Original Article

Aspirin use is associated with the reduced mortality risk in chronic obstructive pulmonary disease with sepsis: a retrospective study using the MIMIC-IV database

Zhao Yu[1], Yuan-Yuan Qian[2]^

[1]Emergency Department, Haining People's Hospital, Haining, China; [2]Department of Respiratory and Critical Care, Haining People's Hospital, Haining, China

Contributions: (I) Conception and design: Z Yu; (II) Administrative support: YY Qian; (III) Provision of study materials or patients: Z Yu; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Yuan-Yuan Qian, BD. Department of Respiratory and Critical Care, Haining People's Hospital, No. 2 Qianjiang West Road, Haizhou Street, Haining 314400, China. Email: 15957345821@163.com.

Background: Sepsis has the characteristics of high morbidity and high mortality in intensive care unit (ICU) patients. Chronic obstructive pulmonary disease (COPD) is an important cause of death. Studies have shown the value of aspirin on COPD and sepsis, separately, but its role in the combined COPD and sepsis patients is unclear. This study aimed to analyze the association of aspirin use after ICU admission with the mortality risk in COPD patients with sepsis.

Methods: We conducted a retrospective study using the Medical Information Mart for Intensive Care (MIMIC)-IV database, enrolling 2,964 COPD patients with sepsis admitted to ICU. They were divided into aspirin users (n=1,642) and non-users (n=1,322). We evaluated the association of aspirin use with in-hospital and 28-day mortality using logistic regression, Kaplan-Meier survival analysis, and Cox proportional-hazards models. The role of aspirin dose and the association of aspirin use with 90-day and 1-year mortality were also assessed.

Results: Aspirin use was associated with lower in-hospital death (13.642% *vs.* 23.676%) and 28-day mortality (17.296% *vs.* 30.257%) (P<0.001). Adjusted models confirmed reduced mortality odds ratio (OR) with aspirin use: OR for in-hospital mortality was 0.574 [95% confidence interval (CI): 0.456, 0.721] and 28-day mortality was 0.539 (95% CI: 0.437, 0.665) in model 3. Survival analyses showed higher survival probabilities for aspirin users. Subgroup analyses supported consistent aspirin benefits across various clinical parameters. Additionally, aspirin users had lower 90-day (21.498% *vs.* 34.191%) and 1-year mortality (27.649% *vs.* 41.982%) (P<0.001).

Conclusions: Aspirin use is significantly related to in-hospital and 28-day mortality risk in COPD patients with sepsis. This highlighted the clinical relevance of aspirin in COPD patients with sepsis.

Keywords: Sepsis; chronic obstructive pulmonary disease with sepsis (COPD with sepsis); critically ill; aspirin; mortality

Submitted Jun 12, 2024. Accepted for publication Aug 23, 2024. Published online Oct 15, 2024.
doi: 10.21037/jtd-24-952
View this article at: https://dx.doi.org/10.21037/jtd-24-952

^ ORCID: 0009-0004-7567-1383.

© AME Publishing Company.

Introduction

Sepsis is a syndrome characterized by physiological, pathological, and biochemical abnormalities caused by an inappropriate host response to infection (1,2). It is a significant threat to global health, with approximately one in five deaths worldwide associated with sepsis (3). Patients with sepsis have hospital stays twice as long as those with other conditions, yet their in-hospital mortality is 20%, and this data reaches 29% in China (4,5).

Previous studies have shown that sepsis patients with comorbidities such as chronic lung disease, chronic kidney disease, peripheral artery disease, and cardiovascular diseases have lower recovery rates and higher mortality (6-8). Chronic obstructive pulmonary disease (COPD) is one of the most common chronic complications in sepsis patients, accounting for about 6.9–16.5% of all sepsis cases (9,10). COPD significantly impacts the treatment and prognosis of sepsis patients. According to Chen *et al.*, the 28-day all-cause mortality rate is higher in COPD with sepsis than in those without COPD (11). Therefore, treating COPD patients with sepsis remains a significant challenge, necessitating effective therapeutic strategies to improve survival rates.

Aspirin is a non-steroidal anti-inflammatory drug widely used in clinical practice for treating cardiovascular diseases, and it exerts anti-inflammatory and anti-platelet effects by inhibiting cyclooxygenase (12). A clinical study suggests that aspirin is a potential therapeutic agent for treating sepsis and acute respiratory distress syndrome (13). Goto *et al.* reported that COPD patients using aspirin were associated with shorter hospital stays and lower in-hospital mortality (14). Kiers *et al.* indicated that Aspirin use was related to improved survival in sepsis patients admitted to the intensive care unit (ICU) (15). Pre-admission aspirin use has been associated with a reduced 90-day mortality rate in sepsis patients (16). However, some studies indicate that aspirin does not significantly treat COPD (17) and s epsis (18), separately. Therefore, further research is needed to explore the specific role of aspirin in sepsis and COPD.

This retrospective study utilized the Medical Information Mart for Intensive Care (MIMIC)-IV database to investigate the association between aspirin use after ICU admission and mortality risk in COPD patients with sepsis. By analyzing a large cohort of critically ill patients, this study aimed to provide insights into the potential function of aspirin therapy in this high-risk population, thereby informing clinical practice and improving patient outcomes in COPD with sepsis. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-952/rc).

Highlight box

Key findings

- Aspirin use was associated with lower mortality risks in chronic obstructive pulmonary disease (COPD) patients with sepsis. This benefit still existed when they were stratified according to various clinical parameters. Higher survival probabilities were observed for aspirin users. Interestingly, aspirin dose had no significant association with mortality outcomes.

What is known and what is new?

- Clinical studies suggest that aspirin is a potential therapeutic agent for treating sepsis and pulmonary complications. However, some studies indicate that aspirin does not significantly treat COPD and sepsis. Therefore, further research is needed to explore the specific role of aspirin in sepsis and COPD.
- This retrospective study utilized the Medical Information Mart for Intensive Care-IV database to investigate the association between aspirin use and mortality risk in COPD patients with sepsis. By analyzing a large cohort of critically ill patients, this study aimed to provide insights into the potential function of aspirin therapy in this high-risk population, thereby informing clinical practice and improving patient outcomes in COPD with sepsis.

What is the implication, and what should change now?

- Our study found that aspirin use was related to lower mortality risks in COPD patients with sepsis. The results implicated that aspirin use should be prospectively studied for validation.

Methods

Data source and study population

This retrospective study with longitudinal follow-up of patients retrieved data from the MIMIC-IV database, which encompasses hospitalization information of patients admitted to the Beth Israel Deaconess Medical Center in Boston, MA, USA from 2008 to 2019. This database is freely accessible and contains various data such as demographics, medication, and laboratory findings. Diagnoses were based on the documents International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10). Patient informed consent was waived since all information was de-identified. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Sepsis patients were diagnosed according to the sepsis

© AME Publishing Company.

3.0 diagnostic criteria: with infection and Sequential Organ Failure Assessment (SOFA) score ≥2 points (19). The SOFA score consists of six organ system scores including respiration, coagulation, live, cardiovascular, central nervous system, and renal, each with a score of 0–4 points (20). COPD was identified using ICD-9 codes 1144, 4162, 4168, and 4169, and ICD-10 codes B381, B391, B401, I2782, J811, and J953. There were 5,119 COPD patients with sepsis aged 18–80 years. Since sepsis is a major cause of ICU admissions and mortality among critically ill patients, and all patients included in the study were admitted to the ICU, our primary focus was on the use or not use of aspirin after ICU admission. For aspirin users, if the time from the start of aspirin use minus ICU admission time was greater than 0, this indicated that aspirin was used after ICU admission. Exclusion criteria: without complete information on vital signs including heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and oxygen saturation (SpO_2) or laboratory findings such as glucose, hematocrit, platelets, white blood cells (WBCs), prothrombin time (Pt), and urine output (n=1,942); ICU stay <24 h (n=156); aspirin use before ICU admission during the current hospitalization (n=57). These inclusion and exclusion criteria finally yielded 2,964 samples: 1,322 samples did not receive aspirin treatment after ICU admission and 1,642 samples received aspirin treatment after ICU admission. Only data from the first admission were used for patients admitted multiple times to the ICU.

Data collection

We extracted and managed data from the MIMIC-IV database using structured query language (SQL). Patient demographics: age, gender, and body mass index (BMI); vital signs: heart rate, SBP, DBP, and SpO_2; comorbidities: renal disease, coronary artery disease, diabetes, and hypertension; treatment: vasopressor use, mechanical ventilation use; and continuous renal replacement therapy (CRRT); score system: Glasgow Coma Scale (GCS), and SOFA; laboratory tests: glucose, hematocrit, platelets, WBC, Pt, and urine output. Only the first value was extracted for variables assessed multiple times. All enrolled variables had no missing value.

Study outcomes

The primary outcomes in the study were the short-term outcomes including in-hospital death and 28-day mortality. Long-term outcomes including 90-day mortality and 1-year mortality served as the secondary outcomes. The 28-day, 90-day, and 1-year were all follow-up times after discharge (the first day to the 28^{th} day, the 90^{th} day, the 365^{th} day).

Statistical analysis

COPD participants with sepsis were divided into aspirin users (with aspirin use after ICU admission) and aspirin non-users (without aspirin use after ICU admission), and the characteristics of the two groups were compared. The Chi-squared test was adopted to compare categorical variables expressed by count (frequency), and continuous characteristics represented by the median [interquartile range] were compared by the Mann-Whitney *U* test. A P value less than 0.05 indicated statistical significance.

Logistic regression models with stepwise regression methods were used to calculate the odds ratio (OR) and 95% confidence interval (CI) for associations of aspirin use with in-hospital death, 28-day mortality, 90-day mortality, and 1-year mortality. When considering survival time, we plotted non-adjusted and adjusted Kaplan-Meier curves to evaluate the survival differences between two aspirin groups using the log-rank tests. Then, the Cox proportional-hazards models were adopted to calculate the hazard ratio (HR) and 95% CI for the relationship between aspirin use and mortality. To consider confounding factors, we included three models. Model 1: age, gender, renal disease, coronary artery disease, diabetes, and hypertension were adjusted; model 2: heart rate, DBP, SBP, SpO_2, glucose, hematocrit, Pt, mechanical ventilation use, and CRRT were adjusted; model 3: all covariates were corrected including age, gender, heart rate, DBP, SpO_2, glucose, hematocrit, Pt, renal disease, coronary artery disease, diabetes, hypertension, mechanical ventilation use, and CRRT. In addition, the multivariable logistic regression model was also employed to assess the independent correlation between aspirin dose and in-hospital death or 28-day mortality. Restricted cubic splines (RCSs) were used to explore the relationship between duration of aspirin use and mortality. Dose of ≤300 mg/d was considered as low-dose aspirin and >300 mg/d as high-dose aspirin (21).

Results

Baseline characteristics

A total of 2,964 COPD patients with sepsis met the inclusion

© AME Publishing Company.

Table 1 Characteristics of COPD patients with sepsis

Variables	Total (n=2,964)	Aspirin non-users (n=1,322)	Aspirin users (n=1,642)	P value
Age (years)	65 [57, 72]	62 [52, 71]	67 [60, 73]	<0.001
Gender				
Male	1,590 (53.644)	651 (49.244)	939 (57.186)	<0.001
Female	1,374 (46.356)	671 (50.756)	703 (42.814)	
BMI (kg/m^2)	28.742 [24.200, 34.100]	28.400 [23.700, 34.300]	28.900 [24.447, 33.900]	0.28
Heart rate (bmp)	71 [62, 82]	75 [63, 87]	69 [61, 79]	<0.001
SBP (mmHg)	86 [78, 95]	87 [78, 97]	86 [78, 95]	0.19
DBP (mmHg)	44 [39, 50]	45 [39, 52]	44 [39, 49]	<0.001
SpO_2 (%)	92 [89, 94]	91 [89, 94]	92 [90, 94]	<0.001
With renal disease	559 (18.860)	197 (14.902)	362 (22.046)	<0.001
With coronary artery disease	951 (32.085)	129 (9.758)	822 (50.061)	<0.001
With diabetes	1,008 (34.008)	351 (26.551)	657 (40.012)	<0.001
With hypertension	1,120 (37.787)	322 (24.357)	798 (48.599)	<0.001
Vasopressor use	1,228 (41.430)	546 (41.301)	682 (41.535)	0.90
Mechanical ventilation use	550 (18.556)	298 (22.542)	252 (15.347)	<0.001
With CRRT	215 (7.254)	124 (9.380)	91 (5.542)	<0.001
GCS	15 [15, 15]	15 [15, 15]	15 [15, 15]	0.06
SOFA	3 [2, 4]	3 [2, 5]	3 [2, 4]	0.85
Glucose (mg/dL)	101 [86, 125]	108 [89, 131]	96 [84, 118]	<0.001
Hematocrit (%)	24.0 [21.0, 28.5]	24.6 [21.0, 29.1]	24.0 [21.0, 28.0]	0.01
Platelets (mL)	161 [113, 231]	169 [106, 247]	158 [116, 220]	0.21
WBC (K/μL)	10.3 [7.3, 13.7]	10.1 [7.0, 14.0]	10.3 [7.6, 13.4]	0.36
Pt (sec)	13.3 [12.0, 15.2]	13.5 [12.1, 16.0]	13.2 [12.0, 14.7]	<0.001
Urine output (mL)	15 [5, 30]	15 [3, 30]	15 [5, 29]	0.78

Categorical variables were expressed by count (frequency), and continuous variables were represented by the median [interquartile range]. COPD, chronic obstructive pulmonary disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO_2, oxygen saturation; CRRT, continuous renal replacement therapy; GCS, Glasgow Coma Scale; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell; Pt, prothrombin time.

and exclusion criteria. During ICU stay, 1,322 patients did not receive aspirin, and 1,642 were treated with aspirin (1,291 users with low-dose aspirin and 351 users with high-dose aspirin). There were 1,590 males and 1,374 females. Detailed information on the patient characteristics is shown in *Table 1*. The aspirin users were older (median age, 67 *vs.* 62 years) and more likely to be males than the non-users (57.186% *vs.* 49.244%) (P<0.001). Individuals who received aspirin treatment had a higher prevalence of renal disease (22.046%), coronary artery disease (50.061%), diabetes (40.012%), and hypertension (48.599%) compared to those without aspirin treatment (all P<0.001). Interestingly, the aspirin user group had a lower percentage of mechanical ventilation use and CRRT treatment (P<0.001). Besides, heart rate (P<0.001), DBP (P<0.001), and the levels of glucose (P<0.001), hematocrit (P=0.01), and Pt (P<0.001) were significantly lower among aspirin users. There was no significant difference in BMI (P=0.28), SBP (P=0.19), vasopressor use (P=0.90), GCS (P=0.06), SOFA (P=0.85), platelets (P=0.21), WBC (P=0.36), and urine output (P=0.78)

© AME Publishing Company.

Table 2 Risk of the primary outcomes among aspirin non-users and aspirin users

Outcomes	Total (n=2,964)	Aspirin non-users (n=1,322)	Aspirin users (n=1,642)	P value
In-hospital death	537 (18.117)	313 (23.676)	224 (13.642)	<0.001
28-day mortality	684 (23.077)	400 (30.257)	284 (17.296)	<0.001

Categorical variables were expressed by count (frequency).

Table 3 Association of aspirin use with primary outcomes using logistic regression analysis

Outcomes	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
In-hospital death						
Aspirin use	0.500 (0.403, 0.620)	<0.001	0.605 (0.493, 0.742)	<0.001	0.574 (0.456, 0.721)	<0.001
28-day mortality						
Aspirin use	0.470 (0.386, 0.573)	<0.001	0.563 (0.467, 0.677)	<0.001	0.539 (0.437, 0.665)	<0.001

Model 1: age, gender, renal disease, coronary artery disease, diabetes, and hypertension were adjusted; model 2: heart rate, DBP, SBP, SpO_2, glucose, hematocrit, Pt, mechanical ventilation use, and CRRT were adjusted; model 3, all covariates adjusted including age, gender, heart rate, DBP, SpO_2, glucose, hematocrit, Pt, renal disease, coronary artery disease, diabetes, hypertension, mechanical ventilation use, and CRRT. OR, odds ratio; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure; SpO_2, oxygen saturation; CRRT, continuous renal replacement therapy; Pt, prothrombin time.

between the two groups.

Association of aspirin use with primary outcomes

Firstly, we assessed the distribution of in-hospital death and 28-day mortality between aspirin non-users and aspirin users. Compared with aspirin non-users, aspirin users had a lower proportion of in-hospital death (13.642% *vs.* 23.676%) and 28-day mortality (17.296% *vs.* 30.257%) (P<0.001) (*Table 2*). Then, the multivariable logistic regression models were adopted to evaluate the odds of mortality. Whether in model 1, model 2, or model 3, there was a decreased odds of in-hospital death and 28-day mortality in the aspirin user group (P<0.001) (*Table 3*). In all covariate-adjusted model 3, the OR values for in-hospital death and 28-day mortality were 0.574 (95% CI: 0.456, 0.721) and 0.539 (95% CI: 0.437, 0.665), respectively. Although vasopressor use was not significantly distributed in the non-aspirin and aspirin user groups, it would clinically be plausible to have an association with mortality, we added this covariate into multivariable logistic and Cox regression analyses. When vasopressor use was adjusted, aspirin use was still associated with reduced odds of in-hospital death and 28-day mortality with OR values of 0.552 and 0.524, respectively (P<0.001) (Tables S1,S2).

Kaplan-Meier analysis showed that aspirin users had a higher survival probability than the aspirin-non users in terms of in-hospital death (P<0.001) and 28-day mortality (P=0.001) (*Figure 1A*,*1B*). After adjusting for all the covariates including age, gender, heart rate, DBP, SpO_2, glucose, hematocrit, Pt, renal disease, coronary artery disease, diabetes, hypertension, mechanical ventilation use, CRRT, and vasopressor use, those with aspirin use still had a favorable in-hospital death (P<0.001) and 28-day mortality (P=0.001) (*Figure 1C*,*1D*). In the multivariable Cox proportional-hazards model, the HRs for in-hospital death in model 1, model 2, and model 3 were 0.676 (95% CI: 0.559, 0.817), 0.680 (95% CI: 0.570, 0.810), and 0.691 (95% CI: 0.570, 0.837), respectively (all P<0.001). As for 28-day mortality, the HRs were 0.807 (95% CI: 0.681, 0.956), 0.791 (95% CI: 0.677, 0.923), and 0.818 (95% CI: 0.688, 0.971), respectively and the P values were 0.01, 0.003, and 0.02, respectively (*Table 4*). Upon vasopressor use adjustment, the negative association of aspirin use with in-hospital death and 28-day mortality still existed (P<0.001) (Tables S3,S4). These results suggested that aspirin use was significantly associated with the reduced risk of in-hospital death and 28-day mortality.

© AME Publishing Company.

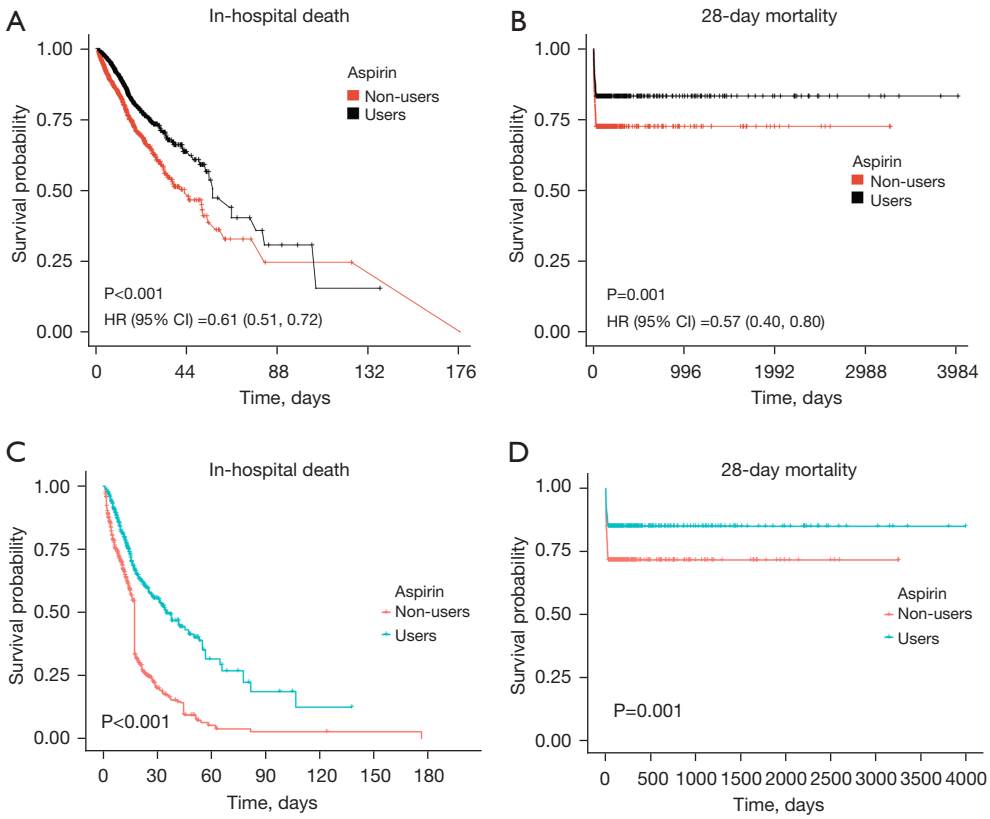

Figure 1 Kaplan-Meier analysis of the survival difference between aspirin non-user and user groups. (A) In-hospital death without adjusting covariates. (B) Twenty-eight-day mortality without adjusting covariates. (C) In-hospital death with adjusting covariates. (D) Twenty-eight-day mortality with adjusting covariates. HR, hazard ratio; CI, confidence interval.

Table 4 Association of aspirin use with primary outcomes using Cox proportional-hazards model

Outcomes	Model 1		Model 2		Model 3	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
In-hospital death						
Aspirin use	0.676 (0.559, 0.817)	<0.001	0.680 (0.570, 0.810)	<0.001	0.691 (0.570, 0.837)	<0.001
28-day mortality						
Aspirin use	0.807 (0.681, 0.956)	0.01	0.791 (0.677, 0.923)	0.003	0.818 (0.688, 0.971)	0.02

Model 1: age, gender, renal disease, coronary artery disease, diabetes, and hypertension were adjusted; model 2: heart rate, DBP, SBP, SpO_2, glucose, hematocrit, Pt, mechanical ventilation use, and CRRT were adjusted; model 3, all covariates adjusted including age, gender, heart rate, DBP, SpO_2, glucose, hematocrit, Pt, renal disease, coronary artery disease, diabetes, hypertension, mechanical ventilation use, and CRRT. HR, hazard ratio; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure; SpO_2, oxygen saturation; CRRT, continuous renal replacement therapy; Pt, prothrombin time.

Subgroup analysis

We conducted a subgroup analysis according to clinical parameters, which was visualized by the forest plot (*Figure 2A*,*2B*). Expectedly, aspirin use was closely connected with in-hospital death and 28-day mortality regardless of gender (P<0.001), renal disease (P<0.001 for without renal disease; P=0.005 for with renal disease), coronary artery disease (P<0.001), diabetes (P<0.001 for

© AME Publishing Company.

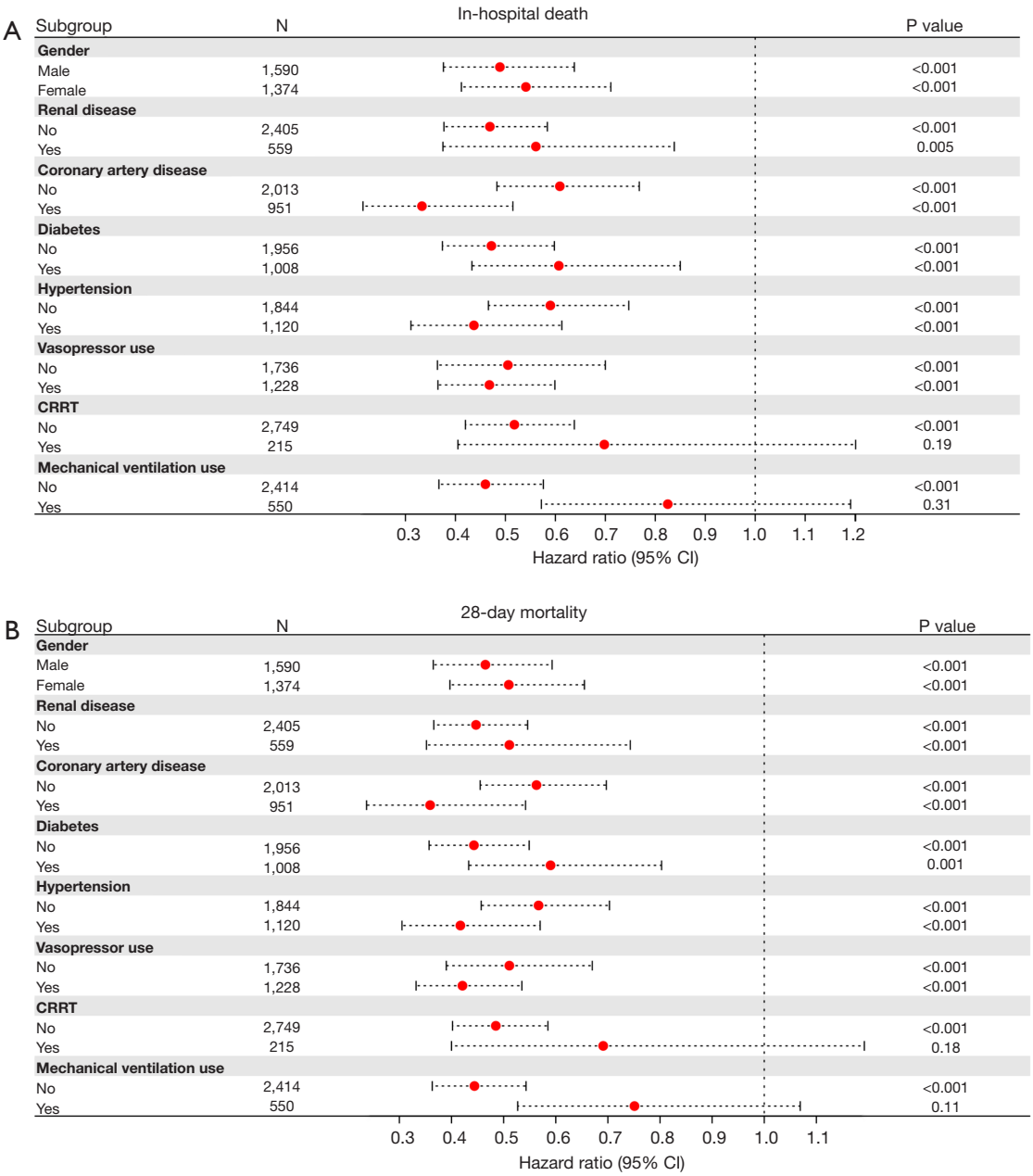

Figure 2 Subgroup analysis of the association of aspirin use and primary outcomes. (A) In-hospital death. (B) Twenty-eight-day mortality. CRRT, continuous renal replacement therapy; CI, confidence interval.

without diabetes; P=0.004 for with diabetes), hypertension (P<0.001), and vasopressor use (P<0.001). In addition, this significant association still existed in the group without CRRT treatment or mechanical ventilation use (P<0.001). This finding again highlighted the vital association of aspirin use with patient short-term survival.

Dose of aspirin and duration of aspirin use

To identify the optimal dose of aspirin in the treatment of COPD patients with sepsis, multivariable logistic regression analysis was performed. Surprisingly, aspirin dose was not associated with in-hospital death (P=0.98) or

© AME Publishing Company.

Table 5 The relationship between aspirin dose and primary outcomes using multivariable logistic regression analysis

Variables	In-hospital death		28-day mortality	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.044 (1.025, 1.064)	<0.001	1.052 (1.035, 1.071)	<0.001
Gender	1.161 (0.843, 1.597)	0.36	1.136 (0.849, 1.517)	0.39
Heart rate	1.007 (0.996, 1.018)	0.23	1.013 (1.003, 1.023)	0.01
DBP	0.986 (0.970, 1.003)	0.11	0.983 (0.967, 0.998)	0.03
SpO_2	0.958 (0.942, 0.974)	<0.001	0.965 (0.95, 0.981)	<0.001
Glucose	1.007 (1.004, 1.011)	<0.001	1.007 (1.004, 1.011)	<0.001
Hematocrit	1.024 (0.994, 1.054)	0.12	1.031 (1.004, 1.059)	0.03
Pt	1.036 (1.010, 1.063)	0.005	1.035 (1.01, 1.062)	0.005
Renal disease	1.463 (1.020, 2.081)	0.04	1.500 (1.081, 2.072)	0.01
Coronary artery disease	0.819 (0.593, 1.129)	0.22	0.828 (0.618, 1.107)	0.20
Diabetes	0.802 (0.572, 1.119)	0.20	0.813 (0.599, 1.099)	0.18
Hypertension	0.807 (0.587, 1.108)	0.19	0.727 (0.544, 0.969)	0.03
Mechanical ventilation use	2.600 (1.796, 3.74)	<0.001	2.210 (1.556, 3.121)	<0.001
CRRT	5.100 (3.062, 8.481)	<0.001	5.062 (3.076, 8.349)	<0.001
Aspirin dose	0.994 (0.682, 1.430)	0.98	1.024 (0.728, 1.426)	0.89

OR, odds ratio; CI, confidence interval; DBP, diastolic blood pressure; SpO_2, oxygen saturation; Pt, prothrombin time; CRRT, continuous renal replacement therapy.

Table 6 Risk of the secondary outcomes among aspirin non-users and aspirin users

Variables	Total (n=2,964)	Aspirin non-users (n=1,322)	Aspirin users (n=1,642)	P value
90-day mortality				<0.001
No	2,159 (72.841)	870 (65.809)	1,289 (78.502)	
Yes	805 (27.159)	452 (34.191)	353 (21.498)	
1-year mortality				<0.001
No	1,955 (65.958)	767 (58.018)	1,188 (72.351)	
Yes	1,009 (34.042)	555 (41.982)	454 (27.649)	

Categorical variables were expressed by count (frequency).

28-day mortality (P=0.89). The tendency to high dose was positively correlated with mortality [OR (95% CI): 1.024 (0.728, 1.426)] (*Table 5*). In addition, we also found that the duration of aspirin use was negatively correlated with in-hospital death (P for overall =0.001) or 28-day mortality (P for overall <0.001) (Figure S1A,S1B) via RCS.

Relationship between aspirin use and secondary outcomes

Subsequently, the significance of aspirin use in the secondary outcomes was evaluated. As shown in *Table 6*, 90-day mortality was 21.498% in the aspirin users, lower than the non-users (34.191%). Besides, 1-year mortality for aspirin users and aspirin non-users was 27.649% and 41.982%, respectively.

Discussion

This study utilized a large cohort from the MIMIC-IV database to investigate the association of aspirin use with

© AME Publishing Company.

mortality in COPD patients with sepsis. Our findings indicated that aspirin use after ICU admission was significantly related to the reduced in-hospital and 28-day mortality risk compared to non-users. This protective effect on COPD patients with sepsis remained significant even after adjusting for demographic and clinical covariates.

Sepsis is characterized by a dysregulated inflammatory and procoagulant response to pathogens (22). In the initial stages of sepsis, the coagulation cascade and inflammatory response trigger platelet activation, leading to thrombosis in the microvascular system and ultimately resulting in multiple organ failure (23). Antiplatelet therapy is a potential way to improve sepsis outcomes (24). Our study showed that aspirin users had favorable prognosis after adjusting for various confounding factors. In addition to short-term mortality, aspirin use reduced 90-day and 1-year mortality rates. This extended survival benefit underscores the long-term positive relationship between aspirin therapy and COPD patients with sepsis.

In the observational cohort study conducted by Lavie *et al.* (25), long-term aspirin use in patients with sepsis was associated with significantly higher survival rates. Herein, both short-term and long-term survival benefits were observed in COPD patients combined with sepsis who received aspirin treatment after ICU admission during the hospitalization. Besides, the longer the duration of aspirin use, the lower the risk of in-hospital mortality and 28-day mortality. This may be due to the relationship between chronic inflammation in COPD patients and platelet activation (26).

We also found no significant difference was observed in mortality outcomes between low- and high-dose aspirin users. This might be due to the uneven distribution between patients using high doses and those using low doses, with a large sample size difference between the two groups, leading to a lack of significant difference. A prospective study on low-dose aspirin in sepsis reported no significant difference in mortality between the aspirin and placebo groups in sepsis patients (18). Another prospective study by Eisen *et al.* (27) showed that the HR for mortality in sepsis patients receiving low-dose aspirin treatment was 0.63, and the OR for mortality in confirmed sepsis patients was 0.52, indicating that low-dose aspirin is a protective factor against sepsis-related death. Herein, a high dose of aspirin tended to correlate positively with mortality but without significance. The authors speculated that high-dose aspirin may be a marker of likely a more comorbid patient, and thus may not have an association with mortality. The above-mentioned prospective studies focused on elderly sepsis patients without specifying whether they were in the ICU. In contrast, our study involved patients aged over 18 years who were admitted to the ICU, who also had COPD. These findings suggest that while aspirin is related to sepsis outcomes, the impact of dosage and specific patient populations requires further detailed investigation through large-scale, multicenter prospective studies.

Additionally, it is widely recognized in numerous studies that these patients often have multiple comorbidities (28,29). We found that many of these patients also had hypertension, diabetes, and coronary artery disease. Particularly during periods of exacerbation, these patients are at an increased risk of acute coronary syndrome, which in turn raises their mortality risk (30). The use of aspirin might reduce the number of complications, thereby lowering mortality rates. However, this hypothesis requires further validation through prospective studies.

Strengths and limitations

This study has several strengths that enhance the validity and reliability of its findings. First, the MIMIC-IV database provided access to a large and diverse patient population, enhancing the generalizability of the results. Second, the detailed baseline characteristics and comprehensive adjustment for potential confounders in the multivariable models improved the robustness of the observed associations. Third, the consistency of the findings across various subgroup analyses and different models strengthened the evidence for the beneficial effects of aspirin. Lastly, including long-term mortality outcomes provided a more comprehensive understanding of aspirin's impact on patient prognosis.

Despite the strengths of this large retrospective study, there are several limitations. First, this study's observational nature precluded causal inference. COPD was defined by ICD-9 codes, which may result in overdiagnosis (11,31). Second, we excluded patients with aspirin use before ICU admission during hospitalization and those with ICU stays <24 h, which might induce sample selection bias and limit generalizability. Third, the database did not provide information on adherence to aspirin therapy or the reasons for aspirin administration, which could influence outcomes. Fourth, all data was collected from the MIMIC-IV, limited to one institution. Future research should focus on prospective, randomized controlled trials to establish a causal relationship between aspirin use and mortality

© AME Publishing Company.

outcomes in COPD patients with sepsis. Additionally, research should explore the mechanisms underlying aspirin's protective effects in this patient population to tailor therapeutic strategies better.

Conclusions

In conclusion, our study provided compelling evidence that aspirin use was associated with reduced in-hospital and 28-day mortality in COPD patients with sepsis. Moreover, no significant relationship was observed between aspirin dose and prognosis, which requires further validation in the future prospective study.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-952/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-952/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-952/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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. Patient informed consent was waived since all information was de-identified. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Huang M, Cai S, Su J. The Pathogenesis of Sepsis and Potential Therapeutic Targets. Int J Mol Sci 2019;20:5376.
2. Pan S, Lv Z, Wang R, et al. Sepsis-Induced Brain Dysfunction: Pathogenesis, Diagnosis, and Treatment. Oxid Med Cell Longev 2022;2022:1328729.
3. Xl L, Gy Z, R G, et al. Ferroptosis in sepsis: The mechanism, the role and the therapeutic potential. Front Immunol 2022;13:956361.
4. Arora J, Mendelson AA, Fox-Robichaud A. Sepsis: network pathophysiology and implications for early diagnosis. Am J Physiol Regul Integr Comp Physiol 2023;324:R613-24.
5. Liu YC, Yao Y, Yu MM, et al. Frequency and mortality of sepsis and septic shock in China: a systematic review and meta-analysis. BMC Infect Dis 2022;22:564.
6. Rincon JC, Efron PA, Moldawer LL. Immunopathology of chronic critical illness in sepsis survivors: Role of abnormal myelopoiesis. J Leukoc Biol 2022;112:1525-34.
7. Wang HE, Shapiro NI, Griffin R, et al. Chronic medical conditions and risk of sepsis. PLoS One 2012;7:e48307.
8. Heung M, Koyner JL. Entanglement of sepsis, chronic kidney disease, and other comorbidities in patients who develop acute kidney injury. Semin Nephrol 2015;35:23-37.
9. Ahlström B, Frithiof R, Larsson IM, et al. A comparison of impact of comorbidities and demographics on 60-day mortality in ICU patients with COVID-19, sepsis and acute respiratory distress syndrome. Sci Rep 2022;12:15703.
10. Xie J, Wang H, Kang Y, et al. The Epidemiology of Sepsis in Chinese ICUs: A National Cross-Sectional Survey. Crit Care Med 2020;48:e209-18.
11. Chen Y, Lu L, Li X, et al. Association between chronic obstructive pulmonary disease and 28-day mortality in patients with sepsis: a retrospective study based on the MIMIC-III database. BMC Pulm Med 2023;23:435.
12. Wang Y, Wang M, Liu C, et al. Hepatoprotective effects of aspirin on diethylnitrosamine-induced hepatocellular carcinoma in rats by reducing inflammation levels and PD-L1 expression. Sci Rep 2023;13:21362.
13. Toner P, McAuley DF, Shyamsundar M. Aspirin as a potential treatment in sepsis or acute respiratory distress syndrome. Crit Care 2015;19:374.
14. Goto T, Faridi MK, Camargo CA, et al. The association of aspirin use with severity of acute exacerbation of chronic obstructive pulmonary disease: a retrospective cohort study. NPJ Prim Care Respir Med 2018;28:7.

© AME Publishing Company.

15. Kiers HD, Kox M, van der Heijden WA, et al. Aspirin may improve outcome in sepsis by augmentation of the inflammatory response. Intensive Care Med 2016;42:1096.
16. Hsu WT, Porta L, Chang IJ, et al. Association Between Aspirin Use and Sepsis Outcomes: A National Cohort Study. Anesth Analg 2022;135:110-7.
17. Yayan J. No significant detectable anti-infection effects of aspirin and statins in chronic obstructive pulmonary disease. Int J Med Sci 2015;12:280-7.
18. Eisen DP, Leder K, Woods RL, et al. Effect of aspirin on deaths associated with sepsis in healthy older people (ANTISEPSIS): a randomised, double-blind, placebo-controlled primary prevention trial. Lancet Respir Med 2021;9:186-95.
19. Pan X, Xie J, Zhang L, et al. Evaluate prognostic accuracy of SOFA component score for mortality among adults with sepsis by machine learning method. BMC Infect Dis 2023;23:76.
20. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801-10.
21. Chen S, Li S, Kuang C, et al. Aspirin reduces the mortality risk of sepsis-associated acute kidney injury: an observational study using the MIMIC IV database. Front Pharmacol 2023;14:1186384.
22. Polat G, Ugan RA, Cadirci E, et al. Sepsis and Septic Shock: Current Treatment Strategies and New Approaches. Eurasian J Med 2017;49:53-8.
23. Cox D. Sepsis - it is all about the platelets. Front Immunol 2023;14:1210219.
24. Wang Y, Ouyang Y, Liu B, et al. Platelet activation and antiplatelet therapy in sepsis: A narrative review. Thromb Res 2018;166:28-36.
25. Lavie I, Lavie M, Gafter-Gvili A, et al. Chronic aspirin use and survival following sepsis-A propensity-matched, observational cohort study. Clin Microbiol Infect 2022;28:1287.e1-7.
26. Campo G, Pavasini R, Pollina A, et al. On-treatment platelet reactivity in patients with chronic obstructive pulmonary disease undergoing percutaneous coronary intervention. Thorax 2014;69:80-1.
27. Eisen DP, Moore EM, Leder K, et al. AspiriN To Inhibit SEPSIS (ANTISEPSIS) randomised controlled trial protocol. BMJ Open 2017;7:e013636.
28. Campo G, Pavasini R, Malagù M, et al. Chronic obstructive pulmonary disease and ischemic heart disease comorbidity: overview of mechanisms and clinical management. Cardiovasc Drugs Ther 2015;29:147-57.
29. Antoniu SA, Mihaescu T. Hospitalizations and mortality in the Lung Health Study. Expert Rev Pharmacoecon Outcomes Res 2002;2:523-6.
30. Pavasini R, d'Ascenzo F, Campo G, et al. Cardiac troponin elevation predicts all-cause mortality in patients with acute exacerbation of chronic obstructive pulmonary disease: Systematic review and meta-analysis. Int J Cardiol 2015;191:187-93.
31. Feng M, McSparron JI, Kien DT, et al. Transthoracic echocardiography and mortality in sepsis: analysis of the MIMIC-III database. Intensive Care Med 2018;44:884-92.

Cite this article as: Yu Z, Qian YY. Aspirin use is associated with the reduced mortality risk in chronic obstructive pulmonary disease with sepsis: a retrospective study using the MIMIC-IV database. J Thorac Dis 2024;16(10):6688-6698. doi: 10.21037/jtd-24-952

© AME Publishing Company.