BMC Anesthesiology

RESEARCH

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Association of acetaminophen use with mortality and renal recovery in patients with sepsis-associated acute kidney injury

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Abstract

Background Sepsis-associated acute kidney injury (SA-AKI) is common and associated with poor outcomes in critically ill patients. Acetaminophen is often used as an antipyretic and analgesic drug, but the association of acetaminophen use with mortality and recovery of renal function in SA-AKI patients remain unclear. We aimed to investigate the association between acetaminophen use and outcomes in SA-AKI patients.

Methods This is a retrospective cohort study based on the MIMIC-IV database. Adult patients with SA-AKI were included in the analysis. The exposure was acetaminophen use within 7 days after the onset of SA-AKI. The primary outcome was 28-day mortality. Secondary outcomes included ICU mortality, in-hospital mortality, 90-day mortality, 1-year mortality, and renal recovery. Cox proportional hazards regression models were used to estimate the hazard ratio (HR) with 95% confidence interval (CI) for mortality. Logistic regression models were used to estimate the odd ratio (OR) with 95% CI for renal recovery.

Results 6752 patients with SA-AKI were included, and 3892 (57.6%) patients received acetaminophen. Acetaminophen use was associated with decreased 28-day mortality (HR 0.69, 95% CI 0.63–0.75), ICU mortality (HR 0.56, 95% CI 0.50–0.63), in-hospital mortality (HR 0.62, 95% CI 0.57–0.69), 90-day mortality (HR 0.73, 95% CI 0.68–0.79), and 1-year mortality (HR 0.62, 95% CI 0.57–0.69). Acetaminophen use also was associated with improved renal recovery (OR 1.15, 95% CI 1.04–1.28).

Conclusions Acetaminophen use is associated with decreased mortality and improved renal recovery in SA-AKI patients.

Keywords Sepsis, Acute kidney injury, Acetaminophen, Mortality, Renal recovery

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Introduction

Sepsis is defined as organ dysfunction resulting from dysregulated host response to infection, and the kidneys are particularly vulnerable among the affected organs [1]. A recent large and multicentre cohort study found that 1 out of every 6 patients admitted to the intensive care unit (ICU) experienced sepsis-associated acute kidney injury (SA-AKI) [2]. SA-AKI is associated with increased mortality and extended hospital stays [2], with survivors facing increased risk of chronic kidney disease [3]. Currently, SA-AKI management mainly revolves around supportive treatment, with no effective and specific pharmacologic interventions, emphasizing the urgent need for research to enhance patient outcomes.

Acetaminophen is frequently used to resolve fever and alleviate pain in critically ill patients [4]. A large, multicenter randomized trial suggested that early administration of acetaminophen for fever due to possible infection did not affect number of ICU-free days or mortality [5]. However, acetaminophen has been reported to reduce mortality in patients with sepsis by mitigating oxidative injury [6]. In terms of renal function, prior studies mainly investigated the association between acetaminophen and the risk of AKI in patients undergoing cardiac surgery, with conflicting results [7–9]. In animal models, acetaminophen reduced oxidative stress markers and alleviated renal dysfunction [10]. Nevertheless, to the best of our knowledge, no studies have evaluated the association of acetaminophen use with mortality and recovery of renal function in SA-AKI patients. Recently, the Acute Disease Quality Initiative Workgroup introduced a consensus definition for SA-AKI and identified research priorities [11]. On this basis, we conducted an analysis using a large public database to investigate the association between acetaminophen use and outcomes in SA-AKI patients.

Methods

Study design and data source

We conducted a retrospective cohort study using data from the Medical Information Mart in Intensive Care (MIMIC)-IV database version 2.0 [12]. MIMIC-IV 2.0 is a large electronic health record dataset encompassing comprehensive data on over 50,000 patients at Beth Israel Deaconess Medical Center (BIDMC) from 2008 to 2019. The data, collected as part of routine clinical care, has been deidentified and is accessible to researchers who have completed the required training and obtained certification. The Institutional Review Board at BIDMC granted a waiver of informed consent and authorized the sharing of the research resource. This study adheres to the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement [13].

Patient, exposure, and outcomes

We identified adult patients aged 18 years and older with SA-AKI using the proposed definition [10]. Briefly, SA-AKI was defined as the simultaneous presence of sepsis (according to the Sepsis-3 criteria [14]) and AKI (according to the KDIGO criteria [15]) when AKI occurs within 7 days after sepsis diagnosis. The workgroup categorized AKI occurring within 48 h after sepsis diagnosis as early SA-AKI and AKI occurring between 48 h and 7 days after sepsis diagnosis as late SA-AKI. Patients who had received acetaminophen before the onset of SA-AKI or had an ICU stay of less than 24 h were excluded. In cases of multiple admissions, we only extract information from the first time. The exposure of interest was the administration of acetaminophen within 7 days after the onset of SA-AKI. The primary outcome was 28-day mortality, and secondary outcomes included ICU mortality, in-hospital mortality, 90-day mortality, 1-year mortality, and renal recovery. Renal recovery was defined as a decrease in serum creatinine levels (less than 1.5 times the baseline value) and the restoration of urine output (more than 0.5 ml/kg/h for 24 h) on ICU discharge [16].

Data extraction

We collected comprehensive patient information, including demographics such as age, sex, race, and weight, as well as Sequential Organ Failure Assessment (SOFA) and Charlson Comorbidity Index scores. Comorbidities were also recorded, including diabetes mellitus, chronic pulmonary disease, congestive heart failure, cerebrovascular disease, liver disease, renal disease, and cancer. Therapeutic interventions included norepinephrine use, invasive mechanical ventilation (IMV), and continuous renal replacement therapy (CRRT). Vital signs (heart rate, mean arterial pressure, respiratory rate, and body temperature) and laboratory tests (white blood cell, hemoglobin, platelet, lactate, and baseline creatinine) were extracted from the patient's first record in ICU.

Statistical analysis

Due to the retrospective nature of this study, a statistical power calculation was not performed beforehand, relying instead on available database data. Missing data is a common phenomenon in databases, and we implemented multiple imputation method [17]. Continuous variables were expressed as median (interquartile range [IQR]) due to skewed distribution and were compared by the Mann-Whitney U test. Categorical variables were expressed as number (percentage) and were compared by the Chi-square test or Fisher's exact test.

The Kaplan-Meier (KM) curve was used to investigate the association between acetaminophen and mortality, with the log-rank test assessing differences in survival between acetaminophen users and non-users. Cox

proportional hazards regression models were used to estimate hazard ratio (HR) with 95% confidence interval (CI) for mortality. Logistic regression models were used to estimate odd ratio (OR) with 95% CI for renal recovery. The multivariable analyses models adjusted for the following variables, including age, sex, race, weight, SOFA, Charlson comorbidity index, invasive mechanical ventilation, continuous renal replacement therapy, respiratory rate, body temperature, white blood cell, platelet, hemoglobin, lactate, and baseline creatinine.

Subgroup analysis

Subgroup analyses were conducted to investigate the association between exposure and the primary outcome (i.e., 28-day mortality) by age (<65 and ≥65 years), sex (male and female), AKI stage (1, 2, and 3), IMV (yes and no), and CRRT (yes and no).

All statistical analyses were conducted using R software (version 4.3.1). A $P<0.05$ was considered statistically significant.

Results

Patient characteristics

Figure 1 illustrates the process of patient selection. Of 6752 patients with SA-AKI, 3892 (57.6%) patients received acetaminophen. Fewer than 1% of relevant variables except lactate were missing (Fig S1). The baseline characteristics are summarized in Table 1. Of these, 6424 (95.1%) were identified as early SA-AKI and 328 (4.9%) were identified as late SA-AKI (Fig S2 and 3). At SA-AKI diagnosis, the majority of patients (71.6%) were categorized as stage 1, with a small proportion at stage 2 (26.4%) and stage 3 (2.0%) (Fig S4). The ICU, in-hospital, 28-day, 90-day, and 1-year mortality was 18.5%, 24.4%, 29.0%, 36.9%, and 46.8%, respectively (Fig S5). The initiating time of acetaminophen is shown in Figure S6. In the majority of the cases (64.6%), acetaminophen use occurred within 48 h after occurrence of SA-AKI. Intravenous administration was the most frequently chosen route, followed by oral/nasogastric administration (Figure S7).

Primary outcome

The 28-day mortality rate was 24.9% (970/3892) in the acetaminophen users and 34.5% (987/2860) in the non-users ($P<0.001$, Table 1). Both the KM curve and the log-rank test showed that acetaminophen users had a higher probability of survival than non-users ($P<0.001$, Fig. 2). Multivariable analysis suggested that acetaminophen was associated with decreased 28-day mortality (HR 0.69, 95% CI 0.63–0.75, $P<0.001$, Table 2).

Subgroup analysis

Figure 3 presents subgroup analyses for 28-day mortality. The results were consistent in all subgroups except for stage 3 of SA-AKI Interactions were presented in subgroups of CRRT and IMV.

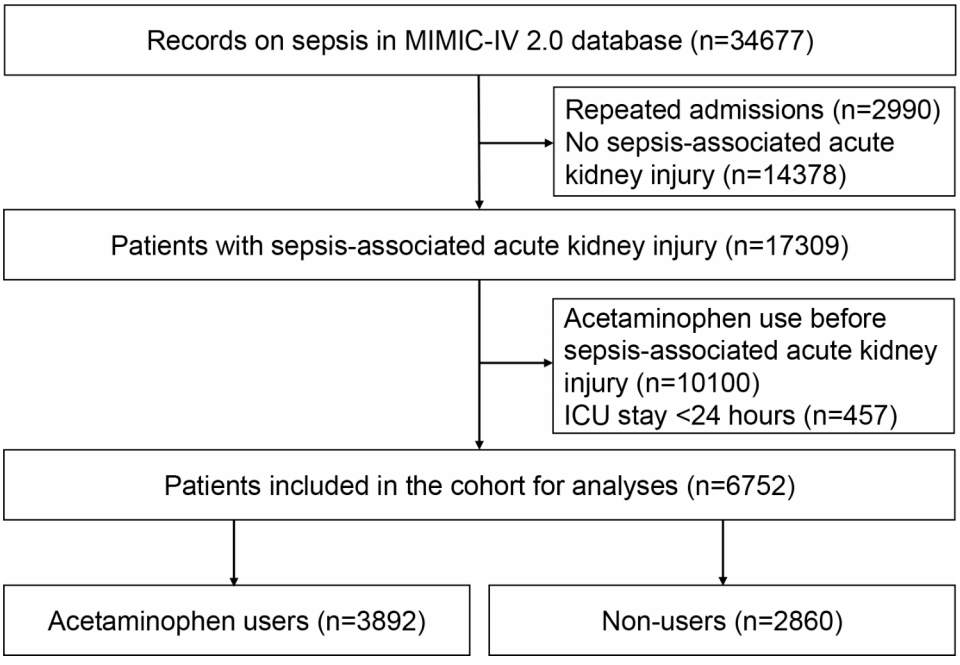

Fig. 1 Flow diagram of patient selection

Table 1 Baseline characteristics

Variables	Total (*n* = 6752)	Acetaminophen users (*n* = 3892)	Non-users (*n* = 2860)	*P*-value
Age, year	68.0 (56, 79)	67 (56, 78)	68 (57, 80)	0.005
Sex				
Male	3888 (57.6)	2203 (56.6)	1685 (58.9)	0.06
Female	2864 (42.4)	1689 (43.4)	1175 (41.1)	
Race				
White	4330 (64.1)	2466 (63.4)	1864 (65.2)	0.007
Black	699 (10.4)	381 (9.8)	318 (11.1)	
Other	1723 (25.5)	1045 (26.8)	678 (23.7)	
Weight, kg	81.1 (68.0, 97.6)	82.0 (68.8, 99.6)	80.0 (66.8, 95.7)	< 0.001
SOFA	3 (2, 5)	3 (2, 5)	3 (2, 5)	< 0.001
Charlson comorbidity index	6 (4, 8)	6 (4, 8)	6 (5, 8)	< 0.001
AKI stage				
1	4833 (71.6)	2823 (72.5)	2010 (70.3)	0.09
2	1783 (26.4)	998 (25.6)	785 (27.4)	
3	136 (2.0)	71 (1.8)	65 (2.3)	
Comorbidities				
Diabetes mellitus	2308 (34.2)	1350 (34.7)	958 (33.5)	0.3
Chronic pulmonary disease	2087 (30.9)	1167 (30.0)	920 (32.2)	0.06
Congestive heart failure	2500 (37.0)	1488 (38.2)	1012 (35.4)	0.02
Cerebrovascular disease	767 (11.4)	480 (12.3)	287 (10.0)	0.004
Liver disease	1728 (25.6)	797 (20.5)	931 (32.6)	< 0.001
Renal disease	1916 (28.4)	1069 (27.5)	847 (29.6)	0.06
Cancer	912 (13.5)	454 (11.7)	458 (16.0)	< 0.001
Treatments				
Norepinephrine	2633 (39.0)	1547 (39.7)	1086 (38.0)	0.1
IMV	3206 (47.5)	1933 (49.7)	1273 (44.5)	< 0.001
CRRT	240 (3.6)	99 (2.5)	141 (4.9)	< 0.001
Vital signs				
Heart rate, beats/minute	90 (77, 105)	90 (77, 105)	90 (77, 104)	0.9
Mean blood pressure, mm Hg	80 (68, 93)	80 (69, 93)	79 (68, 93)	0.2
Respiratory rate, times/minute	20 (16, 24)	20 (16, 24)	19 (16, 24)	0.01
Body temperature, ℃	36.7 (36.3, 37.1)	36.8 (36.4, 37.2)	36.7 (36.3, 37.0)	< 0.001
Laboratory tests				
White blood cell, 10^9/L	11.1 (7.3, 16.4)	11.7 (7.8, 16.8)	10.5 (6.8, 15.7)	< 0.001
Platelet, 10^9/L	180 (116, 251)	186 (126, 254)	172 (102, 244)	< 0.001
Hemoglobin, g/dL	10.5 (9.0, 12.0)	10.6 (9.1, 12.3)	10.3 (8.8, 11.8)	< 0.001
Lactate, mmol/L	1.4 (0.8, 2.2)	1.4 (0.9, 2.2)	1.4 (0.7, 2.1)	0.002
Baseline creatinine, mg/dL	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	0.9 (0.6, 1.1)	< 0.001
Outcomes				
28-day mortality	1957 (29.0)	970 (24.9)	987 (34.5)	< 0.001
ICU mortality	1252 (18.5)	574 (14.7)	678 (23.7)	< 0.001
In-hospital mortality	1647 (24.4)	811 (20.8)	836 (29.2)	< 0.001
90-day mortality	2491 (36.9)	1271 (32.7)	1220 (42.7)	< 0.001
1-year mortality	3162 (46.8)	1628 (41.8)	1534 (53.6)	< 0.001
Renal recovery	2827 (41.9)	1721 (44.2)	1106 (38.7)	< 0.001

Data are expressed as *n* (%) for categorical variables and median (interquartile range) for continuous variables, unless otherwise stated

AKI, acute kidney injury; CRRT, continuous renal replacement therapy; IMV, invasive mechanical ventilation; SOFA, Sequential Organ Failure Assessment

Secondary outcomes

ICU mortality, in-hospital mortality, 90-day mortality, and 1-year mortality

Acetaminophen users had lower ICU mortality, in-hospital mortality, 90-day mortality, and 1-year mortality than non-users (all $P<0.001$, Table 1). Multivariable analyses suggested that acetaminophen was associated with decreased ICU mortality (HR 0.56, 95%

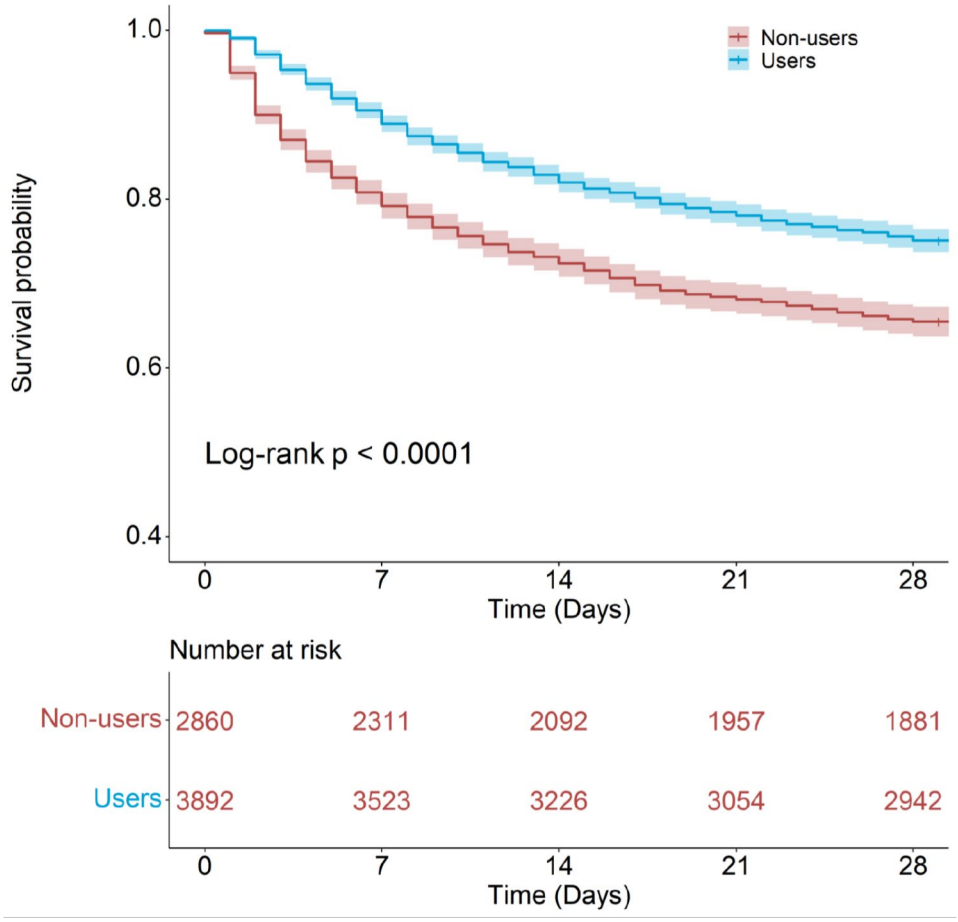

Fig. 2 Kaplan-Meier curve for 28-day mortality according to acetaminophen use

Table 2 The association of acetaminophen use with outcomes

Outcomes	Acetaminophen users (*n* = 3892)	Non-users (*n* = 2860)	Univariable analysis		Multivariable analysis*	
			HR/OR (95% CI)	*P*-value	HR/OR (95% CI)	*P*-value
Primary outcome						
28-day mortality†, n (%)	970 (24.9)	987 (34.5)	0.65 (0.60–0.71)	< 0.001	0.69 (0.63–0.75)	< 0.001
Secondary outcomes						
ICU mortality†, n (%)	574 (14.7)	678 (23.7)	0.50 (0.45–0.56)	< 0.001	0.56 (0.50–0.63)	< 0.001
In-hospital mortality†, n (%)	811 (20.8)	836 (29.2)	0.59 (0.53–0.65)	< 0.001	0.62 (0.57–0.69)	< 0.001
90-day mortality†, n (%)	1271 (32.7)	1220 (42.7)	0.68 (0.63–0.74)	< 0.001	0.73 (0.68–0.79)	< 0.001
1-year mortality†, n (%)	1628 (41.8)	1534 (53.6)	0.69 (0.64–0.73)	< 0.001	0.75 (0.69–0.80)	< 0.001
Renal recovery‡, n (%)	1721 (44.2)	1106 (38.7)	1.26 (1.14–1.39)	< 0.001	1.15 (1.04–1.28)	0.007

*Adjusted for age, sex, race, weight, SOFA, Charlson comorbidity index, CRRT, invasive mechanical ventilation, respiratory rate, body temperature, white blood cell, platelet, hemoglobin, lactate, and baseline creatinine

†HR with 95% CI was calculated using Cox proportional hazards model

‡OR with 95% CI was calculated using logistic regression model

CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; OR, odds ratio

CI 0.50–0.63, $P<0.001$), in-hospital mortality (HR 0.62, 95% CI 0.57–0.69, $P<0.001$), 90-day mortality (HR 0.73, 95% CI 0.68–0.79, $P<0.001$), and 1-year mortality (HR 0.62, 95% CI 0.57–0.69, $P<0.001$, Table 2).

Renal recovery

The proportion of renal recovery was 44.2% (1721/3892) in the acetaminophen users and 38.7% (1106/2860) in the non-users ($P<0.001$, Table 1). Multivariable analyses suggested that acetaminophen was associated with increased

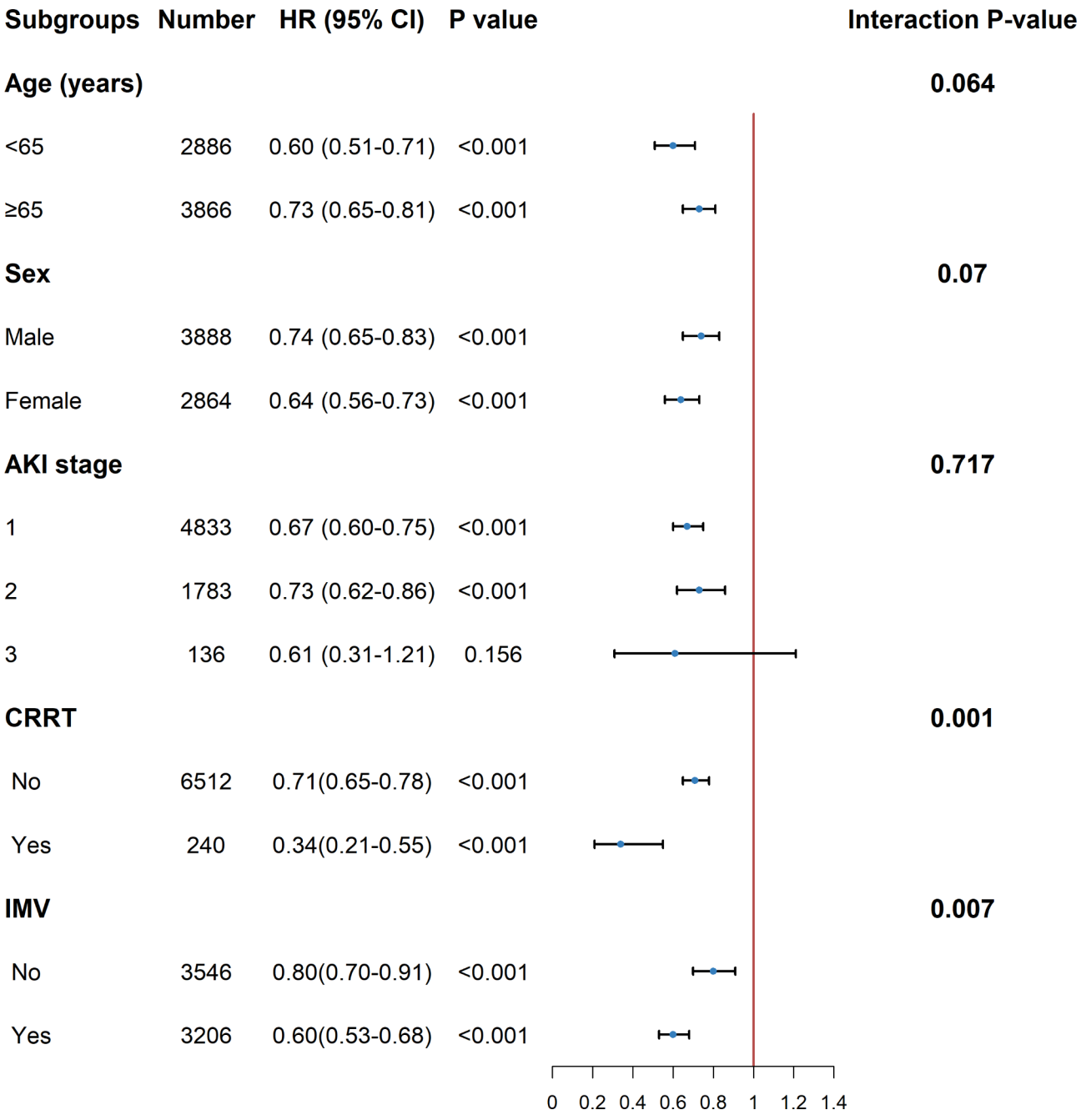

Fig. 3 Subgroup analyses for 28-day mortality

renal recovery (OR 1.15, 95% CI 1.04–1.28, *P*=0.007, Table 2).

Discussion

Main findings

The key findings regarding this large-sample retrospective study are summarized below. First, acetaminophen use was associated with decreased 28-day mortality in SA-AKI patients, and this association was consistent across subgroups. Second, acetaminophen use was associated with decreased ICU mortality, in-hospital mortality, 90-day mortality, and 1-year mortality. Third, acetaminophen use was associated with improved renal recovery.

Possible explanations for findings

Why is acetaminophen use associated with decreased mortality and improved renal recovery in SA-AKI patients? The underlying mechanisms need to be explored. Existing evidence suggests that acetaminophen

may decrease mortality and offer organ protection by targeting cell-free hemoglobin (CFH). Elevated CFH levels are frequently seen in sepsis and can contribute to SA-AKI through various mechanisms, such as tubular obstruction, nitric oxide consumption, oxidative damage, proinflammatory response, and immune dysregulation [18]. Previous studies have suggested that sepsis patients often have elevated CFH plasma levels, which are independently associated with a higher risk of death [6, 19]. Animal studies have also supported these findings [20]. Shaver et al. evaluated the effect of CFH on renal function in an experimental sepsis model, suggesting that CFH exacerbates AKI [21]. Janz et al. reported that early acetaminophen administration may reduce oxidative damage and improve renal function in severe sepsis patients with elevated plasma CFH levels at enrollment [22]. Patients who received acetaminophen exhibited significantly lower oxidative stress levels, as measured by plasma F2-isoprostanes. Additionally, they had lower serum creatinine levels on days 3 and 4 post-randomization and reduced peak serum creatinine levels throughout their hospitalization.

Relation with previous evidence

Acetaminophen is a widely used antipyretic drug in ICUs. Prior evidence consistently found that acetaminophen decreased body temperature among febrile critically ill patients [5, 23, 24]. In our study, we also observed that acetaminophen users had a lower body temperature than non-users (36.7 [36.3−37.0] °C vs. 36.8 [36.4−37.2] °C, $P<0.001$) in SA-AKI patients. A multicenter retrospective observational study showed that acetaminophen administration was associated with decreased in-hospital mortality in critically ill patients [25]. Another retrospective observational study found that acetaminophen had a protective association with in-hospital mortality by reducing CFH-induced oxidative injury [6]. While these findings are in line with our results, our current study placed a stronger emphasis on the role of acetaminophen specifically in SA-AKI patients. Notably, we found the association between acetaminophen use and decreased in-hospital mortality in SA-AKI patients. Furthermore, we explored a broader range of outcomes, including 28-day mortality and mortality at other time points. Additionally, we found a significant association between acetaminophen use and improved renal recovery in SA-AKI patients.

Implications for clinical practice

The consensus report of the 28th Acute Disease Quality Initiative workgroup emphasized the challenges in improving the prognosis of SA-AKI and the critical importance of timely initiation of appropriate supportive measures to limit further kidney damage. Current treatment in SA-AKI patients remains supportive, including fluid management, vasopressor use, and renal replacement therapy, but there are still no specific treatment options. Interestingly, our study has found a potential benefit of acetaminophen in SA-AKI patients, despite it not being advantageous in a broader ICU population. These encouraging findings provide novel insights into the treatment of SA-AKI. Additionally, the widespread use, affordability, and safety of acetaminophen in ICUs highlight the significance of this discovery in improving the prognosis for SA-AKI patients.

Study limitations

Our study has several limitations. First, it was a retrospective observational study with an element of unbalanced baseline information, and despite the multivariable analyses we conducted, there was selection bias and unmeasured confounders that may have affected the reliability of the results. Confirmatory evidence from randomized trials is necessary to validate our findings. Secondly, while acetaminophen is generally considered safe, it has the potential to induce hemodynamic changes. Acetaminophen use may lead to reductions in blood pressure and heart rate, although these reductions may not have significant clinical implications [23, 26]. Third, our analysis was not explored for potential associations between dose and frequency of acetaminophen and outcomes. There may be a dose-response effect, with low doses of acetaminophen potentially lacking the benefits and overdoses possibly posing a nephrotoxic risk. Fourth, we did not consider the effect of other antipyretic drugs or antibiotics on outcomes.

Conclusions

In summary, this retrospective cohort study suggested that acetaminophen use is associated with decreased mortality and improved renal recovery in SA-AKI patients.

Abbreviations

CI	Confidence interval
HR	Hazard ratio
ICU	Intensive care unit
IQR	Interquartile range
OR	Odds ratio
SA-AKI	Sepsis-associated acute kidney injury
SOFA	Sequential Organ Failure Assessment

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-024-02756-7.

Supplementary Material 1: Figure S1 Missing rate of variables in the cohort. Figure S2 Pie diagram for distribution of early and late SA-AKI. Figure S3 The occurrence of SA-AKI after sepsis diagnosis. Figure S4 Pie diagram for distribution of SA-AKI in different stages.Figure S5 The mortality rate at different timepoints in SA-AKI patients. Figure S6 The initiating time of acetaminophen after occurrence of SA-AKI. Figure S7 The route of acet-

aminophen administration

Acknowledgements
Not applicable.

Author contributions
LZL, LMZ, WJG, and MM contributed to the conception and design of the work. All authors contributed to the acquisition, analysis, and interpretation of data for the work. LZL and LMZ contributed to drafting the work. YY contributed to revising it critically for important intellectual content. All authors contributed to the final approval of the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding
This work was supported by the National Natural Science Foundation of China (grant number 82072232), the Science and Technology Program of Guangzhou, China (grant number 202201020028), the Special Projects in Key Areas of General Colleges and Universities in Guangdong Province (grant number 2022ZDZX2003), the 2021 Annual Medical Teaching and Education Management Reform Research Project of Jinan University (grant number 2021YXJG029), the Fundamental Research Funds for the Central Universities (grant number 21623302), the Fundamental Research Funds for The Central Universities (No.21624318), the Medical Scientific Research Foundation of Guangdong Province, China(No. A2024458), and the Science and Technology Program of Guangzhou (grant number SL2024A04J00718).

Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The dataset in this study was obtained from MIMIC-IV v2.0. The data has been deidentified and is accessible to researchers who have completed the required training and obtained certification. The Institutional Review Board at Beth Israel Deaconess Medical Center granted a waiver of informed consent and authorized the sharing of the research resource.

Consent for publication
Not applicable.

Competing interests
The authors report there are no competing interests to declare.

Received: 10 August 2024 / Accepted: 7 October 2024
Published online: 28 November 2024

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