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

PhD thesis

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1. Introduction

Renal biopsy registries are important tools for both clinical practice and research. By collecting demographic and histopathological data from large patient cohorts, they help monitor disease trends, support more accurate classifications, and inform treatment strategies. They also enable long-term follow-up, offering insights into disease progression and therapeutic outcomes.

This is particularly relevant in lupus nephritis, a serious complication of systemic lupus erythematosus affecting 30–50% of patients. It is associated with increased cardiovascular risk, often independent of traditional risk factors, suggesting a role for lupus-specific mechanisms such as chronic inflammation or immunosuppressive therapy.

A renal biopsy database focused on lupus nephritis provides an opportunity to explore the relationship between clinical, histological, and laboratory parameters and cardiovascular outcomes. Such a resource can improve our understanding of the disease and support more personalized, risk-based care.

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

This study was divided into two main parts, and the methodology follows this structure. The research adhered to the Declaration of Helsinki and received approval from the Regional and Institutional Committee of Science and Research Ethics of Semmelweis University, Budapest (SE RKEB 225/2018). All analyses complied with relevant guidelines, and informed consent was obtained from participants or their legal guardians at the time of biopsy.

3.1. Establishment of the Renal Biopsy Database

The first objective was to establish a comprehensive renal biopsy database. Original biopsy reports were recorded on paper and later digitized into electronic medical records (Medsol), necessitating manual data transfer into a structured electronic database (Microsoft Excel 2016). We retrospectively analyzed renal biopsy specimens processed by the Department of Pathology, Forensic, and Insurance Medicine at Semmelweis University from January 2005 to December 2020.

Samples originated from 28 nephrology centers across four counties in Northern and Central Hungary, including Budapest. These centers provided care for both adult and pediatric patients. All biopsy specimens, including those with sampling errors (e.g., adipose tissue), were included.

Recorded data comprised patient age, sex, primary to tertiary diagnoses (if multiple histological findings existed), biopsy institution, and instances of repeat biopsies.

3.1.1. Demographics

Population data from the Hungarian Central Statistical Office served as a reference to compare the biopsy cohort with the general Hungarian population.

3.1.2. Histological Assessment

Specimens were processed according to standard pathological protocols, involving staining methods such as hematoxylin and eosin, periodic acid-Schiff, Masson's trichrome, Congo red, and Jones methenamine silver. Immunofluorescence staining targeted immunoglobulins (IgG, IgA, IgM), complement components (C3c, C4c, C1q),

fibrin, and light chains (kappa, lambda). Cases suspected of Alport syndrome underwent additional collagen IV alpha 5 chain staining.

Between 2006 and 2019, two experienced nephropathologists independently reviewed all samples; a third nephropathologist joined in 2020. Clinical data from treating physicians supported pathological evaluations.

3.1.3. Diagnoses

Different coding systems were used historically, so diagnoses were standardized per the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) coding system. Diagnoses were grouped into seven categories: glomerular diseases, tubulointerstitial diseases, diabetes mellitus, hypertension, systemic diseases, familial nephropathies, and miscellaneous renal disorders. Transplant biopsies were excluded.

For analysis, patients were categorized by age groups: children (≤18 years), adults (19–65 years), and elderly (≥66 years), and by sex.

3.1.4. Statistical Analysis

Categorical variables were analyzed using Chi-square or Fisher's exact tests, while continuous variables were assessed via the Kruskal-Wallis test, guided by the Shapiro-Wilk normality test. Logistic regression was used for binary outcomes. A p-value < 0.05 (two-tailed) indicated statistical significance.

3.2. Cardiovascular Risk Factors in Lupus Nephritis

The second part of the study utilized the established database to investigate cardiovascular risk factors in lupus nephritis patients.

The cohort comprised Caucasian patients aged 18 or older who underwent renal biopsy at Semmelweis University's tertiary care hospital between 2005 and 2020. Systemic lupus erythematosus diagnoses were based on 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR), 2012 Systemic Lupus Collaborating Clinics (SLICC), and 1997 ACR criteria.

Comprehensive clinical data were collected retrospectively from the Medsol system, including physical exams, blood pressure, laboratory parameters, medication use, age,

lupus duration, comorbidities, cardiovascular history, echocardiographic and electrocardiographic data, and smoking status. Variables with ≥75% completeness were included.

Immune serology was performed within three months before biopsy, and routine laboratories at biopsy time. Immunosuppressive therapies were recorded at biopsy and during remission phases. Cardiovascular medication use was documented at biopsy. Blood pressure was measured during hospital admission using automatic devices; smoking status was self-reported.

Major adverse cardiovascular events (MACE) were defined as a composite of nonfatal myocardial infarction, heart failure hospitalization, coronary revascularization, stroke, and cardiovascular death. MACEs were assessed from lupus diagnosis and from biopsy.

3.2.1. Statistical Analysis

Data were anonymized and stored in Excel. Statistical analyses were performed with IBM SPSS Statistics 28; figures were generated using GraphPad Prism 9 and SPSS.

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. We identified independent MACE predictors through multiple logistic regression. Initially, individual logistic regression models were created for significant univariate predictors. Due to the small sample size, predictors were selected based on univariate significance and sufficient data availability. A final multivariate model included all selected variables, with non-significant predictors removed using stepwise elimination.

Model accuracy was assessed using a Receiver Operating Characteristics (ROC) curve and area under the curve (AUC). We developed a risk score for predicting cardiovascular events in lupus nephritis patients, derived from the final logistic regression model and weighted by regression coefficients. Two-tailed p-values <0.05 were considered significant.

4. Results

4.1. Kidney Biopsy-Based Demographic Analyses

4.1.1. Demographics

Between 2006 and 2020, 2140 native kidney biopsies and 111 transplant biopsies were examined; transplant biopsies were excluded, leaving 2296 native biopsy diagnoses. The average population of Hungary was ~9.9 million, with 3.9 million (39.7%) residing in the catchment area. Population density was 107 inhabitants/km², 1.2 times the national and 3.2 times the European average. The male-to-female ratio was nearly equal (49.8% vs. 50.2%), with a mean age of 44.2 ± 21.9 years (range 4 months to 90 years; median 46). Age distribution was 18.3% children, 61.3% adults, and 20.4% elderly. From 2015 to 2020, median age and proportion of adults increased significantly ($p < 0.0001$).

4.1.2. Frequency of the main disease groups

Glomerular diseases (GD, 65.3%) were most common, followed by tubulointerstitial diseases (TID, 8.4%), diabetic nephropathy (DM, 6.1%), kidney disease related to other systemic diseases (OSD, 4.7%), hypertensive/renal vascular diseases (HT/RV, 4.6%), familial/hereditary nephropathies (FHN, 2.9%), and miscellaneous diagnoses (MISC, 7.9%) (Figure 1).

Given that glomerular diseases represented the majority of specimens, we conducted a detailed analysis of this category. 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 anti-neutrophil cytoplasmic antibodies (ANCA) - associated vasculitis (11.3%, with microscopic polyangiitis (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%) (Figure 1).

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

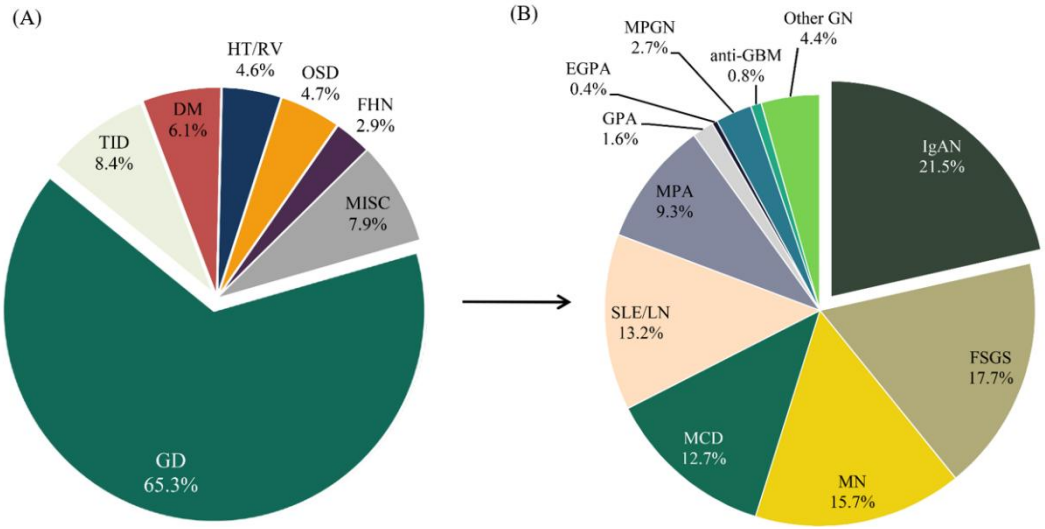

Figure 1. **(A)** Frequencies of the main groups throughout 15 years. GD glomerular diseases, TID tubulointerstitial diseases, DM diabetes mellitus, HT/RV hypertension/renal vascular disease, OSD other systemic disease affecting the kidney, FHN familial/hereditary nephropathies, MISC miscellaneous diseases. **(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.

4.1.3. Three-year trends

GD remained the leading diagnosis throughout. TID significantly declined in 2018–2020 ($p = 0.007$), as did FHN ($p = 0.02$) and HT/RV ($p = 0.009$). The decline in FHN correlated with increased patient age, while HT/RV trends were independent of age. Although DM-related diagnoses increased, this was not statistically significant.

IgAN remained the leading GD. MCD declined significantly over time ($p = 0.038$), as did FSGS in 2018–2020 ($p = 0.027$). ANCA vasculitis, especially MPA, increased ($p = 0.004$ and $p = 0.012$). MPGN also rose significantly in 2018–2020 ($p = 0.021$), independent of age and sex.

The COVID-19 pandemic reduced biopsy numbers in 2020 (43.4 vs. 64.2 per million/year). MN diagnoses decreased ($p = 0.038$), while granulomatous polyangiitis (GPA) cases rose ($p = 0.018$).

4.1.4. Analysis of sex differences

Diagnosis distributions were sex-dependent ($p = 0.0004$). GD was evenly distributed, but DM was more common in males ($p = 0.025$), whereas OSD ($p = 0.002$) and FHN ($p = 0.038$) were more frequent in females.

IgAN was most frequent in males (30.6%), while LN was predominant in females (21.8%). Male predominance was also noted in MN ($p = 0.022$) and IgAN ($p < 0.0001$), while MPA and LN were more common in females ($p < 0.0001$ for both). MCD, MPGN, and anti-GBM showed no sex bias.

4.1.5. Analysis of age-related trends

Diagnosis profiles varied significantly by age ($p < 0.0001$). GD predominated in all groups (60.9–68.4%). Adults and the elderly had higher rates of DM ($p < 0.0001$), HT/RV ($p < 0.0001$), OSD ($p = 0.001$), and miscellaneous categories ($p = 0.012$). FHN was significantly more common in children ($p < 0.0001$).

IgAN was most frequent in children and adults; MN dominated in the elderly (32.3%). MN ($p < 0.0001$), MPA ($p < 0.001$), and EGPA ($p = 0.017$) were more prevalent in older patients. 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.

4.1.6. Sex distribution across age groups

In adults, females were more represented in OSD (6.2% vs. 3.0%; $p = 0.0045$), while in the elderly, DM was more common in males (10.2% vs. 4.8%; $p = 0.0312$).

IgAN showed consistent male dominance across all age groups: children (41.4% vs. 19.7%, $p < 0.0001$), adults (31.6% vs. 12.6%, $p < 0.0001$), and the elderly (14.8% vs. 5.7%, $p = 0.015$). LN had a strong female bias: children (1.4% vs. 14.8%, $p < 0.0001$), adults (6.7% vs. 30.0%, $p < 0.0001$), and the elderly (0% vs. 4.5%, $p = 0.018$), as did childhood MPA (0.7% vs. 6.3%, $p = 0.019$). MN was more frequent in adult males (35.2% vs. 29.9%, $p = 0.001$).

4.2. Cardiovascular risk factors of lupus nephritis

4.2.1. Demographics

Between 2005 and 2020, 91 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. Five patients experienced more than one MACE.

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; $p = 0.012$). They also had lower diastolic blood pressure (DBP) (78.42 vs. 89.51 mmHg; $p < 0.001$), higher leukocyte counts (9.07 vs. 6.99 Giga/liter; $p = 0.026$), and higher absolute neutrophil counts (7.30 vs. 5.15 Giga/liter; $p = 0.01$). The observed elevations in leukocyte count and absolute neutrophil count were not associated with steroid administration or dosage ($r = 0.097$, $p = 0.375$; $r = 0.110$, $p = 0.315$).

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%; $p = 0.003$). Notably, all patients with APS were receiving anticoagulant therapy, though not all anticoagulated patients had APS.

Patients who experienced MACE were more likely to use beta-blockers (50.0% vs. 22.1%; $p = 0.029$) 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 ($p=0.033$).

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

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). 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 (odds ratio (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).

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. 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. 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. Through a stepwise elimination process, the non-significant predictor (anticoagulant use) was removed, leaving three independent risk factors for major adverse cardiovascular events. Using these findings, we developed the CANDE score (Cardiovascular risk-based on Age, Neutrophil count, and Diastolic blood pressure Estimation Score) 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 2).

Figure 2. 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	~ -1
β_2 (Neutrophil count) = 0.278	~ 2
β_3 (Age) = 0.052 → β (10-year age) = 0.52	~ 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 ($p < 0.001$). 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.

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 3). 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 3. 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 3. 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

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; $p = 0.01$).

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.

5. Conclusions

1. We established a comprehensive renal biopsy database with standardized diagnostic nomenclature.
2. Disease distribution was influenced by age:
    - More frequent in adults/elderly: DM, HT/RV, OSD, MN, MPA, EGPA.
    - More frequent in younger individuals: IgAN, SLE/LN, MCD, FSGS
3. Disease distribution was influenced by sex:
    - More frequent in men: DM, MN, IgAN
    - More frequent in women: SLE/LN, MPA, FHN
4. 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.
5. 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. CANDE score showed high sensitivity (78.6%) and specificity (81.9%), confirming its effectiveness in predicting MACE risk in lupus nephritis patients.

6. 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.

7. Bibliography of the candidate's publications

7.1.Publications related to the thesis:

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