Acute kidney injury- attributable mortality in critically ill patients with sepsis (#69669)

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Acute kidney injury- attributable mortality in critically ill patients with sepsis

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Background. To assess whether acute kidney injury (AKI) is independently associated with hospital mortality in ICU patients with sepsis , and estimate the excess AKI-related mortality attributable to AKI. **Methods**. We analyzed adult patients from two distinct retrospective critically ill cohorts: (1) Medical Information Mart for Intensive Care IV (MIMIC IV; n=15,610) cohort and (2) Wenzhou (n=1,341) cohort. AKI was defined by Kidney Disease: Improving Global Outcomes (KDIGO) criteria. We applied multivariate logistic and linear regression models to assess the hospital and ICU mortality, hospital length-of-stay (LOS) , and ICU LOS. The excess attributable mortality for AKI in ICU patients with sepsis was further evaluated. **Results**. AKI occurred in 5,225 subjects in the MIMIC IV cohort (33.5%) and 494 in the Wenzhou cohort (36.8%). Each stage of AKI was an independent risk factor for hospital mortality in multivariate logistic regression after adjusting for baseline illness severity. The excess attributable mortality for AKI was 58.6% (95%CI, 46.8%–70.3%) in MIMIC IV and 44.6% (95% CI, 12.7%–76.4%) in Wenzhou. Additionally, AKI was independently associated with increased ICU mortality, hospital LOS, and ICU LOS. **Conclusion.** Acute kidney injury is an independent risk factor for hospital and ICU mortality, as well as hospital and ICU LOS in critically ill patients with sepsis. Thus, AKI is associated with excess attributable mortality.

Acute kidney injury-attributable mortality in critically ill patients with sepsis

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Abstract

Background. To assess whether acute kidney injury (AKI) is independently associated with hospital mortality in ICU patients with sepsis, and estimate the excess AKI-related mortality attributable to AKI.

Methods. We analyzed adult patients from two distinct retrospective critically ill cohorts: (1) Medical Information Mart for Intensive Care IV (MIMIC IV; n=15,610) cohort and (2) Wenzhou (n=1,341) cohort. AKI was defined by Kidney Disease: Improving Global Outcomes (KDIGO) criteria. We applied multivariate logistic and linear regression models to assess the hospital and ICU mortality, hospital length-of-stay (LOS), and ICU LOS. The excess attributable mortality for AKI in ICU patients with sepsis was further evaluated.

Results. AKI occurred in 5,225 subjects in the MIMIC IV cohort (33.5%) and 494 in the Wenzhou cohort (36.8%). Each stage of AKI was an independent risk factor for hospital mortality in multivariate logistic regression after adjusting for baseline illness severity. The excess attributable mortality for AKI was 58.6% (95%CI, 46.8%–70.3%) in MIMIC IV and 44.6% (95% CI, 12.7%–76.4%) in Wenzhou. Additionally, AKI was independently associated with increased ICU mortality, hospital LOS, and ICU LOS.

Conclusion. Acute kidney injury is an independent risk factor for hospital and ICU mortality, as well as hospital and ICU LOS in critically ill patients with sepsis. Thus, AKI is associated with excess attributable mortality.

Keywords: Acute kidney injury, Attributable mortality, Sepsis, Mortality

Introduction

Acute kidney injury (AKI) is a prevalent clinical complication among patients in Intensive Care Units (ICUs), and an independent risk factor for those in critical conditions (Barrantes et al. 2008; Nisula et al. 2013). Currently, there are no effective drugs available for AKI management (Peerapornratana et al. 2019). Studies have explored the database for critically ill patients and found that each stage of AKI is associated with high mortality (Joannidis et al. 2009; Khadzhynov et al. 2019; Li et al. 2016). Among ICU patients with liver cirrhosis, an analysis of matched population-based cohort revealed excess mortality attributable to severe AKI and mild AKI at 51% and 25%, respectively (du Cheyron et al. 2005). The excess mortality among patients with AKI, that is, the AKI-related death could be avoided without the development of AKI. Sepsis is the leading cause of AKI in critically ill patients (Peerapornratana et al. 2019). It is approximated that one-third of sepsis patients develop AKI (Murugan et al. 2010). Sepsis-associated AKI is a frequent complication in critically ill patients and contributes to high mortality (Peerapornratana et al. 2019; Poston & Koyner 2019). However, the attributable mortality for AKI in ICU patients with sepsis is unknown. Assessment of the AKI attributable mortality would guide in designing clinical trials for the prevention or treatment of AKI.

This study aims to assess whether the development of AKI is an independent risk factor for

mortality in ICU patients with sepsis and to adequately evaluate the excess mortality attributable to AKI.

Materials & Methods

Participants

Critically ill adult patients were enrolled from two distinct retrospective ICU cohorts: (1) Medical Information Mart for Intensive Care IV (MIMIC IV) cohort and (2) Wenzhou cohort study (Zhou et al. 2021). The MIMIC IV cohort was enrolled from a relational database containing comprehensive information on over 250,000 patients hospitalized between 2008 and 2019 at Beth Israel Deaconess Medical Center in Boston, MA, USA. The Wenzhou cohort included critically ill adult patients from ICUs at the Second Affiliated Hospital of Wenzhou Medical University in Wenzhou, Zhejiang, China. The MIMIC IV public database was approved by the institutional review board (IRB). Wenzhou cohort was approved by the Second Affiliated Hospital of Wenzhou Medical University IRB. Informed consent was waived due to retrospective nature of the study.

Primary outcome and additional variables

Inclusion criteria for adult patients followed the definition of sepsis-3 i.e., a known or suspected infection plus acute increase Sequential Organ Failure Assessment (SOFA) ≥ 2 points for organ dysfunction (Levy et al. 2003; Shankar-Hari et al. 2016) from the MIMIC IV and Wenzhou cohorts. We excluded patients with a history of chronic kidney disease (glomerulonephritis, diabetic nephropathy, hypertensive nephropathy, hereditary nephritis, and chronic kidney failure caused by a variety of other diseases), multiple hospitalizations, and ICU length of stay (LOS) less than 24 hours. Patients were defined as having AKI if they met the Kidney Disease: Improving Global Outcomes (KDIGO) serum creatinine diagnostic criteria for AKI (Supplementary materials)(Kellum & Lameire 2013). We defined shock as the need for vasopressor within the first 48 h of hospital admission, while respiratory failure was defined as the need for invasive mechanical ventilation.

In both cohorts, the SOFA score (Vincent et al. 1996), Acute Physiology Score (APS) III (Knaus et al. 1991), Logistic Organ Dysfunction Score (LODS)(Le Gall et al. 1996), and Oxford Acute

Severity of Illness Score (OASIS) (Johnson et al. 2013) were employed to evaluate the severity of illness. Calculations for the modified SOFA score modified APS III and modified LODS were obtained through the exclusion of points associated with renal function. The primary outcome was hospital mortality. The secondary outcomes included ICU mortality, hospital LOS and ICU LOS. According to KDIGO guidelines, we stratified the severity of AKI according to serum creatinine levels (Kellum & Lameire 2013).

Statistical methods

Wilcoxon rank-sum test, Student's t-test, and Chi-squared test were employed to compare the baseline characteristic variables. Before data analysis, the potential confounders and mediating variables between AKI and death were depicted in the directed acyclic graph (DAG) (Supplementary Fig S1)(Lederer et al. 2019). To assess primary and secondary outcomes, we applied the multivariate logistic and linear regression models. A more detailed process is described in the Supplementary materials.

Sensitivity analyses in MIMIC IV were restricted to a given subset of patients presented with pulmonary sepsis and shock and excluded those who died within the first 1 week of hospitalization. We also performed a sensitivity analysis of hospital and ICU LOS for all patients (both survivors and non-survivors). Sepsis-associated AKI was re-defined according to the urine output diagnostic criteria of KDIGO for AKI (Supplementary materials). Furthermore, sensitivity analyses of hospital and ICU mortality were conducted based on the urine output diagnostic criteria.

The attributable fraction (AF) of mortality from AKI (AF_{AKI}) and the population AF of mortality from AKI (population AF_{AKI}) were calculated as reported previously (detail for this calculation is provided in Supplementary materials)(Auriemma et al. 2020; van Vught et al. 2016). The AF_{AKI} denoted the proportion of deaths attributable to AKI in septic patients with AKI. Population AF_{AKI} denoted the proportion of all deaths in the sepsis population attributable to AKI. Estimated value was generated by indirect standardization, performed within strata (additional details for this calculation are provided in Supplementary materials). All statistical analyses were conducted in

R (version 3.6.1) used in our previous study(Weng et al. 2021; Xu et al. 2021); *p*-value < 0.05 denoted statistical significance.

Results

Baseline characteristics and outcomes

Fig 1 illustrates patient selection flow chart, whereas Table 1 outlines the baseline patient characteristics. The Wenzhou cohort tended to be older with higher vasopressor use probability compared to those of the MIMIC IV cohort. The baseline modified SOFA score, modified APS III, modified LODS and OASIS were similar between the two cohorts. The proportion of patients requiring continuous renal replacement therapy (CRRT) were similar, however, more patients acquired AKI in the Wenzhou cohort compared to the MIMIC IV cohort. We reported more cases of stage 1 AKI in the Wenzhou population compared to the MIMIC IV population. While hospital and ICU LOS were longer in the Wenzhou cohort, hospital and ICU mortalities were higher in the MIMIC IV cohort.

Table 1 shows participant characteristics stratified by KAI status. in both cohorts, patients with AKI demonstrated a greater need for mechanical ventilation, vasopressor use, CRRT, and higher illness severity scores than patients without AKI; they also were characterized by higher mortality and longer LOS.

Comparison of clinical outcomes adjusted for severity of illness

MIMIC IV

We reported overall hospital mortality of 13.5%; briefly, 2,118 of 15,610 patients died before discharge (Table 2). Compared to non-survivors, patients who survived were significantly younger, the majority were male and of the white race; they exhibited lower modified SOFA score, modified APS III, modified LODS, and OASIS. Patients who died had a higher tendency to require mechanical ventilation, vasopressors, and CRRT, and a higher probability of AKI. Nearly 66% of non-survivors developed AKI, whereas 28% of survivors developed AKI ($p < 0.001$).

The unadjusted hospital mortality of sepsis with AKI was 27%, while that for sepsis without AKI was 7% (Table 3; OR = 4.82; 95% CI 4.37, 5.31; $p < 0.001$). In constructing the adjusted model,

no other variables except the prespecified variables (illness severity score, age, gender, race, and shock) met the set criteria (variables inclusion criteria are described in Supplementary materials). In the multivariable regression model, the OR values for hospital mortality of patients with AKI were attenuated but remained statistically significant after adjustment for illness severity score (modified APS III, SOFA score, modified LODS, and OASIS), age, gender, race, and shock. In unadjusted and adjusted models, AKI was significantly associated with an increased risk of hospital mortality (Table 3). Sensitivity analyses based on the urine output diagnostic criteria of KDIGO for AKI yielded similar results (Supplementary Table S2). In other sensitivity analyses, in which we included patients with pulmonary sepsis and shock and excluded patients who died within 1 week after hospitalization, the results did not change (data not shown). Septic patients who developed AKI, experienced longer hospital and ICU LOS than patients without AKI, whether among survivors or across all patients (Supplementary Table S3 and S4).

Furthermore, we conducted stratified analyses based on the severity of AKI. And found that stages 1, 2, and 3 AKI were all independently associated with hospital and ICU mortality in adjusted and unadjusted models (Fig 2, Supplementary Table S5). In four adjusted models, stage 3 AKI exhibited the most significant association with increased risk of hospital and ICU mortality. In the MIMIC IV cohort, the AF_{AKI} was 58.6% (CI, 46.8%–70.3%), whereas the population AF_{AKI} was 30.2% (95% CI, 22.7%–37.8%).

Wenzhou

Among 1,341 patients, 155 patients died before discharge, with overall hospital mortality of 10.3% (Table 2). Compared to non-survivors, patients who survived were younger, exhibited lower modified SOFA scores, modified APS III, modified LODS, and OASIS. Besides, patients who died showed a higher tendency to require mechanical ventilation, vasopressors, and CRRT, a higher probability of AKI. Nearly 67% of non-survivors developed AKI, whereas 33% of survivors developed AKI ($p < 0.001$).

The unadjusted hospital mortality of sepsis with AKI was 21% while that for sepsis without AKI was 6% (Table 3; OR = 4.16; 95% CI 2.93, 5.98; $p < 0.001$). Similar to findings in the MIMIC IV

cohort, development of AKI in the Wenzhou population was significantly associated with increased risk of hospital and ICU mortality in multivariate logistic regression after we adjusted for illness severity score (modified APS III, SOFA score, modified LODS and OASIS), age and shock. Similarly, in the sensitivity analyses, AKI was associated with ICU mortality, when we applied the urine output diagnostic criteria of KDIGO for AKI (Supplementary Table S2).

As in the MIMIC IV cohort, patients with AKI had prolonged hospital and ICU (Supplementary Table S3 and S4). Moreover, the correlation of AKI with mortality was stratified according to the severity of AKI. In the Wenzhou cohort, stages 1, 2, and 3 AKI were independently associated with hospital and ICU mortality (Fig 2, Supplementary Table S5). In the Wenzhou cohort, the AF_{AKI} was 44.6% (95% CI, 12.7%–76.4%), whereas the population AF_{AKI} was 26.0% (95% CI, 0%–56.8%).

Discussion

We have revealed the association of AKI with mortality in two critically ill cohorts. Stages 1, 2, and 3 AKI were associated with a longer hospital and ICU LOS, as well as greater hospital and ICU mortality. It is not surprising that patients with stage 3 AKI are characterized by a worse prognosis than those with stages 1- and 2 AKI. Our results provide implicate AKI as an independent risk factor for mortality in patients with sepsis.

Lopes et al. (Lopes et al. 2010) demonstrated that AKI had a negative impact on long-term mortality of patients with sepsis. Uhel et al. (Uhel et al. 2020) reported persistent AKI is independently associated with sepsis mortality compared with transient AKI. Our study yielded similar results to previous studies. However, to our knowledge, this is the first study to explore the excess mortality attributable to AKI in septic patients with severe illness. We applied the KDIGO serum creatinine and urine output diagnostic criteria for AKI. whereas, the potential confounders and mediating variables between AKI and death were depicted in DAG. With this approach, we elucidated the relationship between variables and reduce the selection bias.

Previous reports show that increased severity of AKI is correlated with a stepwise increase in mortality among critically ill patients (Panitchote et al. 2019; Uchino et al. 2006; Uchino et al.

2005), which concurred with our findings. Elsewhere. Vaara et al. reported that stage 1 AKI was not a substantial risk factor for 90-day mortality in critically ill patients (Vaara et al. 2014). Through matched risk-adjusted mortality, Cheyron et al. found that only severe ARF was significantly associated with excess attributable mortality in ICU patients with liver cirrhosis (du Cheyron et al. 2005). Herein, we have reported different results for hospital and ICU mortality compared to the results of Vaara et al. and Cheyron et al., which may be attributed to differences in severity of the disease and that we focused on critically ill patients with sepsis. Additionally, the development of AKI had been associated with long-term risk of mortality and other adverse outcomes, including chronic kidney disease (CKD) and end-stage renal disease (ESRD)(Coca et al. 2009; Fortrie et al. 2019). AKI occurrence was mostly in association with sepsis in critically ill patients. Currently, no effective cure or effective treatment is available yet and clinical interventions are limited (Al-Jaghbeer et al. 2018; Skube et al. 2018). Therefore, the prevention of sepsis-induced AKI is critical in reducing the case fatality rate.

Of note, we estimated the AF_{AKI} and population AF_{AKI} in two cohorts and yielded similar results. The AF_{AKI} is the proportion of deaths attributable to AKI in patients with AKI, whereas the population AF_{AKI} is the proportion of all deaths in the sepsis population attributable to AKI. We found that the AF_{AKI} was 58.6% in MIMIC IV and 44.6% in Wenzhou; the population AF_{AKI} was 32% in MIMIC IV and 26.0% in Wenzhou. Few studies have assessed the attributable mortality of AKI. In one study, the attributable fraction of mortality from critically ill patients with liver cirrhosis was 25% in mild ARF and 51% in severe ARF(du Cheyron et al. 2005), whereas the 90-day mortality attributable to AKI in ICU patients was 8.6%, and population attributable mortality was nearly 20% (Vaara et al. 2014) in another study. It is imperative to apply our results to estimate the attributable mortality of other critically ill patients. The AF of mortality from sepsis was 15% compared to ICU-non-sepsis (Shankar-Hari et al. 2018). The AF of ARDS in patients with sepsis was 27% and 37% in EARLI and VALID cohorts, respectively (Auriemma et al. 2020). Notably, we found that the AF of AKI in patients with sepsis was higher than in other ICU disease states.

There are several highlights in the present study. First, we included two independent large

cohorts of critically ill adult patients hospitalized with sepsis from two countries. The similarity of the association between AKI and mortality in two cohorts strengthens the validity and generalizability of our findings. Second, we reported consistent results we adjusted for four different severity of illness scores in two cohorts. Third, in constructing the adjusted model, the DAG was applied to explore the potential confounders and mediating variables between AKI and death, and we carefully accounted for every possible confounder. Finally, the inclusion criteria for patients strictly followed the latest definitions of sepsis and AKI.

Despite these strengths, this study had some drawbacks. First, being a retrospective cohort study, the residual confounders may remain despite having adjusted for many potential confounders. We hypothesize the acute organ failures were mediators between AKI and death as depicted in the DAG, and not included in the models. However, if the failure of organs such as lung, hepatic, or heart play a predominant role in the association between AKI and mortality, or the organ failures were confounders, our results may not evaluate the precise correlation of AKI with mortality. Second, we enrolled critically ill patients from ICUs, as such, our findings may not apply to the general patients. Finally, because we focused on sepsis, a common cause of AKI, our results may not be generalizable to patients with AKI attributable to other causes.

This study provides the AF_{AKI} and population AF_{AKI} in patients with sepsis. In two retrospective cohorts of ICU patients with sepsis, all stage AKI were independently associated with hospital and ICU mortality, and longer hospital and ICU LOS. Our findings would guide the evaluation of the plausible effect size for future clinical trials regarding the prevention or treatment of AKI.

Conclusions

In two retrospective cohorts of critically ill patients with sepsis, all stage AKI conferred increased risk for hospital mortality, independent of overall severity of illness. Development of AKI was also associated with ICU mortality, hospital and ICU LOS.

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Database.

Ethical Statement

The study was based on existing dataset and was approved by the Ethics Committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. The study was conducted in accordance of the Helsinki Declaration.

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Figure legend

Fig 1 Study flowcharts for the MIMICIV and Wenzhou cohorts

Fig 2 Odds ratios with 95% confidence intervals for in-hospital mortality stratified by severity of AKI. In addition to severity of illness variables listed in the Figure, adjusted models for MIMIC IV include age, gender, race, and shock. Adjusted models for Wenzhou include age, and shock

Figure 1

Fig 1

Study flowcharts for the MIMICIV and Wenzhou cohorts

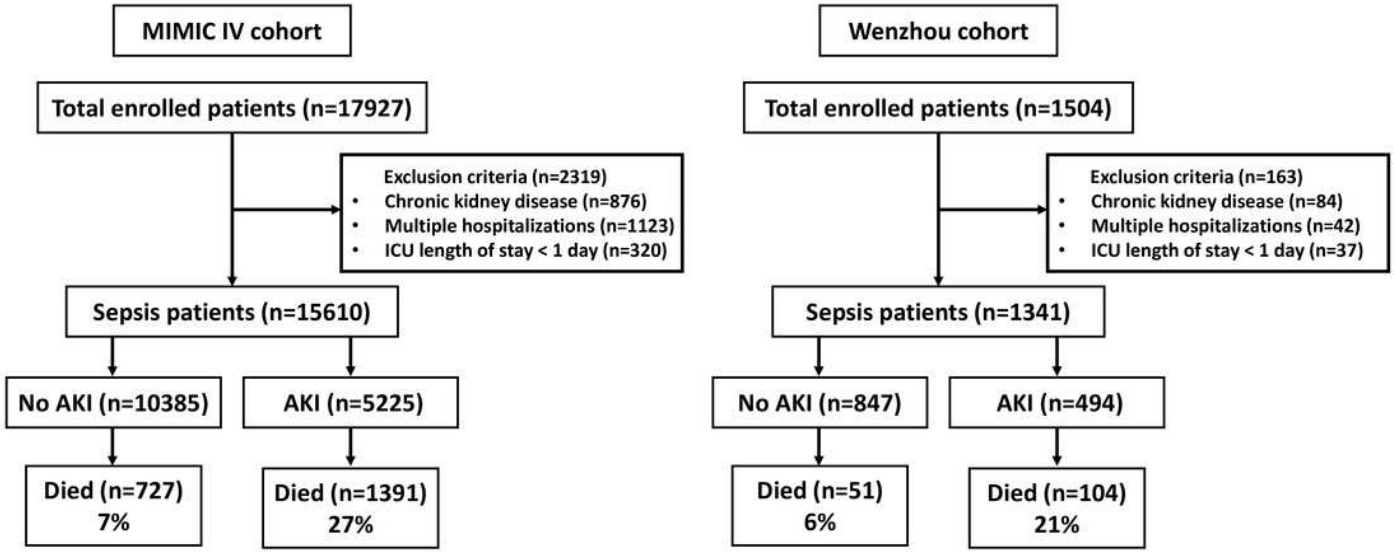

Figure 2

Fig 2

Odds ratios with 95% confidence intervals for in-hospital mortality stratified by severity of AKI. In addition to severity of illness variables listed in the Figure, adjusted models for MIMIC IV include age, gender, race, and shock. Adjusted models for Wenzhou include age, and shock

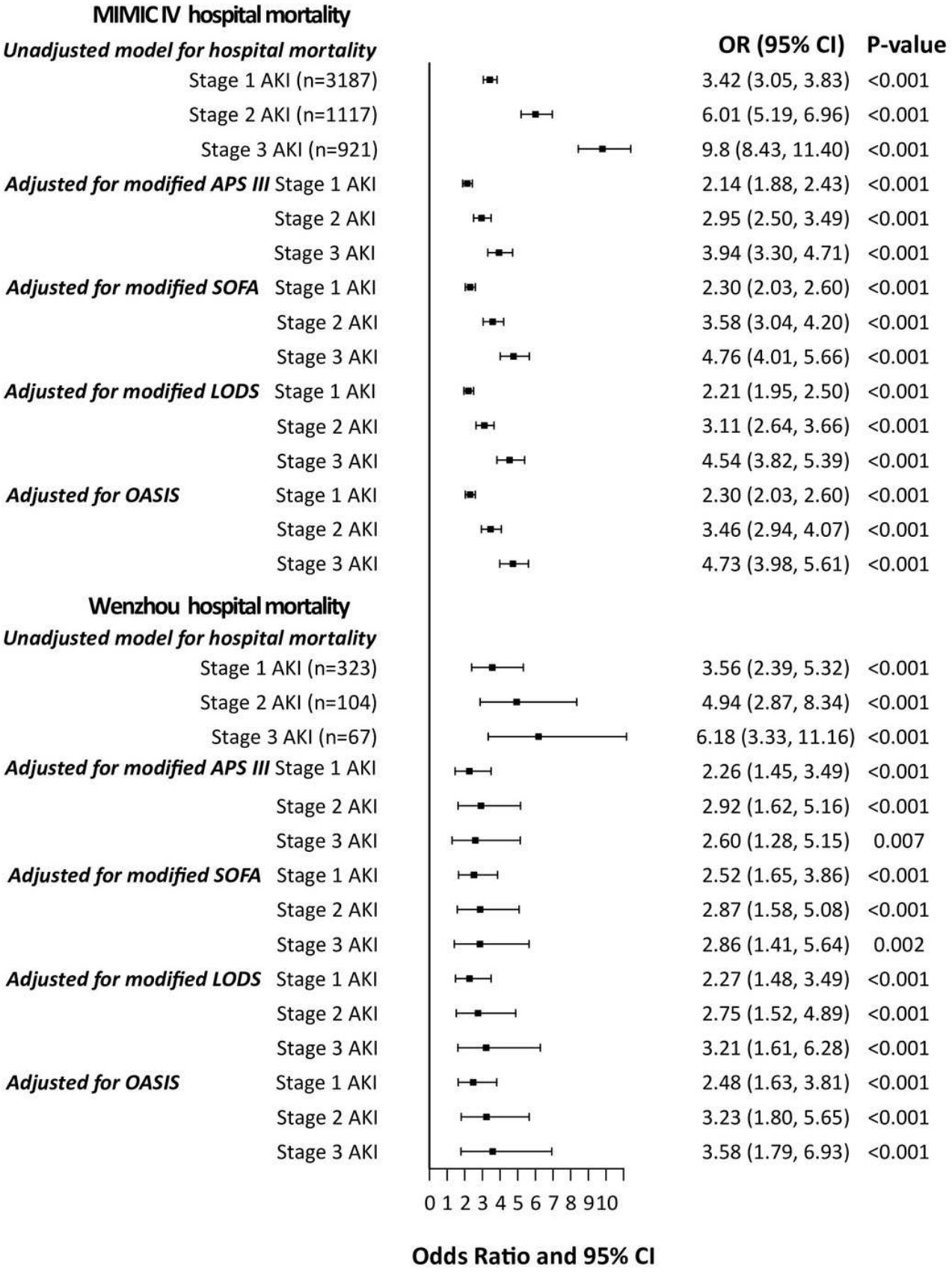
MIMIC IV hospital mortality
Unadjusted model for hospital mortality
OR (95% CI)
P-value
Stage 1 AKI (n=3187)
3.42 (3.05, 3.83)
<0.001
Stage 2 AKI (n=1117)
6.01 (5.19, 6.96)
<0.001
Stage 3 AKI (n=921)
9.8 (8.43, 11.40)
<0.001
Adjusted for modified APS III Stage 1 AKI
2.14 (1.88, 2.43)
<0.001
Stage 2 AKI
2.95 (2.50, 3.49)
<0.001
Stage 3 AKI
3.94 (3.30, 4.71)
<0.001
Adjusted for modified SOFA Stage 1 AKI
2.30 (2.03, 2.60)
<0.001
Stage 2 AKI
3.58 (3.04, 4.20)
<0.001
Stage 3 AKI
4.76 (4.01, 5.66)
<0.001
Adjusted for modified LODS Stage 1 AKI
2.21 (1.95, 2.50)
<0.001
Stage 2 AKI
3.11 (2.64, 3.66)
<0.001
Stage 3 AKI
4.54 (3.82, 5.39)
<0.001
Adjusted for OASIS Stage 1 AKI
2.30 (2.03, 2.60)
<0.001
Stage 2 AKI
3.46 (2.94, 4.07)
<0.001
Stage 3 AKI
4.73 (3.98, 5.61)
<0.001
Wenzhou hospital mortality
Unadjusted model for hospital mortality
Stage 1 AKI (n=323)
3.56 (2.39, 5.32)
<0.001
Stage 2 AKI (n=104)
4.94 (2.87, 8.34)
<0.001
Stage 3 AKI (n=67)
6.18 (3.33, 11.16)
<0.001
Adjusted for modified APS III Stage 1 AKI
2.26 (1.45, 3.49)
<0.001
Stage 2 AKI
2.92 (1.62, 5.16)
<0.001
Stage 3 AKI
2.60 (1.28, 5.15)
0.007
Adjusted for modified SOFA Stage 1 AKI
2.52 (1.65, 3.86)
<0.001
Stage 2 AKI
2.87 (1.58, 5.08)
<0.001
Stage 3 AKI
2.86 (1.41, 5.64)
0.002
Adjusted for modified LODS Stage 1 AKI
2.27 (1.48, 3.49)
<0.001
Stage 2 AKI
2.75 (1.52, 4.89)
<0.001
Stage 3 AKI
3.21 (1.61, 6.28)
<0.001
Adjusted for OASIS Stage 1 AKI
2.48 (1.63, 3.81)
<0.001
Stage 2 AKI
3.23 (1.80, 5.65)
<0.001
Stage 3 AKI
3.58 (1.79, 6.93)
<0.001
0 1 2 3 4 5 6 7 8 9 10
Odds Ratio and 95% CI

Table 1(on next page)

all

Table 1 Baseline characteristics ofMIMIC IV andWenzhou cohorts, together andstratified byAKI

Table 2 Patient characteristics stratified by in-hospital mortality, MIMIC IV and Wenzhou cohorts

Table 3 Association of AKI with mortality in unadjusted and adjusted models, MIMIC IV and Wenzhou cohorts

Table 1 Baseline characteristics of MIMIC IV and Wenzhou cohorts, together and stratified by AKI

Clinical variable*	All patients (n=16951)		MIMIC IV (n=15610)			Wenzhou (n=1341)		
	MIMIC IV (n = 15610)	Wenzhou (n = 1341)	No AKI (n=10385)	AKI (n=5225)	P value	No AKI (n = 847)	AKI (n = 494)	P value
Age, years	64±17	69±10	63±17	64±16	0.27	70 (63, 76)	70 (62, 75)	0.617
Male gender, %	8889 (57)	778 (58)	5863 (56)	3026 (58)	0.086	489 (58)	289 (59)	0.828
White race, %	10537 (68)	-	7143 (69)	3394 (65)	< 0.001	-	-	-
APS III	46 (33, 66)	45 (33, 65)	40 (31, 54)	63 (44, 87)	< 0.001	40 (31, 53)	60 (42, 81)	< 0.001
Modified APS III†	36 (27, 53)	35 (27, 51)	33 (25, 44)	49 (33, 71)	< 0.001	32 (25, 43)	44.5 (32, 66)	< 0.001
SOFA score	5 (4, 8)	5 (4, 8)	5 (3, 7)	8 (5, 11)	< 0.001	4 (3, 6)	7 (5, 11)	< 0.001
Modified SOFA score†	5 (3, 7)	5 (3, 7)	4 (3, 6)	7 (4, 10)	< 0.001	4 (3, 6)	6 (4, 9)	< 0.001
LODS	5 (3, 7)	5 (3, 7)	4 (2, 6)	7 (5, 10)	< 0.001	4 (2, 6)	7 (4, 9)	< 0.001
Modified LODS†	3 (1, 5)	3 (1, 5)	2 (1, 4)	5 (2, 7)	< 0.001	2 (1, 4)	4 (2, 6.75)	< 0.001
OASIS	34 (28, 40)	34 (28, 40)	32 (26, 37)	38 (32, 45)	< 0.001	32 (27, 38)	38 (31, 45)	< 0.001
Vasopressor use in first 48 h, %	7529 (48)	708(53)	4262 (41)	3267 (63)	< 0.001	387 (46)	321 (65)	< 0.001
Mechanical ventilation, %	11334 (73)	986 (74)	6840 (66)	4494 (86)	< 0.001	561 (66)	425 (86)	< 0.001
CRRT, %	561 (4)	45 (3)	26 (0)	535 (10)	< 0.001	1 (0)	44 (9)	< 0.001
AKI, %	5225 (33)	494 (37)	-	-	-	-	-	-
Stage 1 AKI, %	3187 (20)	323 (24)	-	-	-	-	-	-
Stage 2 AKI, %	1117 (7)	104 (8)	-	-	-	-	-	-
Stage 3 AKI, %	921 (6)	67 (5)	-	-	-	-	-	-
Hospital LOS	8 (5, 13)	9 (6, 14)	7 (4,	11 (6,	<	8 (6, 12)	12 (7, 19)	<

			11)	20)	0.001			0.001
Hospital LOS‡	8 (5, 13)	8 (5, 13)	7 (4, 11)	12 (7, 22)	< 0.001	8 (6, 12)	12 (7, 20)	< 0.001
ICU LOS	2 (1, 5)	4 (2, 6)	2 (1, 3)	5 (2, 9)	< 0.001	3 (2, 5)	5 (3, 10)	< 0.001
ICU LOS‡	2 (1, 5)	3 (1, 5)	2 (1, 3)	5 (2, 10)	< 0.001	3 (2, 5)	5 (3, 10)	< 0.001
Hospital mortality, %	2118 (14)	155 (12)	727 (7)	1391 (27)	< 0.001	51 (6)	104 (21)	< 0.001
ICU mortality, %	1478 (9)	111 (8)	413 (4)	1065 (20)	< 0.001	26 (3)	85 (17)	< 0.001

APS: Acute Physiology Score, SOFA: Sequential Organ Failure Assessment, LODS: Logistic Organ Dysfunction Score, OASIS: Oxford Acute Severity of Illness Score, CRRT: Continuous Renal Replacement Therapy, AKI: Acute Kidney Injury, LOS: length of stay

*Data shown as mean ± standard deviation, median (interquartile range) or number (percent) as appropriate

† Modified scores exclude points related to renal function

‡ Restricted to survivor

Table 2 Patient characteristics stratified by in‐hospital mortality, MIMIC IV and Wenzhou cohorts

Clinical variable*	Survived (n = 13492)	Died (n = 2118)	p value
MIMIC IV patient characteristics			
Age, years	64 (53, 76.25)	68 (57, 81)	< 0.001
Male gender, %	7772 (58)	1117 (53)	< 0.001
White race, %	9295 (69)	1242 (59)	< 0.001
APS III	43 (32, 59)	81 (60, 103)	< 0.001
Modified APS III†	34 (26, 48)	64 (46, 83)	< 0.001
SOFA score	5 (3, 7)	9 (6, 13)	< 0.001
Modified SOFA score†	4 (3, 7)	8 (5, 11)	< 0.001
LODS	4 (3, 6)	9 (6, 12)	< 0.001
Modified LODS†	2 (1, 4)	6 (4, 8)	< 0.001
OASIS	32 (27, 38)	43 (36, 49)	< 0.001
Vasopressor use in first 48 h, %	6179 (46)	1350 (64)	< 0.001
Mechanical ventilation, %	9483 (70)	1851 (87)	< 0.001
CRRT, %	235 (2)	326 (15)	< 0.001
AKI, %	3834 (28)	1391 (66)	< 0.001
Hospital LOS	8 (5, 13)	6 (3, 13)	< 0.001
ICU LOS	2 (1, 5)	4 (2, 8)	< 0.001
Clinical variable*	Survived (n = 1186)	Died (n = 155)	p value
Wenzhou patient characteristics			

Age, years	70 (62, 76)	72 (66, 76)	0.029
Male gender, %	692 (58)	86 (55)	0.553
APS III	43 (32, 59)	77 (55, 97.5)	< 0.001
Modified APS III†	34 (26, 48)	59 (42, 80.5)	< 0.001
SOFA score	5 (3, 7)	9 (6, 13)	< 0.001
Modified SOFA score†	5 (3, 7)	8 (5, 11)	< 0.001
LODS	4 (3, 6)	9 (6, 11)	< 0.001
Modified LODS†	2 (1, 4)	6 (4, 8)	< 0.001
OASIS	33 (27, 39)	42 (34.5, 47.5)	< 0.001
Vasopressor use in first 48 h, %	611 (52)	97 (63)	0.012
Mechanical ventilation, %	856 (72)	130 (84)	0.003
CRRT, %	27 (2)	18 (12)	< 0.001
AKI, %	390 (33)	104 (67)	< 0.001
Hospital LOS	9 (6, 14)	8 (4.5, 15.5)	0.074
ICU LOS	4 (2, 6)	5 (3, 8.5)	< 0.001

*Data shown as mean ± standard deviation, median (interquartile range) or number (percent) as appropriate

† Modified APACHE scores exclude points related to renal function

Table 3 Association of AKI with mortality in unadjusted and adjusted models, MIMIC IV and Wenzhou cohorts

MIMIC IV logistic regression models (n = 15610)	OR (95% CI)	p value
Unadjusted model of AKI for in-hospital mortality	4.82 (4.37, 5.31)	<0.001
Adjusted for modified APS III*	2.57 (2.30, 2.87)	<0.001
Adjusted for modified SOFA score*	2.89 (2.59, 3.21)	<0.001
Adjusted for modified LODS*	2.72 (2.44, 3.03)	<0.001
Adjusted for OASIS	2.88 (2.58, 3.20)	<0.001
Unadjusted model of AKI for ICU mortality	6.18 (5.49, 6.97)	<0.001
Adjusted for modified APS III†	2.86 (2.51, 3.27)	<0.001
Adjusted for modified SOFA score†	3.30 (2.90, 3.76)	<0.001
Adjusted for modified LODS†	2.98 (2.61, 3.30)	<0.001
Adjusted for OASIS	3.15 (2.77, 3.59)	<0.001
Wenzhou logistic regression models (n = 1341)	**OR (95% CI)**	**p value**
Unadjusted model of AKI for in-hospital mortality	4.16 (2.93, 5.98)	<0.001
Adjusted for modified APS III*	2.44 (1.65, 3.64)	<0.001
Adjusted for modified SOFA score*	2.64 (1.79, 3.91)	<0.001
Adjusted for modified LODS*	2.48 (1.68, 3.68)	<0.001
Adjusted for OASIS	2.75 (1.88, 4.07)	<0.001
Unadjusted model of AKI for ICU mortality	6.56 (4.22, 10.53)	<0.001
Adjusted for modified APS III†	3.45 (2.12, 5.75)	<0.001

Adjusted for modified SOFA score†	3.85 (2.39, 6.37)	<0.001
Adjusted for modified LODS†	3.38 (2.09, 5.62)	<0.001
Adjusted for OASIS	3.96 (2.46, 6.53)	<0.001

Modified scores exclude points related to renal function

*In addition to severity of illness variable listed in the table, adjusted models include age, gender, race, and shock

† In addition to severity of illness variable listed in the table, adjusted models include age, and shock