Acute Kidney Injury in hospitalized patients with COVID-19 and seasonal influenza: A comparative analysis

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KEY POINTS:

- The rate of AKI is similar in COV-AKI and Flu-AKI though risk of stage 3 AKI is higher in COV-AKI and is associated with a poorer prognosis.
- AA race and mechanical ventilation are associated with a higher risk of COV-AKI. CKD is a major risk factor for AKI in both groups.
- COV-AKI is associated with a 2.3 times higher odds of proteinuria 2+ or more in comparison to Flu-AKI.

ABSTRACT:

Background: Coronavirus disease 2019 (COVID-19) is often compared to seasonal influenza and the two diseases share similarities including the risk of systemic manifestations such as acute kidney injury (AKI). The aim of this study was to perform a comparative analysis of the prevalence, risk factors, and outcomes of AKI in hospitalized patients with COVID-19 and influenza.

Methods: Retrospective cohort study of hospitalized patients with COVID-19 (n=325) or seasonal influenza (n=433). AKI was defined by Kidney Disease: Improving Global Outcomes (KDIGO) criteria. Baseline characteristics and hospitalization data were collected, and multivariable analysis was performed to determine the independent predictors for AKI.

Results: AKI occurred in 32.6% of COVID-19 hospitalizations (COV-AKI) and 33.0% of influenza hospitalizations (FLU-AKI). After adjusting for age, gender, and comorbidity count, the risk of stage 3 AKI was significantly higher in COV-AKI (OR: 3.46; 95% CI 1.63, 7.37). Preexisting CKD was associated with a 6- to 7-fold increased likelihood for FLU-AKI and COV-AKI. Mechanical ventilation was associated with a higher likelihood of developing AKI in the COVID-19 cohort (OR: 5.85; 95% CI 2.30, 15.63). African American race, after adjustment for comorbidities, was an independent risk for COV-AKI.
**Conclusion:** Pre-existing CKD was a major risk factor for AKI in both cohorts. African American race (independent of comorbidities) and mechanical ventilation were associated with a higher risk of developing COV-AKI which is characterized by a higher burden of stage 3 AKI and overall poorer prognosis.
INTRODUCTION:
Coronavirus disease 2019 (COVID-19) is a term encompassing the varied clinical manifestations caused by the novel coronavirus, SARS-CoV-2. This novel RNA virus emerged in the Wuhan province of China in 2019 and as of Dec 3, 2020 has infected 64,863,145 individuals and caused 1,499,586 deaths worldwide with 237,760 deaths in the United States alone[1]. Numerous reports have clearly demonstrated that acute kidney injury (AKI) is a frequent complication of COVID-19 with the incidence of AKI ranging between 8.4-68%[2-7]. Kidney dysfunction in COVID-19 has been demonstrated to be an independent risk factor for mortality in hospitalized patients [8, 9]. The emerging risk factors for AKI in COVID-19 (COV-AKI) include male gender, African American race, hypertension, diabetes mellitus, and congestive heart failure[2, 7]. In addition to AKI, other manifestations of kidney involvement in COVID-19 include electrolyte disorders, hematuria, and proteinuria[10]. Various mechanisms have been proposed for kidney involvement in COVID-19 and these include massive cytokine release, organ crosstalk, and the impact of other organ system involvement on kidney function[5, 11]. Approximately 3.6%-14.6% of patients developing COV-AKI require kidney replacement therapy (RRT)[2, 5]. The surge in COVID-19 cases across the United States resulted in a rapid rise in the need for RRT and the subsequent shortages in dialysis machines, replacement solutions, and consumables has made hospital systems re-evaluate their RRT preparedness.

COVID-19 has been compared to seasonal influenza due to its pandemic potential and risk for severe respiratory failure [12, 13]. It is now clear that the mortality of COVID-19 exceeds that of seasonal influenza and COVID-19 has been associated with a number of novel sequelae[14, 15]. AKI from varying etiologies occurs in seasonal influenza (FLU-AKI) with a reported incidence of ~34-67% and RRT use of 11-36%[16-18]. Whether these two diseases share similar risk factors for AKI and need for RRT remains unknown.
This study seeks to address these questions by performing a comparative analysis focusing on prevalence, risk factors, characteristics, and complications of AKI in hospitalized patients with COVID-19 and seasonal influenza.

**METHODS:**

*Cohort identification.* This study was approved by the Institutional Review Board at the Medical College of Wisconsin. The electronic health record (EHR) was queried to identify hospitalized patients with influenza or COVID-19 within the Froedtert Health system in Milwaukee, WI using ICD-10-CM codes *(Supplementary Table 3).* The Froedtert Health system includes a 735-bed tertiary care hospital and two community hospitals with 272 beds. The inclusion criteria were: 1) adults age 18 years of age and older; 2) admission for influenza related illness between 12/15/17-3/20/18 or COVID-19 related illness between 2/1/20-06/30/20. The exclusion criteria were: 1) history of end stage renal disease 2) history of kidney transplantation and 3) age less than 18 years. The EHR was reviewed by members of the investigative team to: 1) confirm the diagnosis of COVID-19 or seasonal influenza and inpatient admission; 2) confirm the diagnosis and stage of AKI according to KDIGO criteria[19]; 3) abstract urinalysis and urine microscopy data; 4) identify the type and duration of renal replacement therapy; and 5) identify cases of death with rising creatinine and oliguria (DWRCO)[20].

Baseline clinical characteristics abstracted from the EHR included patient demographics, residence on admission, body mass index (BMI), diabetes mellitus (DM), hypertension (HTN), chronic kidney disease (CKD) and stage of CKD, congestive heart failure (CHF), coronary artery disease (CAD), peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), asthma, use of renin angiotensin aldosterone system (RAAS) blocking agents [(angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs)], immunosuppressed status (human immunodeficiency virus positive, use of mycophenolate...
mofetil, cyclophosphamide, or oral corticosteroids, or cancer chemotherapy),
neutrophil/lymphocyte ratio (N/L ratio) and baseline serum creatinine (sCr). Baseline sCr was
determined by chart review as most recent stable sCr value within 1 year prior to admission.
Hospitalization characteristics that were assessed included: nephrology consultation, need for
intensive care unit (ICU) admission, vasopressor and/or inotropic administration, mechanical
ventilation), length of stay (LOS), and in-hospital and 30-day mortality. In those patients
meeting criteria for AKI, the additional variables recorded included: stage of AKI, DRWCO, need
for and type of RRT.

Statistical analysis. Descriptive statistics were conducted to summarize cohort characteristics.
Chi-square and Fisher’s exact test were used for comparison of categorical variables and the
ANOVA test for comparison of continuous values. Comparisons were conducted first in the full
cohort by virus type (COVID-19 and influenza); then by AKI status in the two cohorts; lastly in
the AKI cohort by virus type (COVID-19 and influenza).

Unadjusted and adjusted logistic regression models were used to investigate patient’s
demographics, risk and clinical factors and their relationship with the following outcomes of
interest: 1) AKI, 2) AKI stage 3 and 3) urine findings. We first conducted univariate logistic
models to estimate the odds of having AKI in COVID-19 and influenza cohorts separately.
Based on the univariate analyses and clinic significance, multivariate logistic regression models
for AKI and urine findings were adjusted for demographics (gender, age, ethnicity/race),
comorbidity (DM, HTN, CKD, CHF, CAD) with additional variables of ICU transfer and
mechanical ventilation for AKI only. The AKI stage 3 multivariate regression model was only
adjusted for virus type, gender, age, and comorbidity count due to sample size limitations. All
analyses were performed using SAS version 9.4 (SAS Institute, Cary NC). Two sided tests were
conducted, and p<0.05 was considered statistically significant. Data are presented as median (IQR) for continuous variables or number (%) for dichotomous variables.

RESULTS:
A total of 758 patients were included in this study, 325 in the COVID-19 cohort and 433 in the influenza cohort. The baseline characteristics of the study cohort are shown in Supplementary Table 1. The individuals in the COVID-19 cohort were younger [median age (IQR): 64 (50-77) years] with the majority being males (51.4%) and predominantly African American (51.4%). In contrast, the influenza group was older [median age (IQR): 72 (60-84) years] with a higher proportion of females (60.3%) and non-Hispanic whites (72.3%). The COVID-19 cohort included more individuals (22.8% vs. 12.0%, p<0.001) who were admitted from a long-term care facility (nursing home residents/long term acute care units/rehabilitation homes) rather than home. The median BMI (30.5 vs. 28.1 kg/m$^2$, p=0.007) and prevalence of DM were significantly higher in the COVID-19 group (43.9% vs. 35.6%, p=0.03) while the prevalence of other comorbidities (HTN, CHF, CAD, PVD, COPD, asthma, and CKD) was higher in individuals admitted with influenza. Of these comorbidities, only the higher prevalence of HTN, CAD, COPD, and asthma achieved statistical significance. Individuals with COVID-19 were less likely to be immunosuppressed (11.7% vs 45.5%, p< 0.0001) and were likely to have a lower N/L ratio on admission (4.3 vs. 7.0, p< 0.0001). The proportion of patients with two or more comorbidities was higher in the influenza cohort in comparison to the COVID-19 cohort (67.1% vs 55.5%, p=0.002). There were no statistically significant differences in PVD, CKD, stage of CKD, baseline or admission sCr, or use of RAAS medications between the two cohorts.

Hospital characteristics are presented in Supplementary Table 2. In comparison to the influenza cohort, the rates of nephrology consultation (6.8% vs. 3.2%; p=0.02), vasopressor use (14.2 vs. 9.5%, p=0.045) and mechanical ventilation (12.9% vs. 6.5%; p=0.002) were
significantly higher in the COVID-19 cohort. In-hospital mortality (5.2% vs. 1.6%, p=0.005) and 30-day mortality (12% vs. 6%, p=0.004) were higher in the COVID-19 cohort in comparison to the influenza cohort as was the median LOS [6 (3-12) vs. 4 (2-6) days, p<0.0001]. The rate of ICU admission or inotrope use did not significantly differ between the two groups.

A comparison of the baseline characteristics of the AKI and non-AKI groups in both cohorts is shown in Table 1. A total of 106 COVID-19 patients developed AKI (COV-AKI) while 143 patients developed AKI in the influenza cohort (FLU-AKI). The patients with COV-AKI were older [median age (IQR): 67 (57-81) years], predominantly African American (64.2%) and had a higher prevalence of DM (58.3%), HTN (62.5%), CAD (27.1%), CHF (36.5%) and CKD (53.6%) in comparison to COVID-19 patients without AKI (COV-NoAKI). Most of the COV-AKI patients had Medicare for insurance (71.7%) and 36.5% of COV-AKI patients had a comorbidity count of four or more. The baseline sCr was significantly higher in the COV-AKI group and this group had a higher rate of RAAS medication use than the COV-NoAKI cohort. The remaining variables (gender, BMI, PVD, asthma, COPD, immunosuppression) were not statistically different between the COV-AKI and COV-NoAKI subsets. A comparison of FLU-AKI and FLU-NoAKI groups showed that the predominant race in FLU-AKI subset was non-Hispanic whites and this group was more likely to have underlying CKD, CHF, and a higher comorbidity count (4 or more) than the FLU-NoAKI group. Like COV-AKI, the subjects in the FLU-AKI cohort also had a higher baseline sCr in comparison to the FLU-NoAKI subset.

The characteristics of COV-AKI and FLU-AKI are shown in Figure 1. The COV-AKI group had a higher admission sCr (1.6 mg/dL [1.2-2.2] vs. 1.4 mg/dL [1.1-1.9], p=0.04) while the baseline and discharge sCr were similar though not statistically significant between the two groups. There was also a higher percentage of subjects with stage 3 AKI (24.5% vs. 9.1%, p=0.004) in COV-AKI group vs stage 1 (59.4 vs. 73.4%, p=0.004) and stage 2 AKI (16.0 vs. 17.5%,
p=0.004) which were the dominant stages of AKI in the influenza cohort. The proportion of patients requiring RRT (7.6%), DWRCO (7.6%) and RRT + DWRCO (15.2%) was higher in the COV-AKI cohort. The same rates for the FLU-AKI cohort were: RRT (4.2%), DWRCO (5.6%) and RRT + DRWCO (9.1%) though the rate of RRT use between the two groups was not significantly different. The hospitalization characteristics associated with COV-AKI and FLU-AKI are detailed in **Table 2**. A higher proportion of COV-AKI subjects presented with AKI on admission (71.7% vs. 48.9 %, p=0.0003), required mechanical ventilation (23.6% vs. 11.2%, p=0.009) during hospital stay and experienced a higher rate of in-hospital mortality (11.3% vs. 3.5%, p=0.016) in comparison to FLU-AKI. There were no statistically significant differences between the COV-AKI and FLU-AKI groups with regards to ICU admission, vasopressor and inotrope use, and 30-day mortality.

**Table 3** shows the multivariable logistic regression analysis examining the association between virus type and stage 3 AKI. When only considering age and gender, the risk of stage 3 AKI was significantly higher in the COVID-19 cohort in comparison to influenza (OR: 2.63, 95% CI 1.29, 5.34). After adjusting for comorbidity count, COVID-19 (OR: 3.46, 95% CI 1.63, 7.37), male gender (OR: 2.08, 95% CI 1.03, 4.19), and comorbidity count (OR: 1.35, 95% CI 1.11, 1.65) were significantly associated with stage 3 AKI. **Table 4** shows the multivariable logistic regression analysis examining the association between relevant covariates and AKI, stratified by virus type. When only considering the demographics (age, gender, and race), African Americans were more likely to develop AKI compared to non-Hispanic whites in both the COVID-19 cohort (OR: 2.54, 95% CI 1.47, 4.41) and influenza cohort (OR: 2.37, 95% CI 1.43, 3.91); age increase was significantly associated with higher odds of AKI only in COVID-19 cohort (OR: 1.02, 95% CI 1.01, 1.04). After adjusting for comorbidities, age was no longer significant in COVID-19 cohort, African American race remained significant in the COVID-19 cohort (OR: 2.13, 95% CI 1.11, 4.10) but not in the influenza cohort (OR: 1.89, 95% CI 1.05,
Patients with CKD were more likely to have AKI compared to patients without CKD in both the COVID-19 cohort (OR: 7.03, 95% CI 3.44, 14.38) and influenza cohort (OR: 6.51, 95% CI 3.81, 11.11). In the influenza cohort, patients with CHF were more likely to have AKI than those with no history of CHF (OR: 1.91, 95% CI 1.08, 3.37). Patients requiring mechanical ventilation were more likely to develop AKI (OR: 5.85, 95% CI: 2.30-15.63) in the COVID-19 cohort but not in the influenza cohort (OR: 2.05, 95% CI:0.76-5.58).

Urinalysis results in the COV-AKI and FLU-AKI patients are shown in Figure 2. Clinically significant hematuria and leukocyturia were defined as > 2 RBC’s/HPF and > 2 WBC’s/HPF respectively while clinically significant proteinuria was noted if the urine protein on dipstick was ≥2+. Nephrotic range proteinuria was considered with 3+ proteinuria on urine dipstick[20]. In the COV-AKI group, clinically significant hematuria, leukocyturia, and proteinuria were noted in 30.2%, 38.7% and 26.4% patients. Nephrotic range proteinuria was observed in 5.7% patients. The FLU-AKI group had similar findings with clinically significant hematuria, leukocyturia and proteinuria noted in 34.9%, 35.0% and 20.3%. However, nephrotic range proteinuria was noted in only 2.8% patients. Calculation of p-values was not done due to the high number of missing values for urine findings in both COV-AKI and FLU-AKI groups. A logistic regression model was used to assess the association of urine findings with comorbidities and the findings are shown in Table 5. In comparison to influenza, COVID-19 was associated with 2.3 times higher odds for dipstick proteinuria 2+ or higher in both unadjusted models (OR: 2.31, 95% CI: 1.23-4.40) and after adjusting for comorbidities (OR: 2.33, 95% CI: 1.16-4.77). CAD was the sole comorbidity which was associated with a lower risk of proteinuria in the adjusted model (OR: 0.37, 95% CI: 0.15-0.85). There was no statistically significant association between comorbidities and hematuria and leukocyturia.

**DISCUSSION:**
The clinical manifestations and outcomes of COVID-19 and influenza are often compared but little is known about how the risk of AKI compares between these two illnesses [12, 13]. To our knowledge, this is the first study to compare the prevalence and risk factors for AKI in hospitalized patients with COVID-19 and seasonal influenza. Although the rates of AKI are similar in the hospitalized COVID-19 (32.6%) and influenza cohorts (33%), there are key differences in risk factors. The COV-AKI cohort was younger than the FLU-AKI cohort and had a higher proportion of African American patients and individuals residing in a facility prior to admission. The COV-AKI cohort was more likely to have underlying DM, HTN, CHF, CAD, pre-existing CKD, and a higher comorbidity count (4 or more comorbidities) than the COV-NoAKI cohort. The FLU-AKI cohort was predominantly non-Hispanic whites, and CHF and pre-existing CKD were identified as significant risk factors in comparison with the FLU-NoAKI group. The FLU-AKI group also had a higher comorbidity count (4 or more comorbidities) than FLU-NoAKI. The proportion of individuals with severe AKI, need for mechanical ventilation, and in-hospital mortality were all significantly higher in COV-AKI in comparison to FLU-AKI. The need for mechanical ventilation was associated with higher likelihood of developing COV-AKI in contrast to FLU-AKI. In addition, pre-existing CKD and African American race were two consistent risk factors that were associated with higher odds for AKI in both diseases. African American race was a significant risk factor for COV-AKI independent of comorbidities.

Africans Americans have a higher risk of AKI independent of diabetes, hypertension, and CAD compared with non-Hispanic whites which is consistent with our data demonstrating the two-fold higher risk of COV-AKI and FLU-AKI in African Americans in this study. These study findings are consistent with prior studies that demonstrate African Americans with COVID-19 are more likely to have AKI as a complication compared to non-Hispanic whites[21]. Evidence suggests social risk factors such as low income and lack of access to care could explain some of this disparity[22]. Recently published studies have reported that African Americans are more likely to
be tested for COVID-19 in the emergency department or inpatient settings and are more likely to be admitted to the hospital compared to non-Hispanic whites[23-25]. This is thought to reflect the lack of access to care and delay in seeking care due to lack of trust in the system which results in more advanced disease at the time of presentation[23].

A recently published study by Xie et al. reported a higher overall rate of AKI (37.2% vs. 29.0 %), stage 3 AKI (10.9% vs 3.2%) and RRT use (4.7% vs. 0.9%) in COVID-19 in comparison to influenza. While our study reports a similar higher rate of stage 3 AKI (24.5 % vs. 9.1%) in COVID-19, the overall rates of AKI and RRT use were not significantly different between the COVID-19 and influenza groups in our study. This difference can likely be explained by the higher severity of the influenza season (2017-2018) which was evaluated in our study in contrast to the study by Xie et al where the influenza season from January 2017- December 2019 was used for comparison. This study by Xie et al also describes CKD as a risk factor for death. The study did not specifically evaluate and describe risk factors for AKI since the primary focus was to describe the clinical presentations in the two diseases as well as risk of death and resource utilization. We found a higher rate of mechanical ventilation, vasopressor use, in hospital mortality and LOS in the hospitalized COVID-19 cohort (with and without AKI) similar to the findings reported by Xie et al.

In review of the previously published studies evaluating AKI in COVID-19, our study is comparable in terms of previously reported rates of AKI in New York state (36.6%-46%)[2, 4], Rochester, MN (54.7%)[26] and New Orleans, Louisiana (28%)[20]. These hospital systems were strained early in the COVID-19 pandemic and the number of patients with AKI in these studies was much higher than the present study (161, Mohamed et al; 179, Nimkar et al; 1,993, Hirsch et al; and 1,406, Chan et al.) The risk factor profile for AKI in COVID-19 patients in the current study is consistent with these earlier reports. African American race, hypertension, and
DM have also been identified as risk factors for AKI across these studies[2]. Our findings lend support to the important association of pre-existing CKD with a higher likelihood of AKI in patients with COVID-19 as reported by Chan et al[4]. In the Louisiana study, the median BMI in the AKI group was 34 (16-67) kg/m$^2$ while the median BMI in our COV-AKI study population was 28.6 kg/m$^2$ and not significantly different between the COV-AKI and COV-NoAKI groups. High local prevalence of morbid obesity may thus confer an additional and important risk factor for an increased incidence and severity of AKI during community spread of COVID-19. This may explain the higher rate of RRT requirement in Louisiana (55%). In contrast, the RRT rate in our study was 15.2% which is consistent with the observed RRT rates in New York state and Minnesota [2, 26]. The rate of stage 3 AKI reported in these studies ranged from 20.8% to 66% while the in-hospital mortality ranged from 34.8% to 58%. The proportion of stage 3 AKI (24.5%) and in-hospital mortality (11.3%) was significantly lower in our study. Disease severity on presentation and the ensuing hospital course including need for critical care support may underlie this observed difference in the rates of stage 3 AKI and in-hospital mortality. Since the first wave of COVID-19 in our region was delayed relative to New York and Louisiana, health system readiness and implementation of emerging treatment paradigms (e.g. early proning, less mechanical ventilation, Remdesivir) could further explain lower mortality in our COV-AKI cohort.

AKI in hospitalized patients with influenza has been well documented in various studies based on the clinical experience during the pandemic of 2009[16, 18, 27]While some of these studies focused on AKI in critically ill patients[27], several studies assessed AKI in all hospitalized patients with influenza[16, 18]. The reported incidence of AKI in H1N1 influenza varied between 33.6%-53% with in-hospital mortality of ~36% and RRT rates of 15.6-36% for AKI[16, 18]. Risk factors for AKI in these studies included pregnancy, immunosuppression, DM, COPD and CKD[16, 18, 28]. In the present study, CHF and CKD were associated with a higher risk of AKI in the influenza cohort. While we report a similar incidence of AKI, the in-hospital mortality
(3.5%) and RRT rate (9%) noted in the FLU-AKI cohort were significantly lower. The prevalent strain during the 2017-2018 flu season was H3N2 in contrast to the pandemic H1N1 strain of 2009 which was associated with a higher severity of disease. Differences in pathogenicity of the two strains, efficacy of vaccination against the 2017-2018 H3N2 strain, and the possible early initiation of outpatient anti-viral therapy could have limited the overall disease severity and reduced the burden of AKI in the influenza cohort in our study.

Despite a younger median age, the COV-AKI cohort had more comorbidities relative to the FLU-AKI group indicating that comorbidities may outweigh the benefits of younger age. The severity of AKI was higher in COVID-19 which may indicate a higher overall severity of disease and can also explain the higher in hospital mortality rate (11.3% for COV-AKI vs. 3.5% for FLU-AKI). There was no well-established, highly effective treatment for COVID-19 at the time these patients were hospitalized for COVID-19 and supportive medical management was the mainstay of treatment. Remdesivir has been included in treatment protocols in hospitalized COVID-19 patients and has been shown to shorten the recovery period in these patients from 15 to 11 days[29]. However, its impact on limiting the severity of disease is not well known. On the other hand, the widespread availability of anti-viral drugs for treatment of influenza and early initiation of therapy (which can be done as an outpatient[30]) could have limited the rate of hospitalization and overall severity of disease and associated AKI. Interestingly, in our study, despite a higher rate of stage 3 AKI in COV-AKI, the rate of RRT use or DWRCO was not significantly different between the COV-AKI and FLU-AKI subsets. Hospital systems have been challenged to provide RRT for patients with COV-AKI in a timely and efficient manner[31]. With similar rates of RRT noted in the two groups, it is possible that the need for RRT resources may substantially increase during the seasonal influenza season, assuming a similar rate of hospital admissions, influenza severity, and incidence of AKI as found in the current study.
The pathophysiologic mechanisms of AKI between the two diseases are similar with AKI attributable to hemodynamic insults, myoglobin induced kidney injury in rhabdomyolysis, and thrombotic microangiopathy[32-34]. Hematuria, leukocyturia, and proteinuria are commonly present in patients with AKI in both influenza and COVID-19. The UA findings were similar in the two cohorts in this study though a higher proportion of patients had nephrotic range proteinuria in COV-AKI (5.7% vs 2.8%). COV-AKI is an independent risk factor for development of proteinuria independent of other comorbidities including diabetes and hypertension. This may be explained in part by glomerular involvement by the SARS-CoV-2 virus described in recent reports of collapsing glomerulopathy noted in cases of COV-AKI [20]. Minimal change disease and membranous nephropathy secondary to COVID-19 have also been reported [35].

The limitations of this study include the retrospective, single center nature of the study which may not allow for generalization to the different regions which have seen differential trends of COVID-19 cases and resulting AKI. This study was not designed to assess the impact of available treatment strategies for COVID-19 and influenza on the occurrence of AKI. We were also unable to report and comment on the association of laboratory markers (interleukin-6, C-reactive protein and lactate dehydrogenase) with occurrence and severity of COV-AKI due to variability in the local use of these markers in COVID-19 patients. Nephrology consultation was obtained in only a fraction of patients with AKI in both cohorts, so we are limited in our description of the etiology of AKI in both subsets of patients. Strengths of this study include a direct comparison of the characteristics of AKI in COVID-19 and the last severe influenza season (2017-2018). To the best of our knowledge, this is the first study that reports on the differential aspects of AKI in the two diseases. We also analyzed the patterns of RRT use and mechanical ventilation to understand the differences in resource utilization between COVID-19 and severe seasonal influenza.
In conclusion, AKI occurs frequently in hospitalized patients with COVID-19 and seasonal influenza. The risk of stage 3 AKI is significantly higher in COVID-19 in comparison to seasonal influenza. Pre-existing CKD and African American race confer a higher risk for AKI in both illnesses. The need for mechanical ventilation is associated with a disproportionately higher risk for development of COV-AKI. Understanding the patterns of AKI and need for RRT in these two diseases may help inform and advance our current knowledge of the renal impact of COVID-19 and influenza.

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Table 1. Baseline characteristics by AKI status in the study cohorts.

| Clinical variable          | COVID-19 (n=219) | AKI (n=106) | P-value | COVID-19 (n=290) | AKI (n=143) | P-value |
|---------------------------|------------------|-------------|---------|------------------|-------------|---------|
| Age (years)               | 62 (47-75)       | 67 (57-81)  | 0.01    | 72 (59-85)       | 73 (60-84)  | 0.5     |
| Female                    | 111 (50.7)       | 47 (44.3)   | 0.3     | 180 (62.1)       | 81 (56.6)   | 0.3     |
| Race                      |                  |             | 0.006   |                  |             | 0.02    |
| -African American         | 99 (45.2)        | 68 (64.2)   |         | 58 (20.0)        | 46 (32.2)   |         |
| -non-Hispanic white       | 86 (39.3)        | 28 (26.4)   |         | 221 (76.2)       | 92 (64.3)   |         |
| -Hispanic/Other           | 34 (15.5)        | 10 (9.4)    |         | 11 (3.8)         | 5 (3.5)     |         |
| Primary payor             |                  |             | <0.0001 |                  |             | 0.09    |
| -Medicare                 | 110 (50.2)       | 76 (71.7)   |         | 215 (74.1)       | 116 (81.1)  |         |
| -Medicaid                 | 38 (17.4)        | 13 (12.3)   |         | 32 (11.0)        | 17 (11.9)   |         |
| -Managed care             | 71 (32.4)        | 15 (14.2)   |         | 41 (14.1)        | 9 (6.3)     |         |
| -Other                    | 0                | 2 (1.9)     |         | 2 (0.7)          | 1 (0.7)     |         |
| BMI, kg/m²                | 31.2 (26.3-36.1) | 28.6 (24.4-37.1) | 0.99 | 27.9 (23.9-33.8) | 29.6 (24.7-34.9) | 0.2 |
| Residence on admit        |                  |             | 0.03    |                  |             | 0.07    |
| -Home                     | 177 (80.8)       | 74 (69.8)   |         | 261 (90.0)       | 120 (83.9)  |         |
| -Other                    | 42 (19.2)        | 32 (30.2)   |         | 29 (10.0)        | 23 (16.1)   |         |
| Diabetes mellitus         | 71 (36.8)        | 56 (58.3)   | 0.0005  | 87 (32.5)        | 56 (41.8)   | 0.07    |
| Hypertension              | 96 (49.7)        | 60 (62.5)   | 0.04    | 165 (61.6)       | 93 (69.4)   | 0.1     |
| Heart failure             | 34 (17.6)        | 35 (36.5)   | 0.0004  | 60 (22.4)        | 52 (38.8)   | 0.0005  |
| CAD                       | 31 (16.1)        | 26 (27.1)   | 0.03    | 76 (28.4)        | 41 (30.6)   | 0.6     |
| PVD                       | 14 (7.3)         | 8 (8.3)     | 0.7     | 30 (11.2)        | 15 (11.2)   | 1       |
| COPD                      | 33 (17.1)        | 18 (18.8)   | 0.7     | 103 (38.4)       | 48 (35.8)   | 0.6     |
| Asthma                    | 33 (17.1)        | 22 (22.9)   | 0.2     | 86 (32.1)        | 41 (30.6)   | 0.8     |
| CKD                       | 25 (13.0)        | 52 (53.6)   | <0.0001 | 44 (16.4)        | 76 (56.3)   | <0.0001 |
| Comorbidity count         | 0.0001           |             |         |                  |             | 0.09    |
| -0-1                      | 98 (50.8)        | 30 (31.3)   |         | 98 (36.6)        | 33 (24.4)   |         |
| -2-3                      | 65 (33.7)        | 31 (32.3)   |         | 91 (34.0)        | 43 (31.9)   |         |
| -4+                       | 30 (15.5)        | 35 (36.5)   |         | 79 (29.5)        | 59 (43.7)   |         |
| RAAS medications          | 74 (33.8)        | 53 (50.0)   | 0.005   | 121 (41.7)       | 71 (49.7)   | 0.1     |
| Immunosuppression         | 24 (11.0)        | 14 (13.2)   | 0.6     | 131 (45.2)       | 66 (46.2)   | 0.8     |
| Neutrophil/Lymphocyte ratio | 4.2 (2.6-8.4) | 4.5 (2.9-8.1) | 0.2     | 7.2 (4.0-13.6) | 6.8 (4.0-11.2) | 0.9 |
| Baseline sCr (mg/dL)      | 0.8 (0.7-1.0)    | 1.0 (0.9-1.2) | <0.0001 | 0.8 (0.7-1.0)    | 1.0 (0.8-1.2) | <0.0001 |

Data are presented as median (IQR) or number (%). BMI, body mass index. CAD, coronary artery disease. PVD, peripheral vascular disease. COPD, chronic obstructive pulmonary disease. CKD, chronic kidney disease. RAAS, renin angiotensin aldosterone system. sCr, serum creatinine
Table 2. Hospital characteristics of COVID-19 and Influenza patients with AKI.

| Clinical variable          | COVID-19 (n=106) | Influenza (n=143) | P-value |
|----------------------------|------------------|-------------------|---------|
| AKI on admission, n(%)    | 76 (71.7)        | 70 (48.9)         | 0.0003  |
| ICU admission, n(%)       | 60 (56.6)        | 65 (45.5)         | 0.08    |
| Vasopressor use, n(%)     | 25 (23.6)        | 21 (14.7)         | 0.07    |
| Inotrope use, n(%)        | 3 (2.8)          | 3 (2.1)           | 0.7     |
| Mechanical ventilation    | 25 (23.6)        | 16 (11.2)         | 0.009   |
| In hospital mortality     |                  |                   | 0.016   |
| -Alive                    | 94 (88.7)        | 138 (96.5)        |         |
| -Dead                     | 12 (11.3)        | 5 (3.5)           |         |
| 30-day mortality          |                  |                   | 0.3     |
| -Alive                    | 89 (84.0)        | 127 (88.8)        |         |
| -Dead                     | 17 (16.0)        | 16 (11.2)         |         |

Data are presented as number (%). AKI, acute kidney injury. ICU, intensive care unit.
Table 3. Independent Predictors for Stage 3 AKI.

| Variables            | Model 1          | Model 2          |
|----------------------|------------------|------------------|
| Virus Type           |                  |                  |
| Influenza (Reference)| --               | --               |
| COVID-19             | **2.63**         | **3.46**         |
|                      | (1.29 - 5.34)    | (1.63 - 7.37)    |
| Sex                  |                  |                  |
| Female (Reference)   | --               | --               |
| Male                 | **1.57**         | *2.08*           |
|                      | (0.81 - 3.05)    | (1.03 - 4.19)    |
| Age at admission     | **1.01**         | 0.99             |
|                      | (0.99 - 1.02)    | (0.97 - 1.01)    |
| Comorbidity Count    | **1.35**         |                  |
|                      | (1.11 - 1.65)    |                  |

*p <0.05; **p <0.01; ***p <0.001
Table 4. Independent Predictors for AKI in Patients with COVID-19 vs. Influenza

| Variables                        | Model 1 OR (95% CI) | Model 2 OR (95% CI) | Model 3 OR (95% CI) | Model 1 OR (95% CI) | Model 2 OR (95% CI) | Model 3 OR (95% CI) |
|----------------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Sex                              |                     |                     |                     |                     |                     |                     |
| Female (Reference)               | --                  | --                  | --                  | --                  | --                  | --                  |
| Male                             | 1.42 (0.88 - 2.31)  | 1.62 (0.91 - 2.89)  | 1.49 (0.81 - 2.76)  | 1.42 (0.93 - 2.16)  | 1.43 (0.87 - 2.33)  | 1.37 (0.83 - 2.25)  |
| Age at hospital admission        | 1.02** (1.01 - 1.04)| 0.99 (0.97 - 1.01)  | 1.00 (0.98 - 1.02)  | 1.01 (1.00 - 1.02)  | 1.00 (0.99 - 1.02)  | 1.01 (0.99 - 1.02)  |
| Race/Ethnicity                   |                     |                     |                     |                     |                     |                     |
| NHW (Reference)                  | --                  | --                  | --                  | --                  | --                  | --                  |
| AA                               | 2.54** (1.47 - 4.41)| 2.13* (1.11 - 4.10) | 3.03** (1.52 - 6.27)| 2.37** (1.43 - 3.91)| 1.89 (1.05 - 3.39) | 1.95* (1.07 - 3.54) |
| Hispanic/Other                   | 1.21 (0.51 - 2.86)  | 0.84 (0.28 - 2.53)  | 0.84 (0.26 - 2.52)  | 1.29 (0.43 - 3.91)  | 1.49                | 1.44                |
| Diabetes                         |                     |                     |                     |                     |                     |                     |
| No (Reference)                   | --                  | --                  | --                  | --                  | --                  | --                  |
| Yes                              | 1.53 (0.82 - 2.84)  | 1.39 (0.71 - 2.70)  | 1.01 (0.61 - 1.68)  | 0.97 (0.58 - 1.61)  |                    |                     |
| Hypertension                     |                     |                     |                     |                     |                     |                     |
| No (Reference)                   | --                  | --                  | --                  | --                  | --                  | --                  |
| Yes                              | 1.11 (0.59 - 2.08)  | 1.26 (0.64 - 2.46)  | 0.70 (0.40 - 1.21)  | 0.69 (0.39 - 1.19)  |                    |                     |
| CHF                              |                     |                     |                     |                     |                     |                     |
| No (Reference)                   | --                  | --                  | --                  | --                  | --                  | --                  |
| Yes                              | 1.68 (0.79 - 3.59)  | 1.63 (0.73 - 3.61)  | 1.91* (1.08 - 3.37) | 1.84* (1.04 - 3.29) |                    |                     |
| CAD                              |                     |                     |                     |                     |                     |                     |
| No (Reference)                   | --                  | --                  | --                  | --                  | --                  | --                  |
| Yes                              | 0.76 (0.33 - 1.74)  | 0.82 (0.33 - 1.97)  | 0.63 (0.34 - 1.14)  | 0.63 (0.34 - 1.13)  |                    |                     |
| CKD                              |                     |                     |                     |                     |                     |                     |
| No (Reference)                   | --                  | --                  | --                  | --                  | --                  | --                  |
| Yes                              | 7.03*** (3.44 - 14.38)| 7.84*** (3.69 - 17.52)| 6.51*** (3.81 - 11.11)| 6.66*** (3.92 - 11.58)|                    |                     |
| Mechanical ventilation           |                     |                     |                     |                     |                     |                     |
| No (Reference)                   | --                  | --                  | --                  | --                  | --                  | --                  |
| Yes                              | 5.85*** (2.30 - 15.63)|                    |                    | 2.05 (0.76 - 5.58)  |                    |                     |
| ICU transfer                     |                     |                     |                     |                     |                     |                     |
| No (Reference)                   | --                  | --                  | --                  | --                  | --                  | --                  |
| Yes                              | 1.56 (0.80 - 3.04)  |                    |                    | 1.36 (0.81 - 2.27)  |                    |                     |

*p<0.05; **p<0.01; ***p<0.001. NHW, non-Hispanic White. AA, African American. CHF, congestive heart failure. CAD, coronary heart disease. CKD, chronic kidney disease.
Table 5. Independent clinical predictors of proteinuria, hematuria and pyuria in COVID-19 vs. influenza

| Variables | Dipstick Proteinuria | RBCs/HPF | WBCs/HPF |
|-----------|----------------------|----------|----------|
|           | Unadjusted OR (95% CI) | Adjusted OR (95% CI) | Unadjusted OR (95% CI) | Adjusted OR (95% CI) | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
| Virus type |                      |                      |                      |                      |                      |                      |
| Influenza (Reference) | -- | -- | -- | -- | -- | -- |
| COVID-19 | 2.31* (1.23-4.40) | 2.33* (1.16-4.77) | 0.94 (0.50-1.75) | 1.27 (0.64-2.54) | 1.32 (0.71-2.46) | 1.78 (0.90-3.60) |
| Diabetes |                      |                      |                      |                      |                      |                      |
| No (Reference) | -- | -- | -- | -- | -- | -- |
| Yes | 1.09 (0.53-2.20) | 0.55 (0.27-1.08) | 0.52 (0.26-1.04) |                      |                      |                      |
| Hypertension |                      |                      |                      |                      |                      |                      |
| No (Reference) | -- | -- | -- | -- | -- | -- |
| Yes | 1.87 (0.85-4.26) | 1.54 (0.73-3.29) | 1.07 (0.51-2.26) |                      |                      |                      |
| CHF |                      |                      |                      |                      |                      |                      |
| No (Reference) | -- | -- | -- | -- | -- | -- |
| Yes | 1.04 (0.48-2.29) | 0.82 (0.38-1.75) | 1.55 (0.74-3.30) |                      |                      |                      |
| CAD |                      |                      |                      |                      |                      |                      |
| No (Reference) | -- | -- | -- | -- | -- | -- |
| Yes | 0.37* (0.15-0.85) | 0.84 (0.37-1.89) | 1.36 (0.62-3.06) |                      |                      |                      |
| CKD |                      |                      |                      |                      |                      |                      |
| No (Reference) | -- | -- | -- | -- | -- | -- |
| Yes | 1.00 (0.48-2.06) | 0.86 (0.42-1.75) | 0.79 (0.39-1.58) |                      |                      |                      |

* p<0.05; Dipstick proteinuria (> 2+), RBCs/HPF: >2, WBCs/HPF: > 2; CHF, congestive heart failure. CAD, coronary heart disease. CKD, chronic kidney disease.
FIGURE LEGENDS:

Figure 1. Characteristics of AKI in COVID-19 and influenza. A. Baseline, admission, and discharge serum creatinine in patients with AKI. Data are presented at median (IQR). * p < 0.05. B. Distribution of AKI stages in patients with COVID-19 or influenza. C. RRT requirement in patients with AKI. RRT, renal replacement therapy. DWRCO, death with rising serum creatinine and oliguria.

Figure 2. Urinalysis findings in patients with AKI in the setting of COVID-19 or influenza. Distribution of A. RBCs/HPF, B. WBCs/HPF, and C. dipstick proteinuria. RBCs, red blood cells. WBCs, white blood cells. HPF, high power field.
Figure 2

A. RBCs/HPF

B. WBCs/HPF

C. Dipstick Protein

Graphs showing the comparison between COV-AKI and FLU-AKI for RBCs, WBCs, and Dipstick Protein.