

Impact of Prior Chronic Kidney Disease and Newly Detected eGFR Impairment at Admission on Outcomes and Prognosis of Hospitalized COVID-19 Patients – A Single-Center Cohort Study

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Background and Hypothesis: Chronic kidney disease (CKD) is a major prognostic factor in COVID-19. Little is known about the significance of newly detected renal impairment (RI) for COVID-19 patient outcomes. This study assessed the effect of prior CKD and RI at admission on in-hospital mortality in COVID-19 patients.

Methods: A total of 5191 consecutive patients with COVID-19 admitted between March 6, 2020 and May 31, 2021, to the University Hospital in Krakow were analyzed. The main outcome was in-hospital death from any cause compared between the three study groups – patients with a prior history of CKD (group A), no history of CKD and eGFR on admission <60 mL/min/1.73 m² (group B), and no history of CKD and eGFR on admission >60 mL/min/1.73 m² (group C).

Results: Of 5191 patients, 2348 (45.2%) were women and 2409 (46.4%) were older than 65 years (mean age of 61.98±16.66 years). There were 483 (9.3%) patients in group A, 1009 (22.2%) in group B and 3699 (68.5%) in group C. Groups A and B were older and had higher cardiometabolic burden compared to group C. Multivariable logistic regression showed that older age, higher CRP, WBC, D-dimer levels, HF, and being in groups A or B were associated with higher in-hospital mortality. Group B had the highest risk (OR 3.003, CI 2.298–3.926) compared to group A (OR 2.020, CI 1.636–2.494) and group C (reference).

Conclusion: COVID-19 patients with prior CKD and newly detected RI have higher odds of in-hospital death compared to those with normal kidney function. Special attention is needed for newly detected RI cases in COVID-19 patients.

Keywords: kidney disease, mortality, risk factors, COVID-19, chronic kidney disease, acute kidney injury, SARS-Cov-2

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019 as a novel pathogen in China, causing the worldwide pandemic of coronavirus disease 2019 (COVID-19).¹ Since then, it has caused nearly 770 million confirmed cases with nearly 7 million deaths worldwide according to The World Health Organization.² COVID-19 is primarily a disease of the respiratory tract, however, it has the potential to affect multiple organ systems, including the kidneys.³

Chronic Kidney Disease (CKD) remains an important medical and socio-economic problem, as its prevalence in Poland is estimated to range between 11% and 18%.^{4,5} Patients with CKD show a higher cardiovascular risk, with cardiovascular diseases accounting for ca. 50% of death causes in this group.³ Patients with advanced CKD are also at

higher risk of acquiring infections, acting as a considerable cause of non-cardiovascular morbidity and mortality.⁶ Effective screening for CKD with the use of easily accessible parameters such as estimated glomerular filtration rate (eGFR) calculated based on the serum creatine level, enables detecting CKD at the early stage, slowing down its progression, and preventing its complications.⁷

Older age and numerous chronic comorbidities, including hypertension, diabetes, ischemic heart disease, history of stroke, malignant neoplasms, and overall multimorbidity, were proven to increase the risk of contracting COVID-19, and correlated with a more severe course of the disease, including hospitalization in the intensive care unit (ICU), initiation of mechanical ventilation, and death.^{8,9} The list of such risk factors also includes CKD. CKD, especially in advanced stages and in patients undergoing kidney replacement therapy, was identified as a disease leading to a greater incidence and severity of COVID-19 infection.^{3,10,11} The mortality in CKD patients was 50% to 80% higher than in the population free from this disease.³

Acute kidney injury (AKI) may appear in both CKD patients and populations free from prior kidney disease. There is a bidirectional relationship between AKI and COVID-19, with higher incidence of AKI in COVID-19 patients, but also increased severity of COVID-19 in those affected by AKI.^{12,13}

Considering the high prevalence of CKD and AKI in COVID-19 patients, and the more severe course of disease in COVID-19 patients with kidney dysfunction, it is crucial to continue collecting and reporting data from cohorts of these groups of patients. This seems to be of particular importance during similar viral pandemics that may occur in the future.

The purpose of this study was to assess the impact of prior CKD and at admission newly detected renal impairment (RI) defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1,73 m² on important clinical outcomes such as in-hospital death from any cause, in hospitalized COVID-19 patients.

Methods

In this study, medical records of 5191 consecutive patients admitted between March 6, 2020 and May 31, 2021, to the University Hospital (UH) in Krakow were analyzed. From March 2020, UH was temporarily transformed into the regional COVID-19 center, responsible for the hospitalization of patients with COVID-19 requiring specialized treatment.¹⁴ Diagnosis with COVID-19 was made according to WHO and Polish guidelines with the use of the RT-PCR method.^{15,16} The COVID-19 treatment algorithm was based on constantly updated recommendations of the Polish Association of Epidemiologists and Infectiologists.¹⁵

Demographic and clinical data were extracted from the hospital's digital medical records. Previous reports analyzed selected data from this dataset.^{14,17,18} The database included information on patients' age, sex, date of admission, date of discharge or death, admission to the ICU, and use of mechanical ventilation.

The main outcome analyzed by the study was in-hospital death from any cause. Additionally, we analyzed secondary end points such as Intensive Care Unit (ICU) admission and mechanical ventilation requirements. All these outcomes were evaluated and compared between the three study groups – patients with prior confirmed history of CKD (group A), no history of CKD and eGFR on admission <60 mL/min/1,73 m² (group B) and no history of CKD and eGFR on admission >60 mL/min/1,73 m² (group C). We also compared non-survivors between the three groups A, B and C.

Baseline clinical parameters at admission were extracted. They included heart rate, blood pressure, oxygen saturation, respiratory rate, as well as laboratory results [C-reactive protein (CRP), D-dimer, white blood count (WBC), serum creatinine – at admission and peak during the hospitalization]. eGFR was calculated with the use of Modification of Diet in Renal Disease (MDRD) formula.¹⁹ Patients were stratified based on at admission eGFR: ≥60, 59–30, 29–15, <15 mL/min/1,73 m² (the latter – end-stage renal disease, ESRD). No information was available for previous serum creatinine concentrations. We did not record information on proteinuria at admission or during hospitalization.

The characteristics analyzed also involved comorbidities [previous diagnosis of diabetes, arterial hypertension, heart failure (HF), history of myocardial infarction (MI) or stroke, ischemic heart disease, atrial fibrillation (AF), chronic obstructive pulmonary disease (COPD)] and in-hospital use of renal replacement therapy (RRT). CVD and cardiovascular risk factors were identified on the basis of medical history of prehospital diagnosis and/or treatment and defined in accordance with the current European Society of Cardiology guidelines.²⁰ CKD was identified on the basis of medical

history of prehospital diagnosis and/or treatment. Similarly, other chronic comorbidities were also recognized based on earlier diagnosis available in the medical records.

A model was built for the risk of death in all analyzed patients across different kidney function categories (groups A, B, C), age, sex, CRP, WBC and D-dimer concentrations on admission, hypertension, HF, atrial fibrillation, coronary artery disease, diabetes, COPD and neoplasm.

Ethics

The study was approved by the Jagiellonian University Ethics Committee, decision number 1072.6120.278.2020. The study included a retrospective analysis of data only. As such, the requirement for consent was waived by an ethics committee based on local ethics regulations. The authors, all employees of the University Hospital, had been granted special permission from the Krakow University Hospital authorities to access the data. Data gathered in the study was anonymized and maintained with confidentiality. The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

All statistical analysis was made using the SPSS Imago Pro 9.0. The normality of the continuous variable distribution was assessed using the Shapiro–Wilk test. Differences between groups were analyzed with Student's *t* test and ANOVA, or nonparametric tests (Mann U Whitney and Kruskal–Wallis tests), when appropriate. Continuous variables were presented as arithmetic means ($\pm$ standard deviations (SD) or median (interquartile range; IQR) when the data were not normally distributed. The distribution of categorical variables was shown by counts and percentages. Statistical testing was completed to compare categorical variables using the independent samples chi-square test or Fisher's exact test when appropriate. Bonferroni correction was applied when multiple comparisons were performed. To search for factors associated with hospital death of CKD patients, we performed univariate logistic regression (Table S1). Significant variables were included in the final model. The multicollinearity assumption was fulfilled in the models. The Nagelkerke's index was used as an equivalent of the coefficient of determination, R^2 . The strength of the association was measured by the odds ratio (OR) and the 95% confidence intervals (CI). Statistical inference was based on the criterion $p < 0.05$.

Results

Between March 6, 2020, and May 31, 2021, 5191 individuals were hospitalized due to COVID-19 in the UH in Kraków. Modest male predominance was observed ($N=2843$, 54.8%) with most patients being middle to older aged (46.4%, ≥ 65 years; mean age 61.98 ± 16.66 years). On-admission creatinine serum concentration was available for 5026 individuals. Of these, on admission, 3625 (72.1%) patients had $eGFR \geq 60$ mL/min/1.73 m², 949 (18.9%) 59–30 mL/min/1.73 m², 247 (4.9%) 29–15 mL/min/1.73 m² and 205 (4.1%) <15 mL/min/1.73 m².

Four hundred and eighty-three (9.3%) individuals had prior history of CKD (group A). On-admission creatinine serum concentration was available for 475 of them. Of this number, 83 (17.5%) patients were classified with stage 1 and 2 CKD, 148 (31.2%) with stage 3, 90 (18.9%) with stage 4 and 154 (32.4%) had ESRD.

4708 individuals did not have recorded history of CKD. Among patients with no recorded history of CKD, 1009 had at admission $eGFR < 60$ mL/min/1.73 m² (at admission RI, group B), while the remaining 3699 patients had no history of CKD and retained adequate kidney function ($eGFR > 60$ mL/min/1.73 m²; group C).

Baseline clinical characteristics are summarized in Table 1. Patients from group B were the oldest, followed by group A and group C (74, IQR 67–82 vs 70, IQR 59–79 vs 60, IQR 47–70, $p < 0.001$), there were more males in the group A than in the group B (59.6% vs 52.8%, $p = 0.046$), and patients from group B had the highest BMI. Most comorbidities were more common in both groups A and B than in C, with modest differences between groups A and B. The clinical presentation and laboratory results on admission were similar between groups A and B - patients from both these groups were initially in more severe clinical condition, had higher inflammatory and kidney parameters than those from group C (Table 1). Out of 344 (6.6%) patients requiring renal replacement therapy (RRT) throughout hospitalization, 178 (51.7%) did not have a history of previous CKD.

Table 1 Comparison of Patients With Different Categories of Kidney Dysfunction

Clinical Feature	Kidney Function Category			P value
	A (N=483)	B (N=1009)	C (N=3699)	
Sex [male]	288 (59.6)*	533 (52.8)*	2022 (54.7)	0.046
Age [years]	70 (59–79)*	74 (67–82)*	60 (47–70)*	<0.001
Age class >65 years [N(%)]	285 (59.0)*	790 (78.3)*	1334 (36.1)*	<0.001
BMI [kg/m ²]	27.7 (24.5–32.6)*	29.6 (25.7–34.3)*#	28.1 (25.1–31.6)#	<0.001
RRT [N(%)]	178 (36.9)*	99 (9.8)*	67 (1.8)*	<0.001
CVD [N(%)]	428 (88.6)#	879 (87.1)*	1997 (54.0)*#	<0.001
Hypertension [N(%)]	391 (81.0)#	805 (79.8)*	1832 (49.5)*#	<0.001
Hyperlipidemia [N(%)]	161 (33.3)#	289 (28.6)*	625 (16.9)*#	<0.001
Heart failure [N(%)]	129 (26.7)*	209 (20.7)*	171 (4.6)*	<0.001
Coronary artery disease [N(%)]	157 (32.5)#	303 (30.0)*	404 (10.9)*#	<0.001
History of myocardial infarction [N(%)]	86 (17.8)#	161 (16.0)*	210 (5.7)*#	<0.001
Atrial Fibrillation [N(%)]	101 (20.9)#	228 (22.6)*	312 (8.4)*#	<0.001
History of Stroke [N(%)]	56 (11.6)#	111 (11.0)*	226 (6.1)*#	<0.001
COPD [N(%)]	34 (7.0)#	91 (9.0)*	151 (4.1)*#	<0.001
Diabetes [N(%)]	201 (41.6)#	386 (38.3)*	777 (21.0)*#	<0.001
History of neoplasm [N(%)]	84 (17.4)*	133 (13.2)	407 (11.0)*	<0.001
On-admission presentation				
SBP [mmHg]	130 (115–148)*	124 (107–140)*#	130 (120–144)#	<0.001
DBP [mmHg]	79 (68–88)*	74 (63–85)*	80 (72–90)*	<0.001
Heart rate [bpm]	80 (72–95)#	82 (73–97)*	85 (76–96)*#	<0.001
Respiratory rate [N]	16 (14–20)#	16 (12–20)*	14 (12–17)*#	<0.001
Oxygen saturation [%]	95 (91–97)	95 (90–97)*	95 (92–97)*	<0.001
Laboratory results				
On-admission creatine [μmol/l]	173.0 (111.0–461.0)#	122.0 (106.0–158.0)*	69.6 (58.8–80.9)*#	<0.001
On-admission eGFR [mL/min/1.73m ²]	28.3 (10.5–51.6)#	45.4 (33.0–53.7)*	89.4 (76.0–106.0)*#	<0.001
On-admission eGFR category [N(%)]				<0.001
>60 mL/min/1.73m ²	83 (17.5%)	–	–	
60–30 mL/min/1.73m ²	148 (31.2%)	801 (79.4%)	–	
29–15 mL/min/1.73m ²	90 (18.9%)	157 (15.6%)	–	
<15 mL/min/1.73m ²	154 (32.4%)	51 (5.1%)	–	
Maximal creatine [μmol/l]	223.0 (130.0–525.0)*	135.0 (110.0–195.0)*	74.9 (63.4–87.4)*	<0.001
On-admission CRP [mg/l]	62.8 (25.6–126.0)#	71.8 (28.8–140.0)*	43.6 (11.8–92.4)*#	<0.001
On-admission D-dimer [μg/mL]	1.5 (0.8–3.2)#	1.4 (0.7–3.2)*	0.8 (0.5–1.7)*#	<0.001
On-admission WBC [10 ³ /mm ³]	6.8 (4.7–10.6)#	7.2 (5.0–10.7)*	6.1 (4.5–8.6)*#	<0.001
Endpoints				
In-hospital death [Yes (%)]	188 (38.9)#	372 (36.9)*	397 (10.7)*#	<0.001
Mechanical ventilation [Yes (%)]	88 (18.2)#	215 (21.3)*	340 (9.2)*#	<0.001
Admission to an ICU [n (%)]	85 (17.6)#	205 (20.3)*	344 (9.3)*#	<0.001

Notes: data are presented as median (Q1–Q3); confirmed history of CKD (group A), no history of CKD and eGFR on admission <60 mL/min/1.73 m² (group B), no history of CKD and eGFR on admission >60 mL/min/1.73 m² (group C). *# significant difference post-hoc after correction for multiple comparisons.

Abbreviations: BMI, body mass index; RRT renal replacement therapy, CVD, cardiovascular disease: arterial hypertension, heart failure, history of myocardial infarction or stroke, ischemic heart disease, atrial fibrillation; COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beats per minute; eGFR, estimated glomerular filtration rate; CRP, C reactive protein; WBC, white blood count.

There were no differences in mortality rate between group A and group B (38.9% vs 36.9%), whereas the mortality in group C was significantly lower comparatively (10.7%, $p < 0.001$). Similar observations were made for rates of ICU admission and requirement for mechanical ventilation (Table 1). After adjustment for sex and age, patients from both groups A and B were characterized with higher odds of in-hospital mortality (OR 2.616, 95% CI 2.187–3.128; OR 3.790, 95% CI 3.031–4.739; respectively) when comparing with group C.

Patients who died during hospitalization were generally older, had higher prevalence of heart failure, higher concentrations of inflammatory parameters and more severe presentation on admission than survivors. In groups A and B the prevalence of most of the remaining preexisting conditions was similar between survivors and nonsurvivors, which contrasts with group C (for details see Table 2). When comparing non-survivors across groups, patients with kidney dysfunction (group A and B) were comparable, though significant differences in morbidity, laboratory parameters and clinical presentation were observed with respect to group C (Table 2).

In a multivariable logistic regression model predicting in-hospital mortality, older age, higher CRP, WBC and D-dimer concentrations on admission, HF and kidney dysfunction (group A or B), were associated with higher, whereas hypertension was associated with lower in-hospital mortality (Table 3). In this analysis, patients with a prior history of CKD (group A) and patients with no history of CKD and eGFR at admission <60 mL/min/1.73 m² (at admission RI, group B) had higher odds of in-hospital death than patients without any form of kidney dysfunction (group C, Table 3). Finally, patients from group B had the highest odds of in-hospital death (OR 3.003, CI 2.298–3.926 in group B vs 2.020, CI 1.636–2.494 in group A, group C as reference).

Discussion

This is an observational study investigating the relationship between kidney function and clinical outcomes using a large cohort of hospitalized patients with SARS-CoV2 infection treated at a regional reference center. There are several salient findings of this investigation. Among individuals hospitalized with COVID-19, only 10% had documented history of CKD, most of whom suffered from at least moderate grade disease, with over 30% in end-stage renal disease. Over 20% of patients presented with newly detected RI (at admission eGFR < 60 mL/min/1.73 m²) and no pre-existing CKD. Both cases with prior and new-onset renal dysfunction were correlated with higher odds of in-hospital mortality, as compared with individuals who retained glomerular filtration. However, when accounting for several clinically relevant confounders, we observed the risk of in-hospital death may be enhanced among patients with newly detected RI. Furthermore, out of all patients who required RRT, over half had no prior history of kidney disease.

This study showed that every third patient who required hospitalization due to SARS-CoV2 infection suffered some form of kidney injury, which was associated with a higher risk of mortality. While patients in group A largely represent the case of prevalent CKD, a variable proportion of patients with earlier undiagnosed or unreported CKD and/or AKI likely constitute group B. Based on an array of observational evidence, AKI is recognized as a common complication of COVID-19,²¹ with greater risk tied to the presence of pre-existing CKD.^{22,23} Previous studies have shown that the prevalence of undiagnosed stage 3 CKD is high, even in patients with existing risk factors.²⁴ In line with our findings, prior systematic reviews have also shown that CKD increases the risk of severe COVID-19 by ca. 50%, with a more than a twofold increase in mortality in CKD patients, and case fatality risk in CKD being comparable to that of heart disease (about 50%). Studies consistently show that early referral and timely management strategies carry a benefit in slowing CKD progression and prevention of complications, including cardiovascular events in the general population. This observation indicates an urgent need to institute screening (eg, urinary albumin creatinine ratio; UACR) within the community.^{7,25}

Prior reports have shown that patients with no pre-existing CKD and incident AKI may be at greater risk of mortality than CKD patients developing AKI,²⁶ which falls in line with observations based on a comprehensive review with pooled data from 42 studies.²⁷ In our study, the presence of kidney dysfunction, whether previously confirmed CKD or eGFR on admission <60 mL/min/1.73 m² with no history of CKD, was associated with advanced age, frailty and greater morbidity. Any of these factors alone, or in combination, may have explained the critical progression of COVID-19.^{26,27} Some authors hypothesize that dysregulated immunity in CKD (whether derived from a uremic state or chronic immunosuppression) may affect the inflammatory response in SARS-CoV2 infection. In this unique setting, a tempered

Table 2 Comparison of Survivors and Non-Survivors With Different Categories of Kidney Dysfunction

Clinical Feature	Kidney Function Category									P value for non-survivors A vs B vs C
	A			B			C			
	Survivors	Non-survivors	P value	Survivors	Non-survivors	P value	Survivors	Non-survivors	P value	
Sex [male]	173 (58.6%)	115 (61.1%)	0.581	324 (50.9%)	209 (56.2%)	0.102	1769 (53.6%)	253 (63.7%)	<0.001	0.098
Age [years]	66 (54–75)	74 (64–83)*	<0.001	73 (65–80)	77 (70–84)* ^{‡‡}	<0.001	59 (45–68)	71 (63–78) [‡]	<0.001	<0.001
Age class >65 years [N(%)]	148 (50.2%)	137 (72.9%)*	<0.001	478 (75.0%)	312 (83.9%)* ^{‡‡}	0.001	1062 (32.2%)	272 (68.5%)* [‡]	<0.001	<0.001
BMI [kg/m ²]	28.0 (24.5–32.3)	27.7 (24.3–32.9)	0.901	29.4 (25.8–33.9)	30.0 (25.4–34.4)	0.666	28.1 (25.1–31.6)	27.8 (25.4–32.2)	0.843	0.044
RRT [N(%)]	93 (31.5%)	85 (45.2%)* ^{‡‡}	0.002	25 (3.9%)	74 (19.9%)*	<0.001	13 (0.4%)	54 (13.6%)* [‡]	<0.001	<0.001
CVD [N(%)]	266 (90.2%)*	162 (86.2%)	0.177	563 (88.4%)	316 (84.9%)* [‡]	0.116	1712 (51.8%)	285 (71.8%)* ^{‡‡}	<0.001	<0.001
Hypertension [N(%)]	244 (82.7%)	147 (78.2%)*	0.217	522 (81.9%)	283 (76.1%)* [‡]	0.025	1589 (48.1%)	243 (61.2%)* ^{‡‡}	<0.001	<0.001
Hyperlipidemia [N(%)]	106 (36.0%)	55 (29.2%)* ^{‡‡}	0.129	200 (31.4%)	89 (23.9%)	0.011	559 (16.9%)	66 (16.6%)* ^{‡‡}	0.878	<0.001
Heart failure [N(%)]	60 (20.3%)	59 (36.7%)* ^{‡\$}	<0.001	121 (19.0%)	88 (23.7%)* ^{‡‡}	0.078	117 (3.5%)	54 (13.6%)* ^{‡\$}	<0.001	<0.001
Coronary artery disease [N(%)]	88 (29.8%)	69 (36.7%)*	0.116	188 (29.5%)	115 (30.9%)* [‡]	0.640	320 (9.7%)	84 (21.2%)* ^{‡‡}	<0.001	
History of myocardial infarction [N(%)]	47 (15.9%)*	39 (20.7%)	0.018	100 (15.7%)	61 (16.4%)*	0.770	162 (4.9%)	48 (12.1%)*	<0.001	0.021
Atrial Fibrillation [N(%)]	52 (26.7%)	49 (26.1%)*	0.026	136 (21.4%)	92 (24.7%)* [‡]	0.215	245 (7.4%)	67 (16.9%)* ^{‡‡}	<0.001	<0.001
History of Stroke [N(%)]	30 (10.2%)	26 (13.8%)	0.221	72 (11.3%)	39 (10.5%)	0.688	181 (5.5%)	46 (11.6%)	<0.001	0.506
COPD [N(%)]	20 (6.8%)	14 (7.8%)	0.780	54 (8.5%)	37 (9.9%)	0.432	111 (3.4%)	40 (10.1%)	<0.001	0.560
Diabetes [N(%)]	118 (40.0%)	83 (44.1%)*	0.367	240 (37.7%)	146 (39.2%)	0.620	648 (19.6%)	129 (32.5%)*	<0.001	0.016
History of neoplasm [N(%)]	60 (20.3%)	24 (12.8%)	0.032	91 (14.3%)	42 (11.3%)*	0.175	338 (10.2%)	69 (17.4%)*	<0.001	0.044
On-admission presentation										
SBP [mmHg]	134 (120–150)	121 (109–140)	<0.001	127 (114–145)	118 (98–140)*	<0.001	131 (120–144)	127 (110–142)*	<0.001	<0.001
DBP [mmHg]	80 (70–89)	75 (60–86)*	0.003	76 (68–86)	70 (60–80)* ^{‡‡}	<0.001	80 (73–90)	75 (64–83)* [‡]	<0.001	<0.001
Heart rate [bpm]	80 (71–91)	84 (72–100)	<0.001	80 (72–93)	85 (75–100)	<0.001	84 (76–95)	88 (75–100)	0.013	0.420
Respiratory rate [N]	15 (12–18)	18 (14–24)	<0.001	15 (12–18)	18 (14–24)	<0.001	14 (12–16)	18 (14–22)	<0.001	0.396
Oxygen saturation [%]	95 (92–97)	94 (89–96)	0.002	95 (92–97)	92 (85–96)	<0.001	95 (93–97)	93 (88–96)	<0.001	0.152
Laboratory results										
On-admission creatine [μmol/l]	172.5 (107.8–477.3)	181.0 (118.5–443.0)* ^{‡‡}	0.611	117.0 (99.8–139.5)	138.5 (114.0–200.0)*	<0.001	69.2 (58.9–80.7)	73.2 (57.2–86.0)* [‡]	<0.001	<0.001
On-admission eGFR [mL/min/1.73m ²]	30.2 (10.4–55.6)	26.8 (10.5–46.0)* ^{‡‡}	0.433	48.5 (37.9–55.5)	38.4 (25.9–49.2)*	<0.001	89.8 (76.7–106.3)	84.1 (70.5–102.0)* [‡]	<0.001	<0.001
On-admission eGFR category			0.087			<0.001	–	–	–	<0.001
>60 mL/min/1.73m ²	58 (20.0%)	25 (13.5%)		–	–		–	–	–	
60–30 mL/min/1.73m ²	88 (30.3%)	60 (32.5%)*		551 (86.5%)	250 (67.2%)*		–	–	–	
29–15 mL/min/1.73m ²	50 (17.3%)	40 (21.6%)		62 (9.7%)	95 (25.5%)		–	–	–	
<15 mL/min/1.73m ²	94 (32.4%)	60 (32.4%)*		24 (3.8%)	27 (7.3%)*		–	–	–	
Maximal creatine [μmol/l]	187.0 (117.5–577.5)	279.0 (154.0–504.0)* ^{‡\$}	0.019	120.0 (104.0–150.0)	187.0 (135.0–260.0)* ^{‡‡}	<0.001	73.9 (62.9–85.4)	91.9 (71.7–152.0)* ^{‡‡\$}	<0.001	<0.001
On-admission CRP [mg/l]	49.8 (19.9–100.2)	92.9 (41.1–159.0)*	<0.001	52.7 (19.3–105.0)	110.0 (56.0–197.0)* ^{‡‡}	<0.001	38.4 (10.1–84.2)	94.2 (50.3–155.8)* [‡]	<0.001	0.003
On-admission D-dimer [μg/mL]	1.2 (0.7–2.3)	2.3 (1.0–6.0)	<0.001	1.1 (0.6–2.2)	2.1 (1.2–6.2)	<0.001	0.8 (0.5–1.5)	1.6 (0.9–5.3)	<0.001	0.734
On-admission WBC [10 ³ /mm ³]	6.1 (4.3–8.9)	9.0 (5.9–13.8)	<0.001	6.5 (4.8–9.4)	9.0 (6.2–14.1)	<0.001	6.0 (4.5–8.2)	8.5 (5.4–12.5)	<0.001	0.252

Notes: data are presented as median (Q1–Q3); confirmed history of CKD (group A), no history of CKD and eGFR on admission <60 mL/min/1.73 m² (group B), no history of CKD and eGFR on admission >60 mL/min/1.73 m² (group C). *#/\$ significant difference post-hoc after correction for multiple comparisons.

Abbreviations: BMI, body mass index; RRT, renal replacement therapy; CVD, cardiovascular disease: arterial hypertension, heart failure, history of myocardial infarction or stroke, ischemic heart disease, atrial fibrillation); COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beats per minute; eGFR, estimated glomerular filtration rate; CRP, C reactive protein; WBC, white blood count.

Table 3 Multivariable Logistic Regression Analysis for the Risk of in-Hospital Death in Patients With Different Categories of Kidney Dysfunction

Variable	OR	95% CI	P value
Age [years]	1.058	1.049–1.066	<0.001
Sex [females vs males]	0.886	0.734–1.070	0.886
(Log 10) CRP on admission [mg/l]	4.094	3.295–5.087	<0.001
WBC on admission [$10^3/\text{mm}^3$]	1.050	1.033–1.066	<0.001
D-dimer on admission [$\mu\text{g/mL}$]	1.038	1.026–1.050	<0.001
Kidney function category			<0.001
Group A vs group C	2.020	1.636–2.494	
Group B vs group C	3.003	2.298–3.926	
Diabetes [Yes/No]	1.262	1.041–1.530	0.018
Hypertension [Yes/No]	0.719	0.580–0.891	0.003
Heart failure [Yes/No]	1.742	1.332–2.277	<0.001
Atrial fibrillation [Yes/No]	0.934	0.727–1.200	0.594
COPD [Yes/No]	1.069	0.770–1.483	0.691
Neoplasm [Yes/No]	0.989	0.758–1.289	0.932
Coronary artery disease [Yes/No]	1.167	0.932–1.462	0.179

Notes: confirmed history of CKD (group A), no history of CKD and eGFR on admission $<60 \text{ mL/min/1.73 m}^2$ (group B), no history of CKD and eGFR on admission $>60 \text{ mL/min/1.73 m}^2$ (group C).

Abbreviations: OR, odds ratio; CKD, chronic kidney disease; CRP, C reactive protein; WBC, white blood count; COPD, chronic obstructive pulmonary disease, Nagelkerke's $R^2 = 0.352$.

immune response may be protective against the tissue injury that is characteristic of the hyperinflammatory response to COVID-19.^{26,28}

Patients with CKD are characterized by diminished innate and adaptive immune responses.²⁹ This is supported by data from observational studies, which indicate CKD is a major risk factor for severe infection, such as the development of bacteremia and sepsis.^{30,31} When compared with individuals who retain adequate kidney function, higher mortality from specific causes, such as pneumonia, has also been reported.³⁰ As we transition towards the endemic phase of COVID-19, the association between CKD and greater susceptibility to SARS-CoV2 should be recognized. Renal impairment is inadvertently tied to poor prognosis in SARS-CoV2 infection, whether reflected in higher rates of hospitalization, complications and/or mortality.^{3,10,27,32} For patients with prevalent CKD who develop AKI, the risk of unfavorable outcomes may be compounded.³² Taken together, individuals with COVID-19 who present with renal impairment (eGFR $< 60 \text{ mL/min/1.73m}^2$) should be treated as a special population, regardless of the temporal nature of the kidney dysfunction.

We observed that the odds of in-hospital death were numerically similar across both groups with kidney dysfunction. However, after adjustment for several clinically relevant confounders, patients without pre-existing kidney disease and at admission eGFR $< 60 \text{ mL/min/1.73m}^2$ appeared to be at greater risk of mortality. While the prevalence of specific comorbidities was comparable, patients with newly detected eGFR $< 60 \text{ mL/min/1.73m}^2$ were, on average, older, had higher indices of systemic inflammation and more severe clinical presentation on admission. Congruently, the markers of kidney function were poorest, baseline creatine concentrations highest and eGFR values lowest, in group A.

Interestingly, the history of arterial hypertension in the multivariable model reduced the odds of in-hospital death. To date data on the impact of hypertension on the prognosis in COVID-19 showed either poorer, or no differences, in prognosis.^{33–36} It is possible that this surprising finding could have resulted from bias related to confounders, probably due to the retrospective design of the study and uneven dispersion of these confounding factors. To confirm this hypothesis, we performed additional analyses in different subgroups by building models for individual categories of kidney dysfunction, with additional age stratification (data not shown). They revealed that odds for in-hospital death were significantly lower only in patients with no history of CKD or new onset kidney dysfunction and with age >70 years old, with insignificant impact in the rest of analyzed groups, regardless of age group (data not shown). This finding, that the risk of in-hospital death associated with hypertension may be lower in older, but relatively healthy, patients with no history of kidney dysfunction, was also reported in some previous studies.³⁷ This may be explained by the fact that patients with a recorded history of hypertension could have received more medical care than those with undetected medical problems. Secondly, lower blood pressure on admission is a recognized risk factor for increased mortality in COVID-19 patients,³⁸ thus older patients with hypertension may be protected. The odds for in-hospital death were higher in those with a history of diabetes and HF in our study. This is in line with the available data, suggesting that cardiovascular complications that appear along COVID-19, such as new onset or exacerbation of HF, are more pronounced in patients with CKD.³⁹ Diabetes is an identified risk factor for a severe course of COVID-19,^{18,38} and this risk is amplified by comorbid CKD.

The limitations of this study must be addressed. Patients were categorized into groups based on a clinically established cut-off for decreased glomerular filtration, and further regarding evidence of pre-existing CKD. While medical chart review is a convenient data source, it is prone to several sources (incompleteness, misattribution, and recall) of bias inherent to retrospective studies. Further, the lack of an independent control group limits our ability to establish causal attribution. While the division of patients into groups is guided by clinical principle, whenever a continuous variable (ie, eGFR) is dichotomized, some information is lost. Variable distribution of subjects with worse renal function and heterogeneity in terms of excess comorbidity can affect the conclusions drawn from multivariable models. Due to the retrospective nature of this study, we are also not able to verify the diagnosis of AKI (according to the KDIGO criteria⁴⁰).

Conclusions

Using a large tertiary care cohort of hospitalized patients with SARS-CoV2 infection, we showed that the odds of in-hospital death were higher for patients with previous CKD and newly-detected cases of renal impairment than in subjects with adequate kidney function. The highest risk of in-hospital death was recorded among patients with no history of CKD and at admission eGFR < 60 mL/min/1.73m². These findings support the concept of kidney disease as a major poor prognostic factor in COVID-19, thus, adding one more argument for CKD screening using simple and common laboratory parameters in order to slow down its progression. Newly detected cases of COVID-19 and RI should be treated with special attention.

Data Sharing Statement

The data analyzed in the paper is available from the corresponding author upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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