Original Clinical Research Quantitative

Incidence and Outcomes of Acute Kidney Injury in Patients Admitted to Hospital With COVID-19: A Retrospective Cohort Study

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Abstract

Background: The incidence of acute kidney injury (AKI) in patients with COVID-19 and its association with mortality and disease severity is understudied in the Canadian population.

Objective: To determine the incidence of AKI in a cohort of patients with COVID-19 admitted to medicine and intensive care unit (ICU) wards, its association with in-hospital mortality, and disease severity. Our aim was to stratify these outcomes by out-of-hospital AKI and in-hospital AKI.

Design: Retrospective cohort study from a registry of patients with COVID-19.

Setting: Three community and 3 academic hospitals.

Patients: A total of 815 patients admitted to hospital with COVID-19 between March 4, 2020, and April 23, 2021.

Measurements: Stage of AKI, ICU admission, mechanical ventilation, and in-hospital mortality.

Methods: We classified AKI by comparing highest to lowest recorded serum creatinine in hospital and staged AKI based on the Kidney Disease: Improving Global Outcomes (KDIGO) system. We calculated the unadjusted and adjusted odds ratio for the stage of AKI and the outcomes of ICU admission, mechanical ventilation, and in-hospital mortality.

Results: Of the 815 patients registered, 439 (53.9%) developed AKI, 253 (57.6%) presented with AKI, and 186 (42.4%) developed AKI in-hospital. The odds of ICU admission, mechanical ventilation, and death increased as the AKI stage worsened. Stage 3 AKI that occurred during hospitalization increased the odds of death (odds ratio [OR] = 7.87 [4.35, 14.23]). Stage 3 AKI that occurred prior to hospitalization carried an increased odds of death (OR = 5.28 [2.60, 10.73]).

Limitations: Observational study with small sample size limits precision of estimates. Lack of nonhospitalized patients with COVID-19 and hospitalized patients without COVID-19 as controls limits causal inferences.

Conclusions: Acute kidney injury, whether it occurs prior to or after hospitalization, is associated with a high risk of poor outcomes in patients with COVID-19. Routine assessment of kidney function in patients with COVID-19 may improve risk stratification.

Trial registration: The study was not registered on a publicly accessible registry because it did not involve any health care intervention on human participants.

Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection (COVID-19) was originally thought to be a primarily respiratory illness; however, as the pandemic has evolved, its multisystem effects have been increasingly recognized.[1] A binding site for SARS-CoV-2, the angiotensin-converting enzyme 2 (ACE2) receptor, is expressed in abundance in the kidneys and may allow for direct kidney damage.[2] Consequently, the impact of COVID-19 on kidney outcomes is of interest, based on both the potential for acute kidney injury (AKI) and the recognized association between AKI and poor outcomes for hospitalized patients in other diseases.

The reported incidence of AKIs in individuals with COVID-19 varies widely from 2.9% to 46% in various studies, with similar degrees of heterogeneity in mortality rates.[3-5] There is a dearth of studies investigating the association between AKIs in COVID-19 outcomes regarding severity of COVID-19, pre-existing comorbidities, length of admission, admission to intensive care unit (ICU), and mortality. There are still fewer studies investigating outcome measures that stratify individuals based on the severity of their AKI and AKI acquired in the community.[6,7]

While AKI is associated with poor outcomes in individuals with COVID-19, there are uncertainties and gaps in our knowledge. Our objective is to determine whether AKI conferred an increased odds of death for patients admitted to hospital with COVID-19, as well as disease severity in terms of admission to ICU and mechanical ventilation.

Methods

Study Design and Population

The McMaster Multi-Regional Hospital Coronavirus Registry (COREG) is a registry of patients admitted to any of 3 community and academic hospitals in southern Ontario with a positive SARS-CoV-2 polymerase chain reaction (PCR) test. We followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines to structure the paper.[8] Details on the registry data collection can be found in supplementary file 1. The region serves approximately 1 000 000 persons. COREG received approval from the Hamilton Integrated Research Ethics Board and Tri-Hospital Research Ethics Board.

Study Population

We included all patients admitted to hospital with a positive SARS-COV-2 PCR nasal swab test. The majority of the PCR samples used the Allplex 2019-nCOV assay for testing.[9] We used serum creatinine measurements in COREG admitted between March 4, 2020, and April 15, 2021.

Exposures

We defined AKI according to the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline, based on changes in serum creatinine.[10] We reported each stage according to the KDIGO framework as stage 1, 2, and 3. These correspond to 1.5 to 1.9 times their baseline creatinine, 2 to 2.5 times their baseline creatinine, and 3 or more times their baseline creatinine or newly required dialysis. Urine output was not considered due to its limited data collection in routine inpatient care at these hospitals. Particularly, ward patients were unlikely to have corrected in and out calculations. Change in creatinine was calculated by comparing the peak creatinine during hospitalization to the lowest creatinine during hospitalization, under the assumption that the lowest creatinine would best represent baseline kidney function. In addition, we assessed preadmission AKI by comparing the admission creatinine to the lowest creatinine during hospitalization. This was done to determine whether AKI was present at the time of admission. Out-of-hospital AKI was defined as an increase of creatinine by greater than 26.5 μmol/L. We calculated this by subtracting their admission creatinine by their lowest recorded creatinine during their hospital stay.

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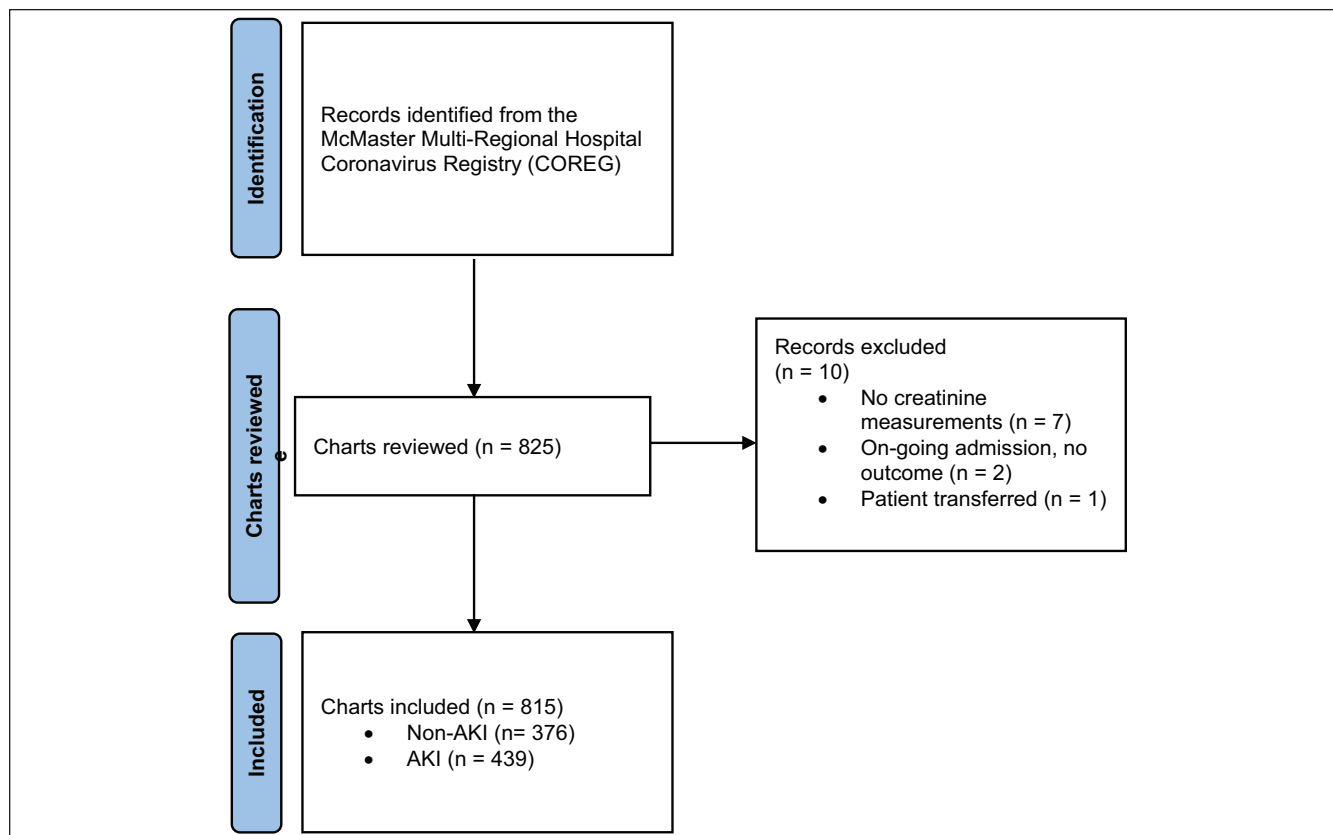
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Figure 1. Flow diagram of inclusion process of studies.
Note. AKI = acute kidney injury.

Outcomes

Primary outcomes included odds of death (all-cause in-hospital mortality), admission to intensive care unit (ICU) admission, and odds of mechanical ventilation.

Statistical Methods

We described patient characteristics using median (25th to 75th percentile) and frequency (percentage) as appropriate for the distribution of data. Frequencies less than 6 are reported only as <6, to ensure the anonymity of patients. Comparison of baseline characteristics was performed using Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables. We reported the incidence of AKI by stages in the study population and the crude outcome rates by stage of AKI. We then assessed the associations of interest using unadjusted and adjusted binary logistic regressions, between stage of AKI and in-hospital mortality, ICU admission, and mechanical ventilation. We decided on covariates for our regression models based on previously described associations with AKI in both the COVID-19 and general medical literature. These included ages, chronic kidney disease (CKD) defined as the presence of kidney damage or decreased function for 3 or more months,[11] diabetes mellitus defined by clinician report, and hypertension, defined as persistently elevated blood pressure above 140 systolic or 90 diastolic.[12-18] We reported odds ratios (ORs) with 95% confidence intervals. We performed an independent audit of the COREG study database to ensure no missing data was due to collection error. All analyses were done using R 4.0.

Results

Basic Characteristics

We included 815 patients admitted with SARS-CoV-2 in this analysis. Figure 1 has more detail on the inclusion process. Patients who developed AKI were more likely to have diabetes, hypertension, and CKD. Patients who developed AKI had higher baseline creatinine, blood urea nitrogen, and neutrophil counts on admission. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARB), and non-steroidal anti-inflammatory drugs (NSAIDs) were used at similar rates in both groups. Table 1 has more detail on baseline characteristics.

Incidence of AKI

The presence of AKI was common in our cohort of patients with COVID-19, representing about 53.9% of patients. 22.8% of the patients admitted to hospital with COVID-19

Table 1. Patient Characteristics by AKI Status.

	Non-AKI (n = 376)	Stage 1 (n = 261)	Stage 2 (n = 86)	Stage 3 (n = 92)	P value
Demographics					
Age, years	71 (57, 83)	77 (66, 86)	74 (63, 84)	72 (63, 83)	<.001
Sex, male	182 (48.4)	145 (55.6)	56 (65.1)	58 (63.0)	.001
Comorbidities					
Chronic obstructive pulmonary disease	110 (29.3)	60 (23.0)	22 (25.6)	22 (23.9)	.33
Coronary artery disease	74 (19.7)	63 (24.1)	13 (15.1)	31 (33.7)	<.001
Prior deep vein thrombosis or pulmonary embolism	18 (4.8)	19 (7.3)	<6	9 (9.8)	<.001
Diabetes	109 (29.0)	102 (39.1)	32 (37.2)	54 (58.7)	<.001
Hypertension	198 (52.7)	179 (68.6)	56 (65.1)	67 (72.8)	<.001
Chronic kidney disease	18 (4.8)	39 (14.9)	16 (18.6)	36 (39.1)	<.001
Admit blood work					
Creatinine (μmol/L)	77 (66, 86)	99 (82, 132)	103 (74, 146)	186 (99, 365)	<.001
Urea (mmol/L)	86 (68, 98)	56 (40, 80)	55 (36, 83)	26 (12, 57)	<.001
WBC ($\times 10^9$/L)	5.9 (4.2, 7.9)	8.6 (6.0, 12.6)	9.3 (5.3, 16.4)	12.3 (8.3, 20.3)	<.001
Lymphocytes ($\times 10^9$/L)	6.3 (4.7, 8.5)	7.0 (5.0, 10.0)	6.2 (4.7, 9.7)	8.0 (5.6, 11.4)	.003
Neutrophils ($\times 10^9$/L)	1.0 (0.7, 1.4)	0.9 (0.6, 1.2)	0.8 (0.6, 1.3)	0.8 (0.6, 1.3)	.003
Hemoglobin (g/L)	4.4 (3.0, 6.4)	5.2 (3.5, 7.9)	4.5 (3.2, 7.6)	6.3 (4.2, 9.0)	<.001
	132 (118, 144)	128 (111, 142)	127 (107, 139)	118 (102, 134)	<.001
Pre-admission drugs					
Angiotensin-converting enzyme inhibitor	77 (20.5)	69 (26.4)	27 (31.4)	22 (23.9)	<.001
Angiotensin receptor blocker	54 (14.4)	46 (17.6)	12 (14.0)	22 (23.9)	<.001
Non-steroidal anti-inflammatory drugs	20 (5.3)	24 (9.2)	14 (16.3)	<6	<.001
Creatinine					
Highest/lowest	1.20 (1.08, 1.29)	1.60 (1.47, 1.73)	2.25 (2.11, 2.15)	3.41 (2.27-4.60)	<.001
Highest-lowest	13 (6, 18)	38 (31, 52)	78 (47, 105)	200 (140-316)	<.001

Note. Data are presented as frequency (%) except for age, admit blood work, and creatinine, which are presented as median (Q1, Q3). AKI = acute kidney injury; WBC = white blood cell.

eventually developed AKI and 31.04% of admitted patients to hospital presented with AKI. The incidence of stage 1 was the most common (n = 261, 59.45%), with approximately equal numbers of stage 2 (n = 86, 19.6%) and 3 (n = 92, 20.1%).

Wave 1 went from March 2020 until August 31, with 318 patients included. Wave 2 and some of the third wave extend from September 1, 2021, until April 2021, with 497 patients. The overall incidence of AKI was 53.4% in the first wave and 54.7% in the second wave. There were more patients with stage 1 AKI requiring mechanical ventilation in wave 1 than wave 2 (20.0% vs 9.9%) and more patients with stage 2 AKI requiring mechanical ventilation in wave 2 compared to wave 1 (44.9% vs 29.7%). Table 2 summarizes the results.

Outcomes of Patients With AKI

There were 199 (24.4%) deaths in our cohort, 58 in the non-AKI group and 141 in the AKI group. Forty patients in the non-AKI group were admitted to the ICU and 171 admitted to ICU in the AKI group. Six patients in the non-AKI group required mechanical ventilation, whereas 111 in the non-AKI group required mechanical ventilation. These findings are summarized in Table 3.

Our binary logistic regression model showed that for patients who developed AKI in hospital, the odds of death increased for those with stage 2 (OR = 2.46 [1.37, 4.43]) and stage 3 (OR = 7.87 [4.35, 14.23]) but not stage 1 (OR = 1.47 [0.95, 2.25]). Patients were significantly more likely to be admitted to ICU and require mechanical ventilation in all stages of AKI. Table 4 summarizes these results.

For patients who developed AKI prior to admission, there was a similar pattern of odds of death. The binary logistic regression model showed that the odds of death increased for those with stage 2 (OR = 2.75 [1.41, 5.36]) and stage 3 (OR = 5.28 [2.60, 10.73]) but not stage 1 (OR = 1.31 [0.78, 2.22]). Patients who developed AKI outside of hospital in all stages were similarly more likely to be admitted to ICU and require mechanical ventilation. Table 4 summarizes these results.

Table 2. Wave Comparison of Prevalence of AKI by Kidney Disease: Improving Global Outcomes System Stage and Outcomes of Death, ICU Admission, and Invasive Ventilation.

Measure	Stage 0 (%)	Stage 1 (%)	Stage 2 (%)	Stage 3 (%)
Wave 1 (until August 31, 2020, n = 318)				
Prevalence of AKI	46.7	32.4	9.9	11.1
Death in-hospital	16.0	23.0	27.0	56.8
Admitted to ICU	7.6	28.0	35.1	56.8
Invasive ventilator	<6	20.0	29.7	46.0
Wave 2+ (September 1, 2020 and beyond, n = 497)				
Prevalence of AKI	45.3	31.5	11.6	11.6
Death in-hospital	15.1	26.7	32.7	50.9
Admitted to ICU	12.5	29.3	57.1	61.8
Invasive ventilator	<6	9.9	44.9	45.5

Note. AKI = acute kidney injury; ICU = intensive care unit.

Table 3. Outcomes of Kidney Disease: Improving Global Outcomes System Classes of AKI and Death, ICU Admission, and Invasive Ventilation.

Outcomes	Non-AKI (n = 376)	Stage 1 (n = 261)	Stage 2 (n = 86)	Stage 3 (n = 92)	P value
In-hospital deaths	58 (15.4)	66 (25.3)	26 (30.2)	49 (53.3)	<.001
Admitted to ICU	40 (10.6)	75 (28.7)	41 (47.7)	55 (59.8)	<.001
Invasive ventilator	6 (1.6)	36 (13.8)	33 (38.4)	42 (45.7)	<.001
Dialysis in-hospital	0 (0)	0 (0)	0 (0)	34 (40.0)	<.001

Note. Data are presented as numbers (%). AKI = acute kidney injury; ICU = intensive care unit.

Discussion

Main Findings

This multicenter cohort study of patients admitted to hospital with COVID-19 in Canada found AKI was common (53.9% of patients). Whether AKI occurred prior to or after admission, it was associated with a graded odds of increased mortality, admission to the ICU, and mechanical ventilation, as seen in previous literature.[1-3,5,12-23] These findings underscore the importance of assessing kidney function in patients with COVID-19. Importantly, these findings suggest that whether you develop AKI in or outside of hospital, your odds of serious outcomes increase significantly.

In Relation to Other Findings

Our findings are in agreement with pre-existing studies indicating no difference in mortality rates between community- and hospital-acquired AKI, albeit with increased comorbid status.[6,7] Importantly, we had more community-acquired AKI than inpatient AKI, which may point to a more direct biologic association. This is furthermore consistent with a study conducted by Hansrivijit et al, where most COVID-19 associated AKIs were community acquired and attributed to pre-renal origins. This is in contrast with the more severely staged hospital-acquired AKI originating from intrinsic etiologies and requiring a higher need for renal replacement therapy.[24]

Studies of AKI in COVID-19 in North America remain outnumbered by international studies, particularly from Asia. In other North American cohorts of admitted patients with COVID-19, AKI occurs with similar frequency compared to our cohort and the association between AKI and death is similar.[12,13,15,25] In terms of specific risk factors for AKI among patients with COVID-19, common risk factors across reviewed literature include older age, CKD, and critical respiratory status.[1-3,5,12-23]

In addition, our findings follow how AKI incidences and severity have changed throughout waves 1 and 2 of the pandemic, with wave 2 having increased ventilator requirement for stage 2 patients and decreased requirement for stage 1. These findings may be the result of changes in resource allocation, threshold for mechanical ventilation, and triaging for mechanical ventilation in hospital settings, as the pandemic progressed.[26]

In Relation to AKI in Other Disease

SARS-CoV-2 is hypothesized to directly injure kidneys and/ or to have a high risk of AKI. The risk of AKI in patients

Table 4. Adjusted and Unadjusted Associations Between Kidney Disease: Improving Global Outcomes Classes of AKI and Death, ICU Admission, and Invasive Ventilation.

Stage (n = 815)	Odds ratio (vs none)			Adjusted odds ratio[a] (vs None)		
	Dead	ICU	Ventilated	Dead	ICU	Ventilated
None	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
Stage 1	1.86 (1.25, 2.76)	3.39 (2.22, 5.17)	9.87 (4.09, 23.8)	1.47 (0.95, 2.25)	5.58 (3.48, 8.97)	20.10 (7.92, 51.00)
Stage 2	2.38 (1.39, 4.07)	7.65 (4.48, 13.07)	38.39 (15.36, 95.99)	2.46 (1.37, 4.43)	12.31 (6.82, 22.20)	82.36 (30.41, 223.05)
Stage 3	6.25 (3.8, 10.3)	12.49 (7.3, 21.22)	51.8 (21.0, 128.0)	7.87 (4.35, 14.23)	24.92 (13.28, 46.77)	147.72 (52.87, 412.73)
Excluding those who developed AKI in hospital						
Stage (n = 639)	Dead	ICU	Ventilated	Dead	ICU	Ventilated
None	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
Stage 1	1.73 (1.08, 2.77)	3.28 (2.01, 5.34)	7.06 (2.68, 15.58)	1.31 (0.78, 2.22)	5.07 (2.96)	11.85 (4.31, 32.60)
Stage 2	2.42 (1.32, 4.45)	8.40 (4.63, 15.25)	38.95 (14.99, 101.2)	2.75 (1.41, 5.36)	12.30 (6.42, 23.55)	68.14 (22.56, 176.68)
Stage 3	4.24 (2.33, 7.75)	12.60 (6.70, 23.69)	44.32 (16.83, 116.73)	5.28 (2.60, 10.73)	20.59 (10.03, 42.29)	85.19 (28.80, 252.01)

Note. AKI = acute kidney injury; ICU = intensive care unit.
[a]Adjusted for age, diabetes, hypertension, and chronic kidney disease.

hospitalized with COVID-19 in our study was just over 50%. In cohorts of patients admitted with pneumonia, the risk of AKI was 18.0% to 34%, although severity of pneumonia varied (7.0%-52% ventilated). Similarly, in a cohort of patients admitted to the ICU with influenza in Korea, only 22.6% developed AKI.[27] Lower rates of AKI could simply reflect lesser severity of infection in non-COVID-19 cohorts, which may reflect attitudes toward admissions for patients with COVID-19. Our findings of AKI incidence in patients with COVID-19 are consistent with a systematic review conducted which found around 50% frequency of AKI in severe COVID-19 populations, with an incidence of around 15% for AKI in patients with COVID-19 not stratified for severity.[28] It is interesting that AKI was so substantially more common in our cohort, when one considers the biologic rationale for direct kidney injury by the virus, compared to the commonly hypothesized ischemia-reperfusion injury.

A recent multicenter cohort study further introduced how occurrence of AKI remained associated with COVID-19 and was not fully explained by adjustment for known renal risk factors such as demographic variables, comorbidities, and laboratory results.[29]

Whether the mechanism by which COVID-19 causes AKI is shared with other infections, its association with poor outcomes is very consistent. A meta-analysis of AKI in a mixture of surgical and critical care settings suggests mild, moderate, and severe AKI are associated with risk ratios for death of 1.67, 2.73, and 3.04, respectively.[30] Newly published studies follow the same trend of increasing mortality with increasing AKI severity, indicating little respite despite advances in clinical management.[31] Individual studies vary considerably in the magnitude of the association (eg, 1.60 to 29.17 for severe AKI) and our estimates are consistent within these ranges. While the relative risks of death associated with AKI are consistent, it is important to note that the absolute risk of death in our study is high at almost 15% for those without AKI and over 50% for those with AKI, while existing literature notes absolute risk difference for AKI mortality to be 21.5% and relative risk at 3.63 (cumulative incidence of 29.6% in patients with AKI and 8.1% in non-AKI patients). These findings underscore the potential severity of COVID-19 infections in patients admitted to hospital. Clinicians and investigators should be aware of these high risks of AKI, poor outcomes, and plan resources accordingly.

Limitations

An important limitation of our study is the relatively small number of patients and events. Our results, however, are consistent with others globally. While the lack of precision in the associations between AKI, ICU admission, and mechanical ventilation may be only due to sample size, AKI, particularly requiring dialysis, may be a reason for admission to the ICU. In addition, the indication for dialysis may be lower in patients with severe respiratory failure and may also contribute to the broad confidence intervals for these outcomes. In addition, the lack of non-COVID control limits ability to understand the degree to which the observations are COVID specific. Our study is also limited to hospitalized patients, so it is unclear whether AKI occurs frequently in non-admitted patients, which would likely weaken the association between non-severe AKI and other outcomes.

Conclusions

AKI is associated with disease severity in patients with COVID-19 admitted to hospital and portends significant odds of death, ICU admission, and mechanical ventilation, whether AKI is developed outside of hospital or in-hospital. Canadian patients with AKI are similarly at risk than those patients in other non-Western and Western nations.

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Ethics Approval and Consent to Participate

Consent for Publication

Availability of Data and Materials

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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