OPEN

Association Between Acute Kidney Injury During Invasive Mechanical Ventilation and ICU Outcomes and Respiratory System Mechanics

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OBJECTIVES: Compare ICU outcomes and respiratory system mechanics in patients with and without acute kidney injury during invasive mechanical ventilation.

DESIGNS: Retrospective cohort study.

SETTINGS: ICUs of the University of California, San Diego, from January 1, 2014, to November 30, 2016.

PATIENTS: Five groups of patients were compared based on the need for invasive mechanical ventilation, presence or absence of acute kidney injury per the Kidney Disease: Improving Global Outcomes criteria, and the temporal relationship between the development of acute kidney injury and initiation of invasive mechanical ventilation.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: A total of 9,704 patients were included and 4,484 (46%) required invasive mechanical ventilation; 2,009 patients (45%) had acute kidney injury while being treated with invasive mechanical ventilation, and the mortality rate for these patients was 22.4% compared with 5% in those treated with invasive mechanical ventilation without acute kidney injury ($p <$ 0.01). Adjusted hazard of mortality accounting for baseline disease severity was 1.58 (95% CI, 1.22–2.03; $p < 0.001$]. Patients with acute kidney injury during invasive mechanical ventilation had a significant increase in total ventilator days and length of ICU stay with the same comparison (both $p < 0.01$). Acute kidney injury during mechanical ventilation was also associated with significantly higher plateau pressures, lower respiratory system compliance, and higher driving pressures (all $p < 0.01$). These differences remained significant in patients with net negative cumulative fluid balance.

CONCLUSIONS: Acute kidney injury during invasive mechanical ventilation is associated with increased ICU mortality, increased ventilator days, increased length of ICU stay, and impaired respiratory system mechanics. These results emphasize the need for investigations of ventilatory strategies in the setting of acute kidney injury, as well as mechanistic studies of crosstalk between the lung and kidney in the critically ill.

KEY WORDS: acute hypoxemic respiratory failure; acute kidney failure; breathing mechanics; mechanical ventilation; multiple organ dysfunction syndrome; ventilator-induced lung injury

Invasive mechanical ventilation (IMV) is one of the most used life support modalities throughout the world (1). The mortality of mechanically ventilated patients is increased as additional organs fail, particularly in the setting of acute kidney injury (AKI) (2). However, the magnitude of this contribution is poorly described, as is the impact of AKI on pulmonary function during IMV.

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There are several mechanisms by which AKI would be predicted to have a negative impact on ventilator outcomes. For example, AKI poses a challenge to implementing lung protective ventilation with low tidal volumes, as patients with AKI have diminished capacity to correct for the hypercapnic acidosis often required with this strategy (3–5). Furthermore, volume overload in the setting of oliguria or anuria would be expected to decrease respiratory system compliance (6–8); thus, more lung stress may be required to achieve adequate gas exchange. Finally, prior studies have demonstrated that inflammatory crosstalk exists between the lung and kidney such that injury to one organ contributes to injury and inflammation in the other (9–14). Therefore, patients with AKI may be more prone to ventilator-induced lung injury, a major contributor to multiple organ failure and death in the critically ill.

Small, retrospective studies have suggested that AKI contributes independently to poor outcomes from IMV, such as failure to wean (15–17). Contrarily, a larger, prospective study found that AKI was not associated with longer duration of mechanical ventilation or an increased length of ICU stay (18). These investigations were conducted prior to developing the current Kidney Disease: Improving Global Outcomes (KDIGO) criteria for AKI diagnosis (19), and no study, to our knowledge, has investigated the association between AKI and respiratory system mechanics during IMV.

The objective of this study was to address these uncertainties by performing a large, retrospective cohort study comparing mortality, duration of IMV, and respiratory system mechanics in critically ill patients who required IMV with and without AKI. We hypothesized that AKI would have a negative impact on these outcomes in ventilated patients. A better understanding of the impact of AKI on ICU outcomes in patients treated with IMV, including ventilator parameters, will inform clinicians and researchers regarding prognosis, resource utilization, and opportunities for novel treatment approaches.

MATERIALS AND METHODS

This retrospective cohort study included all adult patients admitted to medical and surgical ICUs at all hospitals sites within the University of California, San Diego (UCSD) Health System between January 1, 2014, and November 30, 2016. The study was approved by the UCSD Institutional Review Board (IRB) with IRB 170011 (approved 2/3/21), and the need for informed consent was waived given the anonymity of data and noninterventional study design. All research procedures were conducted in accordance with the ethical standards set by the UCSD IRB and the Helsinki Declaration of 1975. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were used to disseminate the results. Patients were included if they were greater than 18 years old and excluded if they had ICU stays of less than 48 hours, preexisting end-stage renal disease, or history of kidney transplant.

We extracted demographic, sex, race, and comorbidity (using *International Classification of Diseases*, 10th Revision) data from the electronic health record, EPIC. Five ICU location groups were identified. To account for multiple admissions during the study period, we used each index ICU admission. IMV cases were identified based on the oxygen device recorded as "Tracheostomy—mechanical ventilation" or "Endotracheal Tube" in the medical record at any point during their ICU index admission. Duration of IMV was counted as the sum of days over which a patient was recorded to require IMV as defined above. Ventilator and gas exchange parameters were studied using the following: median of a daily mean value of the plateau pressure in cm H_2O, respiratory system compliance in mL/cm H_2O, driving pressure in cm H_2O, and Pao_2/Fio_2 ratio defined by the Po_2 in arterial blood divided by the Fio_2 delivered.

Our main exposure of interest was AKI. Patients were identified as having AKI during their ICU stay according to the KDIGO criteria, which define AKI as an increase in serum creatinine of greater than or equal to 0.3 mg/dL within 48 hours or a 50% increase from a baseline serum creatinine (19). Baseline serum creatinine was determined by the lowest serum creatinine during the previous 7 days of the current hospital admission, and no outpatient or prior hospital admission serum creatinine values were used. AKI was further divided into three stages of severity based on the KDIGO creatinine criteria. Baseline disease severity was measured using the Sequential Organ Failure Assessment (SOFA) Score recorded at admission after accounting for the exposure (kidney failure), that is, the nonrenal

SOFA (nrSOFA). Dialysis indication and prescription were performed by the nephrology team. The choice between intermittent or continuous renal replacement therapy (CRRT) was based on hemodynamic status, use of vasopressors, and rate of fluid removal necessary to achieve target fluid balance. Intermittent dialysis was performed daily or every other day based on obligated fluid intake and ultrafiltration tolerance. Continuous venovenous hemodiafiltration with the PrismaFlex system and citrate anticoagulation are used at UCSD.

Five groups were identified based on three factors: the need for IMV, development of AKI, and the temporal relationship between the development of AKI and initiation of IMV (**Fig. 1**). Among patients who did not require IMV, those who did not develop AKI were defined as "No AKI, No IMV"; whereas those who developed AKI during their ICU index admission were defined as "AKI, No IMV." The rest of the patients required IMV at some point during their index admission. These patients were divided into three groups. Those who did not develop AKI before or during IMV were defined as "No AKI before/during IMV." Patients who developed AKI before IMV was initiated and continued to have a serum creatinine level that met their respective KDIGO criteria for AKI after the initiation of IMV were grouped into "AKI before & during IMV." Those who developed AKI after the initiation of IMV were grouped "AKI during IMV."

The primary outcomes were ICU survival measured by patient survival status at the end of the index ICU stay, duration of IMV, and ICU and hospital lengths of stay defined as the number of days in the ICU and the hospital, respectively, from the day of admission to the recorded day of discharge or death. Analyses of duration of IMV and ICU and hospital lengths of stay were limited to the survivors to account for shorter durations that may be due to deaths. Secondary outcomes were plateau pressures, respiratory system compliance, driving pressures, and Pao_2/Fio_2 ratio. Cumulative fluid balance (CFB) over the ICU index admission was used to study the impact of volume overload on respiratory system mechanics and gas exchange during IMV. Here, CFB was defined as the difference between all documented intakes and all documented outputs for the entire hospital stay starting on the day of admission and calculated up to each hospital day. In order to understand if there was a relationship between volume status and plateau pressures, respiratory system compliance, driving pressures, and Pao_2/Fio_2 ratio during IMV, the mean value for CFB from hospital admission up to each day during IMV was calculated. For the "AKI before & during IMV" and "AKI during IMV" groups, we limited CFB and respiratory system mechanics and gas exchange comparisons to days in which patients had AKI while being treated with IMV. Differences in severity of AKI and need for continuous or intermittent renal replacement therapy were also evaluated.

Descriptive continuous variables and categorical variables within the four study groups were compared using Wilcoxon rank-sum test for medians and χ^2 test for proportions, respectively. Differences between independent proportions were compared using *Z*-test for independent proportions. The primary outcome of ICU mortality was assessed using Cox proportional hazard regression. Mortality was adjusted for age, sex, nrSOFA score, ICU location, and comorbidities (chronic kidney disease, lung disease, acute coronary dysfunction, congestive heart failure, diabetes

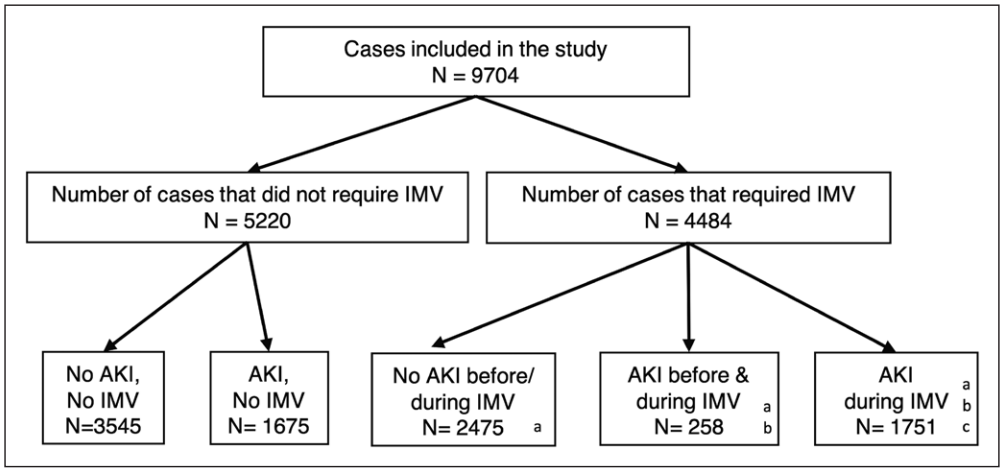


Figure 1. Flowchart of the study. [a]Significant difference ($p < 0.05$) when compared with "acute kidney injury (AKI), no invasive mechanical ventilation (IMV)." [b]Significant difference ($p < 0.05$) when compared with "No AKI before/during IMV." [c]Significant difference ($p < 0.05$) when compared with "AKI before & during IMV." *n* = number of cases.

mellitus, hypertension, and cerebral vascular accident). Both hazard ratios for study groups for each predictor and the overall model are presented. Subanalyses of mortality were carried out by ICU location adjusting for the above covariates. Neurology/neurosurgery and Burns and Plastic Surgery ICUs were omitted from this analysis because mortality in these subgroups did not exceed 10%. Kolmogorov-Smirnov goodness of fit and Shapiro-Wilk tests were used to test for normality. A two-tailed *p* value of 0.05 before the Bonferroni test for multiple comparisons was considered statically significant for all the above tests. All statistical analyses were carried out using IBM SPSS Statistics for Macintosh (Version 26, IBM, Armonk, NY).

RESULTS

We identified 9,704 patients that met our inclusion criteria, and 4,484 (46%) of these patients required IMV (Fig. 1). Of the patients treated with IMV, 1,751 (39%) developed AKI after initiating IMV, and the incidence of AKI in this group was significantly greater than those never treated with IMV (39% vs 32%; $p < 0.05$). Finally, there were additional 258 patients who already had AKI at the time IMV was initiated. Thus, we found a total of 2,009 patients (45%) in our cohort who were treated with IMV and had AKI concomitantly.

Patient demographics and baseline characteristics are outlined in **Table 1**. The average age of the study population was 58.6 years with the "AKI before & during IMV" and "AKI during IMV groups" being of slightly younger age. The population consisted of 2,298 (38.8%) women with a small, but significant difference between the "AKI, no IMV" and the "AKI during IMV" group (43% vs 34%; $p < 0.01$). The cohort was 56.5% Caucasian, 23% Hispanic/Latino, 8.3% African American, and 7.3% Asian/Pacific Islander with no significant differences in race between the groups. Patients who had "AKI before & during IMV" were more likely to be from the medical ICU, and this group had a higher frequency of comorbidities. Nr-SOFA at admission was slightly higher in the "AKI during IMV" group compared with "No AKI before/during IMV" (7 [4–10] vs 6 [4–8]; $p < 0.01$), whereas the "AKI before & during IMV" group had an nrSOFA at admission that was significantly lower than "No AKI before/during IMV" (3 [1–6] vs 6 [4–8]; $p < 0.01$).

Survival at 30 days was significantly lower in the "AKI before & during IMV" and "AKI during IMV" groups compared with "No AKI before/during IMV" (**Fig. 2**). The ICU mortality rate was 28.7% in the "AKI before & during IMV" group and 21.5% in the "AKI during IMV" group compared with 5% in the "No AKI before/during IMV" ($p < 0.01$ for both comparisons) (**Table 2**). Thus, the combined mortality rate for patients treated with IMV who had AKI concomitantly was 22.4% compared with 5% in patients treated with IMV without AKI ($p < 0.01$). The unadjusted hazard ratios for mortality in the "AKI before & during IMV" and "AKI during IMV" groups were 1.69 (95% CI, 1.26–2.28) and 1.59 (95% CI, 1.28–1.97), respectively, compared with "No AKI before/during IMV" ($p < 0.001$) (**Supplemental Table 1**, http://links.lww.com/CCX/B20). The adjusted hazard ratios for age, sex, nrSOFA, ICU location, and comorbidities were 1.77 (1.22–2.56) and 1.55 (1.20–2.01), respectively, with the same comparison. The adjusted hazard ratio for the "AKI before & during IMV" and "AKI during IMV" groups combined was 1.58 (95% CI, 1.22–2.03; $p < 0.001$) compared with the "No AKI before/during IMV" group. Most deaths occurred in the medical ICU with 71.6% of total deaths in the "AKI before & during IMV" group and 51.4% of total deaths in the "AKI during IMV" groups occurring in the medical ICU. Risk of mortality in the "AKI before & during IMV" and "AKI during IMV" groups was also highest in the medical ICU with adjusted hazard ratios of 2.99 (1.76–5.06) and 2.26 (1.46–3.49), respectively, compared with 1.77 (0.79–4.00) and 1.44 (0.90–2.30), respectively, in the surgical ICU (Supplementary Table 1, http://links.lww.com/CCX/B20). Total days requiring IMV (4 [2–7] and 6 [3–12] vs 2 [2–3] median days; $p < 0.01$); ICU length of stay (13 [8–19] and 9 [6–17] vs 5 [3–7] median days; $p < 0.01$); and hospital length of stay (17 [12–30] and 13 [7–22] vs 6 [4–9] median days; $p < 0.01$) were significantly higher in the "AKI before & during IMV" and "AKI during IMV" groups compared with "No AKI before/during IMV" (Table 2).

IMV was associated with more severe AKI, as patients in the "AKI, no IMV" group had a significantly higher percentage of stage 1 AKI compared with the "AKI before & during IMV" and "AKI during IMV"" groups (61% vs 23%, $p < 0.01$; 61% vs 43%, $p < 0.01$, respectively) (**Supplemental Table 2**, http://links.lww.com/CCX/B20). AKI cases in the "AKI during IMV"

TABLE 1.
Patient Characteristics

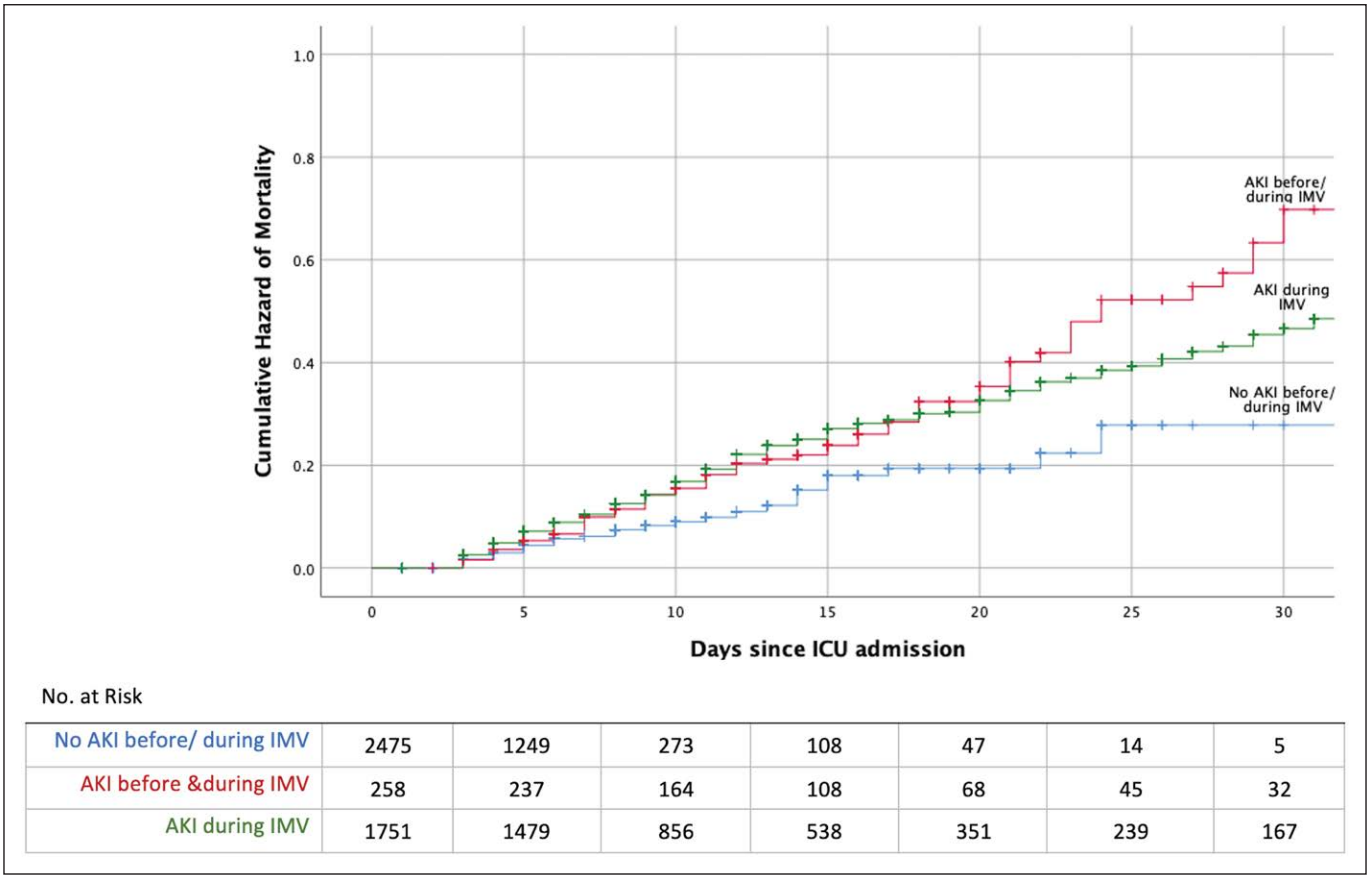
Characteristics	No AKI, No IMV ($n = 3,545$)	AKI, No IMV ($n = 1,675$)	No AKI Before/ During IMV ($n = 2,475$)	AKI Before & During IMV ($n = 258$)	AKI During IMV ($n = 1,751$)
Age					
Mean + SD	59.8 ± 18.0	59.6 ± 17.6	58.2 ± 17.0	56.7 ± 16.3	56.5 ± 16.9[a,b]
Sex, *n* (%)					
Men	2,078 (59)	960 (57)	1,578 (64)	169 (66)	1,154 (66)[a]
Women	1,467 (41)	715 (43)	897 (36)	89 (35)	597 (34)[a]
Race, *n* (%)					
Caucasian	2,003 (57)	927 (55)	1,426 (58)	142 (55)	982 (56)
Hispanic or Latino	840 (24)	390 (23)	533 (22)	63 (24)	402 (23)
African	252 (7)	157 (9)	239 (10)	17 (7)	139 (8)
Asian or Pacific Islander	274 (8)	128 (8)	148 (6)	23 (9)	131 (8)
American Indian/ Alaska Native	8 (0.2)	7 (0.5)	9 (0.4)	1 (0.4)	4 (0.2)
Multiracial	4 (0.1)	0 (0)	2 (0.1)	0 (0)	2 (0.1)
Other	164 (5)	66 (4)	118 (5)	12 (5)	91 (5)
ICU location, *n* (%)					
Surgery	1,320 (37)	499 (30)	1,438 (58)	84 (33)[b]	743 (42)[a,b,c]
Medical	1,009 (29)	768 (46)	615 (25)	117 (45)[b]	630 (36)[a,b,c]
Cardiac	447 (13)	266 (16)	170 (7)	44 (17)[b]	168 (10)[a,c]
Neuro/neurosurgical	686 (19)	106 (6)	225 (9)	6 (2)[a,b]	120 (7)[c]
Burns	83 (2)	36 (2)	27 (1)	7 (3)	90 (5)[b]
Comorbidities, *n* (%)					
Chronic kidney disease	55 (2)	36 (2)	41 (2)	9 (4)	38 (2)
Lung disease	112 (3)	67 (4)	95 (4)	10 (4)	58 (3)
Acute coronary dysfunction	235 (7)	104 (6)	188 (8)	20 (8)	109 (6)
Congestive heart failure	377 (11)	215 (13)	293 (12)	36 (14)	199 (11)
Diabetes mellitus	341 (10)	231 (14)	199 (8)	34 (13)[b]	164 (9)[a,c]
Hypertension	412 (12)	181 (11)	239 (10)	21 (8)	150 (9)
Cerebral vascular accident	133 (4)	30 (2)	64 (3)	3 (1)	39 (2)
Nonrenal Sequential Organ Failure Assessment score					
Median (25–75)	1 (1–3)	2 (1–4)	6 (4–8)	3 (1–6)[a,b]	7 (4–10)[a,b,c]

AKI = acute kidney injury, IMV = invasive mechanical ventilation.

[a]Significant difference ($p < 0.01$) when compared with "AKI, No IMV."

[b]Significant difference ($p < 0.01$) when compared with "No AKI before/during IMV."

[c]Significant difference ($p < 0.01$) when compared with "AKI before and during IMV."



No. at Risk

No AKI before/ during IMV	2475	1249	273	108	47	14	5
AKI before &during IMV	258	237	164	108	68	45	32
AKI during IMV	1751	1479	856	538	351	239	167

Figure 2. 30-d survival plot. Plot shows the 30-d hazard of ICU mortality in study groups adjusted for age, gender, nonrenal Sequential Organ Failure Assessment score, ICU location, and the following comorbidities: chronic kidney disease, lung disease, acute coronary dysfunction, congestive heart failure, diabetes mellitus, hypertension, and cerebral vascular accident. Log-rank test, $p < 0.001$. AKI = acute kidney injury, IMV = invasive mechanical ventilation.

group developed an average of 1.0 (95% CI, 1.0–3.0) median days after starting IMV. Total days with AKI were higher in the "AKI before & during IMV" and "AKI during IMV" groups compared with those not exposed to IMV (11 [7–19] vs 3 [2–5], $p < 0.01$; 7 [4–13] vs 3 [2–5], $p < 0.01$, respectively) (Supplementary Table 2, http://links.lww.com/CCX/B20). Sixty-one patients (23.6%) in the "AKI before & during IMV" group and 286 patients (16.3%) in the "AKI during IMV" group were treated with CRRT compared with 51 patients (3%) in the "AKI, no IMV" group ($p < 0.01$ for both comparisons) (Supplemental Table 2, http://links.lww.com/CCX/B20).

Finally, we compared the impact of AKI on respiratory system mechanics and blood oxygenation. Groups treated with IMV who had AKI ("AKI before & during IMV" and "AKI during IMV") had significant differences in respiratory system mechanics compared with "No AKI before/during IMV" regardless of CFB including: higher plateau pressures (19.2 [16.5–23.3] and 18.9 [16.0–22.0] vs 16.9 [14.5–19.3]; $p < 0.01$ in positive CFB and 19.5 [17.0–22.0] and 19.5 [17.0–23.2] vs 18.0 [16.0–21.0], $p < 0.01$ in negative CFB), lower respiratory system compliance (38.4 [28.7–49.4] and 41.6 [31.2–51.9] vs 47.8 [38.0–60.0], $p < 0.01$ in positive CFB and 36.0 [30.8–46.8] and 40.0 [31.0–51.0] vs 46.5 [37.0–56.0], $p < 0.01$ in negative CFB), and higher driving pressures (13.0 [10.5–17] and 12.8 [10.4–15.5] vs 11.0 [9.3–13.8], $p < 0.01$ in positive CFB and 13.3 [11.6–16] and 13.0 [11–15.7] vs 12.0 [10–14.3], $p < 0.01$ in negative CFB) (**Table 3**). Oxygenation, as assessed by the Pao_2/Fio_2 ratio, was significantly lower in the "AKI during IMV" group compared with "No AKI before/during IMV" (233 [172–302.8] vs 271.1 [195.0–356.8], $p < 0.01$ in positive CFB and 204.2 [159.2–278.6] vs 233.9 [166.0–316.0], $p < 0.01$ in negative CFB). The "AKI before & during IMV" had a significantly lower Pao_2/Fio_2 ratio compared with "No AKI before/during IMV" only in patients with positive CFB (217 [165.4–316.5] vs 271.1 [195.0–356.8],

TABLE 2.
Primary Outcomes

Characteristics	No AKI Before/ During IMV ($n = 2,475$)	AKI Before & During IMV ($n = 258$)	AKI During IMV ($n = 1,751$)
Total days with IMV, median (25–75)	2 (2–3)	4 (2–7)[a]	6 (3–12)[a,b]
ICU length of stay, d, median (25–75)	5 (3–7)	13 (8–19)[a]	9 (6–17)[a,b]
Hospital length of stay, d, median (25–75)	6 (4–9)	17 (12–30)[a]	13 (7–22)[a,b]
Overall mortality, *n* (%)	124 (5)	74 (28.7)[a]	377 (21.5)[a,b]
ICU mortality, *n* (% mortality)			
Surgery	43 (34.7)	12 (16.2)	93 (24.7)
Medical	39 (31.5)	53 (71.6)	204 (54.1)
Cardiac	10 (8.1)	8 (10.8)	32 (8.5)
Neurosurgery	32 (25.8)	1 (1.4)	30 (8.0)
Burns	0 (0)	0 (0)	18 (4.8)

AKI = acute kidney injury, IMV = invasive mechanical ventilation.
[a]Significant difference ($p < 0.01$) when compared with "no AKI before/during IMV."
[b]Significant difference ($p < 0.01$) when compared with "AKI before and during IMV."

$p < 0.01$) (Table 3). Subanalyses of ventilator parameters and Pao_2/Fio_2 ratio between patients with positive and negative CFB showed no relevant differences.

DISCUSSION

This retrospective cohort study found that 45% of patients who required IMV had AKI at some point concomitantly. We also show that having AKI is associated with poor ICU outcomes, including mortality, and worse respiratory system mechanics. Interestingly, significant differences in respiratory system mechanics remained present in patients with negative CFB.

Open-lung protective ventilation with low tidal volumes and permissive hypercarbic acidosis has been proven to improve mortality and increase AKI-free days in patients with acute respiratory distress syndrome (ARDS) (3). This approach remains standard for treating patients with AKI who require IMV. Our results showing worse respiratory system mechanics in patients with AKI suggest that lung protective ventilation may be more challenging in these patients. For example, higher driving pressures have been found to be the variable that best predicts mortality in patients with ARDS (20), and we found that AKI is associated with significantly higher driving pressures in addition to lower respiratory system compliance. The fact that these associations are independent of CFB indicates that there may be mechanisms involved beyond volume overload. These results also suggest that there may be limitations to a conservative fluid management strategy in patients with AKI, which has previously been shown to improve lung function and reduce the duration of mechanical ventilation in patients with ARDS (8).

Most AKI cases in our study occurred after the initiation of mechanical ventilation, and IMV was associated with more severe AKI, longer duration of AKI, and a greater need for CRRT compared with patients with AKI who did not require IMV. These results are interesting, but not surprising, as the detrimental impact of mechanical ventilation on the kidney has been recognized for decades. In 1947, Drury et al (21) first identified an association between positive pressure ventilation and a "circulatory stress" that impairs venous return, reduces cardiac output, and leads to impaired urea clearance. Other groups have identified neurohormonal mechanisms, such as sympathetic activation and antidiuretic hormone release, that may contribute to kidney injury via alterations in intrarenal blood flow and sodium reabsorption (22–25). In 2003, Imai et al (14) discovered that inflammatory mediators (i.e., Fas-ligand) released into the circulation during injurious mechanical ventilation contribute directly to kidney damage via a process termed biotrauma. Unfortunately, despite decades of research, there are still limited treatment strategies available to prevent

TABLE 3.
Ventilator Outcomes

Parameter	No AKI Before/ During IMV ($n = 2,475$)	AKI Before & During IMV ($n = 258$)	AKI During IMV ($n = 1,751$)
Plateau pressure in cm H_2O, median (25–75)			
NEG mean CFB	18.0 (16.0–21.0)	19.5 (17.0–22.0)[a]	19.5 (17.0–23.2)[a]
POS mean CFB	16.9 (14.5–19.3)	19.2 (16.5–23.3)[a]	18.9 (16.0–22.0)[a]
Respiratory system compliance, mL/cm H_2O, median (25–75)			
NEG mean CFB	46.5 (37.0–56.0)	36.0 (30.8–46.8)[a]	40.0 (31.0–51.0)[a]
POS mean CFB	47.8 (38.0–60.0)	38.4 (28.7–49.4)[a]	41.6 (31.2–51.9)[a]
Driving pressure, cm H_2O, median (25–75)			
NEG mean CFB	12.0 (10.0–14.3)	13.3 (11.6–16.0)[a]	13.0 (11.0–15.7)[a]
POS mean CFB	11.0 (9.3–13.8)	13.0 (10.5–17.0)[a]	12.8 (10.4–15.5)[a]
Pao_2/Fio_2 ratio, median (25–75)			
NEG mean CFB	233.9 (166.0–316.0)	231.7 (186.9–295.3)	204.2 (159.2–278.6)[a]
POS mean CFB	271.1 (195.0–356.8)	217.0 (165.4–316.5)[a]	233.0 (172.0–302.8)[a]

AKI = acute kidney injury, CFB = cumulative fluid balance, IMV = invasive mechanical ventilation, NEG = negative, POS = positive.
[a]Significant difference ($p < 0.01$) when compared with "no AKI before/during IMV."

ventilator induced kidney injury, and our study shows that the risk of AKI in mechanically ventilated patients remains high. The COVID-19 pandemic has highlighted this association further, as 40–70% of patients with COVID-19 who require IMV will develop AKI concomitantly, and the associated mortality rate for these patients is well over 50% (26–29).

Although we cannot prove causality in this retrospective analysis, we provide a strong rationale for investigations focused on novel strategies to prevent AKI in patients treated with IMV and to provide ventilatory support to patients with AKI who develop respiratory failure. For example, biomarkers or predictive models for AKI could be investigated as tools to determine which patients are early candidates for advanced therapies, such as extracorporeal membrane oxygenation or extracorporeal CO_2 removal, which may prevent further injury to both the lung and kidney by allowing for a reduction in driving pressures (30). Mechanistic studies focused on novel mediators of lung and kidney inflammatory crosstalk that may be modifiable should also continue to be explored.

This study does have several limitations that warrant discussion. As mentioned, this is an observational study not a randomized controlled trial; thus, the associations between IMV and AKI that we demonstrate are not proven to be causal. Second, we only have data from two hospitals in one hospital system in the United States. Therefore, local management strategies, such as early versus late CRRT, may impact outcomes in other centers throughout the world. Third, patients who developed AKI during IMV may have had a higher degree of critical illness based on higher nrSOFA scores at admission compared with the IMV group without AKI. However, nrSOFA was significantly lower in patients with AKI before and during IMV, and nrSOFA was included in the adjusted hazard ratios. Fourth, there is a higher percentage of surgical patients in the groups without AKI. These patients had better mortality and ICU outcomes overall; thus, we attempted to control for this observation by adjusting for ICU location. Fifth, we did not have robust data available on the use of noninvasive positive pressure ventilation (NIPPV). NIPPV may lead to similar hemodynamic and neurohormonal effects to IMV, yet patients treated with NIPPV would have been included in the groups designated as "no IMV" based on our methodology.

CONCLUSIONS

In conclusion, this large, retrospective cohort study found that nearly half the patients being treated with IMV had AKI, and AKI is associated with increased

duration of IMV, increased length of ICU stays, and higher ICU mortality. AKI is also associated with impaired respiratory system mechanics and gas exchange, which may contribute to these adverse outcomes during IMV. This information emphasizes the need for mechanistic studies into kidney-ventilator interactions, and novel treatment strategies focused on patients with AKI who require mechanical ventilatory support.

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