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Kidney involvement in acute COVID-19 and long-term cardiovascular outcomes: The role of inflammation and endothelial dysfunction

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Abstract. *COVID-19 is associated with long-term cardiovascular (CV) complications, potentially driven by persistent inflammation, coagulopathy, and endothelial dysfunction. The contribution of kidney dysfunction to this risk remains insufficiently characterized. The aim of this study was to evaluate the association between kidney involvement during acute COVID-19 and the development of CV events within one year after hospital discharge.*

Methods. This prospective cohort study included 328 patients hospitalized with moderate to severe COVID-19, without known kidney or cardiovascular disease, followed for 12 months after discharge. Kidney involvement was defined as newly detected proteinuria >150 mg/L, an increase in serum creatinine ≥26 μmol/L, or a decline in estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73 m^2 during hospitalization. Additional assessments included C-reactive protein (CRP), D-dimer, and intercellular adhesion molecule-1 (ICAM-1). The primary endpoint was a composite of new-onset heart failure, therapy-requiring hypertension, arrhythmias, ischemic stroke or transient ischemic attack (TIA), and myocardial infarction within one year.

Results. CV complications occurred in 105 of 328 patients (32.0%) during follow-up. The most frequent were major adverse cardiovascular events (40.8%), arrhythmias (20.0%), and new-onset hypertension (16.8%); heart failure developed in 13.6%, myocardial infarction in 5.6%, and stroke/TIA in 3.2%. Patients with complications had higher serum creatinine (92.0 ± 50.8 vs. 81.8 ± 40.1 μmol/L; p=0.042), lower eGFR (83.2 ± 27.2 vs. 87.3 ± 25.5 mL/min/1.73 m^2; p=0.092), and more frequent proteinuria. In multivariable logistic regression, each 10 mL/min/1.73 m^2 decrease in eGFR was associated with an 8% increase in CV risk (OR 1.08; 95% CI 1.01–1.16; p=0.044), while each 10 μmol/L rise in creatinine increased risk by 6% (OR 1.06; 95% CI 1.01–1.12; p=0.037). Patients with adverse outcomes had significantly higher D-dimer (2.90 ± 0.11 vs. 1.89 ± 0.07 mg/L; p<0.001), whereas CRP showed only a trend (38.3 ± 2.0 vs. 35.1 ± 1.1 mg/L; p=0.066). ICAM-1 concentrations remained threefold higher one year later in patients with CV events (522.7 ± 113.1 pg/mL) compared with controls (193.6 ± 93.7 pg/mL).

Conclusions. Kidney dysfunction during acute COVID-19 is an independent predictor of long-term CV complications. Persistent inflammation, hypercoagulability, and endothelial activation may represent the underlying mechanisms. These findings emphasize the need for integrated cardiorenal monitoring in COVID-19 survivors.

Keywords: *COVID-19; estimated glomerular filtration rate; proteinuria; cardiovascular outcomes; inflammation; endothelial dysfunction.*

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Ураження нирок під час гострого COVID-19 та віддалені серцево-судинні наслідки: роль запалення та ендотеліальної дисфункції

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Резюме. *COVID-19 асоціюється з віддаленими серцево-судинними (СС) ускладненнями, механізм яких асоційований з персистуючим запаленням, коагулопатією та ендотеліальною дисфункцією. Роль ниркової дисфункції у формуванні цього ризику залишається недостатньо вивченою. Метою дослідження було визначити зв'язок між ураженням нирок під час гострого періоду COVID-19 та розвитком СС подій протягом року після виписки.*

Методи. У проспективне когортне дослідження було включено 328 пацієнтів із середньотяжким та тяжким перебігом COVID-19 (без попередньо відомих захворювань нирок та СС системи), яких спостерігали протягом 12 місяців після виписки. Ураження нирок визначали за вперше виявленої потеїнурії понад 150 мг/л, підвищення креатиніну ≥26 мкмоль/л або зниження розрахункової швидкості клубочкової фільтрації (рШКФ) <60 мл/хв/1,73 м^2 під час госпіталізації. Оцінювали також конецнтрації С-реактивного білку (СРБ), D-димеру та молекули міжклітинної адгезії-1 (ICAM-1)). Первинною кінцевою точкою була поява нової серцевої недостатності, артеріальної гіпертензії, що потребує терапії, аритмій, ішемічного інсульту чи транзиторної ішемічної атаки (ТІА), а також інфаркту міокарда протягом року після виписки.

Результати. СС-ускладнення протягом року після виписки відзначались у 105 із 328 пацієнтів (32,0%). Найчастіше реєструвались великі несприятливі серцево-судинні події (40,8%), аритмії (20,0%) та вперше виявлена артеріальна гіпертензія (16,8%); серцева недостатність виникла у 13,6%, інфаркт міокарда — у 5,6%, інсульт/ТІА — у 3,2%. Пацієнти з ускладненнями мали вищі рівні креатиніну (92,0 ± 50,8 vs 81,8 ± 40,1 мкмоль/л; p=0,042), нижчу рШКФ (83,2 ± 27,2 vs 87,3 ± 25,5 мл/хв/1,73 м^2; p=0,092) та частішу протеїнурію. У багатофакторному логістичному аналізі кожне зниження рШКФ на 10 мл/хв/1,73 м^2 асоціювалося з 8% підвищенням ризику СС-подій (OR 1,08; 95% CI 1,01–1,16; p=0,044), а підвищення креатиніну на 10 мкмоль/л — з 6% зростанням ризику (OR 1,06; 95% CI 1,01–1,12; p=0,037). Пацієнти з ускладненнями мали достовірно вищий рівень D-димеру (2,90 ± 0,11 vs 1,89 ± 0,07 мг/л; p<0,001), тоді як СРБ показав лише тенденцію (38,3 ± 2,0 vs 35,1 ± 1,1 мг/л; p=0,066). Концентрація ICAM-1 залишалась утричі вищою через рік у пацієнтів з СС подіями (522,7 ± 113,1 pg/мл) порівняно з контрольною групою (193,6 ± 93,7 pg/мл).

Висновки. Ураження нирок під час гострого періоду COVID-19 є незалежним предиктором віддалених СС-ускладнень. Персистуюче запалення, гіперкоагуляція та ендотеліальна активація можуть бути ключовими патогенетичними механізмами. Отримані результати підкреслюють необхідність інтегрованого кардіоренального моніторингу пацієнтів після COVID-19.

Ключові слова: *COVID-19; швидкість клубочкової фільтрації, протеїнурія, серцево-судинні наслідки, запалення, ендотеліальна дисфункція.*

Introduction. Coronavirus disease 2019 (COVID-19) is increasingly recognized as a multisystem illness with a substantial post-acute cardiovascular (CV) burden. Large population cohorts have shown that, beyond the acute phase, survivors carry elevated 1-year risks of incident heart failure, arrhythmias, thromboembolism, stroke, and myocardial infarction – even after non-severe infection – implicating persistent vascular injury as a unifying mechanism [1].

Among candidate pathways, injury to the kidney during acute COVID-19 may be pivotal. Acute kidney injury (AKI) is frequent in hospitalized patients and is a well-established amplifier of future CV risk in non-COVID settings; COVID-19 appears to accelerate this cardiorenal vulnerability by promoting chronic kidney function loss. In a contemporary comparative cohort, post-COVID trajectories showed faster annual eGFR decline than post-pneumonia, particularly among those hospitalized with COVID-19, underscoring the plausibility that a renal "hit" could prime later CV events [2].

Long-term CV sequelae after COVID-19 span multiple phenotypes. Incident heart failure following recovery has been documented in national datasets after adjustment for conventional risk factors [3], while several nationwide analyses highlight an excess of atrial arrhythmias beyond the acute illness [4]. Additionally, quantitative syntheses suggest an increased risk of new-onset hypertension after infection [5], with signals also seen after non-severe disease [6] – findings that collectively support a persistent hemodynamic and electrophysiologic imprint.

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Endotheliopathy links these observations across organs. Reviews and syntheses converge on sustained endothelial activation and microvascular dysfunction in acute and post-acute COVID-19, with elevations in adhesion molecules, inflammatory markers and coagulation abnormalities. Persistence of these abnormalities months after infection supports a pathobiologic bridge between kidney injury, vascular dysfunction and downstream CV events [7–9]. Critically, there is emerging (but still limited) evidence that the nature and recovery of kidney injury during the index COVID-19 hospitalization stratify post-discharge CV risk. In a health-system cohort, COVID-19 survivors with in-hospital AKI experienced higher rates of major adverse cardiovascular events (MACE), with longer AKI recovery times conferring the greatest hazard within the first 90 days – suggesting that kidney injury dynamics carry prognostic information for subsequent CV outcomes [10]. However, effects beyond the early post-discharge period and in populations without advanced pre-existing chronic kidney disease (CKD) or cardiovascular disease (CVD) remain under-characterized.

Although a growing body of evidence highlights the long-term cardiovascular burden of COVID-19, the role of kidney involvement during the acute phase remains insufficiently characterized. It is unclear whether renal abnormalities observed in hospitalized patients represent only transient consequences of acute illness or whether they signal a sustained vulnerability to future complications. At the same time, the contribution of systemic inflammation, coagulation disturbances, and persistent endothelial dysfunction to this cardiorenal continuum has not been fully established. Thus, our study sought to explore the relationship between kidney dysfunction in hospitalized COVID-19 patients and the risk of cCV events during 1-year follow-up. We further investigated whether biomarkers reflecting inflammation, thrombosis, and endothelial activation could provide additional insights into the mechanisms that link acute infection with long-term outcomes. By addressing these gaps, we aim to contribute to a better understanding of post-COVID risk stratification and the potential need for integrated cardiorenal monitoring.

Materials and methods. This prospective cohort study included 328 patients who were hospitalized with moderate to severe COVID-19 between March 2021 and December 2022 at Central City Clinical Hospital of Chernivtsi and at the Department of Propedeutics of Internal Medicine of Bukovinian State Medical University. All participants had a positive PCR test for SARS-CoV-2 and radiological signs of pneumonia. Patients with chronic kidney disease, previous dialysis or kidney transplantation, as well as those with a known history of myocardial infarction, stroke, or symptomatic heart failure, were excluded in order to minimize the influence of pre-existing cardiorenal pathology. Patients with active malignant disease, systemic autoimmune conditions, or missing follow-up data were also excluded.

After applying these criteria, 328 patients were followed for twelve months after discharge. Cardiovascular outcomes were identified through review of electronic medical records, outpatient visits, and cardiology consultations. Based on these results, the study population was divided into two groups: 105 patients who developed cardiovascular complications during follow-up and 223 patients without cardiovascular outcomes.

During hospitalization, blood samples were taken for standard laboratory testing. Inflammatory and endothelial markers were also assessed, including C-reactive protein (CRP), D-dimer, neutrophil and lymphocyte counts with calculation of the neutrophil-to-lymphocyte ratio, together with routine hematological indices such as hemoglobin, white blood cells, and platelets.

Kidney function was evaluated using serum creatinine, urea, and estimated glomerular filtration rate (eGFR) calculated by the CKD-EPI equation. For the purposes of this study, COVID-19-associated kidney dysfunction was defined as either (i) an increase in serum creatinine ≥26 μmol/L compared with the value at admission during the index hospitalization, or (ii) a reduction in eGFR to <60 mL/min/1.73 m^2 at any point during hospitalization. These thresholds were chosen to differentiate kidney involvement from expected age-related decline in kidney function.

The main endpoint was the occurrence of major adverse cardiovascular events within one year of discharge, defined as a composite of new-onset heart failure, arterial hypertension requiring therapy, clinically significant arrhythmias, ischemic stroke or transient ischemic attack, and myocardial infarction. Each of these outcomes was also analyzed separately.

In addition, a smaller substudy was conducted to evaluate intercellular adhesion molecule-1 (ICAM-1) as a biomarker of endothelial activation. This included three groups of 20 participants each: healthy controls with no history of COVID-19, patients during the acute phase of infection, and patients one year after hospitalization who had developed cardiovascular complications.

All data were entered into Google Sheets and analyzed using Python. Descriptive statistics summarized the study population; normality was tested with the Shapiro–Wilk. Group comparisons used the t-test or Mann–Whitney U for continuous variables and χ^2 or Fisher's exact test for categorical variables. Two multivariable logistic regression models were constructed: one with kidney dysfunction (eGFR <90 mL/min/1.73 m^2) as the outcome and predictors of diabetes, age, sex, and BMI; the other with 12-month cardiovascular outcomes as the dependent variable and kidney function indicators (creatinine, eGFR) as predictors. Results are presented as odds ratios (OR) with 95% confidence intervals (CI); $p < 0.05$ was considered significant.

The study was approved by the Bukovinian State University Ethics Committee (protocol №1, 22.09.2022). All procedures were conducted in accordance with the principles of the Declaration of Helsinki

(2013 revision) and national ethical regulations. Written informed consent was obtained from all participants where applicable. In the ICAM-1 substudy, all patients and healthy controls provided written informed consent before blood sampling.

Results. Patients with cardiovascular outcomes (n = 105) had a mean age of 57,7 years (IQR 50–65), while those without outcomes (n = 223) had a mean age of 56,6 years (IQR 48–66). Thus, the two groups were similar in age distribution. However, the sex structure differed: among patients with outcomes, 60 (57,1%) were men and 45 (42,9%) women, whereas in the group without outcomes, men accounted for 105 (47,1%) and women for 118 (52,9%). This difference was not strongly, but statistically significant (p < 0,1), suggesting that male sex was more common among patients who later developed cardiovascular complications.

Kidney abnormalities were already common during hospitalization for COVID-19. According to our predefined criteria, COVID-19–associated kidney dysfunction (a rise in serum creatinine ≥26 μmol/L during hospitalization or an eGFR <60 mL/min/1.73 m) was observed in a notable proportion of patients. Mean serum creatinine and urea levels were 92,0 ± 50,8 μmol/L and 9,3 ± 4,8 mmol/L, respectively. Nearly half of the cohort (45.7%) had eGFR values below 90 mL/min/1.73 m^2, and more than one-fifth met the threshold of <60 mL/min/1.73 m^2. Proteinuria was also widespread: only 42,1% of patients had negative results, while 22,0% showed trace amounts, 22,3% mild proteinuria (+), and about 14% had moderate to severe proteinuria (++/+++). These findings indicate that kidney involvement was present in a large proportion of patients already during the acute phase of infection, before cardiovascular outcomes became evident.

After discharge, patients were followed for 12 months. Among the 105 patients who experienced cardiovascular complications, the most common events were major adverse cardiovascular events (40,8%), arrhythmias (20,0%), and new-onset arterial hypertension (16,8%). Heart failure occurred in 13,6% of cases, while myocarditis (5,6%) and cardiomyopathy (3,2%) were less frequent. Totally 32,0% of all patients had any type of cardiovascular dysorders during 12 months after acute COVID-19.

Our analysis showed that patients who later developed cardiovascular complications already tended to have more pronounced kidney impairment during hospitalization. Their creatinine and urea values were higher, while eGFR was lower (83,2 ± 27,2 vs 87,3 ± 25,5 mL/min/1,73 m^2) compared with patients who remained event-free. Although these differences did not always reach statistical significance, the reduction in eGFR showed at least a tendency toward significance (p between 0.05 and 0.1 in adjusted analyses) (Table 1). Proteinuria was also more frequent among those who subsequently developed cardiovascular outcomes, reinforcing the link between early kidney involvement during COVID-19 and long-term cardiorenal vulnerability. Group comparisons were performed using the Mann-Whitney U-test for continuous variables and the χ^2 test for categorical variables.

Table 1

Comparative analysis of kidney function between groups

Variable	With outcomes (mean±SD)	Without outcomes (mean±SD)	p-value
Creatinine, μmol_L	92,0 ± 50,8	81.8 ± 40.1	0.0423
Urea, mmol/L	9,3 ± 4,8	8.5 ± 3.2	0.1689
eGFR, mL/min/1,73m^2	83,2 ± 27,2	87.3 ± 25.5	0.0923

Diabetes was a common comorbidity in this cohort. Overall, 26,8% of the patients had either known diabetes mellitus or were first diagnosed during hospitalization, while two-thirds had no history of the disease. Specifically, 16,7% had previously diagnosed diabetes and 10,1% were identified with first-time hyperglycemia meeting diagnostic criteria during admission.

When kidney function was analyzed in relation to diabetes (DM) status, the prevalence of reduced eGFR (<90 mL/min/1.73 m^2) was high in both groups, affecting almost half of the patients regardless of diabetes. Similarly, the occurrence of moderate dysfunction (eGFR <60 mL/min/1.73 m^2) did not differ significantly between diabetics and non-diabetics. The only tendency was found in proteinuria levels among these groups of patients with p=0,073 – proterinuria was more often in patients with DM. This may prove that kidney dysfunction found in studied population was related to acute infection and was not a result of chronic kidney disease in people with DM.

To further explore the potential interaction between diabetes and kidney injury, a multivariable logistic regression model was performed with kidney dysfunction (eGFR <90 mL/min/1,73 m^2) as the dependent variable, and diabetes, age, sex, and body mass index as predictors. In this model, diabetes was not independently associated with kidney dysfunction (OR 1,04, 95% CI 0,64–1,67, p = 0,88). By contrast, age emerged as the dominant predictor: each additional year of age was associated with a 5% increase in the odds of reduced eGFR (OR 1,05 per year, 95% CI 1,02–1,07, p < 0,001). Neither sex nor body mass index showed significant associations with kidney impairment (Fig.1).

In multivariable regression, indicators of kidney function during hospitalization showed an association with cardiovascular outcomes at one year. Each 10 mL/min/1.73 m^2 decrease in eGFR was linked to an 8% higher risk of subsequent complications (aOR 1.08, 95% CI 1.01–1.16, p = 0.044), suggesting that even mild reductions in filtration capacity may carry prognostic weight. Similarly, elevated serum creatinine was independently associated with later events: for every 10 µmol/L increase, the odds of cardiovascular outcomes rose by approximately 6% (aOR 1.06, 95% CI 1.01–1.12, p = 0.037). These findings support the concept that impaired kidney function during the acute phase of COVID-19 is not only a marker of illness severity but also a predictor of long-term cardiovascular vulnerability (Fig. 1).

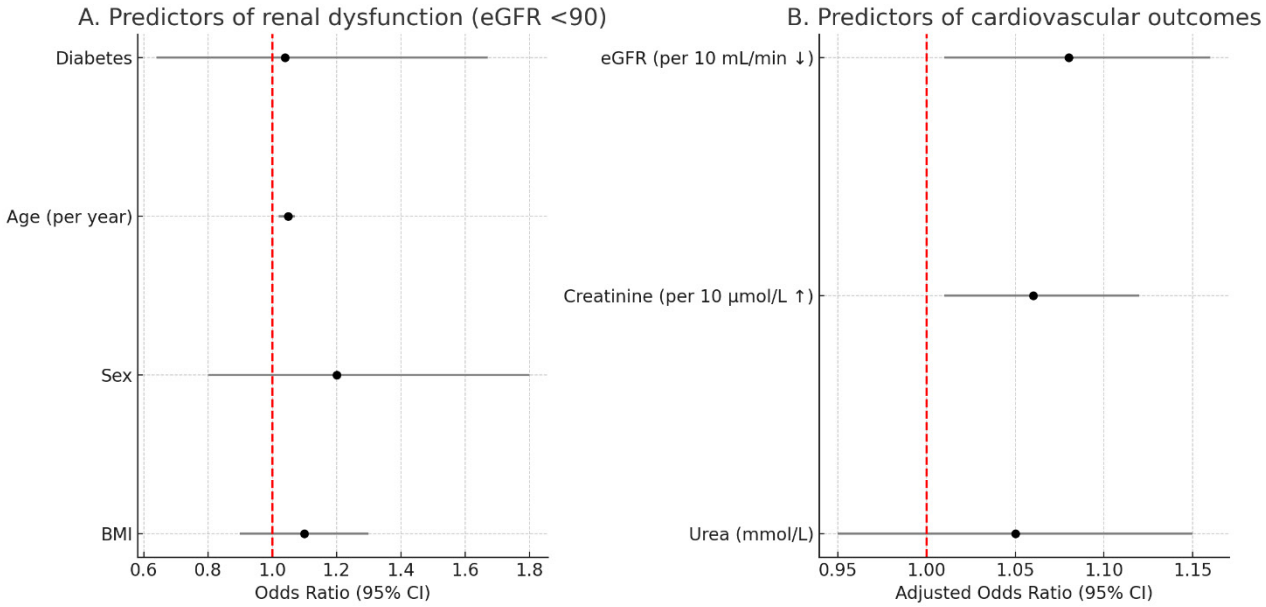

Fig. 1. Multivariable logistic regression results. (A) Predictors of kidney dysfunction during COVID-19 hospitalization: age showed a significant association with reduced eGFR, whereas diabetes, sex, and BMI demonstrated non-significant trends. (B) Predictors of 12-month cardiovascular outcomes: a 10 mL/min/1.73 m^2 decrease in eGFR and a 10 µmol/L increase in creatinine were associated with higher odds of events; urea showed a non-significant trend. Points indicate odds ratios; horizontal bars show 95% CIs; dashed vertical line marks OR=1.

C-reactive protein (CRP) levels during hospitalization were higher in participants who later developed cardiovascular outcomes (38,28 ± 1,99 mg/L) compared to those without events (35,11 ± 1,12 mg/L). Although this difference did not reach conventional statistical significance, the p value was <0,1 (p = 0,0661), indicating a tendency toward elevated CRP in patients at risk of cardiovascular complications, reflecting the systemic inflammation processes during COVID-19 and afterwards (Table 2). In contrast, D-dimer levels were significantly different between groups, being almost 1 mg/L higher in participants with cardiovascular outcomes (2,90 ± 0,11 mg/L) compared with those without complications (1,89 ± 0.07 mg/L, p < 0,001), confirming the role of coagulation and thrombosis (Table 2).

Table 2

Laboratory markers in patients with and without CV outcomes during 1 year after COVID-19

Marker	With CV outcomes	Without CV outcomes	p
CRP, mg/L	38,28 ± 1,99 [5,60; 70,70]	35,11 ± 1,12 [5,00; 70,36]	0.0661
D-Dimer, mg/L	2,90 ± 0,11 [0,52; 4,84]	1,89 ± 0,07 [0,03; 4,08]	<0.01

In the ICAM-1 substudy, healthy controls (n = 20) had low baseline levels (mean 193,6 ± 93,7 pg/mL). Patients in the acute phase of COVID-19 (n = 20) demonstrated markedly elevated concentrations (mean 569,1 ± 105,6 pg/mL). Importantly, patients one year after hospitalization who developed cardiovascular complications (n = 20) continued to show persistently high ICAM-1 values (mean 522,7 ± 113,1 pg/mL) (Fig. 2). Although slightly lower than in the acute phase, these levels remained nearly three times higher than in healthy individuals, highlighting long-lasting endothelial dysfunction in those prone to post-COVID cardiovascular disease.

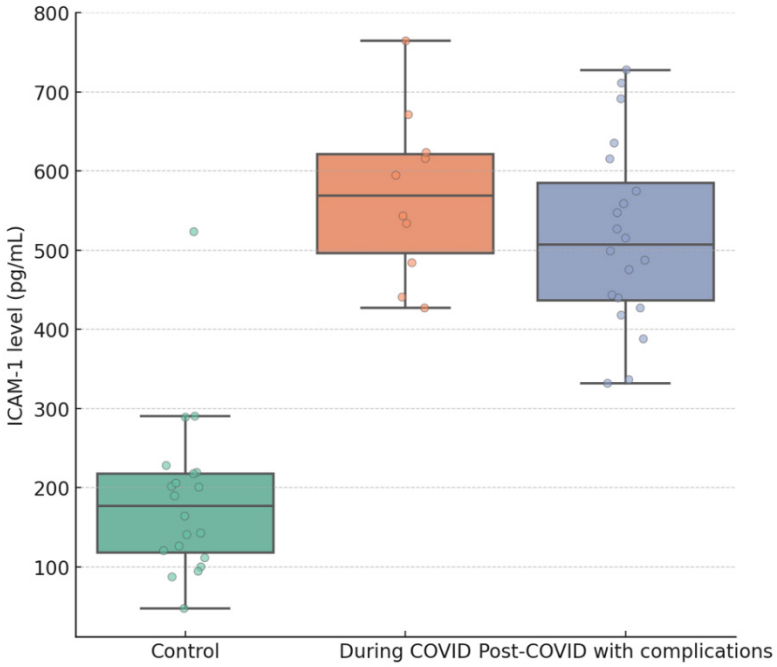

Fig. 2. ICAM-1 levels in healthy individuals, patients during acute COVID-19, and 1 year after COVID-19 with cardiovascular outcomes. Levels were significantly higher in acute COVID and in post-COVID patients with CV events compared to healthy controls (both p<0.001), while a trend was observed between acute and post-COVID groups (p=0.086).

Discussion. This prospective cohort study provides new evidence that kidney dysfunction during acute COVID-19 hospitalization is closely linked to the subsequent development of CV complications over one year of follow-up. Three principal findings emerge. First, a substantial proportion of hospitalized patients exhibited biochemical or urinary evidence of kidney involvement at the time of admission, including elevated creatinine, reduced eGFR, and proteinuria. Second, these abnormalities were not explained by underlying CKD or DM, supporting the concept of COVID-related acute kidney injury. Third, patients who developed CV complications more frequently demonstrated early kidney impairment and higher levels of inflammation, thrombosis, and endothelial activation, as reflected by CRP, D-dimer, and ICAM-1. Together, these findings suggest that kidney injury in COVID-19 is not merely an epiphenomenon but a mechanistic contributor to post-acute cardiorenal vulnerability.

Consistent with prior studies, kidney abnormalities were widespread in our cohort. Nearly half of the patients had reduced eGFR (<90 mL/min/1,73m^2), and proteinuria was observed in more than half. Importantly, regression analyses showed that diabetes was not independently associated with reduced eGFR, while age was the strongest predictor. Moreover, proteinuria was only weakly related to diabetes status (p = 0,073). This argues against chronic diabetic nephropathy as the major driver and instead indicates that kidney dysfunction in our study reflected acute COVID-associated kidney injury. This is in line with recent reports documenting that COVID-19 survivors, even without pre-existing CKD, experience accelerated kidney function decline compared to matched post-pneumonia controls [**2, 6, 11**]. Literature reviews also indicate that SARS-CoV-2 itself can provoke acute kidney injury, supporting our observation of frequent kidney involvement during COVID-19 [**12**].

Long-term CV complications were frequent, affecting almost one-third of the cohort. Arrhythmias, hypertension, and major adverse cardiovascular events predominated. These outcomes were more common among patients with kidney impairment during hospitalization, consistent with the established cardiorenal link whereby acute kidney injury (AKI) accelerates vascular vulnerability [**2, 10**]. Our findings reinforce the notion that COVID-19 acts as a "second hit", precipitating persistent renal and vascular sequelae that manifest clinically as CV events. Previous national cohorts have similarly shown elevated 1-year risks of heart failure, arrhythmias, and stroke after COVID-19, even in non-severe cases [**1, 3–5**]. The stronger association of CV events with kidney dysfunction at baseline suggests that the kidney is not only a marker of disease severity but also a mediator of future risk.

Our biomarker findings provide important mechanistic insight into the long-term sequelae of COVID-19. Although the predefined clinical endpoints of this study were cardiovascular outcomes, the observed pattern of biomarker alterations suggests that nephrological pathology should also be considered a relevant and potentially preventable consequence of COVID-19. Elevated CRP, higher D-dimer concentrations, and persistently increased ICAM-1 levels collectively point to a triad of systemic inflammation, thrombo-inflammation, and endothelial activation, all of which may represent the biological substrate for both cardiovascular and kidney complications in survivors of COVID-19.

CRP is a sensitive marker of systemic inflammation and reflects IL-6–driven acute phase response. In our cohort, patients who subsequently developed cardiovascular outcomes already had higher CRP levels during hospitalization, and the difference, though modest, reached borderline statistical significance. These findings are consistent with previous studies demonstrating that even low-grade elevations in CRP can persist after acute infection and may contribute to sustained endothelial activation and vascular dysfunction [7, 11, 13]. Persistent inflammatory activation has been implicated in platelet hyperreactivity, vascular permeability, and maladaptive tissue repair, mechanisms that provide a plausible explanation for both cardiovascular and renal sequelae of COVID-19.

The role of coagulation and thrombosis is underscored by our observation of significantly elevated D-dimer in patients who later developed cardiovascular complications. Elevated D-dimer reflects ongoing fibrin formation and degradation and has been repeatedly shown to remain abnormally high in convalescent COVID-19 patients, often independent of the acute phase response [11, 13]. This prolonged hypercoagulability suggests that a persistent immunothrombotic state, rather than residual acute illness, underlies the observed laboratory abnormalities. Clinically, elevated D-dimer is strongly associated with venous thromboembolic events, but it also signals widespread endothelial and microvascular injury, which can compromise kidney as well as cardiovascular health [14, 15].

Perhaps the most interesting finding in our study was the persistence of elevated ICAM-1 one year after hospitalization in patients who developed cardiovascular events. ICAM-1 is a leukocyte adhesion molecule expressed by activated endothelial cells and is a central mediator of leukocyte-endothelium interactions, promoting transendothelial migration and vascular inflammation. Our results align with prior research showing that endothelial biomarkers (ICAM-1, VCAM-1, E-selectin, von Willebrand factor) remain elevated months after infection and correlate with impaired functional recovery and thrombotic risk [7–9, 16, 17]. Importantly, large-scale cohort studies outside of the COVID context demonstrate that higher levels of these adhesion molecules independently predict incident CKD and accelerated eGFR decline [14]. Taken together, these findings suggest that ICAM-1 is not merely a biomarker but also a mechanistic bridge between systemic endotheliopathy, cardiovascular pathology, and kidney disease progression.

The kidney is particularly susceptible to the downstream effects of this persistent endotheliopathy. Autopsy and biopsy series have demonstrated complement deposition in renal microvasculature, endothelial swelling, and peritubular capillary thrombosis in severe COVID-19, supporting the concept of "endothelialitis" as a driver of kidney injury [18,19]. Experimental work also highlights endothelial-to-mesenchymal transition, glycocalyx shedding, and oxidative stress as processes that contribute to capillary rarefaction and interstitial fibrosis [17]. These pathophysiological mechanisms may explain why COVID-19 survivors, even without pre-existing CKD, demonstrate accelerated kidney function decline and higher risk of CKD progression compared to matched controls [6, 11–14]. Other recent studies also emphasize the contribution of pro- and anti-inflammatory cytokines to the development of kidney dysfunction, highlighting the complex immunological background of possible COVID-19-related kidney injury. In this context, our findings acquire additional significance. Patients in our cohort who experienced cardiovascular outcomes not only had higher CRP and D-dimer during hospitalization but also showed more pronounced kidney involvement, including lower eGFR and higher prevalence of proteinuria. The persistence of elevated ICAM-1 one year later provides evidence of ongoing endothelial activation in this high-risk subgroup. These converging abnormalities suggest that kidney injury in COVID-19 is both a marker and a mediator of systemic endotheliopathy, linking acute infection to chronic cardiovascular and kidney disease.

Therefore, we suggest that kidney outcomes should be integrated into post-COVID surveillance strategies. Beyond cardiovascular follow-up, systematic kidney screening – including serum creatinine, eGFR, and albuminuria – should be performed in patients hospitalized for COVID-19, particularly those who experienced AKI or presented with abnormal biomarkers. Monitoring kidney trajectories in such patients could allow earlier detection of CKD progression and provide opportunities for targeted interventions.

Conclusions. This prospective cohort study shows that kidney dysfunction is highly prevalent during hospitalization for COVID-19 and represents an acute consequence of infection. Patients with impaired kidney function at baseline were more likely to develop long-term cardiovascular complications over 12 months of follow-up, underscoring the kidney as both a marker and mediator of systemic vulnerability.

Biomarker analysis revealed a persistent pattern of systemic inflammation (CRP), coagulation activation (D-dimer), and endothelial dysfunction (ICAM-1) in patients with adverse outcomes. These findings provide a mechanistic link between kidney involvement in acute COVID-19 and long-term CVD.

Taken together, our results highlight the importance of integrated cardiorenal monitoring after COVID-19. We propose that patients with kidney involvement during hospitalization should undergo structured follow-up, including kidney function tests and CV evaluation. ICAM-1 and related endothelial markers may serve as promising tools for identifying individuals at the highest risk, although further research is warranted.

Ethics statement. The study protocol was reviewed and approved by the Ethics Committee of the Bukovinian State Medical University, Chernivtsi, Ukraine, approval number №1, 22.09.2022. All participants pro-

vided written informed consent prior to enrollment in the study and for the collection and analysis of their clinical and laboratory data.

Conflict of interest statement. The authors have no conflicts of interest to declare.

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Authors' contributions.

Anastasiia Hovornyan: conception and study design, data collection, statistical analysis, drafting of the manuscript.

Tetiana Ilashchuk: supervision, critical revision of the manuscript for important intellectual content, guidance in study design and interpretation.

Both authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Data availability statement. The datasets analyzed during the current study are not publicly available due to institutional privacy regulations but are available from the corresponding author on reasonable request.

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