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Outcome Comparison in Hospitalized COVID-19 Patients With and Without AKI

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Abstract

Aim: **Patients hospitalized with COVID-19 have a higher incidence of Acute Kidney Injury (AKI) compared with non-COVID patients. Previous observational studies showed AKI in hospitalized patients with COVID-19 was associated with significant increased mortality rate. We conducted a retrospective cohort study in a large mid-Atlantic health system to investigate whether COVID-19 associated AKI during hospitalization would lead to worse outcomes in a predominant Black patient population, compared to COVID-19 without AKI.**

Methods: **We reviewed health records of patients (aged≥18 years) admitted with symptomatic COVID-19 between March 5, 2020, and Jun 3, 2020, in 9 acute care facilities within the MedStar Health system. Patients were followed up until 3 months after discharge. Primary outcome was inpatient mortality. Secondary outcomes were need for ICU level of care, need for intubation, length of ICU stay, length of hospital stay, need for renal replacement therapy, recovery of renal function.**

Results: **Among 1107 patients admitted with symptomatic COVID-19, the AKI incidence rate was 35 %. African American patients made up 63 % of the total patient population and 74 % of the total AKI population. Inpatient mortality in the AKI group and the non-AKI group was 163 (41.9 %) and 71 (9.9 %), respectively. COVID-19 patients with AKI had significant higher risk of in-patient mortality (OR, 4.71 [95 % CI, 3.38−6.62], P < 0.001), ICU admission (OR, 4.27 [95 % CI, 3.21−5.72], P < 0.001) and need of intubation (OR, 6.18 [95 % CI, 4.45−8.68], P < 0.001).**

Conclusions: **AKI in hospitalized patients with COVID-19 was associated with higher mortality rate, need for intubation and ICU admission compared to COVID-19 patients without AKI group.**

Keywords: Covid-19, Acute kidney injury, Mortality, Intensive care units

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by viral pathogen severe acute respiratory coronavirus 2 (SARS-CoV-2) broke out in December 2019. Renal involvement in COVID-19 infection was widely recognized and studied during the past three years.[1] In a meta-analysis of 22 observational cohort studies in the US, the pooled incidence of AKI in COVID-19 patients reached 11.0 % (7.4−15.1).[2] Observational studies suggested patients hospitalized with COVID-19 have a higher incidence of severe Acute Kidney Injury (AKI) compared with non-COVID patients and were less likely to recover kidney function.[3] Despite this, it is still unclear if AKI plays a major role in mortality in the context of COVID-19 infection. Therefore, we conducted a retrospective cohort study to compare clinical features of COVID-19 infection with and without AKI, in the mid-Atlantic health system.

2. Methods

2.1. Study population

During the COVID-19 pandemic, MedStar Health system was a large multicenter network with 9 acute

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care hospitals to provide health care for COVID-19 patients in the mid-Atlantic area. We performed a retrospective cohort study to investigate the outcomes of hospitalized COVID-19 patients with AKI on presentation within 9 acute care facilities of the MedStar Health system, compared to COVID-19 patients without AKI, between March 5, 2020, and Jun 3, 2020. Hospitalized adult patients with a positive COVID-19 confirmatory test, defined by RT-PCR assay of specimen collected from a nasopharyngeal swab during the study period were included. Patients with asymptomatic COVID-19 infection, baseline end-stage kidney disease (ESKD) or missing creatinine values were excluded. The study population is shown in Fig. 1.

The Institutional Review Board from MedStar Health Research Institute approved this study on October 11, 2021. Informed consent was waived, and only de-identified data were analyzed.

2.2. Data collection

We reviewed health records of patients (aged≥18 years) admitted with symptomatic COVID-19 between March 5, 2020, and Jun 3, 2020, in 9 acute care facilities within the MedStar Health system. Convenience sampling was adopted. We identified 1107 COVID-19 patients after excluded 301 patients with ESKD at baseline and 101 patients with missing creatinine values or asymptotic COVID-19 infection. Data on sociodemographic factors (age, gender, race), comorbidities (hypertension, hyperlipidemia, diabetes, obesity, CKD, coronary artery disease, arrhythmia, congestive heart failure, stroke, asthma, COPD, malignancy, HIV infection) was extracted. Information on creatinine, inpatient mortality, intensive care unit (ICU) admission, the need for mechanical ventilation, or dialysis in all modalities were extracted. Patients were followed up until 3 months after discharge.

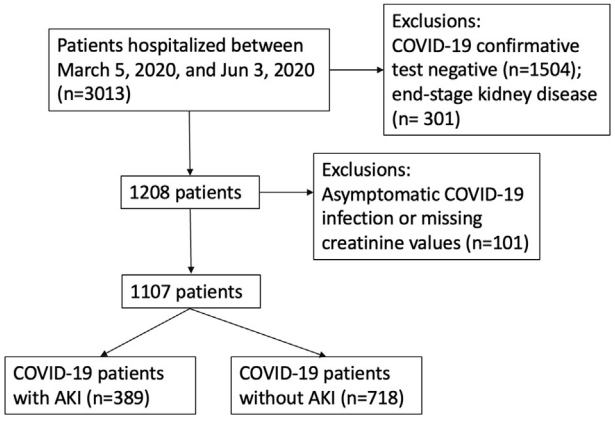

Fig. 1. Study population.

2.3. Measurements and variable definitions

AKI was defined by either an increase in serum creatinine by greater than or equal to 0.3 mg/dL within 48 h, or an increase in serum creatinine by greater than or equal to 1.5 times baseline, based on KDIGO guideline.[4]

Baseline creatinine was defined by the median outpatient serum creatinine value 90 days before this hospitalization.[5] For participants with missing pre-hospitalization data, we applied the method that Siew et al. recommended, by using lowest inpatient serum creatinine.[6]

2.4. Outcomes

Primary outcome was inpatient mortality. Secondary outcomes included need for ICU level of care, need for intubation, length of ICU stay, length of hospital stay, need for renal replacement therapy, recovery of renal function.

2.5. Statistical analyses

Demographic characteristics, comorbidities and other inpatient records were summarized and stratified by the presence or absence of AKI. Summary statistics included frequency (%) for categorical variables and mean ± SD or median [IQR] (if non-normal) for continuous variables. D'Agostino-Pearson test was used to test normality. Fisher exact test (for categorical variables), Student's t-test (for normal continuous variable) and Wilcoxon rank sum test (for non-normal continuous variable) were performed to compare the differences between groups. Multivariate logistic regression was used to compute adjusted odds ratio regarding 3 outcomes: Inpatient mortality, ICU admission, and need of intubation. All statistical analyses were conducted with R software 4.0.3. All P values were presented, no adjustment was made for multiple tests.

3. Results

3.1. Baseline characteristics

Baseline characteristics of patients enrolled in this study are outlined in Table 1. Between March 5, 2020, and Jun 3, 2020, by convenience sampling, 1107 symptomatic COVID-19 positive patients hospitalized at the MedStar Health system were included in this study, in which 718 patients without

Table 1. Baseline characteristics of hospitalized patients positive for COVID-19.

Characteristics	Overall	COVID-19 positive without AKI	COVID-19 positive with AKI	P Value
N	1107	718	389	
Age on Admission (median [IQR])	63.0 [52.0, 74.0]	60.0 [48.0, 72.0]	67.0 [60.0, 78.0]	<0.001
(mean (SD))	62.6 ± 16.0	59.6 ± 16.4	68.1 ± 13.5	<0.001
Sex (%)				0.13
Female	525 (47.4)	353 (49.2)	172 (44.2)	
Male	582 (52.6)	365 (50.8)	217 (55.8)	
Race (%)				<0.001
Black or African American	684 (63.0)	398 (56.9)	286 (73.9)	
Other Race	244 (22.5)	201 (28.8)	43 (11.1)	
White	158 (14.5)	100 (14.3)	58 (15.0)	
Clinical Comorbidities, n (%)				
Hypertension	716 (64.7)	419 (58.4)	297 (76.3)	<0.001
Hyperlipidemia	373 (33.7)	215 (29.9)	158 (40.6)	<0.001
Diabetes on insulin	153 (13.8)	82 (11.4)	71 (18.3)	0.003
Diabetes not on insulin	253 (22.9)	153 (21.3)	100 (25.7)	0.1
Obesity (BMI≥ 30)	469 (42.4)	310 (43.2)	159 (40.9)	0.484
CKD Stage IIIb or higher	90 (8.1)	24 (3.3)	66 (17.0)	<0.001
Coronary artery disease	121 (10.9)	57 (7.9)	64 (16.5)	<0.001
Cardiac arrhythmia history not atrial fibrillation or atrial flutter	18 (1.6)	8 (1.1)	10 (2.6)	0.082
Atrial Fib or flutter	101 (9.1)	52 (7.2)	49 (12.6)	0.004
Congestive heart failure	148 (13.4)	62 (8.6)	86 (22.1)	<0.001
Stroke	127 (11.5)	73 (10.2)	54 (13.9)	0.075
Asthma	95 (8.6)	64 (8.9)	31 (8.0)	0.654
Chronic Obstructive Pulmonary Disease	98 (8.9)	46 (6.4)	52 (13.4)	<0.001
Chronic active cancer	41 (3.7)	18 (2.5)	23 (5.9)	0.007
human immunodeficiency virus infection	25 (2.3)	14 (1.9)	11 (2.8)	0.398
Transplant patient	15 (1.4)	3 (0.4)	12 (3.1)	<0.001
Charlson Comorbidity Index Score (median [IQR])	3.0 [1.0, 5.0]	2.0 [1.0, 5.0]	4.0 [3.0, 6.0]	<0.001
(mean (SD))	3.5 ± 2.6	2.9 ± 2.6	4.4 ± 2.4	<0.001
Baseline creatinine (median [IQR])	1.0 [0.8, 1.3]	1.0 [1.0, 1.0]	1.0 [0.8, 1.3]	
Baseline GFR (median [IQR])	60.0 [52.0, 60.0]	60.0 [60.0, 60.0]	60.0 [52.0, 60.0]	
Highest creatinine during hospitalization (median [IQR])	2.5 [1.6, 4.4]	1.1 [1.1, 1.1]	2.5 [1.6, 4.4]	
Creatinine on day of discharge or the day of death (median [IQR])	1.4 [1.0, 2.8]	0.9 [0.9, 0.9]	1.4 [1.0, 2.8]	

AKI and 389 patients with AKI. Mean age for the groups was 62.6 ± 16.0, and the AKI group was significantly older than the non-AKI group ($P < 0.001$). No gender differences were noticed between 2 groups. African American patients made up 63 % of the total patient population and 74 % of the total AKI population, significantly higher than the non-AKI group ($P < 0.001$). The two groups showed same median baseline creatinine, overall, 1.0 [0.8, 1.3]. The clinical comorbidity profile of the 2 groups also showed stark differences. The AKI group had higher prevalence of hypertension, hyperlipidemia, insulin dependent diabetes, CKD stage IIIb or higher, coronary artery disease, congestive heart failure, atrial flutter or fibrillation, chronic active cancer, and organ transplant; no differences were noted in obesity, non-insulin dependent diabetes, cardiac arrhythmia (not atrial flutter or fibrillation), stroke, asthma, or HIV infection. Overall, the mean Charlson Comorbidity Index Score was 3.5 ± 2.6 in this study, with 2.9 ± 2.6 in the non-AKI group, and 4.4 ± 2.4 in the AKI group ($P < 0.001$).

3.2. Outcomes

The outcomes of this study were displayed in Table 2. A total of 1107 COVID-19 positive patients were admitted during March 5, 2020, and Jun 3, 2020. Inpatient mortality of this study was 21.2 %, with 9.9 % in non-AKI group and 41.9 % in AKI group ($P < 0.001$). Higher ICU admission and needs for intubation were also observed in AKI group, compared to non-AKI group. Similar tendency was also noticed in needs for ICU stay, hospital stay, new inpatient hemodialysis. After controlling age, gender, race and Charlson Comorbidity Index Score, AKI group still showed significantly higher inpatient mortality, ICU admission and needs for intubation.

Table 2. Outcome comparation between COVID-19 AKI group and non-AKI group.

Total Cohort	Overall	COVID-19 positive without AKI	COVID-19 positive with AKI	P value
Inpatient Mortality	234 (21.2)	71 (9.9)	163 (41.9)	<0.001
ICU admission	408 (37.0)	183 (25.6)	225 (57.8)	<0.001
Mechanical ventilation	256 (23.1)	87 (12.1)	169 (43.4)	<0.001
Inpatient hemodialysis new for patient	89 (8.1)	1 (0.1)	88 (22.7)	<0.001
ICU stay (median [IQR])	6.0 [2.0, 13.0]	4.0 [1.0, 9.0]	8.0 [4.0, 16.8]	<0.001
Hospital stay (median, [IQR])	9.0 [5.0, 15.0]	7.0 [4.0, 13.0]	12.0 [7.0, 21.0]	<0.001

Table 3. Associations between selected factors and primary outcomes.

Factors	Inpatient Mortality (n = 1073, event = 227)		ICU Admission (n = 1071, event = 395)		Intubation (n = 1073, event = 250)	
	Odd Ratio (95 % CI)	P Value	Odd Ratio (95 % CI)	P Value	Odd Ratio (95 % CI)	P Value
COVID-19 associated AKI	4.71 (3.38, 6.62)	<0.001	4.27 (3.21, 5.72)	<0.001	6.18 (4.45, 8.68)	<0.001
Age	1.03 (1.01, 1.04)	<0.001	0.98 (0.97, 0.99)	0.001	0.99 (0.97, 1)	0.041
Gender Male vs. Female	1.44 (1.03, 2.01)	0.033	1.31 (1, 1.72)	0.051	1.14 (0.84, 1.56)	0.404
Race Other Race vs African American	0.93 (0.56, 1.51)	0.768	0.74 (0.52, 1.05)	0.098	0.88 (0.57, 1.33)	0.542
Race White vs African American	1.11 (0.7, 1.73)	0.653	0.82 (0.55, 1.22)	0.337	0.98 (0.61, 1.52)	0.915
Charlson Comorbidity Index Score	1.12 (1.03, 1.22)	0.005	1.04 (0.97, 1.12)	0.267	0.99 (0.91, 1.07)	0.8

Odd ratios (and 95 % confidence intervals) from Multivariate logistic regression analysis identifying associations between selected factors and primary outcomes. Multivariate logistic regression was used to compute adjusted odds ratio regarding 3 outcomes: Inpatient mortality, ICU admission, and intubation. AKI group had significant higher mortality, ICU admission and needs for intubation, even after age, gender, race, and Charlson Comorbidity Index Score were controlled.

Risk factors for inpatient mortality, ICU admission and mechanical ventilation, were conducted with multivariate logistic regression analyses to compute adjusted odds ratio, as shown in Table 3. COVID-19 associated AKI (adjusted odds ratio, 4.71; 95 % CI (3.38, 6.62), P < 0.001), age (adjusted odds ratio, 1.03; 95 % CI (1.01, 1.04), P < 0.001), male vs. female (adjusted odds ratio, 1.44; 95 % CI (1.03, 2.01), P = 0.033), Charlson Comorbidity Index Score (adjusted odds ratio, 1.12; 95 % CI (1.03, 1.22), P = 0.005) significantly increased the risk of inpatient mortality. COVID-19 associated AKI was associated with higher odds of ICU admission and needs for intubation.

4. Discussion

In this retrospective cohort study, we collected hospitalization data between March 5, 2020, and Jun 3, 2020, in a large mid-Atlantic health system with unique patient population, to compare baseline characteristics, outcomes, and investigate risk factors for primary outcomes between COVID-19 positive AKI group and non-AKI group. In our study, there was a strikingly high incidence of inpatient mortality, need for ICU care and intubation in COVID-19 patients with AKI compared to those without AKI.

Reported incidence of AKI in COVID-19 during the first wave (between March and August 2020) ranged from 28 % to 46 %.[7-9] Notably, the incidence in China was overall 4.5 %, in a meta-analysis of data before May 2020.[10] Possible explanations include early intervention in China preventing the development of severe cases, and lower baseline susceptibility of Chinese population, enlightened by epidemiological data before this pandemic.[11]

In our study, AKI group was associated with older age, African American race and multiple comorbidities at baseline, compared to non-AKI group. These patient factors are also known to be associated with increased risk for AKI, even outside the COVID-19 context.[12-14] African American patients made up about 2/3 in both groups of this study. The connection between ethnicity and risk of AKI remains unclear though could be multifactorial and include comorbid profile, systemic inequalities, and socioeconomic factors. Recently, a large multicenter prospective cohort study with data from pre-COVID era found the modest effect of racial disparities on AKI incidence was attenuated and no longer significant after adjusted for prehospitalization clinical risk factors.[15] Nevertheless, observational studies indicated black patients carry higher risk of AKI in COVID-19 infection, even after adjusting for socioeconomic factors, and comorbidities.[3,16]

Our study found that patients with COVID-19 associated AKI were independently associated with higher inpatient mortality, ICU admission and needs for intubation, compared to COVID-19 positive but non-AKI patients. Additionally, male gender, older age, and higher Charlson Comorbidity

Index Score increased the risk of inpatient mortality. These outcomes remained significant after conducting multivariate logistic regression analysis controlled for age, gender, race, and Charlson Comorbidity Index Score. Our findings are similar to prior studies.[17-20] Notably, a wide variability in the inpatient mortality exists among different studies. One possible explanation is the different threshold for admission at the beginning of the pandemic, leading to different inpatient disease severity, proven by lower mortality in Chinese population.[21,22] Also, along with the pandemic evolving, raising public awareness of the importance of vaccination, implementation of protective measures and evolution of treatment methods for COVID-19 infection played more important roles in decreasing mortality.[23,24]

Due to missing data, we cannot comment on either recovery from AKI or development of CKD, although these are the most common consequences of AKI. Observation studies showed, by hospital discharge, the majority (74.1 %) COVID-19 associated AKI stage 1–3 survivors achieved recovery of kidney function, with 30.6 % remaining on dialysis at discharge among AKI stage 3D survivors.[25] However, in STOP-COVID Cohort study,[26] among AKI patients who received kidney replacement therapy (KRT) in ICU, only 22 % achieved kidney recovery by the time of discharge. Also, lower baseline eGFR and reduced urine output at initiation of KRT were independently associated with kidney nonrecovery among ICU patients with COVID-19 infection. A large UK cohort involving 1248 inpatients, of whom 39 % experienced AKI, demonstrated that AKI was a strong predictor of 30-day mortality and 30.7 % AKI stage 3 survivors had newly diagnosed renal impairment at 3–6 months.[27] Another large cohort study of US Veterans found that compared to non-infected controls, 30-day survivors had higher incidence of eGFR decline, and ESKD, including those non-hospitalized, hospitalized and admitted to ICU during acute COVID-19 infection.[28] In contrast, a prospective uncontrolled cohort study revealed the vast majority of 4-month survivors can recover kidney function as only 2 patients (2.1 %) developed new-onset AKI.[29]

The mechanism of kidney injury in COVID-19 infection is still unknown. Histologically, early autopsy studies revealed that acute tubular injury was the main finding in AKI,[30,31] which is most likely caused by volume depletion, hypotension/shock, sepsis and other pathophysiological pathways that can cause local or systemic inflammation response to COVID-19 infection.[32,33] Persistent tubular injury from acute tubular injury would contribute to the progression of CKD.[34] Autopsy and clinical studies also suggested micro or macrovascular injury,[35,36] and podocytopathy collapsing glomerulopathy,[37,38] ANCA associated vasculitis,[39] anti-GBM nephropathy[40] and IgA nephropathy[41] may also contribute to the CKD progression in COVID-19 associated AKI patients.

Defining a high-risk population for post COVID-19 renal function decline can be challenging. Although the risk of CKD progression is higher in patients with severe AKI and COVID-19, the eGFR decline also existed in patients without overt AKI.[42] This finding could be explained by subclinical AKI, with persistent subclinical inflammation and injury, resulting in a progressive decline in eGFR that leads to CKD over many months.[17,43] Therefore, close renal function surveillance upon discharge is of great significance. It is important to note that muscle loss is quite common in COVID-19 patients,[44] causing creatinine an insensitive marker for detecting kidney damage.[29] A prospective study of hospitalized COVID-19 patients suggested urinary AKI biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL) and Interleukin 18 (IL-18), were associated with adverse renal outcomes up to 2 months, including subclinical AKI.[45] Future studies are needed to investigate the long-term prognostic significance of blood and urine AKI biomarkers in COVID-19.

Our study has several limitations. First, as an observational study adopting convenient sampling, is subject to selection bias, missing data and possible unnoticed data entry errors. Second, the effect of AKI on mortality would be confounded by its influences on clinical management. Third, a significant portion of our patients were black, although this provided valuable information of this specific patient population, clinicians and researchers should keep cautious regarding result generalization. Finally, due to missing data were unable to compare outcomes beyond the index hospitalization.

5. Conclusions

AKI in hospitalized patients with COVID-19 was associated with higher inpatient mortality rate, need for intubation and ICU admission, compared to COVID-19 patients without AKI. Our study adds on the current body of knowledge regarding outcomes of COVID-19 with AKI in a primary Black patient population.

Disclaim

This article has never been submitted to other publications. The abstract of this article was poster

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Disclosures

All authors have nothing to disclose.

Conflict of interest

The authors declare no conflict of interest.

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