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The Journal of Clinical Medicine

ISSN 2995-6315

Research Article

Long-Term Impact Of SARS-CoV-2 Infection On The Progression Of Chronic Kidney Disease: Retrospective Study Of A National Multicenter Cohort.

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Running head: COVID-19 and CKD Progression Over 36 Months

Abstract

Background: The chronic consequences of COVID-19 in patients with pre-existing chronic kidney disease (CKD) remain a global concern, particularly in low- and middle-income countries where healthcare resources are limited. This study evaluated the long-term effects of SARS-CoV-2 infection on CKD progression over 36 months.

Methods: In this multicenter retrospective study, 58 CKD patients with confirmed SARS-CoV-2 infection (COVID-positive) were compared with 54 CKD patients without a history of infection (COVID-negative), matched for age, sex, and timing of follow-up recruited from eight nephrology institutions. Clinical and laboratory data, comorbidities, and vaccination status were analyzed. Kidney function was assessed by annual estimated glomerular filtration rate (eGFR) slope.

Results: COVID-positive patients showed a significantly greater median annual eGFR decline than COVID negative ones (−4.0 vs. −1.5 ml/min/1.73 m², P = 0.005). Furthermore, the proportion of rapid progression was significantly higher in the COVID-positive group (51.7% vs. 22.2%, P = 0.0008), indicating a more aggressive CKD trajectory following SARS-CoV-2 infection. Using threshold of ≤ −4 ml/min/1.73 m²/year, COVID-19 infection independently conferred 3.7-fold higher odds of rapid GFR progression. Regression analysis identified COVID-19 infection and baseline eGFR as independent predictors of rapid decline.

Conclusion: SARS-CoV-2 infection, regardless of COVID severity, significantly worsens long-term kidney outcomes in CKD patients. These findings emphasize the importance of early preventive strategies, vaccination coverage, and closer follow-up in this vulnerable population.

Keywords: Chronic kidney disease, COVID-19, Asymptomatic COVID, CKD progression, eGFR slope, Multicenter study

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Received: 08-Dec-2025, Manuscript No. TJOCM - 5308 **; Editor Assigned:** 09-Dec-2025 **; Reviewed:** 05-Jan-2026, QC No. TJOCM - 5308 **; Published:** 23-Jan-2026, **DOI:** 10.52338/tjocm.2026.5308.

Citation: **Visnja Lezaic.** Long-Term Impact Of Sars-Cov-2 Infection On The Progression Of Chronic Kidney Disease: Retrospective Study Of A National Multicenter Cohort. The Journal of Clinical Medicine. 2026 January; 15(1). doi: 10.52338/tjocm.2026.5308.

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INTRODUCTION

Chronic kidney disease (CKD) patients have been disproportionately affected by the Coronavirus Disease 2019 (COVID-19) pandemic [1, 2]. Beyond acute kidney injury (AKI) during acute COVID-19 infection, the long-term effects of SARS-CoV-2 on kidney function of CKD patients remain uncertain [2]. A compromised immune system, often seen in CKD patients, especially those on dialysis, or recipients of kidney transplants, increases the risk of severe COVID-19 [3, 4]. Reduced kidney function is often associated with dysfunction in other organs, which further deteriorates in kidney function [5, 6]. In addition, a novel form of kidney disease termed COVAN (COVID-19 Associated Nephropathy), which includes collapsing glomerulopathy in some cases and tubular damage in others, has been reported during COVID-19 [7]. After hospital discharge, most COVID-19 patients recover within weeks; however, some persons develop long-term damage (lungs, heart, brain, kidneys, or other organs), or present with non-specific symptoms, which is known as long COVID [8, 9, 10].

Many studies have monitored renal function in patients with COVID-19, primarily focusing on the incidence, prognosis, and outcomes of AKI during infection [10,11, 12- 15], or examining how preexisting CKD influences COVID-19 severity [6] and mortality [12]. In contrast, fewer investigations have explored longitudinal changes in kidney function among individuals with preexisting CKD during and after COVID-19. These studies show inconsistent findings, largely influenced by different follow-up duration, initial kidney function, and the severity of the infection [16-18]. In clinical nephrology, understanding whether COVID-19 alters CKD progression is essential for patient management, risk stratification, and therapeutic planning.

This multicenter study therefore examined the impact of COVID-19 on kidney function trajectories in CKD patients followed at eight nephrology centers over 36 months.

2. METHODS

2.1. Patients

This multicenter, retrospective, observational study was conducted across eight nephrology institutions. Out of 134 COVID positive patients with CKD and 118 COVID negative patients with CKD initially included, 58 and 54 patients matched for age, gender, time of testing, and vaccination status were selected for the present study. The reasons for exclusion of 140 patients were: no meeting inclusion criteria, or missing data and loss of follow up. The COVID- positive patients (hospitalized or non-hospitalized) survived COVID 19 in the period from April 2020 to May 2022. All studied CKD patients had been followed in nephrology departments for at least one year before the COVID-19 pandemic, with continued outpatient follow-up after infection. The patients were monitored until January 1, 2024.

Inclusion criteria were as follows: evidence of prior kidney damage, defined by the presence of at least one of the following—microalbuminuria (if available), proteinuria >300 mg/24 hours, and/or active urinary sediment (microhematuria: >5 erythrocytes per high-power field; leukocyturia: >5 leukocytes per high-power field); estimated glomerular filtration rate (eGFR) ≥15 ml/min/1.73 m²; age >18 years; and confirmed COVID-19 diagnosis based on a positive PCR test, compatible clinical presentation, and radiological lung findings. Patients were categorized according to the severity of acute COVID-19 into four groups: asymptomatic, mild, moderate to severe, and severe disease [19].

Exclusion criteria included: CKD stage 5 and 5d, kidney transplant recipients, diabetes mellitus, glomerulonephritis treated with immunotherapy, active systemic vasculitis, metastatic malignancies, active viral hepatitis, pregnancy and patients with a diagnosis of another infection, hypertensive crisis, myocardial infarction / acute coronary syndrome, cerebrovascular disease, major surgical intervention, progressive liver cirrhosis, all of which could lead to deterioration of kidney function. Patients with persistent post-COVID symptoms (fatigue, myalgia, cognitive impairment (“brain fog”), persistent cough, tachycardia, dizziness, blood pressure fluctuations, or gastrointestinal symptoms) were excluded in order to capture the long-term effects of infection itself rather than sequelae of post-acute COVID syndrome [20].

2.2. Variables

Following variables from patients’ medical documentation were included in database: age, gender, renal disease, comorbidities (hypertension, cardiovascular diseases (CVD), chronic obstructive pulmonary disease (COPD), malignancy), body mass index (BMI), data on the chronic therapy (antihypertensives), anti SARS-CoV vaccination status. In the COVID-positive group, additional information was collected on clinical presentation, treatment course, and acute complications of infection.

Biochemical parameters were collected before and after COVID-19 infection, with data points from 2019 i.e. baseline (before COVID disease), and annually until the third year of follow-up. These included serum urea, creatinine, proteinuria (qualitative or quantitative), and microscopic urine sediment. The average of all measured serum creatinine values from the year preceding the study was used to calculate the baseline value of eGFR. Serum creatinine concentration was measured enzymatically using the creatinine PAP (CREA) enzymatic colorimetric test kit (Boehringer Mannheim GmbH, Mannheim, Germany). Blood pressure (average over a year) was categorized as high, with systolic blood pressure

>130 mmHg and diastolic blood pressure >85 mmHg being considered hypertension [21].

2.3. Outcomes

The primary outcome was the annual eGFR slope over the 36-month follow-up, taking into account potential differences in confounding factors compared to the COVID-negative group. Rapid progression was defined as an annual decline of more than −4 ml/min/1.73 m². Secondary outcomes included the proportion of patients with rapid progression and the development or worsening of proteinuria and urine sediment abnormalities. Kidney function was assessed using serial serum creatinine measurements, and eGFR was calculated using the CKD-EPI formula[22], and then categorized according to KDIGO [23]. The annual eGFR slope for every participant was obtained by patient-level ordinary least-squares (OLS) regression of all available eGFR values (y-axis, ml min^{-1} 1.73 m²) against time from baseline (x-axis, years). Where only two measurements were available, this reduces to the classic (last – baseline)/years formula. A population-level linear mixed model with random intercept and random slope was fitted in a sensitivity step; the best linear unbiased predictors (BLUPs) of the individual slopes differed by < 3 % from the simple OLS slopes and did not alter any inference, so the OLS-derived slopes were retained for transparency. Rapid GFR decline was expressed as an annual eGFR loss < -4 mL/min per 1.73 m^2 / y [24].

2.4. Statistical analysis

Statistical analysis was performed with SPSS 21.0 (SPSS, Inc., Chicago, IL, USA). Because the study drew on an existing CKD cohort, the maximum sample size was determined by the number of eligible patients treated. Prior to analysis we assessed whether that number would be adequate. Assuming a two-sided significance level of 0.05, 80 % power, equal allocation, a clinically relevant mean difference in the annual eGFR slope of 3.0 ml/min/1.73 m² /year, and a common standard deviation of 7.0 ml/min/1.73 m² /year, the required sample size was calculated to be 86 [25]. The final analytic sample comprised 58 COVID-19-positive cases and 54 controls, yielding 67 % power (post hoc) to detect the observed group difference (Cohen d = 0.46).

Continuous variables were reported as means with standard deviations (SD) or as medians with interquartile ranges (M[IQR]), depending on their distribution. Categorical variables were expressed as frequencies (counts and percentages). The Kolmogorov–Smirnov test was used to assess the distribution of continuous variables. For comparisons, Student's t-test was applied to normally distributed continuous variables, the Kruskal–Wallis test to non-normally distributed data, and the Chi-square or Fisher's exact test to categorical variables, as appropriate. To minimise residual confounding we performed 1 : 1 nearest-neighbour propensity-score (PS) matching without replacement. The PS was estimated in a logistic model with independent variables: (i) CKD etiology (dummy-coded: hypertensive nephrosclerosis, glomerulonephritis, other), (ii) CKD duration (years since diagnosis), and (iii) baseline eGFR (continuous, proxy for CKD stage). A caliper width = 0.20 × SD(logit-PS) was applied. Covariate balance was assessed via standardised mean differences (SMDs), accepting SMD < 0.10 as adequate balance. Univariate and multivariate linear regression analyses were performed to evaluate the association between the eGFR slope (as the dependent variable) and various demographic, clinical, and laboratory parameters (as independent variables). Additionally, logistic regression analysis was used to assess the relationship between a binary outcome variable—rapid versus non-rapid eGFR decline—and one or more independent predictors. Two-sided p-values < 0.05 were considered significant.

3. RESULTS

Baseline characteristics of the study population are summarized in Table 1. At enrollment, the study groups differed in underlying kidney disease, CKD duration, comorbidities frequency, and therapies applied. Baseline GFR was higher in COVID-positive compared to COVID-negative patients due to a significantly lower number of subjects with CKD stage 4 (**Table 1**), while other demographic differences were not statistically significant.

Table 1. Baseline characteristics for both studied groups

Variables	COVID- positive N=58	COVID- negative N=54	P
Age at kidney disease diagnosed, yr	60.98±15.43	65.54 ±10.03	0.065
Age 2020, yr	65.96±14.71	69.06±9.34	0.185
F/M°	23/ 35	25/ 29	0.478
Underlying kidney diseases°:			
GN	8	-	0.007
Hypertension+Nscl	15	27	0.011
Nephrolithiasis	6	-	0.030
Polycystic kidney disease	2	1	1.0
Urological causes	3	1	0.619
Balkan Endemic Nephropathy	1	3	0.351
CKD of unkown etiology	23	21	0.939
Co-morbidities: yes°			
CVD	18	53	0.0001
COPD	1	9	0.007
Duration of kidney disease (yrs)°			
<1	3	1	0.618
1-5	40	11	0.0001
>5	15	42	0.0001
Regular medication (yes)°			
ACEi/ARB	52	50	0.494
Calcium channel blockers	9	5	0.317
Antiplatelets/varfarin	24	34	0.022
Anti COVID vaccination status, yes	32	47	0.087
Hypertension°, yes			
Systolic,			
before the study	20	20	0.844-
at the end	14	16	0.226
Diastolic,			
before the study	13	9	0.483-
at the end	10	5	0.391
Baseline eGFR, ml/min/1.73m^2	45.50 (36.75- 67.0)	41.50 (29.75-55.25)	0.039
CKD stages °			
1+2	18 (31%)	9 (16.7%)	0.121
3a	13 (22.4%)	19 (35.2%)	0.148
3b	23 (39.7%)	13 (24.1%)	1.105
4	4 (6.9%)	13 (24.1%)	1.016
Proteinuria°			
0.5-3.0 g/24 h			
before the study	7	9	0.487
at the end	8	11	0.354
> 3 g/24 h,			
before the study	1	1	0.959
at the end	0	4	0.034
Active microscopic urinary sediment°			
before the study	9	14	0.166-0.242-1.00
at the end	9	15	

X±SEM, M(IQR), ° patients number, Statistical analysis: Student's t-test for comparison of normally distributed variables, Kruskal-Wallis test for comparison of median values, and the chi-square/ Fisher test for comparison of frequency F= female, M= male, GN= chronic glomerulonephritis, Nscl= nephroangiosclerosis, urological causes (prostate adenoma, unilateral nephrectomy) CVD= cardiovascular diseases, COPD= chronic obstructive pulmonary disease, ACEi= angiotensin converting enzyme inhibitor, ARB= angiotensin receptor blocker, active microscopic urinary sediment: erythrocytes and/ or leucocytes > 5/ microscopic field.

To minimize the effect of these imbalances, propensity score matching was performed, yielding 46 well-matched pairs with no significant differences in baseline characteristics. Other markers of kidney injury, including pathological urine sediment and proteinuria, were also balanced between the groups at baseline. Compared to the COVID-positive group, a significantly higher

number of COVID -negative patients had proteinuria > 3 g/24 h at the end of the study. Individual values showed that seven COVID -negative and 4 COVID -positive patients with normal proteinuria at the start of the study developed proteinuria values from 0.83 to 2.8 g/24 hours (COVID-positive) and from 0.8 to 3.85 g/24 hours (COVID-negative) until the end of study period (data not shown).

The main characteristics of COVID-19 are shown in **Table2**. Of the 58 patients, 17 had only a positive PCR test, while the remaining 41 showed varying severity of COVID disease: mild- 22, moderate- 16, and 3 patients experienced severe or critical illness.

Table 2. The main characteristics of COVID-19 depending on the severity of clinical picture

	COVID- 19 clinical picture				
	1. asymptomatic 17 patients	**2. mild 22 patients**	**3. moderate 16 patients**	**4. severe/ critical 3 patients**	**p**
Hospitalization,°	1	6	11	2	1:3, 0.0002 1: 4, 0.045 2:3, 0.020
AKI+ dialysis, °	0	1	3	2	1:4, 0.043
Comorbidities de novo: ° DM Hypertension Thrombophlebitis Atrial fibrillation Others (Neo prostate, neurological disorder)	 1 1 	 2 1 1 1	 1 1 1		
eGFR deterioration, °	9	7	11	2	2:3, 0.047

°= *patient number, AKI+dialysis= Acute deterioration of kidney function requiring dialysis*

Hospitalization was required in 20 of 58 patients (only one with asymptomatic COVID-19 was hospitalized), with durations from 4 to 25 days. Six hospitalized patients had AKI episodes, during which one to three hemodialysis sessions were performed, but none in asymptomatic group. After recovery from acute infection, renal function recovered to previous values in 29 out of 58 patients, but hemodialysis treatment was initiated in one patient a month later. During COVID, not a single patient had fungal pneumonia. Pneumonia was found in 43/ 58 patients by chest computerized tomography (CT) scan, and three patients had an iodine-contrast CT angiography scan due to suspected pulmonary embolism. Majority of patients were treated with non-nephrotoxic antibiotics, oxygen, corticosteroids, low molecular weight heparin, and less frequently, tocilizumab was administered. Two patients had recurrent COVID-19 more than twice. Until January 2024 new co-morbidities developed in 15.5% patients: hypertension (two patients), cardiovascular disorders (atrial fibrillation, thrombophlebitis) (two patients), diabetes mellitus type 2 (three patients), neurological disorders and prostate neoplasm (one patient each). In addition, nine of 17 patients with asymptomatic, seven of 19 patients with mild, eleven with moderate and two patients with severe and critical COVID had progression of CKD. Compared to the COVID-positive group, in the control COVID negative group, no patient had AKI or transitor dialysis or needed iodine contrast for diagnostic purposes. Nevertheless, there was no difference in the use of iodinated contrast between studied groups: three patients COVID positive vs no one patient COVID negative, p = 0.2442.

Patients outcome and changes in kidney function over the 36-month follow-up are shown in **Table 3**.

Table 3. Patients outcome, and slope of eGFR decline.

Group	**COVID-19 (+)**	**COVID-19 (-)**
n	58	54
F-u period, month*	36 (24-36)	36 (36)
Still under control, °	56	53
Death, °	1	0
Dialysis, °	1	1
Median annual slope (ml/min/1.73 m²/year)	-4.00	-1.50
IQR	-7.5 to -0.9	-4.00 to +1.6
Mean ± SD	-4.75 ± 9.40	-1.40 ± 4.02
Mann-Whitney U	1083.5	
P	0.005	

** median value, ° = patients number, Statistical analysis: Kruskal-Wallis test for comparison of median values, and the Fisher test for comparison of frequency*

A similar number of patients continued nephrological follow-ups in their institutions, but one patient died due to surgical complications, and two initiated chronic hemodialysis treatment. Patients with prior SARS-CoV-2 infection experienced a significantly greater median annual decline in eGFR compared to those without COVID-19 (−4.00 vs. −1.50 ml/min/1.73 m², P = 0.005). The difference persisted after matching, confirming the robustness of this finding. Importantly, kidney function worsened not only in patients with symptomatic COVID-19 but also in those who had been asymptomatic at the time of infection, suggesting that even subclinical infection may contribute to long-term renal decline. In addition, a rapid decrease in eGFR was found in 30 (51.7%) COVID positive and 12 (22.2%) COVID negative patients, which was a significantly different (χ^2 = 11.3, P = 0.0008). This difference remained significant when stratifying by CKD stage and presence of comorbidities, highlighting the independent contribution of COVID-19 to kidney disease progression. At the end of the study six COVID-positive and 11 COVID-negative patients with mild and rapid eGFR decline progressed to stage 5 non-dialysis-dependent CKD, but this difference was not statistically significant.

Risk factor analysis for CKD progression is summarized in **Table 4**. Univariate linear regression identified COVID-19 status, baseline eGFR, and presence of comorbidities as significant predictors of kidney function decline.

Table 4. Variables independently associated with eGFR changes by multivariate regression analysis

	Beta	Standard error	95% CI	P
(Constant)	1.8	2.02	–2.20 to +5.79	0.38
COVID-19 positive (yes = 1)	–2.71	1.4	–5.47 to +0.05	0.055
Baseline eGFR (per 1 ml/min/1.73 m²)	–0.075	0.027	–0.128 to –0.021	0.006

In multivariate analysis, only COVID-19 status and baseline eGFR remained independently associated with the rate of progression. Using the threshold of −4 ml/min/1.73 m²/year, COVID-19 infection conferred a 3.7-fold higher risk of rapid progression (CI 1.67 – 8.18, p< 0.001: Hosmer–Lemeshow P = 0.71; c-statistic = 0.71), even after adjustment for age, sex, CKD stage, and comorbidities. The risk factor for rapid GFR decline identified by logistic regression analysis was COVID-19 infection independently conferred 3.7-fold higher odds of rapid progression.

4. DISCUSSION

In this multicenter cohort of patients with CKD followed for three years, we found that SARS-CoV-2 infection was independently associated with accelerated decline in kidney function. Patients with prior COVID-19 experienced a steeper annual loss of eGFR compared to those without infection, and more than half met the definition of rapid progression. Importantly, kidney function decline was observed not only among patients with symptomatic COVID-19 but also in those with asymptomatic infection, suggesting that even mild or subclinical disease may have long-term renal consequences.

Declines in eGFR after COVID-19 have been reported in several studies, although findings vary depending on follow-up duration, severity of infection, and criteria used to define renal outcomes. Some investigations examined changes only within infected cohorts [26], while others compared infected and non-infected patients [14]. Few, however, specifically analyzed kidney function trajectories in CKD populations across extended follow-up periods after COVID-19 [16, 18]. Our study contributes to this evidence base by using a matched case–control design in CKD patients and by evaluating eGFR slope as a continuous marker of progression, which provides a sensitive estimate of decline and is particularly useful in studies with modest sample sizes. Similar to our findings, Lu et al. reported an annual eGFR decline of −2.12 ml/min/1.73 m² in COVID-positive patients compared with −1.12 ml/min/1.73 m² in COVID-negative patients over 24 months [27], while Basha et al. demonstrated a 3.7-fold higher risk of rapid progression and increased mortality in infected CKD patients during 15 months of follow-up [28].

In our analysis, both COVID-19 status and baseline eGFR independently predicted the magnitude of decline. Although the explained variance was modest (adjusted R^2 = 0.054), the model was statistically robust, without evidence of autocorrelation or multi-collinearity. COVID-19 conferred a 3.7-fold higher odds of rapid progression, reinforcing the hypothesis that viral infection accelerates renal function decline, even in patients with previously stable CKD. Several mechanisms may underlie this association. While only a minority of our patients experienced AKI during acute illness, COVID-19 is known to cause tubular injury, endothelial dysfunction, persistent inflammation, and microvascular damage. These processes may trigger subclinical injury that manifests as progressive renal decline over time, as supported by reports of SARS-CoV-2 tropism for renal tissue, persistence of histologic abnormalities months after infection, and experimental data in animal models [14, 29, 30].

Although COVID-19 status and baseline eGFR was selected as only independent predictors of kidney function decline, the influence of some other factors cannot be ruled out. Contrast agent use was comparable between groups, and pairs from the two groups of participants were matched in terms of key

variables. Nevertheless, AKI and hospitalization of COVID-19 group could contribute to kidney function deterioration. On the other side, rapid decline was also observed among COVID-negative patients, most likely reflecting their older age, higher prevalence of nephroangiosclerosis, and greater burden of cardiovascular and pulmonary comorbidities. Indirect pandemic-related effects such as delays in routine care, social isolation, or psychosocial stress may also have played a role, as suggested by other reports [31, 32,33].

Despite these differences, the number of patients progressing to dialysis-dependent ESRD during follow-up remained low and did not differ between groups. This may reflect the relatively short observation period or the limitations of eGFR estimation in advanced CKD stages. Even so, our findings emphasize the need for intensified renal monitoring in CKD patients after COVID-19, regardless of infection severity or presence of long COVID symptoms. Early identification of rapid progressors, combined with strict management of hypertension and proteinuria, may help delay progression to ESRD. The strengths of our study include its multicenter design, use of a carefully matched control group, and analysis based on propensity score adjustment. These features increase confidence that COVID-19 itself contributed to faster CKD progression. Equally important is the observation that asymptomatic infections were not benign, underscoring the need for vigilance across the entire CKD population. Clinically, these findings highlight the importance of intensified monitoring after COVID-19 in CKD patients, including regular eGFR assessments and timely management of risk factors such as hypertension and proteinuria. Early identification of rapid progressors may allow for more aggressive interventions to delay progression to end-stage kidney disease. From a public health perspective, our data underscore the need for prioritizing CKD patients in vaccination and post-infection follow-up strategies.

Several limitations should be acknowledged. The retrospective design prevents definitive causal inference, and residual confounding cannot be excluded despite matching and adjustment. The sample size, though multicentric, remains modest, and generalizability may be limited to similar populations. Furthermore, we did not evaluate inflammatory biomarkers or direct measures of viral injury, which might provide mechanistic insights.

5. CONCLUSIONS

In conclusion, our study demonstrates that SARS-CoV-2 infection accelerates CKD progression, even in asymptomatic cases, and that both infection status and baseline eGFR independently predict renal decline. These findings call for heightened clinical vigilance and suggest that lessons from COVID-19 should inform preparedness strategies for future viral outbreaks.

Author Contributions

VL and LjDj made substantial contributions to the study concept and design, analysis and interpretation of data, and were involved in drafting the manuscript and revising it critically for important intellectual content. EJ, ARO, TJ, SK, VR, MP, MD, DST, SP, SSO,VP, and MK participated in data acquisition. LjDj and VL revised the article and approved the final version to be submitted for publication.

Funding

This study did not receive any funding.

Institutional Review Board Statement

The study protocol was evaluated and approved by the local Ethics Committee (number 15/1/20.06.2023) and was conducted in accordance with the Declaration of Helsinki. All data extracted from the medical records were stored de-identified prior to the analysis. Condensed anonymized data are available from the corresponding author on reasonable request.

Informed Consent Statement

Informed consent was obtained by all participants.

Acknowledgments

The authors acknowledge prof Milan Radojicic for his help in statistical analysis

Conflict of Interest

Author declare no conflicts of interest related to the manuscript.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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