-blocker and no beta-blocker use. Chi-square test and Mann-Whitney U test were used to analyze the differences between the groups. MACE major adverse cardiovascular event, BB beta-blocker (13).

Patients with MACE were less likely to have anti-dsDNA (anti-double stranded deoxyribonucleic acid) positivity (63.6% vs. 90.5%; p = 0.016) (Figure 7A). Additionally, anti-dsDNA positivity was associated with a lower absolute neutrophil count (5.08 vs. 7.44 Giga/liter; p = 0.035) (Figure 7B). Proteinuria did not have a statistically significant effect on the occurrence of MACE (p = 0.359).

Figure 7. Association of Distribution of anti-dsDNA positivity and association of anti-dsDNA positivity with absolute neutrophil count

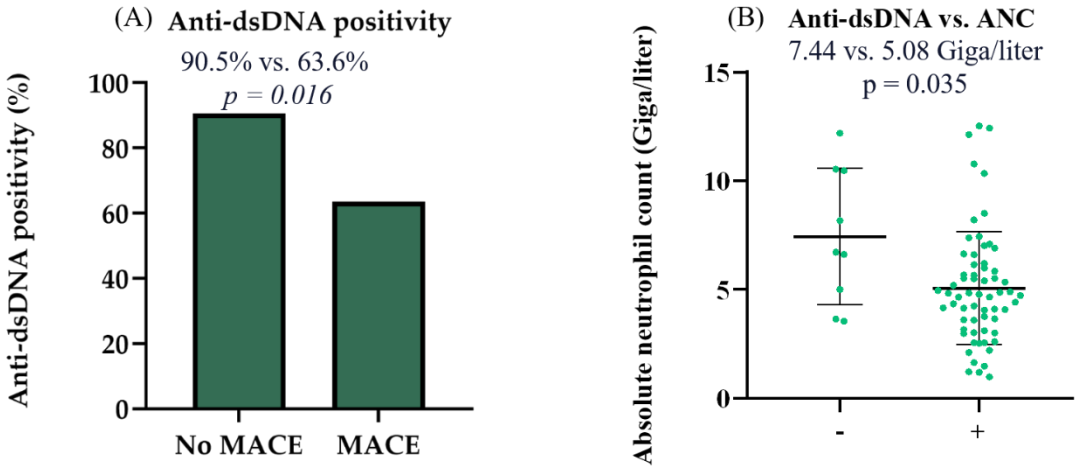

Figure 7. (A) Distribution of anti-dsDNA positivity in patients with MACE and no MACE at the time of the biopsy. **(B)** Absolute neutrophil count of patients with anti-dsDNA positivity and negativity. Chi-square test and Mann-Whitney U-test were used to analyze the differences between the groups. Anti-dsDNA anti-double-stranded deoxyribonucleic acid, MACE major adverse cardiovascular event, ANC absolute neutrophil count (13).

Pulse pressure was slightly wider among individuals with MACE compared to those without (54.07 vs. 51.66 mmHg), though the difference was not statistically significant (p = 0.842) (Table 7).

No significant relationship was found between MACE occurrence and remission status, including no remission (p = 0.953), partial remission (p = 0.790), or 3-year relapse (p = 0.953).

Out of these parameters, univariate logistic regression identified several factors associated with MACE, including older age (OR 1.059 per year, 95% confidence interval (CI) 1.013-1.017, p = 0.011), lower diastolic blood pressure (OR 0.889 per mmHg, 95% CI 0.824-0.958, p = 0.002), higher absolute neutrophil count (OR 1.248 per G/l, 95% CI 1.039-1.499, p = 0.018), use of anticoagulants (OR 6.000, 95% CI 1.795-20.052, p = 0.004) and beta-blockers (OR 3.529, 95% CI 1.087-11.462, p = 0.036), absence of anti-dsDNA positivity (OR 0.184, 95% CI 0.042-0.816, p = 0.026), presence of APS (OR 6.574, 95% CI 1.663-25.990, p = 0.007), and history of deep vein thrombosis (OR 6.000, 95% CI 1.759-20.461, p = 0.004) (Table 8).

Table 8. Risk factors for major adverse cardiovascular events in univariate logistic regression

OR odds ratio, dsDNA double-stranded deoxyribonucleic acid (13).

Variables	B	*p*	OR	Confidence Interval for OR	
				Lower	Upper
Univariate Logistic Regression					
Age (years)	0.057	***0.002***	1.059	1.013	1.017
Diastolic blood pressure (mmHg)	-0.118	***0.002***	0.889	0.824	0.958
Leukocyte count (G/l)	0.148	0.053	1.160	0.998	1.347
Neutrophil count (G/l)	0.222	***0.018***	1.248	1.039	1.499
Anticoagulant	1.792	***0.004***	6.000	1.795	20.052
Beta-blocker	1.261	***0.036***	3.529	1.087	11.462
Anti-dsDNA	-1.692	***0.026***	0.184	0.042	0.816
Antiphospholipid syndrome	1.883	***0.007***	6.574	1.663	25.990
Deep vein thrombosis	1.792	***0.004***	6.000	1.759	20.461

4.2.3. Subgroup analysis of patients with a history of major adverse cardiovascular events

Although limited by the small sample size, several noteworthy associations were observed in the subgroup analysis.

Patients with a history of coronary revascularization showed a significantly elevated neutrophil-platelet ratio (0.06 vs. 0.02; p = 0.02). Those who had experienced a stroke were older (56.20 vs. 36.20 years; p = 0.017) and had lower diastolic blood pressure (78.00 vs. 88.34 mmHg; p = 0.018). Patients hospitalized due to heart failure were more likely to be smokers (78.0% vs. 25.4%; p = 0.031) and had higher levels of C-reactive protein (18.13 vs.

7.52 mg/L; p = 0.021). During the study period, myocardial infarction occurred in two patients, and two individuals died from cardiovascular causes.

4.2.4. Assessment of long-term cardiovascular risk in lupus nephritis patients

To evaluate long-term cardiovascular risk in lupus nephritis patients, we developed a risk prediction model using logistic regression (Figure 8). Since logistic regression is commonly used for binary classification, it served as the foundation for our model. To ensure the model's effectiveness, we first identified independent variables that best predicted major adverse cardiovascular events. For the final multivariable prediction model, we selected one variable from each set of interrelated factors (neutrophil count and anti-dsDNA negativity, age and beta-blocker use, deep vein thrombosis, antiphospholipid syndrome, and anticoagulant use) based on univariate model fit and data availability (Table 9). The variable with the highest R-square value in each group (age, diastolic blood pressure, neutrophil count, and anticoagulant use) was included in the initial model (Table 10). Through a stepwise elimination process, the non-significant predictor (anticoagulant use) was removed, leaving three independent risk factors for major adverse cardiovascular events (Table 10-11).

Using these findings, we developed the CANDE score (Cardiovascular risk-based on Age, Neutrophil count, and Diastolic blood pressure Estimation Score) (Figure 9) to predict MACE risk in lupus nephritis patients at the time of renal biopsy. Predictor weights were derived from the final logistic regression model's β coefficients' nearest integer, with age categorized into 10-year intervals to simplify calculations. The CANDE score represents a linear combination of these weighted variables.

Figure 8. Risk prediction model with logistic regression

$$log\ (\frac{P\ (Y=1)}{1-P(Y=1)}) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ ...\beta_n X_n$$

$P\ (Y = 1)$ is the probability that MACE occurs

$\frac{P\ (Y=1)}{1-P(Y=1)}$ The ratio is the odds, which compares the probability of MACE occurring to the probability of MACE not occurring.

β_0 is the intercept, which represents the log-odds when all predictors are zero

$\beta_1, \beta_2, ...\beta_n$ are regression coefficients showing how each predictor influences the log-odds of the outcome

$X_1, X_2, ... X_n$ are the independent variables

Table 9. Step 1 to select variables based on R square values and availability of data points within the group of interrelated variables (13)

Interrelated variables	Number of data points	R square from the univariate model
Absolute neutrophil count	87	0.108
Anti-dsDNA	74	0.105
Age	91	0.124
Beta-blocker use	91	0.08
Anticoagulant use	91	0.155
Deep vein thrombosis	91	0.145
Antiphospholipid syndrome	91	0.123

Table 10. Step 2 to select independent risk factors for MACE

OR odds ratio, mmHg millimeter of mercury, G/l giga/liter, CI confidence interval (13).

Variables	B	*p*	OR	95% CI for OR	
				Lower	Upper
Multivariate Logistic Regression					
Diastolic blood pressure (mmHg)	-0.099	***0.027***	0.906	0.830	0.989
Neutrophil count (G/l)	0.247	***0.042***	1.281	1.009	1.626
Age (years)	0.061	***0.031***	1.063	1.006	1.123
Anticoagulant	1.462	0.062	4.314	0.931	19.979
Constant	2.079	0.604	7.995		

Table 11. Step 3 to select independent risk factors for MACE

OR odds ratio, mmHg millimeter of mercury, G/l giga/liter, CI confidence interval (13).

Variables	B	*p*	OR	95% CI for OR	
				Lower	Upper
Multivariate Logistic Regression					
Diastolic blood pressure (mmHg)	-0.124	***0.005***	0.884	0.810	0.964
Neutrophil count (G/l)	0.278	***0.020***	1.320	1.044	1.668
Age (years)	0.052	***0.048***	1.053	1.000	1.109
Constant	4.877	*0.188*	131.211		

Figure 9. Development of CANDE score

$$CANDE\ score\ (point) = \beta_1\ x\ diastolic\ blood\ pressure + \beta_2\ x\ neutrophil\ count + \beta_3\ 10\ years\ age$$

$$CANDE\ score\ (point) = -0.124\ x\ diastolic\ blood\ pressure + 0.278\ x\ neutrophil\ count + 0.52\ x\ 10\ age$$

Nearest integer of beta values for easier calculation:

β_1 (Diastolic blood pressure) = -0.124 $\sim$ -1

β_2 (Neutrophil count) = 0.278 $\sim$ 2

β_3 (Age) = 0.052 $\rightarrow$ β (10-year age) = 0.52 $\sim$ 4

$$CANDE\ score = -1\ x\ diastolic\ blood\ pressure + 2\ x\ neutrophil\ count + 4\ x\ 10\ years\ age$$

By applying logistic regression with the CANDE score, as the independent variable, we found that each 1-point increase in the score corresponded to a 13.7% rise in the MACE risk ($p < 0.001$) (Table 12). The model demonstrated good calibration, as confirmed by the Hosmer-Lemeshow test ($\chi^2 = 2.322$, $p = 0.970$).

The logistic regression model provides a framework to directly estimate the absolute risk of MACE for each patient based on their specific CANDE score. Using the model's intercept (β_0) and coefficient (β), individual point scores can be converted into probabilities (Figure 10).

Table 12. Relative risk: CANDE score (point) and MACE association

OR odds ratio, CI confidence interval (13).

Variables	B	*p*	OR	95% CI l for OR	
				Lower	Upper
Point	0.128	***<0.001***	1.137	1.062	1.217
Constant	5.414	*0.003*	224.531		

Figure 10. Converting log-odds to probability

$$p = \frac{1}{1+e^{-(\beta_0+\beta \text{ x points})}}$$

$$p = \frac{1}{1+e^{-(5.414+0.128 \text{ x points})}}$$

Figure 10. Converting log-odds to probability. This formula outputs a probability between 0 and 1, making logistic regression useful for predicting risk probabilities

To enhance clarity and practical application, we developed a risk assessment table and a graph allowing healthcare providers to estimate absolute MACE risk for lupus nephritis patients based on their CANDE score (Figure 11-12). For example, the CANDE score of a 37-year-old patient, with absolute neutrophil count 7 Giga/liter, and diastolic blood pressure 75 mmHg is -46,2 (CANDE score = -1x75 + 2x7 + 4x3.7 = -46,2), which corresponds to a 38.36% MACE risk.

Figure 11. Absolute risk: risk assessment table for MACE in lupus nephritis at the time of the biopsy

CANDE score (point)	Risk of MACE	95% confidence interval
-30	82.8%	49-96%
-35	71.8%	41-90%
-40	57.3%	32-79%
-45	41.4%	24-61%
-50	27.2%	16-42%
-55	16.4%	8-29%
-60	9.4%	4-20%
-65	5.2%	2-15%
-70	2.8%	1-11%
-75	1.5%	0-8%
-80	0.8%	0-6&
-85	0.4%	0-4%
-90	0.2%	0-3%

Figure 11. Risk assessment table for MACE in lupus nephritis at the time of the biopsy. The rounded β values (coefficients) from the final multivariable logistic regression were used as weighting factors for the calculation of the CANDE score. The logistic regression model provides a framework for estimating these probabilities to calculate the absolute risk of MACE directly for each patient based on their specific CANDE score (points). The risk assessment table facilitates the practical use of the score. MACE major adverse cardiovascular event, G/l Giga/liter, mmHg millimeters of mercury (13).

Figure 12. CANDE score and probability

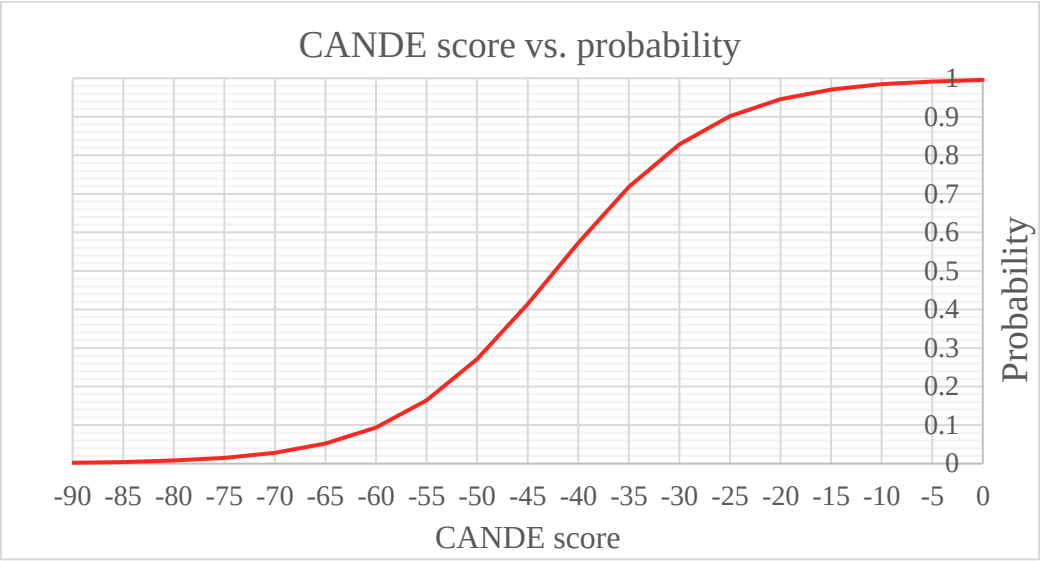

Figure 12. The graph illustrates the relationship between the CANDE score and probability. It shows an exponentially increasing curve, indicating that a higher CANDE score corresponds to a greater probability.

The CANDE score was validated in both the group where MACE was assessed over the entire medical history (OR 1.137; $p < 0.001$) and the subset where MACE was observed following renal biopsy (OR 1.081; $p = 0.01$) (Table 13). The ROC curve analysis confirmed the model's strong predictive power, with an AUC of 0.866 (95% CI: 0.768–0.965). At the optimal cut-off value of -53.73, the CANDE score achieved a sensitivity of 78.6% and a specificity of 81.9%, supporting its utility in predicting long-term cardiovascular risk in lupus nephritis patients (Figure 13).

Table 13. CANDE score

OR, odds ratio, CANDE, Cardiovascular risk - based on Age, Neutrophil count, and Diastolic blood pressure Estimation Score, MACE, major adverse cardiovascular event, CI confidence interval (13).

Variables	B	*p*	OR	95% CI for OR	
				Lower	Upper
CANDE score					
MACE in medical history	0.128	***<0.001***	1.137	1.062	1.217
MACE after the kidney biopsy	0.078	***0.030***	1.081	1.019	1.147

Figure 13. Receiver operating characteristic (ROC) curve and area under the curve (AUC) for CANDE score

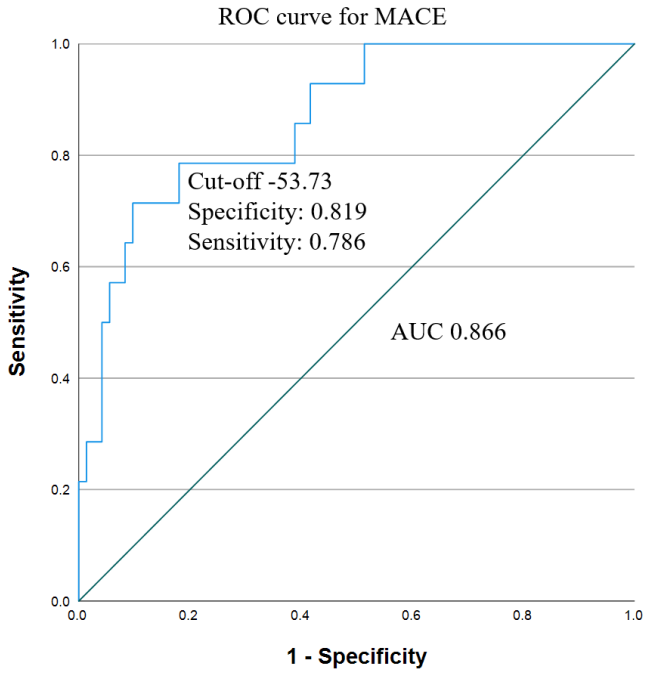

Figure 13. Receiver operating characteristic (ROC) curve and area under the curve (AUC) with cut-off value, sensitivity and specificity for CANDE score predicting MACE. MACE major adverse cardiovascular event (13).

5. Discussion

A well-organized renal biopsy database is a crucial resource for epidemiological and clinical research. It not only provides valuable insights into disease prevalence and progression, but it also streamlines clinical investigations by enabling the efficient identification of target patient populations. Through systematically collecting and categorizing biopsy data, researchers can analyze patterns, assess treatment outcomes, and find potential biomarkers for disease prognosis. Moreover, a comprehensive database supports multicenter collaborations, enhances the reproducibility of studies, and contributes to developing evidence-based guidelines for patient management.

Numerous countries maintain such registries and databases to enhance clinical research and improve diagnostic accuracy. This study underscores the importance of developing robust national and international biopsy registries, as cross-border comparisons can contribute to quality control and global improvements in nephrology care.

5.1. Epidemiologic analysis of the database

Our comprehensive 15-year retrospective analysis of renal biopsy data offers valuable insights into the demographics and prevalence of kidney diseases in Hungary. Although our study was conducted at a single pathology center, it encompasses nearly half of the Hungarian population, allowing for broader generalization of the findings.

Our database exhibits a slight female predominance, which may be attributed to the declining male-to-female demographic ratio with advancing age (14). However, the biopsy rate among males was relatively higher, aligning with findings from other European studies (1).

The mean patient age was 44.2 ± 21.9 years, consistent with data from similar registries (1). Including additional non-pediatric tertiary nephrology centers within our catchment area can partly explain the increased biopsy samples from 2014. However, the aging population and the subsequent rise in biopsy rates among elderly patients also likely played a role. This trend suggests an extended life expectancy and may indirectly reflect improvements in healthcare and social conditions (15).

The average renal biopsy rate of 36.3 per one million person-years remains lower than most European reports (1). However, since 2015, our data collection rate has significantly increased, suggesting a trend toward catching up. Several factors may explain the historically lower biopsy rates, including the geographically dispersed catchment area, the limited number of hospitals maintaining regular collaboration with the university pathology department, and a traditionally conservative approach to biopsy indications. Financial constraints may have also contributed (1, 16).

Nevertheless, in the most recent years, there has been a notable increase in biopsy rates, likely driven by advancements in procedural proficiency, improved safety outcomes, and a growing number of nephrologists skilled in renal biopsy techniques. Increased confidence among nephrologists regarding their colleagues' expertise has further facilitated biopsy requests. Additionally, shifts in medical training paradigms, the increasing presence of nephrologists trained abroad, and greater exposure to biopsy techniques during training have contributed to this trend. As a result, biopsy rates may continue to rise in the future (17). The widespread accessibility of online medical literature and databases has also played a role in reducing the threshold for biopsy indications. Additionally, the actual incidence of kidney diseases may have increased due to an aging and expanding patient population, as certain renal pathologies and systemic disease manifestations become more prevalent over time.

Our findings reaffirm that glomerular diseases constitute the predominant renal pathology, a trend consistent with most biopsy registries (18-42). Among these, IgA nephropathy emerged as the most common diagnosis, in agreement with data from another Hungarian database and multiple international studies (16, 18-21, 29, 30, 43-62). Interestingly, while IgA nephropathy dominates in Hungary and several other regions, other countries - particularly outside Europe - report membranous nephropathy (22, 23, 26, 37, 63, 64) or focal segmental glomerulosclerosis/minimal change disease (24, 25, 32-36, 39, 41, 65-74) as the most frequently diagnosed conditions. Furthermore, membranoproliferative glomerulonephritis has been observed to prevail in African and Eastern populations (41, 74-80). In certain regions, lupus nephritis, diffuse endocapillary glomerulonephritis, IgM nephropathy, and hereditary nephropathies are more prevalent among biopsy-confirmed cases (Figure 14) (42, 81-85). These geographical variations in disease prevalence reflect

differences in genetic predisposition, lifestyle, environmental factors, and, most importantly, biopsy indication practices.

Figure 14. Overview of the most frequent renal diseases in renal registries and studies around the world

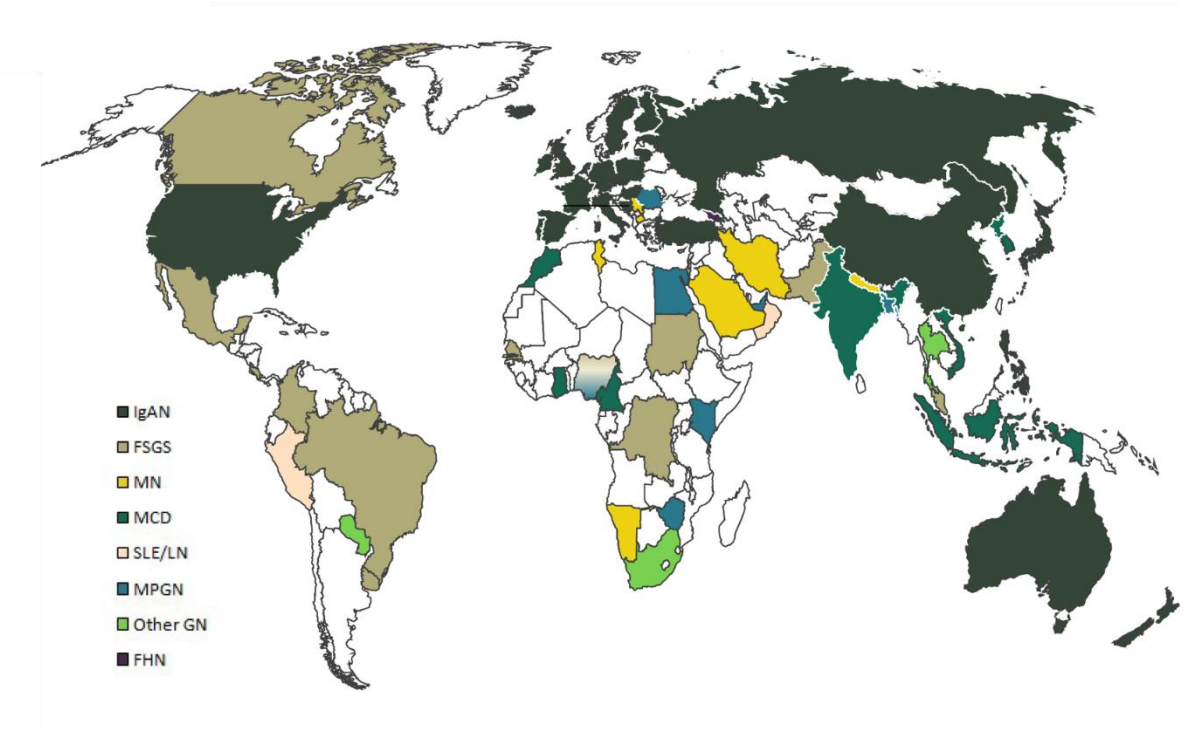

Figure 14. Overview of the most frequent renal diseases in renal registries and studies around the world. Biopsy indication was heterogeneous except in Cameroon, Senegal, Ghana, and Zaire, where only nephrotic syndrome was considered. Information was not found from countries left white. IgAN IgA nephropathy – histologically proven and Henoch-Schönlein purpura/nephritis, FSGS focal segmental glomerulosclerosis, MN membranous nephropathy (primary and secondary), MCD minimal change disease, SLE/LN systemic lupus erythematosus/lupus nephritis, MPGN membranoproliferative glomerulonephritis, Other GN other glomerulonephritis, FHN familial/hereditary nephropathies, MISC miscellaneous diseases (12).

Hypertension prevalence increases with age, and renal manifestations may parallel this trend (86). However, our study observed a relatively low and decreasing frequency of hypertension or renovascular disease-related diagnoses in biopsy trends despite the aging population. This may reflect improved medical management and blood pressure control, even among elderly patients. Alternatively, a dilution effect cannot be excluded: the rise in overall

biopsy rates may have led to a proportionally lower representation of hypertensive nephropathy as the primary diagnosis. It is important to note that while many biopsy specimens exhibited arterial hyalinosis indicative of hypertension, these were not classified as primary hypertensive nephropathy unless no other significant renal pathology was identified.

Over time, the declining incidence of tubulointerstitial diseases can be attributed to several key factors. While the etiology of this heterogeneous disease group was historically unclear in many cases, a significant proportion has been linked to drug-induced nephrotoxicity. Increased awareness of nephrotoxic agents has led to a more cautious use of drugs (e.g., non-steroid anti-inflammatory drugs) known to cause tubulointerstitial injury.

Immune-mediated tubulointerstitial injury represents another major etiology. Advances in immunosuppressive therapies have significantly improved the management of autoimmune disorders such as Sjögren's syndrome, thereby reducing renal involvement and minimizing disease progression. Additionally, better screening tools enable routine blood and urine tests help to detect early kidney dysfunction before it progresses to significant tubulointerstitial damage.

We could not exclude the decrease due to improved regulations and workplace safety measures: environmental and occupational exposure to nephrotoxins, particularly heavy metals, has markedly declined due to stricter regulations and improved workplace safety measures. These preventive efforts have likely contributed to the observed reduction in the incidence of tubulointerstitial diseases (87).

Over the years, our study also noted an increasing incidence of microscopic polyangiitis, a trend consistent with previous epidemiological studies (88). Given that ANCA-associated vasculitis (AAV) is more prevalent among older individuals, population aging likely contributes to this trend (89). This is also funded by the decline in competing mortality: in the past, many patients with AAV may not have survived long enough for diagnosis due to severe infections or other comorbidities. With improved overall healthcare and better management of chronic diseases, more individuals reach an age where AAV becomes clinically apparent. However, the observed rise in cases may also reflect improved diagnostic awareness and testing. Advances in serological testing, such as more widespread

and sensitive ANCA assays, have led to increased detection rates (90). Additionally, heightened awareness among clinicians – fostered by improved medical education – may have contributed to increased case recognition (88). Nevertheless, the possibility of a genuine biological increase in disease incidence cannot be ruled out. Moreover, shifts in environmental factors, including alterations in infectious patterns, which have been implicated in the pathogenesis of AAV, may also contribute to the observed rise in cases (91).

MPA is typically reported to exhibit a slight female predominance, whereas GPA is more frequently observed in males. Our findings align with these reports, demonstrating a significant female predominance across all age groups in MPA and a mild male predominance in GPA (88). This sex-based difference is likely to be driven by a complex interplay of hormonal, genetic, and environmental factors. The higher prevalence of MPA in females further underscores potential differences in immune regulation between these two forms of ANCA-associated vasculitis.

Historically, the incidence of MPGN has been on the decline in most developed countries, including those in Europe (1). This trend is largely attributed to improved management of underlying conditions associated with MPGN, such as infections and autoimmune diseases. The reason why MPGN increased over time is inconclusive, particularly because, in our study, this trend was both age and sex independent. This suggests that demographic shifts alone cannot fully account for the rising incidence. Further investigation is needed to explore potential contributing factors, including evolving diagnostic criteria, heightened clinical awareness, improvements in biopsy practices, and changes in underlying etiologies (infections, immune-mediated disorders, complement dysregulations, or monoclonal gammopathies).

The observed decline in the incidence of familial and hereditary nephropathies, minimal change disease, and focal segmental glomerulosclerosis over time can be attributed to demographic shifts, particularly the aging population and the proportional decrease in pediatric cases within our cohort. Given that these conditions are more commonly diagnosed in younger individuals, their relative frequency naturally declines as the study population skews toward older age groups.

Membranous nephropathy was found to increase with age and demonstrated a male predominance, a trend likely driven by the aging population and its associated rise in malignancy incidence (92). This finding aligns with international reports (93). Additionally, environmental factors such as increasing air pollution levels may contribute to MN prevalence (94). Notably, Hungary has one of the highest global incidences of lung and colorectal cancer, along with significant rates of ovarian and bladder cancers, which may partly explain the higher proportion of MN cases observed in our study compared to neighboring countries (95). Furthermore, our findings suggest that MN manifests at a younger age in males, potentially due to lower participation in screening programs, dietary factors, and lifestyle differences (96). The introduction of anti-PLA2R (phospholipase A2 receptor) titer measurements has expanded diagnostic capabilities, potentially reducing the need for biopsy in primary MN cases (97).

Diabetic nephropathy exhibited a higher prevalence among elderly individuals and males. This trend aligns with the established epidemiological patterns. Men are at greater risk of developing type 2 diabetes mellitus, and there is also a relative male predominance in type 1 diabetes mellitus as well. Additionally, men are often diagnosed with diabetes at a younger age, which extends their exposure to chronic hyperglycemia and increases the likelihood nephropathy progression over time (98). Beyond glycemic factors, men also exhibit a higher prevalence of aggravating comorbidities, including dyslipidemia and hypertension, both of which accelerating glomerular injury, endothelial dysfunction and renal fibrosis (99). These factors collectively contribute to the observed male predominance in diabetic nephropathy.

The reported prevalence of diabetic nephropathy varies across studies. In our cohort, its incidence exceeded that of most countries, consistent with Hungary's high obesity and overweight rates (14). However, a Western German study reported a 3.6-fold higher prevalence of diabetic nephropathy, highlighting potential differences in biopsy indications (18). The lower incidence observed in our study may stem from the practice of reserving renal biopsy for diabetic patients only in cases of unexpected proteinuria severity or unexplained renal function decline. Notably, advanced structural damage can be present even in early diabetic nephropathy, despite normal renal function. This underscores the potential

benefits of a less restrictive approach to biopsy indications and highlights the need for improved secondary prevention strategies in Hungary.

Younger patients exhibited higher frequencies of lupus nephritis, IgA nephropathy, minimal change disease, and focal segmental glomerulosclerosis, suggesting potential genetic predispositions contributing to the early onset of these conditions.

The female predominance observed in amyloidosis cases corresponds with the higher prevalence of amyloid A (AA) amyloidosis, which was frequently associated with underlying rheumatoid arthritis – a disease more common in females. Additional cases were linked to inflammatory bowel disease, reinforcing the relationship between chronic inflammatory conditions and AA amyloidosis prevalence.

The COVID-19 pandemic significantly impacted healthcare systems worldwide, including renal biopsy practices. In 2020, biopsy rates in Hungary declined compared to previous years, as many nephrology departments shifted focus to urgent COVID-19 care. Additionally, patients with stable kidney disease may have postponed hospital visits due to concerns about viral exposure. As a result, only cases of rapidly progressive renal disease or those requiring histopathological confirmation for treatment decisions were prioritized for biopsy. Interestingly, the incidence of MN diagnoses decreased significantly during this period, likely due to the increased use of anti-PLA2R serology, which in primary MN cases may preclude the need for biopsy, particularly in resource-constrained settings. The rise in granulomatosis with polyangiitis cases during the pandemic could reflect improved disease recognition, although a direct impact of COVID-19 cannot be ruled out. Further data are needed to elucidate these trends.

Our retrospective analysis provides long-term insights into kidney disease trends diagnosed via renal biopsy in Hungary.

Scientific societies should actively support the establishment and expansion of national and international biopsy registries. These registries are vital for advancing nephrology research, standardizing clinical practice, and improving patient outcomes worldwide. Hungary has already established a renal biopsy registry, which enables better epidemiological tracking of kidney diseases and contributes valuable data to international collaborative studies aimed at optimizing renal care.

5.2. Lupus nephritis and MACE

Our decision to conduct a more in-depth analysis of lupus nephritis was based on the following considerations. Lupus nephritis represents a well-defined clinical entity that, according to established guidelines, almost invariably requires a renal biopsy for accurate diagnosis and classification. This mandatory biopsy requirement provides a distinct advantage in research, as it allows for a direct correlation between clinical presentation, laboratory findings, and histopathological features. Given these factors, focusing on this patient group allows for robust, pathology-supported clinical research with significant implications for patient care and possible future therapeutic advancements.

Our 16-year retrospective cohort study provides valuable insights into cardiovascular risk factors present at the time of biopsy in lupus nephritis patients. We identified lower diastolic blood pressure, higher neutrophil count, and age as independent predictors of major adverse cardiovascular events. Using multivariate logistic regression, we developed the CANDE score – an assessment tool designed to aid in predicting MACE risk in lupus nephritis patients. The CANDE score has the potential to be a rapid, cost-effective, and easily accessible method for evaluating cardiovascular risks at the time of biopsy. Our study highlights the critical need for proactive cardiovascular risk screening in this high-risk patient group.

While our predictive model cannot prove cause and effect, its main factors are clearly connected to cardiovascular complications.

Diastolic hypotension has been recognized as an independent risk factor for heart failure (100). Unlike the direct correlation between systolic blood pressure (SBP) and cardiovascular (CV) risk, diastolic blood pressure follows a J-shaped relationship with cardiovascular disease (101). Data from NHANES III (National Health and Nutrition Examination Survey III) and the Framingham Heart Study indicate that pulse pressure (PP) increases as DBP declines in later decades of life, primarily due to arterial stiffness caused by atherosclerosis (102, 103). This arterial stiffening leads to reduced elasticity, diminished arterial compliance, and lower DBP. Over time, these changes contribute to increased afterload, rising SBP, and widening PP – factors linked to adverse cardiovascular and renal

outcomes (104). The resulting elevated myocardial oxygen demand can ultimately lead to ischemia and both systolic and diastolic dysfunction (100).

DBP also plays a crucial role in left coronary perfusion. During diastole, the myocardium relaxes, relieving extravascular compression on the coronary arteries and allowing full perfusion. However, coronary perfusion is dependent on the difference between aortic diastolic pressure and left ventricular end-diastolic pressure (105). A decline in DBP reduces coronary blood flow, increasing the risk of myocardial hypoxia and contractile dysfunction. These physiological relationships are particularly relevant for lupus nephritis patients, who face an elevated risk of atherosclerosis, arterial stiffness, coronary artery disease, and left ventricular hypertrophy compared to the general population and SLE patients without renal involvement (106).

Although our study did not observe isolated diastolic hypotension (DBP ranged from 60-114 mmHg) or significant variations in PP, we found that patients who experienced MACE had slightly lower DBP, suggesting an underlying acceleration of atherosclerosis – even among relatively young individuals. This finding reinforces the necessity for comprehensive cardiovascular risk screening and prevention strategies in this patient group.

Atherosclerosis is a complex process involving vascular and immune cells, occurring alongside chronic inflammation. Subclinical atherosclerosis is present in 25-56% of SLE patients and progresses at a significantly faster rate than in the general population (10% vs. 5% per year) (107). Given that immune dysregulation is central to SLE, it significantly contributes to atherosclerosis. Our study underlines the possible role of neutrophils in the development of MACE.

Dysregulation of the innate immune system – particularly involving neutrophil granulocytes – plays a key role in the cardiovascular complications observed in SLE patients. Neutrophils, the most abundant and rapidly responsive immune cells, have a potent antimicrobial defense but can also cause tissue damage and release autoantigens. A subset of neutrophils known as low-density granulocytes (LDGs) exhibits a highly proinflammatory phenotype in SLE, contributing to atherosclerosis through inflammatory cytokine release, increased neutrophil extracellular trap (NET) formation, and mitochondrial reactive oxygen species production. NETosis, an inflammatory process, further accelerates atherosclerosis.

NETs also promote both arterial and venous thrombosis by acting as a scaffold for platelet aggregation. Additionally, localized hypoxia triggers the release of endothelial procoagulant factors, enhancing thrombogenesis (108). These findings underscore the significant impact of innate immune dysregulation – particularly involving neutrophils and NETs – in driving cardiovascular complications in SLE patients.

Long-term glucocorticoid use further exacerbates cardiovascular risk by promoting dyslipidemia, obesity, diabetes, and hypertension. Glucocorticoids impair insulin sensitivity, enhance lipolysis, and promote gluconeogenesis, ultimately contributing to visceral obesity – a major cardiovascular risk factor. Additionally, glucocorticoids interfere with vasodilation, increase cardiac contractility, and expand plasma volume, which can lead to hypertension and cardiac hypertrophy (109, 110). Glucocorticoids also enhance coagulation by increasing procoagulant factors, hematocrit, and blood viscosity, contributing to endothelial dysfunction and a hypercoagulable state (111). Multiple SLE cohort studies have linked higher cumulative glucocorticoid doses to an increased incidence of cardiovascular events (112-115). However, our study was not designed to quantify cumulative steroid and immunosuppressive (ISU) doses, which may explain why ISU use did not significantly influence MACE occurrence. Furthermore, many of our patients were on low-dose glucocorticoid therapy, limiting our ability to establish a meaningful control group.

Anti-dsDNA positivity is typically associated with increased cardiovascular risk due to its link to inflammatory mediators, endothelial dysfunction, and accelerated atherosclerosis. It is also correlated with elevated NET-derived molecules, such as neutrophil elastase and myeloperoxidase (116, 117). However, in contrast to prior studies, our findings suggest that anti-dsDNA positivity was associated with fewer MACE cases. Notably, neutrophil counts were higher in anti-dsDNA-negative cases, which aligns with previous research showing that anti-dsDNA accelerates neutrophil apoptosis (118-120). Variability in measurement methods over time may have influenced our results, and further investigation is needed to clarify these findings.

APS significantly increases the risk of atherosclerosis, myocardial infarction, stroke, and valvular heart disease. Antiphospholipid antibodies interact with endothelial β2-glycoprotein 1 (β2-GP1) receptors, leading to endothelial dysfunction through multiple

mechanisms. By inhibiting endothelial nitric oxide synthesis, these antibodies disrupt leukocyte adhesion, endothelial cell growth, vascular permeability, and smooth muscle proliferation. APS antibodies enhance the expression of leukocyte adhesion molecules while simultaneously triggering endothelin-1 and tissue factor production, leading to thrombocyte aggregation (121). Furthermore, anti-β2-GP1 and anticardiolipin antibodies contribute to atherosclerosis by promoting the uptake of oxidized low-density lipoproteins by macrophages (122, 123). Valvular involvement is another common cardiac complication of APS, affecting approximately 15-30% of patients. This typically presents as thickening, dysfunction, or vegetations on the atrial side of the mitral valve or the vascular surface of the aortic valves. While the exact mechanism remains unclear, it is believed that anti-β2-GP1 antibodies bind to β2-GP1 on valvular endothelial cells, leading to endothelial dysfunction and complement activation (124).

Despite the heightened cardiovascular risk in SLE patients, particularly those with renal involvement, there are no specific primary prevention guidelines tailored to this population aside from APS management (125-127). General recommendations emphasize smoking cessation, diabetes control, and physical activity (128). Statin therapy in SLE patients is advised based on American Heart Association and American College of Cardiology guidelines (129). Additionally, individuals with sustained blood pressure levels of 130-139/80-89 mmHg over two years have a markedly higher risk of developing atherosclerosis compared to normotensive individuals (130). While no specific antihypertensive regimen is recommended for lupus patients, angiotensin convertase enzyme inhibitors (ACE-I) are commonly used due to their renal protective effects. The LUMINA study proposed that ACE inhibitors could delay renal complications and lower disease activity in SLE, offering potential for primary prevention (131). Furthermore, ACE inhibitors significantly reduce proteinuria, a key cardiovascular risk factor. As a result, the European Alliance of Associations for Rheumatology (EULAR) and the European Renal Association (ERA) recommend renin-angiotensin-aldosterone system blockade, even in the absence of lupus nephritis (125, 128, 132). However, our study revealed that only 50.6% of SLE patients were on ACE-I/ARB therapy at biopsy, and 9.8% of hypertensive patients were not receiving

ACE-I/ARB treatment, highlighting gaps between clinical practice and guideline recommendations.

Although well-established risk factors exist in SLE, primary prevention remains ineffective for several reasons. Since SLE primarily affects younger individuals, traditional risk factors are often overlooked. Additionally, routine screening for cardiovascular risk factors like LDL cholesterol, BMI, and diabetes is frequently neglected, reflecting a general lack of awareness – a limitation that was also evident in our study, where inconsistent documentation precluded a detailed analysis of traditional cardiovascular risk factors in lupus nephritis patients. The limited literature on targeted preventive measures and the absence of comprehensive guidelines that address the disease's interdisciplinary nature further contribute to this gap. Moreover, many major clinical trials exclude active lupus nephritis patients, leaving a void in evidence-based recommendations. This shortfall is also evident in clinical practice, where physicians tend to focus on urgent, specialized concerns while neglecting long-term preventive strategies.

Conventional cardiovascular risk assessment tools, such as the Framingham Risk Score and ASCVD (Atherosclerotic Cardiovascular Disease) Score, primarily consider traditional risk factors and overlook the impact of chronic inflammation and prolonged steroid use in SLE (133). The QRISK3 (Quantitative Risk Assessment for Individuals version 3) calculator offers a more accurate risk estimate for SLE patients by incorporating both traditional and disease-specific risk factors, such as chronic kidney disease and SLE itself (134). The CANDE score is the first CV risk calculator specifically designed for lupus nephritis patients. Its key advantage lies in its ability to be applied at the time of biopsy, offering a quick and accessible method for predicting MACE risk.

Our study has limitations, including a relatively small patient cohort, single-center data, and retrospective design. Additionally, racial diversity was lacking, as the study population was limited to Caucasian patients in Hungary. Despite these limitations, after external validation, the CANDE score may become a widely accessible and cost-effective risk assessment tool for lupus nephritis patients. We encourage further independent validation studies to refine and enhance its clinical utility.

Our findings emphasize the need for continued renal biopsy-based research to enhance risk stratification and improve patient outcomes. The expansion of regional renal biopsy registries will not only refine our understanding of renal disease trends but also facilitate global data comparisons, ultimately informing healthcare policies and resource allocation.

Moving forward, future studies should focus on validating the CANDE model in larger, multi-center cohorts to assess its generalizability and clinical utility. If successfully implemented, the CANDE score could aid clinicians in identifying high-risk lupus nephritis patients early, potentially guiding preventive cardiovascular interventions. Additionally, further research is needed to explore the mechanistic pathways linking inflammation, nephropathy, and cardiovascular disease in lupus patients.

6. Conclusions

We established a comprehensive renal biopsy database with standardized diagnostic nomenclature.

Between 2006 and 2020, the biopsy rate in Hungary increased, and this rise was accompanied by a significant increase in the median age of biopsy recipients, reflecting a growing burden of age-related kidney diseases.

The distribution of glomerular diseases remained stable, with IgA nephropathy being the most common diagnosis. Age and sex influenced disease patterns. In trends, we observed an increasing incidence of ANCA-associated vasculitis, and the COVID-19 pandemic reduced biopsy rates and altered disease distribution, leading to a lower proportion of membranous nephropathy diagnoses.

These findings align with global trends, where population aging and shifts in disease patterns necessitate adaptive nephrology practices. These observations emphasize the need for flexible healthcare strategies that respond to demographic shifts and emerging public health challenges.

Developing and maintaining renal biopsy registries are fundamental to understanding epidemiological trends, optimizing healthcare resource allocation, and advancing nephrology research. Systematic data collection allows for meaningful comparisons across populations, providing insights into socioeconomic, genetic, and environmental factors influencing renal disease prevalence and progression.

Beyond epidemiological analysis, we leveraged our renal biopsy database to investigate cardiovascular risk in lupus nephritis patients, a population with significantly elevated MACE risk.

In our retrospective analysis of lupus nephritis patients, the independent risk factors of MACE included older age, higher neutrophil counts, and lower diastolic blood pressure.

Based on these findings, we introduce the CANDE model (Cardiovascular Risk Based on Age, Neutrophil Count, and Diastolic Blood Pressure Estimation Score), a practical and efficient tool for estimating MACE risk in lupus nephritis patients.

To enhance clinical applicability, we developed a risk assessment table to help healthcare providers estimate MACE risk in lupus nephritis patients. CANDE score showed

high sensitivity (78.6%) and specificity (81.9%), confirming its effectiveness in predicting MACE risk in lupus nephritis patients.

By incorporating three easily measurable clinical parameters, CANDE serves as a practical tool for early cardiovascular risk assessment, supporting timely interventions and personalized treatment strategies.

In conclusion, this study underscores the critical role of renal biopsy registries in nephrology research and highlights the need for targeted cardiovascular risk assessment in lupus nephritis patients. By developing a predictive model, we can improve early detection, optimize therapeutic strategies, and improve long-term renal and cardiovascular outcomes in high-risk patient populations. Future research should focus on validating CANDE in larger, multicenter cohorts and integrating it into clinical decision-making algorithms for broader applicability.

7. Summary

Background: Renal biopsy registries are crucial for tracking disease trends, optimizing resources, and advancing research.

Objectives: Our study aimed to establish a standardized renal biopsy database to analyze Hungarian trends in renal disease distribution and temporal changes. We also investigated cardiovascular (CV) risk in lupus nephritis patients, a cohort requiring mandatory renal biopsy.

Methods: We retrospectively analyzed 2140 renal biopsies (2006–2020) from 28 nephrology centers in Northern and Central Hungary, using standardized diagnostic criteria. Lupus nephritis patients (biopsied 2005–2020) were further examined for clinical and pathological data. Major adverse cardiovascular events (MACE) included myocardial infarction, heart failure hospitalization, stroke, coronary revascularization, and cardiovascular death. Statistical analysis was conducted with IBM SPSS v28 and GraphPad Prism v9.0.

Results: IgA nephropathy was the most common diagnosis, followed by focal segmental glomerulosclerosis and membranous nephropathy. Disease distribution varied by age and sex: diabetic and membranous nephropathy were more common in men, while lupus nephritis and microscopic polyangiitis predominated in women. ANCA-associated vasculitis increased over time. Among 91 lupus nephritis patients, 15.38% experienced MACE over a mean follow-up of 62 ± 48 months. Older age, higher neutrophil counts, and lower diastolic blood pressure were independent risk factors. We introduced the CANDE model (Cardiovascular Risk Based on Age, Neutrophil Count, and Diastolic Blood Pressure Estimation Score) to predict MACE risk. 1 point increase in CANDE correlated with a 13.7% higher relative MACE risk. The model demonstrated high sensitivity (78.6%) and specificity (81.9%).

Conclusions: Our findings highlight evolving renal disease patterns in Hungary and emphasize the importance of CV risk assessment in lupus nephritis patients. The CANDE model provides a simple, effective tool for early risk prediction, supporting timely interventions and improved patient outcomes.

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9. Bibliography of the candidate's publications

9.1. Publications directly related to the PhD dissertation

- **Molnár, Adél**; Juha, Márk; Bulajcsík, Klaudia; Tabák, Ádám Gy.; Tislér, András; Ledó, Nóra: Proposal of a novel cardiovascular risk prediction score in lupus nephritis; FRONTIERS IN IMMUNOLOGY 15 P: 1405463 , 12 p. (2024) IF: 5.7 (2023)
- **Molnár, Adél**; Thomas, Mbuotidem Jeremiah; Fintha, Attila; Kardos, Magdolna; Dobi, Deján; Tislér, András; Ledó, Nóra; Kidney biopsy-based epidemiologic analysis shows growing biopsy rate among the elderly; SCIENTIFIC REPORTS 11 : 1 Paper: 24479 , 14 p. (2021) IF: 4.997

9.2. Publications not directly related to the PhD dissertation

- Juha, Márk; **Molnár, Adél**; Jakus, Zoltán; Ledó, Nóra: NETosis: an emerging therapeutic target in renal diseases; FRONTIERS IN IMMUNOLOGY 14 P: 1253667, 23 p. (2023) IF: 5.7 (2023)
- **Molnár, Adél**; Tislér, András; Dobi, Deján; Pethő, Ákos; A unique case of anti-GBM disease with concomitant anti-PLA2R positivity; BMC NEPHROLOGY 23 : 1 Paper: 337 , 5 p. (2022) IF: 2.3 (2022)
- **Molnár, Adél**; Studinger, Péter; Ledó, Nóra; Diagnostic and Therapeutic Approach in ANCA-Associated Glomerulonephritis: A Review on Management Strategies; FRONTIERS IN MEDICINE 9 Paper: 884188 , 20 p. (2022) IF: 3.9 (2021)
- Schneider, Miklós; **Molnár, Adél**; Angeli, Orsolya; Szabó, Dorottya; Bernáth, Fruzsina; Hajdú, Dorottya; Gombocz, Eszter; Máté, Bálint; Jiling, Bálint; Nagy, Balázs Vince Nagy, Zoltán Zsolt; Pető, Tünde; Papp, András.; Prevalence of Cilioretinal Arteries: A systematic review and a prospective cross-sectional observational study; ACTA OPHTHALMOLOGICA 99 : 3 pp. e310-e318. , 9 p. (2021) IF: 3.988
- **Molnár, Adél**; Gombocz, Eszter; Nagy, ZZs; Schneider, Miklós; A Nap sötét oldala: retinopathia solaris esetének multimodális bemutatása; ORVOSI HETILAP 161 : 16 pp. 632-636. , 5 p. (2020) IF: 0.540

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