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

Zhiyi Wang[1,2,*], Jie Weng[1,*], Jinwen Yang[3], Xiaoming Zhou[1], Zhe Xu[4], Ruonan Hou[1], Zhiliang Zhou[1], Liang Wang[5], Chan Chen[3] and Shengwei Jin[6]

[1] Department of General Practice, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, China

[2] Center for Health Assessment, Wenzhou Medical University, Wenzhou, Zhejiang, China

[3] Department of Geriatric Medicine, The First Affiliated Hospital, Wenzhou Medical University, Wenzhou, China

[4] Department of Emergency Intensive Care Unit, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, China

[5] Department of Public Health, Robbins College of health and Human Sciences, Baylor University, Waco, TX, United States of America

[6] Department of Anesthesia and Critical Care, the Second Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

[*] These authors contributed equally to this work.

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.

Subjects Emergency and Critical Care, Infectious Diseases, Nephrology

Keywords Acute kidney injury, Attributable mortality, Sepsis, Mortality

Submitted 11 January 2022
Accepted 7 March 2022
Published 25 March 2022

Corresponding author
Shengwei Jin, jinshengwei69@163.com

Academic editor
Cristina Capusa

Additional Information and Declarations can be found on page 12

DOI **10.7717/peerj.13184**

How to cite this article Wang Z, Weng J, Yang J, Zhou X, Xu Z, Hou R, Zhou Z, Wang L, Chen C, Jin S. 2022. Acute kidney injury-attributable mortality in critically ill patients with sepsis. *PeerJ* **10**:e13184 http://doi.org/10.7717/peerj.13184

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, Zou & Xu, 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*). 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*). *Kellum et al. (2016)* reported that sixty-day hospital mortality was 6.2% for septic Shock patients without AKI, 16.8% for those with stage 1, and 27.7% for stages 2–3. Currently, all available literature only reports sepsis-related AKI mortality (*Chang et al., 2015*; *Uhel et al., 2020*). 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.

Patients

Inclusion criteria for adult patients followed the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) *i.e.,* a known or suspected infection plus acute increase Sequential Organ Failure Assessment (SOFA) $\geq$ 2 points for organ dysfunction (*Shankar-Hari et al., 2016*; *Singer 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 (only the first hospitalization was considered), and ICU length of stay (LOS) less than 24 h. 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, Kramer & Clifford, 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 shock and respiratory failure variables were both collected. 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.

Outcomes

AKI is the primary outcome. Patients were defined as having AKI if they met the Kidney Disease: Improving Global Outcomes (KDIGO) serum creatinine diagnostic criteria for AKI (Supplemental Information) (*Kellum et al., 2012*). The presence of AKI and its severity were defined according to KDIGO criteria. The secondary outcomes included hospital and ICU mortality, hospital LOS and ICU LOS.

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) (Fig. 1) (*Lederer et al., 2019*). Potential confounders are variables related to both the exposure and outcome of interest, and therefore should be controlled for in analyses. Variables that may be on the indirect causal path between the exposure and outcome partially mediate the association between exposure and outcome. It would be incorrect to control for these factors, as that would partially close the causal path, attenuating the observed association between the exposure and outcome (*Lederer et al., 2019*).

Guided by the conceptual model illustrated in the DAG, multivariate logistic, and linear binomial regression models were developed for primary and secondary outcomes. Specifically, we assessed each of the variables identified on the DAG and listed in Table 1 for inclusion in the final multivariable model along with several pre-specified variables considered clinically significant pre-hoc. Pre-specified variables included illness severity score (modified APS III, SOFA score, modified LODS and OASIS), age, gender, race, and shock. Chronic co-morbidity variables for the final model were selected after assessing how each potential confounder affected the overall odds ratio (OR) when added to a multivariable model with the pre-specified variables. In generating final models, we retained only variables that altered the OR by greater than 10%, so as to avoid over-fitting.

We 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 (sensitivity analysis with urine output criteria, considered only urine output criteria, not the worse between serum creatinine and urine

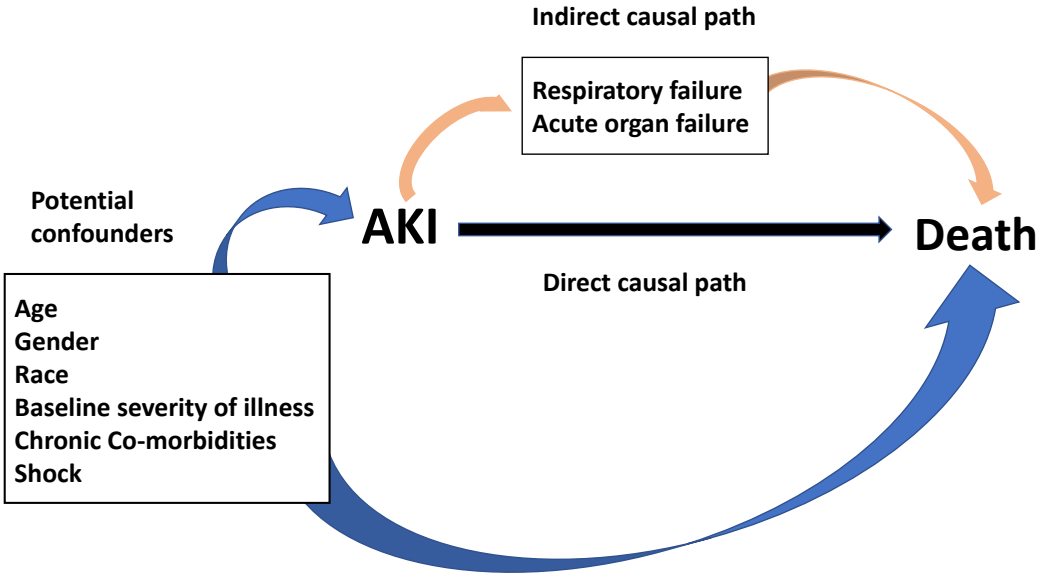

Figure 1 **Direct acyclic graph for the relationship between AKI and death.**
Full-size DOI: 10.7717/peerj.13184/fig-1

Table 1 **Variables screened for inclusion into models of attributable mortality.**

Pre-specified variables for inclusion in Models
Age
Baseline severity of illness (modified APS III, modified SOFA, modified LODS, OASIS)
Demographics
Gender
Race*
Chronic Co-morbidities
Heart disease (myocardial infarct, congestive heart failure)
Liver disease
Chronic pulmonary disease
Rheumatic disease
Diabetes
Cancer (metastatic cancer, non-metastatic cancer)
AIDS
Cerebrovascular disease
Acute Co-morbidities
Shock (use of vasopressors)
Respiratory failure (receive mechanical ventilation)

Notes.
*Variables only considered within MIMIC IV cohort, not present within Wenzhou cohort.

output criteria) (Supplemental Information). 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 (A F_{AKI}) and the population AF of mortality from AKI (population A F_{AKI}) were calculated as reported previously

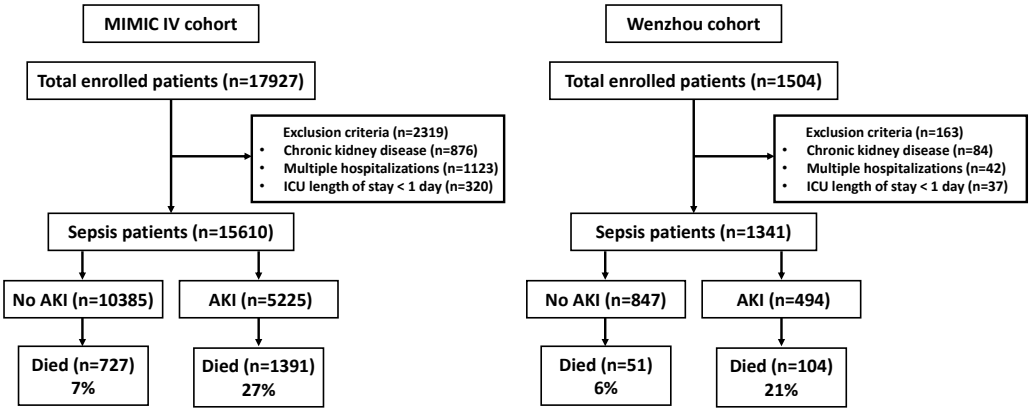

Figure 2 **Study flowcharts for the MIMIC IV and Wenzhou cohorts.**
Full-size DOI: 10.7717/peerj.13184/fig-2

(detail for this calculation is provided in Supplemental Information) (*Auriemma et al., 2020*; *Van Vught et al., 2016*). The A F_{AKI} denoted the proportion of deaths attributable to AKI in septic patients with AKI. Population A F_{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 Supplemental Information). 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

Figure 2 illustrates patient selection flow chart, whereas Table 2 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 2 shows participant characteristics stratified by AKI 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.

Table 2 Baseline characteristics of MIMIC IV and Wenzhou cohorts, together and stratified by AKI.

Clinical variable*	All patients ($n = 16,951$)			MIMIC IV ($n = 15,610$)			Wenzhou ($n = 1,341$)		
	MIMIC IV ($n = 15,610$)	Wenzhou ($n = 1,341$)	*P* value	No AKI ($n = 10,385$)	AKI ($n = 5,225$)	*P* value	No AKI ($n = 847$)	AKI ($n = 494$)	*P* value
Age, years	64 ± 17	69 ± 10	<0.001	63 ± 17	64 ± 16	0.27	70 (63, 76)	70 (62, 75)	0.617
Male gender, %	8,889 (57)	778 (58)	0.464	5,863 (56)	3,026 (58)	0.086	489 (58)	289 (59)	0.828
White race, %	10,537 (68)	–	–	7,143 (69)	3,394 (65)	<0.001	–	–	–
APS III	46 (33, 66)	45 (33, 65)	0.447	40 (31, 54)	63 (44, 87)	<0.001	40 (31, 53)	60 (42, 81)	<0.001
Modified APS III[a]	36 (27, 53)	35 (27, 51)	0.151	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)	0.605	5 (3, 7)	8 (5, 11)	<0.001	4 (3, 6)	7 (5, 11)	<0.001
Modified SOFA score[a]	5 (3, 7)	5 (3, 7)	0.57	4 (3, 6)	7 (4, 10)	<0.001	4 (3, 6)	6 (4, 9)	<0.001
LODS	5 (3, 7)	5 (3, 7)	0.901	4 (2, 6)	7 (5, 10)	<0.001	4 (2, 6)	7 (4, 9)	<0.001
Modified LODS[a]	3 (1, 5)	3 (1, 5)	0.732	2 (1, 4)	5 (2, 7)	<0.001	2 (1, 4)	4 (2, 6.75)	<0.001
OASIS	34 (28, 40)	34 (28, 40)	0.827	32 (26, 37)	38 (32, 45)	<0.001	32 (27, 38)	38 (31, 45)	<0.001
Vasopressor use in first 48 h, %	7,529 (48)	708(53)	0.001	4,262 (41)	3,267 (63)	<0.001	387 (46)	321 (65)	<0.001
Mechanical ventilation, %	11,334 (73)	986 (74)	0.488	6,840 (66)	4,494 (86)	<0.001	561 (66)	425 (86)	<0.001
CRRT, %	561 (4)	45 (3)	0.708	26 (0)	535 (10)	<0.001	1 (0)	44 (9)	<0.001
AKI, %	5,225 (33)	494 (37)	0.013	–	–	–	–	–	–
Stage 1 AKI, %	3,187 (20)	323 (24)		–	–	–	–	–	–
Stage 2 AKI, %	1,117 (7)	104 (8)		–	–	–	–	–	–
Stage 3 AKI, %	921 (6)	67 (5)		–	–	–	–	–	–
Hospital LOS	8 (5, 13)	9 (6, 14)	<0.001	7 (4, 11)	11 (6, 20)	<0.001	8 (6, 12)	12 (7, 19)	<0.001
Hospital LOS[b]	8 (5, 13)	9 (6, 14)	<0.001	7 (4, 11)	12 (7, 22)	<0.001	8 (6, 12)	12 (7, 20)	<0.001
ICU LOS	2 (1, 5)	4 (2, 6)	<0.001	2 (1, 3)	5 (2, 9)	<0.001	3 (2, 5)	5 (3, 10)	<0.001
ICU LOS[b]	2 (1, 5)	4 (2, 6)	<0.001	2 (1, 3)	5 (2, 10)	<0.001	3 (2, 5)	5 (3, 10)	<0.001
Hospital mortality, %	2,118 (14)	155 (12)	0.042	727 (7)	1,391 (27)	<0.001	51 (6)	104 (21)	<0.001
ICU mortality, %	1,478 (9)	111 (8)	0.165	413 (4)	1,065 (20)	<0.001	26 (3)	85 (17)	<0.001

Notes.

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.

[a]Modified scores exclude points related to renal function.

[b]Restricted to survivor.

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 3). Nearly 66% of non-survivors developed AKI, whereas 28% of survivors developed AKI ($p < 0.001$). More patient characteristics were shown in Table 3.

Table 3 Patient characteristics stratified by in-hospital mortality, MIMIC IV and Wenzhou cohorts.

Clinical variable*	Survived ($n = 13,492$)	Died ($n = 2,118$)	p value
MIMIC IV patient characteristics			
Age, years	64 (53, 76.25)	68 (57, 81)	<0.001
Male gender, %	7,772 (58)	1,117 (53)	<0.001
White race, %	9,295 (69)	1,242 (59)	<0.001
APS III	43 (32, 59)	81 (60, 103)	<0.001
Modified APS III[a]	34 (26, 48)	64 (46, 83)	<0.001
SOFA score	5 (3, 7)	9 (6, 13)	<0.001
Modified SOFA score[a]	4 (3, 7)	8 (5, 11)	<0.001
LODS	4 (3, 6)	9 (6, 12)	<0.001
Modified LODS[a]	2 (1, 4)	6 (4, 8)	<0.001
OASIS	32 (27, 38)	43 (36, 49)	<0.001
Vasopressor use in first 48 h, %	6,179 (46)	1,350 (64)	<0.001
Mechanical ventilation, %	9,483 (70)	1,851 (87)	<0.001
CRRT, %	235 (2)	326 (15)	<0.001
AKI, %	3,834 (28)	1,391 (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[a]	34 (26, 48)	59 (42, 80.5)	<0.001
SOFA score	5 (3, 7)	9 (6, 13)	<0.001
Modified SOFA score[a]	5 (3, 7)	8 (5, 11)	<0.001
LODS	4 (3, 6)	9 (6, 11)	<0.001
Modified LODS[a]	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

Notes.

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

[a]Modified APACHE scores exclude points related to renal function.

The unadjusted hospital mortality of sepsis with AKI was 27%, while that for sepsis without AKI was 7% (Table 4; 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. In the multivariable regression model, the OR values for hospital mortality of patients with AKI were attenuated but

Table 4 Association of AKI with mortality in unadjusted and adjusted models, MIMIC IV and Wenzhou cohorts.

MIMIC IV logistic regression models (n = 15,610)	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[a]	2.57 (2.30, 2.87)	<0.001
Adjusted for modified SOFA score[a]	2.89 (2.59, 3.21)	<0.001
Adjusted for modified LODS[a]	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[b]	2.86 (2.51, 3.27)	<0.001
Adjusted for modified SOFA score[b]	3.30 (2.90, 3.76)	<0.001
Adjusted for modified LODS[b]	2.98 (2.61, 3.30)	<0.001
Adjusted for OASIS	3.15 (2.77, 3.59)	<0.001
Wenzhou logistic regression models (n = 1,341)	**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[a]	2.44 (1.65, 3.64)	<0.001
Adjusted for modified SOFA score[a]	2.64 (1.79, 3.91)	<0.001
Adjusted for modified LODS[a]	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[b]	3.45 (2.12, 5.75)	<0.001
Adjusted for modified SOFA score[b]	3.85 (2.39, 6.37)	<0.001
Adjusted for modified LODS[b]	3.38 (2.09, 5.62)	<0.001
Adjusted for OASIS	3.96 (2.46, 6.53)	<0.001

Notes.
Modified scores exclude points related to renal function.
[a]In addition to severity of illness variable listed in the table, adjusted models include age, gender, race, and shock.
[b]In addition to severity of illness variable listed in the table, adjusted models include age, gender and shock.

remained statistically significant after adjustment for illness severity score (modified APS III, SOFA score, modified LODS, and OASIS), age, gender, race, and shock. Sensitivity analyses based on the urine output diagnostic criteria of KDIGO for AKI yielded similar results (Table S1). Septic patients who developed AKI, experienced longer hospital and ICU LOS than patients without AKI, whether among survivors or across all patients (Tables S2 and S3).

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. 3, Table S4). 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%]).

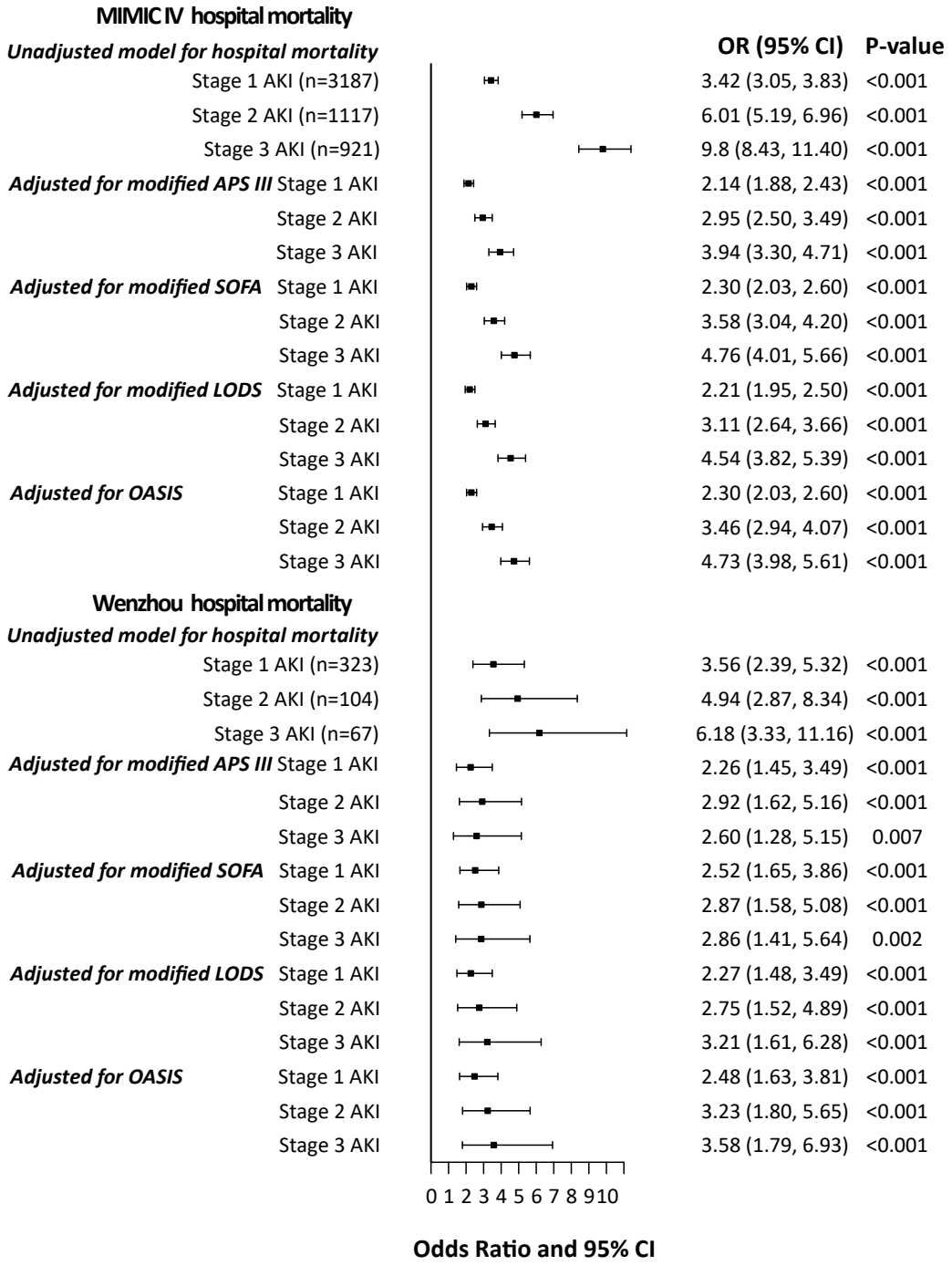

Figure 3 Odds ratios with 95% confidence intervals for in-hospital mortality stratified by severity of AKI. In addition to severity of illness variables listed in the Figure, adjusted models for MIMIC IV include age, gender, race, and shock. Adjusted models for Wenzhou include age, gender and shock.

Full-size DOI: 10.7717/peerj.13184/fig-3

Wenzhou

Among 1,341 patients, 155 patients died before discharge, with overall hospital mortality of 10.3% (Table 3). Nearly 67% of non-survivors developed AKI, whereas 33% of survivors developed AKI ($p < 0.001$). More patient characteristics were shown in Table 3.

The unadjusted hospital mortality of sepsis with AKI was 21% while that for sepsis without AKI was 6% (Table 4; 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 (Table S1).

As in the MIMIC IV cohort, patients with AKI had prolonged hospital and ICU (Tables S2 and S3). 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. 3, Table S4). In the Wenzhou cohort, the A F_{AKI} was 44.6% (95% CI [12.7%–76.4%]), whereas the population A F_{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. (2010) demonstrated that AKI had a negative impact on long-term mortality of patients with sepsis. *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 avoided including mediator variables.

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. (2014)* reported that stage 1 AKI was not a substantial risk factor for 90-day mortality in critically ill patients. Through matched risk-adjusted mortality, Cheyron et al. found that only severe AKI 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, De Geus & Betjes, 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. Few studies have assessed the attributable mortality of AKI. In one study of critically ill patients with liver cirrhosis, the AF_{AKI} from mild AKI was 25% and the AF_{AKI} from severe AKI was 51% (*Du Cheyron et al., 2005*), whereas the 90-day AFAKI in ICU patients was 8.6%, and population AFAKI 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. In ICU patients, the AF of mortality from sepsis was 15% (*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*).

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, the definition of AKI and baseline creatinine are not possible to be address for the intrinsic nature of this retrospective analysis. Third, 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.

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.

ACKNOWLEDGEMENTS

We wish to thank the intensivists, data managers, and other staff in the participating MIMIC IV Database.

ADDITIONAL INFORMATION AND DECLARATIONS

Funding

This study was supported by National Natural Science Foundation of China, No. 81772054 and 82100074. The Key R&D Program of Zhejiang Province (2019C03011), Wenzhou Major Science and Technology Innovation Project (2018ZY006), Clinical Research Fundation of the 2nd Affiliated Hospital of Wenzhou Medical University (SAHoWMU-CR2018-11-134). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Grant Disclosures

The following grant information was disclosed by the authors:
National Natural Science Foundation of China: 81772054, 82100074.
The Key R&D Program of Zhejiang Province: 2019C03011.
Wenzhou Major Science and Technology Innovation Project: 2018ZY006.
Clinical Research Fundation of the 2nd Affiliated Hospital of Wenzhou Medical University: SAHoWMU-CR2018-11-134.

Competing Interests

The authors declare there are no competing interests.

Author Contributions

- Zhiyi Wang, Jie Weng, Chan Chen and Shengwei Jin conceived and designed the experiments, analyzed the data, authored or reviewed drafts of the paper, and approved the final draft.
- Jinwen Yang, Xiaoming Zhou, Zhe Xu, Ruonan Hou, Zhiliang Zhou and Liang Wang performed the experiments, prepared figures and/or tables, and approved the final draft.

Human Ethics

The following information was supplied relating to ethical approvals (*i.e.*, approving body and any reference numbers):

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. Informed consent was waived due to retrospective nature of the study. The

study was conducted in accordance of the Helsinki Declaration. Committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University.

Data Availability

The following information was supplied regarding data availability:

The raw measurements are available in the Supplemental Files.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.13184#supplemental-information.

REFERENCES

Al-Jaghbeer M, Dealmeida D, Bilderback A, Ambrosino R, Kellum JA. 2018. Clinical decision support for in-hospital AKI. *Journal of the American Society of Nephrology* **29**:654–660 DOI 10.1681/asn.2017070765.

Auriemma CL, Zhuo H, Delucchi K, Deiss T, Liu T, Jauregui A, Ke S, Vessel K, Lippi M, Seeley E, Kangelaris KN, Gomez A, Hendrickson C, Liu KD, Matthay MA, Ware LB, Calfee CS. 2020. Acute respiratory distress syndrome-attributable mortality in critically ill patients with sepsis. *Intensive Care Medicine* **46**:1222–1231 DOI 10.1007/s00134-020-06010-9.

Barrantes F, Tian J, Vazquez R, Amoateng-Adjepong Y, Manthous CA. 2008. Acute kidney injury criteria predict outcomes of critically ill patients. *Critical Care Medicine* **36**:1397–1403 DOI 10.1097/CCM.0b013e318168fbe0.

Chang JW, Jeng MJ, Yang LY, Chen TJ, Chiang SC, Soong WJ, Wu KG, Lee YS, Wang HH, Yang CF, Tsai HL. 2015. The epidemiology and prognostic factors of mortality in critically ill children with acute kidney injury in Taiwan. *Kidney International* **87**:632–639 DOI 10.1038/ki.2014.299.

Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. 2009. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. *American Journal of Kidney Diseases* **53**:961–973 DOI 10.1053/j.ajkd.2008.11.034.

Du Cheyron D, Bouchet B, Parienti JJ, Ramakers M, Charbonneau P. 2005. The attributable mortality of acute renal failure in critically ill patients with liver cirrhosis. *Intensive Care Medicine* **31**:1693–1699 DOI 10.1007/s00134-005-2842-7.

Fortrie G, De Geus HRH, Betjes MGH. 2019. The aftermath of acute kidney injury: a narrative review of long-term mortality and renal function. *Critical Care* **23(1)**:24 DOI 10.1186/s13054-019-2314-z.

Joannidis M, Metnitz B, Bauer P, Schusterschitz N, Moreno R, Druml W, Metnitz PG. 2009. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. *Intensive Care Medicine* **35**:1692–1702 DOI 10.1007/s00134-009-1530-4.

Johnson AE, Kramer AA, Clifford GD. 2013. A new severity of illness scale using a subset of Acute Physiology And Chronic Health Evaluation data elements

shows comparable predictive accuracy. *Critical Care Medicine* **41**:1711–1718 DOI 10.1097/CCM.0b013e31828a24fe.

Kellum JA, Chawla LS, Keener C, Singbartl K, Palevsky PM, Pike FL, Yealy DM, Huang DT, Angus DC. 2016. The effects of alternative resuscitation strategies on acute kidney injury in patients with septic shock. *American Journal of Respiratory and Critical Care Medicine* **193**:281–287 DOI 10.1164/rccm.201505-0995OC.

Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, Herzog CA, Joannidis M, Kribben A, Levey AS, MacLeod AM, Mehta RL, Murray PT, Naicker S, Opal SM, Schaefer F, Schetz M, Uchino S. 2012. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney International Supplements* **2(1)**:1–138 DOI 10.1038/kisup.2012.1.

Khadzhynov D, Schmidt D, Hardt J, Rauch G, Gocke P, Eckardt KU, Schmidt-Ott KM. 2019. The incidence of acute kidney injury and associated hospital mortality. *Deutsches Ärzteblatt International* **116**:397–404 DOI 10.3238/arztebl.2019.0397.

Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A, HarrellJr FE. 1991. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* **100**:1619–1636 DOI 10.1378/chest.100.6.1619.

Le Gall JR, Klar J, Lemeshow S, Saulnier F, Alberti C, Artigas A, Teres D. 1996. The logistic organ dysfunction system. A new way to assess organ dysfunction in the intensive care unit. ICU Scoring Group. *The Journal of the American Medical Association* **276**:802–810 DOI 10.1001/jama.276.10.802.

Lederer DJ, Bell SC, Branson RD, Chalmers JD, Marshall R, Maslove DM, Ost DE, Punjabi NM, Schatz M, Smyth AR, Stewart PW, Suissa S, Adjei AA, Akdis CA, Azoulay É, Bakker J, Ballas ZK, Bardin PG, Barreiro E, Bellomo R, Bernstein JA, Brusasco V, Buchman TG, Chokroverty S, Collop NA, Crapo JD, Fitzgerald DA, Hale L, Hart N, Herth FJ, Iwashyna TJ, Jenkins G, Kolb M, Marks GB, Mazzone P, Moorman JR, Murphy TM, Noah TL, Reynolds P, Riemann D, Russell RE, Sheikh A, Sotgiu G, Swenson ER, Szczesniak R, Szymusiak R, Teboul JL, Vincent JL. 2019. Control of confounding and reporting of results in causal inference studies. Guidance for authors from editors of respiratory, sleep, and critical care journals. *Annals of the American Thoracic Society* **16**:22–28 DOI 10.1513/AnnalsATS.201808-564PS.

Li M, Zou H, Xu G. 2016. The prevention of statins against AKI and mortality following cardiac surgery: a meta-analysis. *International Journal of Cardiology* **222**:260–266 DOI 10.1016/j.ijcard.2016.07.173.

Lopes JA, Fernandes P, Jorge S, Resina C, Santos C, Pereira A, Neves J, Antunes F, Gomesda Costa A. 2010. Long-term risk of mortality after acute kidney injury in patients with sepsis: a contemporary analysis. *BMC Nephrology* **11**:9 DOI 10.1186/1471-2369-11-9.

Murugan R, Karajala-Subramanyam V, Lee M, Yende S, Kong L, Carter M, Angus DC, Kellum JA. 2010. Acute kidney injury in non-severe pneumonia is associated with

an increased immune response and lower survival. *Kidney International* **77**:527–535 DOI 10.1038/ki.2009.502.

Nisula S, Kaukonen KM, Vaara ST, Korhonen AM, Poukkanen M, Karlsson S, Haapio M, Inkinen O, Parviainen I, Suojaranta-Ylinen R, Laurila JJ, Tenhunen J, Reinikainen M, Ala-Kokko T, Ruokonen E, Kuitunen A, Pettilä V. 2013. Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. *Intensive Care Medicine* **39**:420–428 DOI 10.1007/s00134-012-2796-5.

Panitchote A, Mehkri O, Hastings A, Hanane T, Demirjian S, Torbic H, Mireles-Cabodevila E, Krishnan S, Duggal A. 2019. Factors associated with acute kidney injury in acute respiratory distress syndrome. *Annals of Intensive Care* **9**:74 DOI 10.1186/s13613-019-0552-5.

Peerapornratana S, Manrique-Caballero CL, Gómez H, Kellum JA. 2019. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. *Kidney International* **96**:1083–1099 DOI 10.1016/j.kint.2019.05.026.

Poston JT, Koyner JL. 2019. Sepsis associated acute kidney injury. *BMJ* **364**:k4891 DOI 10.1136/bmj.k4891.

Shankar-Hari M, Harrison DA, Rowan KM, Rubenfeld GD. 2018. Estimating attributable fraction of mortality from sepsis to inform clinical trials. *Journal of Critical Care* **45**:33–39 DOI 10.1016/j.jcrc.2018.01.018.

Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, Angus DC, Rubenfeld GD, Singer M. 2016. Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). *The Journal of the American Medical Association* **315**:775–787 DOI 10.1001/jama.2016.0289.

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, Van der Poll T, Vincent JL, Angus DC. 2016. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *The Journal of the American Medical Association* **315**:801–810 DOI 10.1001/jama.2016.0287.

Skube SJ, Katz SA, Chipman JG, Tignanelli CJ. 2018. Acute kidney injury and sepsis. *Surgical Infections* **19**:216–224 DOI 10.1089/sur.2017.261.

Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C. 2006. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. *Critical Care Medicine* **34**:1913–1917 DOI 10.1097/01.Ccm.0000224227.70642.4f.

Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Ronco C. 2005. Acute renal failure in critically ill patients: a multinational, multicenter study. *The Journal of the American Medical Association* **294**:813–818 DOI 10.1001/jama.294.7.813.

Uhel F, Peters-Sengers H, Falahi F, Scicluna BP, Van Vught LA, Bonten MJ, Cremer OL, Schultz MJ, Van der Poll T. 2020. Mortality and host response aberrations associated with transient and persistent acute kidney injury in critically ill patients

with sepsis: a prospective cohort study. *Intensive Care Medicine* **46**:1576–1589 DOI 10.1007/s00134-020-06119-x.

Vaara ST, Pettila V, Kaukonen KM, Bendel S, Korhonen AM, Bellomo R, Reinikainen M, Finnish Acute Kidney Injury Study G. 2014. The attributable mortality of acute kidney injury: a sequentially matched analysis*. *Critical Care Medicine* **42**:878–885 DOI 10.1097/CCM.0000000000000045.

Van Vught LA, Klein Klouwenberg PM, Spitoni C, Scicluna BP, Wiewel MA, Horn J, Schultz MJ, Nürnberg P, Bonten MJ, Cremer OL, Van der Poll T. 2016. Incidence, risk factors, and attributable mortality of secondary infections in the intensive care unit after admission for sepsis. *The Journal of the American Medical Association* **315**:1469–1479 DOI 10.1001/jama.2016.2691.

Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG. 1996. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European society of intensive care medicine. *Intensive Care Medicine* **22**:707–710 DOI 10.1007/bf01709751.

Weng J, Hou R, Zhou X, Xu Z, Zhou Z, Wang P, Wang L, Chen C, Wu J, Wang Z. 2021. Development and validation of a score to predict mortality in ICU patients with sepsis: a multicenter retrospective study. *Journal of Translational Medicine* **19**:322 DOI 10.1186/s12967-021-03005-y.

Xu J, Weng J, Yang J, Shi X, Hou R, Zhou X, Zhou Z, Wang Z, Chen C. 2021. Development and validation of a nomogram to predict the mortality risk in elderly patients with ARF. *PeerJ* **9**:e11016 DOI 10.7717/peerj.11016.

Zhou S, Zeng Z, Wei H, Sha T, An S. 2021. Early combination of albumin with crystalloids administration might be beneficial for the survival of septic patients: a retrospective analysis from MIMIC-IV database. *Annals of Intensive Care* **11**:42 DOI 10.1186/s13613-021-00830-8.