Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Aspirin reduces the mortality risk of Acute Respiratory Failure: an observational study using the MIMIC IV database

ZhenHong Jiang
Affiliated Hospital of Hangzhou Normal University
Jinming Xia
Affiliated Hospital of Hangzhou Normal University
Shijin Lv
Affiliated Hospital of Hangzhou Normal University
Guohu Zhang
Affiliated Hospital of Hangzhou Normal University
Zengyan Fu
Affiliated Hospital of Hangzhou Normal University
Le Jiang
jiangle025@163.com
Affiliated Hospital of Hangzhou Normal University

Article

Keywords: Acute Respiratory Failure, aspirin, critically ill, mimic iv, mortality

Posted Date: August 6th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9777748/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Acute respiratory failure (ARF) presents high mortality with excessive inflammation and hypercoagulation. Aspirin exerts anti-inflammatory and antiplatelet effects, yet its clinical benefits in ARF remain controversial. This study aimed to explore the association between aspirin use and clinical outcomes in ARF patients and provide evidence for its rational administration.

Methods

Data were retrieved from the MIMIC-IV 2.2 database. Propensity score matching balanced baseline differences between aspirin and non-aspirin groups. Kaplan-Meier survival analysis and multivariate Cox regression were adopted to assess the prognostic value of aspirin.

Results

Among 4008 matched ARF patients, aspirin users had significantly lower 30-day and 90-day mortality. Multivariate analysis confirmed aspirin as an independent protective factor for 90-day mortality. Aspirin also shortened mechanical ventilation duration, despite a slightly prolonged median ICU stay.

Conclusion

Aspirin effectively decreases short-term mortality and reduces ventilation time, serving as a promising adjuvant therapy for ARF patients.

INTRODUCTION

Acute respiratory failure (ARF) is a critical condition characterized by the abrupt inability of the lungs to maintain adequate oxygenation and ventilation, leading to life-threatening respiratory distress[1]. The etiology of ARF is diverse, including pneumonia, sepsis, trauma, and other non-infectious causes such as pancreatitis or drug-induced lung injury[2]. ARF, a life-threatening condition, affects 2 million Americans hospitalized yearly in the USA, with annual costs exceeding $50 billion[3]. About 50% of acute respiratory failure patients require invasive mechanical ventilation, with over 20% not surviving hospitalization[3].Current ARF treatments focus mainly on supportive care, including mechanical ventilation, oxygen therapy, and hemodynamic support[4,5]. Despite advances in critical care, there remains a lack of targeted pharmacological therapies that directly address the underlying pathophysiology of ARF. This condition involves complex coagulation-inflammation interactions, with the endothelium central to its progression[6]. In ARF pathophysiology, endothelial cells shift from normal antithrombotic, anti-inflammatory phenotypes to prothrombotic, proinflammatory states. This transition involves increased pulmonary vascular procoagulant activity and reduced fibrinolytic capacity, causing fibrin deposition and alveolar damage[7,8]. Fibrin deposition may initially aid gas exchange and tissue repair but can cause further pulmonary dysfunction and fibrosis if unchecked[5]. Ongoing research increasingly seeks novel therapeutic targets and biomarkers to improve ARF outcomes.

Aspirin, a widely used drug, is known for reducing fever, pain and inflammation via its action on cyclooxygenases—key enzymes in inflammation, blood clotting and immune modulation[9,10]. Emerging studies highlight aspirin's versatility: it inhibits platelet aggregation to reduce subsequent heart attacks in cardiovascular patients and may help prevent colorectal cancer[11].

According to relevant reports, aspirin has the capability to suppress platelet activity and dampen inflammation, leading to enhanced outcomes[10]. And aspirin is a special antiplatelet drug because different dosage of aspirin has different function [12]. Low-dose aspirin, typically ranging from 75 to 100 milligrams per day, is recognized for its ability to inhibit platelet aggregation, while higher doses, exceeding 300 milligrams per day, not only affect platelet function but also possess anti-inflammatory properties. Several studies have reported aspirin as a promising treatment option for acute respiratory distress syndrome (ARDS)[9,13,14]. A study by Wang et al., based on the MIMIC-IV database, found that aspirin use is associated with a reduction in the 28-day mortality rate of patients with community-acquired pneumonia (CAP)[15]. However, Daryl J et al. have reported that the use of aspirin compared with placebo did not reduce the risk of ARDS at 7 days[16]. Philip et al. have discovered that aspirin did not improve oxygenation index (OI) or other physiological outcomes[17]. Currently, there are relatively few articles on aspirin in relation to acute respiratory failure, with most focusing on its associations with ARDS and CAP. ARDS, as a specific type of acute respiratory failure, still has diverging results in relevant research. Our research findings further indicate that there is a certain correlation between aspirin and diseases such as respiratory failure. Therefore, we carried out an examination of the MIMIC IV database to explore the association between the use of aspirin and the clinical outcomes in patients suffering from ARF. Additionally, our aim was to ascertain the optimal dosing regimen for aspirin treatment within this patient population.

METHODS

Medical Information Mart for Intensive Care IV (MIMIC-IV)

MIMIC-IV, the fourth iteration of the Medical Information Mart for Intensive Care, is a comprehensive, single-site database that offers open access to a vast trove of information. Specifically, it encompasses records from over 730,000 intensive care unit (ICU) admissions at the Beth Israel Deaconess Medical Center in the U.S., with data spanning from 2008 through 2019[18]. This resource can be found at https://physionet.org/content/mimiciv/2.2/. Author Zhenhong Jiang retrieved clinical data, encompassing patient demographics, laboratory findings, and medication records, from the MIMIC database (with certification number: 12918901). Utilization of this database received endorsements from the institutional review boards at MIT and BIDMC. This project was

conducted in accordance with the ethical guidelines outlined in the Declaration of Helsinki. Given the de-identified status of the participants and the structured data in the database, further ethical committee clearance was not deemed necessary for this investigation.

Patient selection

The exclusion criteria were: 1) Patients aged < 18 years (0 patients); 2) Data from subsequent hospitalizations were excluded (6,942 patients); 3) ICU stay duration < 48 h (discharged or death, 3,515 patients). The inclusion criteria were: Patients diagnosed with acute respiratory failure based on ICD codes (9,063 patients); 2) Patients with complete relevant data (6,663 patients). The variables in our study had missing values, so we would remove them. The final cohort comprised 6,663 patients, consisting of 2,813 aspirin users and 3,850 non-users. After propensity score matching (PSM), 2,004 pairs of patients were matched (Supplementary Fig. 1).

Data collection

Using the Navigate Premium tool, version 16, Structured Query Language (SQL) queries were employed to retrieve information pertaining to patients from the MIMIC-IV database (version 2.2). The following ARF comorbidities were recorded: cancer, diabetes mellitus, sepsis, chronic obstructive pulmonary disease (COPD), hypertension, acute pancreatitis and renal disease. Subsequently, the laboratory indexes within the first day of ICU admission were extracted, including hemoglobin, white blood cells (WBC), platelets (PLT), prothrombin time (PT), and OI. Simplified acute physiology (SAPS II) scores, Sequential organ failure assessment (SOFA) scores and Oxford acute severity of illness score (OASIS) were calculated at ICU admission. The following treatment information was noted: use of mechanical breathing, vasopressors, renal replacement therapy (RRT) and continuous renal replacement therapy (CRRT).

Primary and secondary outcomes

The primary outcome of this study was the 90-day mortality. The secondary outcomes included 30-day mortality, hospital stay duration and ICU stay duration.

Statistical analysis

The variables in our study were missing value, so we would remove them. Patients diagnosed with ARF who administered aspirin during their stay in ICU were categorized into the experimental cohort. Conversely, ARF patients who did not receive aspirin therapy comprised the control cohort. For continuous variables that did not follow a normal distribution, the Mann-Whitney U test was applied, and the results were presented using medians accompanied by interquartile ranges. Categorical variables between the two groups were depicted by counts and their respective proportions, and differences were evaluated utilizing the chi-squared test. All statistical analyses were conducted using SPSS Statistics software version 26.0 and R version 4.4.2. A p-value of 0.05 or below was considered indicative of statistical significance.

To minimize the disparity in baseline characteristics between the two cohorts, a propensity score matching technique (PSM) was employed with a caliper width set at 0.02. This method helps to create more comparable groups by matching participants based on their probability of receiving the treatment or exposure, thereby reducing selection bias and confounding factors.

Through the application of Kaplan-Meier estimators, graphical representations demonstrated the proportions of ARF patients surviving up to 30 days and 90 days, further highlighting the midpoint of survival times for the cohort. To evaluate the effect of aspirin treatment on the risk of dying within 30 days and 90 days in patients with acute respiratory failure, we utilized the Cox proportional-hazards model to calculate the hazard ratios and corresponding confidence intervals. We utilized the Cox proportional-hazards model to calculate the hazard ratios and corresponding confidence intervals. Firstly, univariate Cox regression was employed to screen out significant variables ($p < 0.05$). Variables that met this criterion were then subjected to multivariate Cox regression analysis. Further, acute respiratory failure patients were grouped by demographic and clinical criteria, encompassing age, gender, race, comorbid conditions, severity assessment scores (SAPS II, SOFA, OASIS), and interventions such as RRT, CRRT, mechanical breathing support, and use of vasoactive agents. Individual subgroup analyses were performed to ascertain hazard ratios and the corresponding 95% confidence intervals for each category.

RESULTS

Patient characteristics

Patient selection for this study is shown in Supplementary Fig. 1; 6,663 ARF patients met the inclusion criteria. Comprehensive clinical data (including aspirin therapy timelines and dosage) for these 6,663 ARF patients is in Supplementary Table 1.No aspirin treatment details are available for non-users. In our study, 2,286 patients took the most common dose of 81 mg/d, while 462 used high doses (> 300 mg/d). Our retrospective study is prone to confounding variables. PSM, a common statistical technique, mitigates this by pairing treatment and control individuals with similar baselines. 6,663 patients with ARF were extracted from the MIMIC IV 2.2 database. PSM paired 4,008 individuals, reducing confounding variables. Post-matching, aspirin administration became the key factor, with other confounders minimized, enabling clearer analysis of aspirin's correlation with outcomes. Table 1 shows ARF patients' clinical data pre- and post-PSM: 2,813 received aspirin, 3,850 did not during ICU stay. Among them, 920 (13.8%) had cancer, 2,159 (32.4%) diabetes, 2,527 (37.9%) congestive heart failure. A total of 1,276 patients (19.2%) had experienced myocardial infarction, and the percentage of patients with sepsis stood at 87.9% (5,860 cases). Additionally, 2,251 cases (33.8%) had Chronic Obstructive Pulmonary Disease (COPD). Moreover, the proportions of patients with hypertension, acute pancreatitis, and renal disease were 53.5% (3,565 cases), 3.5% (233 cases), and 25.3% (1,687 cases), respectively. Compared to subjects who did not receive

aspirin, patients who were on aspirin therapy had higher prevalence rates of diabetes (16.20%), congestive heart failure (54.90%), myocardial infarction (34.10%), COPD (38.30%), hypertension (60.40%), and renal disease (33.70%). Furthermore, the median age in the group receiving aspirin was greater than in the non-user group, but the mortality rate of the former (22.5% vs 34.3% for 30 day mortality, 31.8% vs 41.4% for 90 day mortality, both $p < 0.001$) was significantly lower than that of the latter (Table 1). From Table 1 and Supplementary Fig. 2, it can be observed that there is no significant difference between the two groups after PSM.

Table 1
Clinical information of ARF patients before PSM and after PSM.SOFA;SAPS II;OASIS;MBP;OI;RRT;CRRT

	Before PSM				After PSM	
	ALL patients (n = 6663)	Non-users (n = 3850)	Aspirin users (n = 2813)	*P* value	ALL patients (n = 4008)	Non-users (n = 200
Age	67.19(55.91,78.05)	63.02(51.66,75.52)	71.33(61.93,80.50)	< 0.001	69.74(59.59,79.92)	70.18(59.34,80.69)
Gender (female %)	2854(42.8)	1737(45.1)	1117(39.7)	< 0.001	1709(42.6)	857(42.8)
Race (White %)	4136(62.1)	2337(60.7)	1799(64.0)	0.007	2533(63.2)	1266(63.2)
Cancer (%)	920(13.8)	624(16.2)	296(10.5)	< 0.001	485(12.1)	232(11.6)
Diabetes (%)	2159(32.4)	1006(26.1)	1153(41.0)	< 0.001	1430(35.7)	716(35.7)
Congestive heart failure (%)	2527(37.9)	984(25.6)	1543(54.9)	< 0.001	1702(42.5)	828(41.3)
Myocardial infarct (%)	1276(19.2)	318(8.30)	958(34.1)	< 0.001	654(16.3)	307(15.3)
Sepsis (%)	5860(87.9)	3375(87.7)	2485(88.3)	0.402	3550(88.6)	1773(88.5)
COPD (%)	2251(33.8)	1174(30.5)	1077(38.3)	< 0.001	1467(36.6)	732(36.5)
Hypertension (%)	3565(53.5)	1867(48.5)	1698(60.4)	< 0.001	2346(58.5)	1177(58.7)
Acute pancreatitis (%)	233(3.5)	179(4.6)	54(1.9)	< 0.001	100(2.5)	51(2.5)
Renal disease (%)	1687(25.3)	738(19.2)	949(33.7)	< 0.001	1091(27.2)	543(27.1)
SOFA	7.00(5.00,10.00)	7.00(5.00,10.00)	7.00(5.00,10.00)	0.113	7.00(5.00,10.00)	7.00(5.00,10.00)
SAPS II	44.00(35.00,54.00)	43.00(33.00,53.00)	45.00(37.00,54.00)	< 0.001	44.00(36.00,54.00)	44.00(35.00,54.00)
OASIS	38.00(33.00,44.00)	38.00(33.00,44.00)	38.00(33.00,44.00)	0.054	38.00(33.00,43.00)	38.00(33.00,44.00)
Heart rate mean	86.86(75.57,99.86)	89.25(77.34,102.40)	84.13(73.78,96.16)	< 0.001	84.91(74.72,97.51)	84.60(74.55,97.74)
MBP	75.56(70.00,82.30)	76.04(70.33,82.92)	74.92(69.60,81.46)	< 0.001	75.38(69.77,81.92)	75.53(69.68,81.88)
Resp rate	20.00(17.52,22.94)	20.15(17.55,23.17)	19.86(17.47,22.60)	0.002	19.89(17.43,22.62)	19.87(17.39,22.53)
White blood cell(×10^9/L)	14.5(10.3,19.9)	14.2(10,19.9)	14.8(10.8,20.05)	0.001	14.6(10.3,20)	14.2(10.1,19.875)
Hemoglobin(g/dL)	9.70(8.20,11.40)	9.90(8.20,11.50)	9.60(8.20,11.20)	0.002	9.70(8.20,11.40)	9.80(8.20,11.40)
Platelets(×10^9/L)	171.00(112.00,234.00)	167.00(105.00,231.00)	174.00(121.00,238.00)	< 0.001	175.00(118.25,239.75)	179.00(118.00,241.
Prothrombin (time s)	14.80(12.80,19.30)	14.80(12.80,19.60)	14.80(12.90,18.90)	0.862	14.70(12.80,19.20)	14.75(12.80,19.48)
OI	125.00(77.50,220.00)	129.50(78.00,235.00)	119.00(76.00,202.50)	< 0.001	126.00(77.60,218.00)	126.00(77.50,222.0
Vasoactive drugs (%)	4372(65.6)	2409(62.6)	1963(69.8)	< 0.001	2695(67.2)	1353(67.5)
Ventilation (%)	6266(94.0)	3636(94.4)	2630(93.5)	0.116	3767(94.0)	1893(94.5)
RRT (%)	1057(15.9)	577(15.0)	480(17.1)	0.023	609(15.2)	295(14.7)
CRRT (%)	814(12.2)	448(11.6)	366(13.0)	0.096	470(11.7)	232(11.6)
30day-mortality (%)	1924(28.9)	1239(32.2)	685(24.4)	< 0.001	1139(28.4)	688(34.3)
90day-mortality (%)	2451(36.8)	1508(39.2)	943(33.5)	< 0.001	1467(36.6)	830(41.4)

Association between aspirin and mortality outcomes

ARF patients were categorized into two groups based on whether they received aspirin during their hospitalization. Compared to the non-user group, the aspirin group demonstrated lower risks of death at both 30 days and 90 days (HR: 0.59, 95%CI: 0.53–0.67; HR: 0.59, 95% CI: 0.53–0.67), as revealed by univariate Cox regression analysis (Supplementary Table 2). The Kaplan-Meier curves for 30-day and for 90-day survival in Fig. 1. According to the Kaplan-Meier survival analysis, the 30-day and 90-day survival rates were significantly higher in the aspirin user group than in the non-user group (Log-rank test: p-value < 0.001). Univariable Cox regression analysis was conducted on the variables presented in Supplementary Table 2. Variables with a p-value less than 0.05 were then included in the subsequent multivariable Cox regression analysis. The aspirin group showed a lower risk of death at 30 days and 90 days compared to the non-users group (HR = 0.59, 95% CI: 0.53–0.67; HR = 0.69, 95% CI: 0.62–0.76), as determined by multivariable Cox proportional hazards analysis (Table 2). The remaining results of the multivariable Cox regression analysis are presented in Table 2.

Table 2
Multivariable Cox regression analysis for 30-day and 90-day outcomes.

	30 days		90days	
	p	HR(95%CI)	p	HR(95%CI)
Aspirin	< 0.001	0.59(0.53–0.67)	< 0.001	0.69(0.62–0.76)
Cancer	< 0.001	1.32(1.12–1.55)	< 0.001	1.37(1.18–1.58)
Myocardial infarct	< 0.001	1.33(1.15–1.54)	< 0.001	1.25(1.10–1.43)
Vasoactive drug	< 0.001	1.28(1.10–1.48)	< 0.001	1.19(1.04–1.35)
Age	< 0.001	1.03(1.02–1.04)	< 0.001	1.03(1.02–1.04)
SAPS II	< 0.001	1.02(1.01–1.03)	< 0.001	1.02(1.01–1.03)
Respiration rate	< 0.001	1.04(1.03–1.06)	< 0.001	1.04(1.02–1.05)

Association of aspirin with composite outcomes

The group receiving aspirin had longer stays in the ICU and in the hospital, but notably shorter durations of mechanical ventilation (Table 3). Despite longer ICU/hospital stays, aspirin recipients needed less mechanical respiratory support, potentially reflecting better respiratory function, faster recovery, and higher survival. Notably, ARF ICU patients on aspirin had a significantly higher prevalence of comorbidities (e.g., diabetes, heart failure, hypertension; Table 1) than non-users. Studies show patients with comorbidities face higher cardiovascular risk, leading to more frequent aspirin use to prevent thrombosis[19–22]. Thus, such ICU patients receive more intensive medical care, raising the likelihood of aspirin prescription for respiratory and cardiovascular needs[20–22]. This, in turn, contributes to longer hospital stays and ICU stays.

Table 3
Composite outcomes of the aspirin use group and the non-users group.

Composite outcomes	Non-users	Users-Aspirin	p-value
Length of ICU stay, median (inter-quartile range)	6.08(3.68,11.18)	6.93(3.87,11.95)	**0.004**
Length of hospital stay, median (inter-quartile range)	11.78(6.96,19.20)	14.13(8.77,22.78)	**< 0.001**
Surviving patients	1393(69.5%)	1594(79.5%)	**< 0.001**
Mechanical ventilation length	58.00(27.00,117.16)	54.95(22.50,122.00)	**< 0.001**

Subgroup analyses

ARF patients were divided into different subgroups according to age, gender, race, cancer, co-morbidity, SOFA scores, vasoactive drug, ventilation, RRT and CRRT. The impact of aspirin on 90-day mortality within the subgroups of ARF patients was explored, and the findings were visually represented using a forest plot (Fig. 2). The analysis demonstrated that, across all subgroups, a significant correlation ($p < 0.05$) was identified between aspirin use and 90-day mortality, excluding the subgroups of sepsis, acute pancreatitis, ventilation, and CRRT. Regarding the interaction analysis, significant interactions were detected within two specific subgroups: the categorization of patients into white and non-white racial groups, and the presence or absence of acute pancreatitis, with corresponding p-values of 0.002 and 0.017, respectively. In contrast, the remaining subgroups did not exhibit statistically significant interactions.

Dose of aspirin

To comprehensively assess the influence of aspirin dosage on patients with ARF during their ICU admission, we analyzed the following key data aspects. In terms of the event - patient distribution, within the low-dose aspirin group, 497 events were recorded among 1631 patients (Supplementary Table 3). In contrast, the high-dose aspirin group presented 140 events out of 373 patients, with a significant p-value of 0.010, highlighting a notable difference in event incidence between the two groups. Regarding the length of hospital stay, the low-dose group had a median value of 14.21 days (8.78, 23.02). The high-dose group exhibited a median of 13.75 days (8.73, 21.53). This comparison indicated no significant difference in hospital stay duration ($p = 0.184$). For the length of ICU stay, the low-dose group had a median of 6.78 days (3.84, 11.75), while the high-dose group had a median of 7.51 days (4.0, 13.33), demonstrating a

significant disparity in ICU stay length (p = 0.029). Concerning the hazard ratios, the unadjusted HR for the high-dose group relative to the low-dose group was 1.30, with a 95%CI ranging from 1.08 to 1.57 (p = 0.006). The adjusted HR was also 1.30, with a 95% CI of 1.07 to 1.57 (p = 0.007). Collectively, these results revealed significant differences in event occurrence and ICU stay length between the low- dose aspirin and high-dose aspirin groups. The higher hazard ratios in the high-dose group suggest an elevated risk associated with high-dose aspirin use in ARF patients during their ICU stay.

DISCUSSION

Aspirin's therapeutic benefits for ARF patients are unclear. This observational study aimed to determine its positive impact on ARF outcomes, finding that aspirin use in ICU ARF patients may reduce 30-day and 90-day mortality but slightly prolong hospital and ICU stays.

Even with progress in the treatment of ARF, the death rate remains significantly high. A life-threatening condition with alveolar damage, barrier disruption, edema and impaired gas exchange. Platelet activation drives ARF by destabilizing cadherins, causing leak and raised alveolar-capillary permeability[23]. In ARF's inflammation-procoagulation-barrier breakdown cascade, aspirin's pleiotropy offers a novel therapy[5,24,25]. And platelets, by expressing CD40, have the capacity to trigger the activation of additional platelets and endothelial cells. They also secrete a variety of signaling molecules such as cytokines and chemokines, which contribute to the inflammatory process. Furthermore, platelets are involved in the activation of the complement system, a component of the immune response, which enhances inflammation during ARF[23,26].A study targeting sepsis-related respiratory failure patients has shown that pre-ICU exposure to aspirin is associated with a reduction in 28-day mortality, 60-day mortality, and in-hospital mortality in S-ARF (sepsis-associated acute respiratory failure) patients[27]. Aspirin was the first antiplatelet agent introduced into clinical practice and remains widely used today. By inhibiting COX-1, it blocks the synthesis of thromboxane A2, a potent platelet activator[28].

Aspirin's advantage in ARF patients likely stems from inhibiting platelet function; studies show antiplatelet drugs reduce ARF patients' death risk. Aspirin-induced resolvin D1 inhibits oxygen-induced pulmonary edema, permeability, and inflammation in mice[29]. An observational study of ICU ARDS patients showed lower ICU mortality with aspirin (OR 0.38, 95% CI 0.15–0.96, P = 0.04)[30]. Aspirin is a potential anti-fibrotic drug for the treatment of patients infected with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)[31].

The three fundamental mechanisms of ARF include microvascular dysfunction, inflammation, and metabolic reprogramming[23]. Aspirin's potent anti-inflammatory effects stem from blocking prostanoid production and promoting lipoxin and resolvin generation[32]. Previous studies show aspirin-triggered resolvin D1 (AT-RvD1) downregulates LPS(lipopolysaccharide)-induced ARF mice's inflammation, reducing alveolar cells in endotoxin-induced ARF[29]. Resolvin D1 (RvD1), an anti-inflammatory bioactive compound, downregulates NF-κB signals, showing potential as an ARF therapeutic target[33,34].

The efficacy of aspirin is contingent upon the dosage administered. Low-dose aspirin irreversibly inhibits cyclooxygenase-1 (COX-1), reducing platelets' ability to synthesize and release thromboxane A2, a secondary aggregator[12]. High-dose aspirin inhibits both COX-1 and COX-2 more broadly, boosting anti-inflammatory activity[35]. However, in our study, we found that high-dose aspirin was associated with increased mortality. This finding is consistent with that of Mujaj et al. (2021), who reported an increased risk of incident heart failure with aspirin use[36]. Welin et al. (2009) found that aspirin increased mortality in diabetic patients without cardiovascular disease[37]. This discrepancy may stem from higher aspirin doses raising side effect risks: gastrointestinal bleeding, platelet dysfunction, allergies, Reye's syndrome, kidney damage, and drug interactions[38–43]. Our finding of no hospital stay difference between low and high aspirin doses aligns with Bundhun et al. (2016) showing no mortality or myocardial infarction differences[44].

This study has limitations: focusing on critically ill ICU patients, despite propensity score matching, ICU complexity may affect mortality beyond aspirin; as an observational, non-random study, residual confounding may persist; its retrospective nature precludes establishing a causal link between aspirin and ARF outcomes; and long-term effects can't be assessed due to lacking follow-up data. Further research—animal studies and more prospective cohorts—is needed to explore aspirin's relation to ARF prognosis. Subgroup analysis shows greater benefits in non-Caucasians and non-acute pancreatitis patients, but related studies are few and require more exploration.

CONCLUSION

Aspirin may reduce the 30-day or 90-day mortality risk in ARF patients and shorten the duration of mechanical ventilation. Aspirin could be an effective medication in the treatment of ARF patients. However, further studies are required to investigate the specific mechanism underlying aspirin benefiting ARF patients.

Declarations

Ethics statement

This project complied with the Helsinki Declaration and approval from the ethics committee was not required due to participant anonymity and data standardization in this database.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

number: 2023KY185

Author Contribution

ZhenHong Jiang: Conceptualization, Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing – original draft; obtained the database access certification and performed the main data extraction, processing and statistical analysis.Jinming Xia: Funding acquisition, Resources, Supervision; secured research funding support and provided project resources.Shijin Lv: Data curation, Investigation, Methodology; assisted with data validation and study design refinement.Guohu Zhang: Investigation, Project administration, Resources; contributed to clinical data interpretation and project coordination.Zengyan Fu: Formal analysis, Visualization, Writing – review & editing; supported statistical result interpretation and manuscript revision.Le Jiang: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing; corresponding author, designed the study, supervised the research, revised the manuscript and approved the final version for submission.

Acknowledgement

AcknowledgementsWe gratefully acknowledge the Medical Information Mart for Intensive Care (MIMIC-IV) database for providing the clinical data used in this study. We also thank the developers and maintainers of the database for their valuable work.

Data Availability

Data availabilityThe data used in this study were obtained from the MIMIC-IV database (version 2.2), which is publicly available upon completion of the required training and data use agreement. All analyses were performed in compliance with the database access policies. The authors do not have the right to redistribute the raw data. Code used for data extraction and analysis is available from the corresponding author upon reasonable request.

References

1. Bitton, E. et al. An international survey of adherence to Surviving Sepsis Campaign Guidelines 2016 regarding fluid resuscitation and vasopressors in the initial management of septic shock. *J. Crit. Care*. **68**, 144–154 (2022).
2. Thompson, B. T., Chambers, R. C. & Liu, K. D. Acute Respiratory Distress Syndrome. *N. Engl. J. Med.* **377**, 562–572. 10.1056/NEJMra1608077 (2017).
3. Brodie, D., Slutsky, A. S. & Combes, A. Extracorporeal Life Support for Adults With Respiratory Failure and Related Indications: A Review. *JAMA J. Am. Med. Association*. **322**, 557 (2019).
4. Phua, J., Badia, J. R., Adhikari, N., Friedrich, J. O. & Ferguson, N. D. Has mortality from acute respiratory distress syndrome decreased over time? A systematic review. *Am. Rev. Respir. Dis.* **179**, 220–227 (2009).
5. Xiao, L. et al. Exploring the therapeutic role of early heparin administration in ARDS management: a MIMIC-IV database analysis. *J. intensive care*. **12** 10.1186/s40560-024-00723-5 (2024).
6. Matthay, M. A., Ware, L. B. & Zimmerman, G. A. The acute respiratory distress syndrome. *Jama J. Am. Med. Association*. **307**, 2542 (2012).
7. BROADDUS. *Murray and Nadel's Textbook of Respiratory Medicine* (Murray and Nadel's Textbook of Respiratory Medicine, 2016).
8. Cepkova, M. & Matthay, M. A. Pharmacotherapy of Acute Lung Injury and the Acute Respiratory Distress Syndrome. *J. Intensive Care Med.* **21**, 119–143 (2006).
9. Papadakos, P. J. An aspirin a day keeps the acute respiratory distress syndrome away. *Crit. Care Med.* **41**, 659 (2013).
10. Chen, S. et al. Aspirin reduces the mortality risk of sepsis-associated acute kidney injury: an observational study using the MIMIC IV database. *Front. Pharmacol.* **14**, 1186384. 10.3389/fphar.2023.1186384 (2023).
11. Patrono, C., Andreotti, F., Arnesen, H., Badimon, L. & Verheugt, F. Antiplatelet agents for the treatment and prevention of atherothrombosis. *Eur. Heart J.* **32**, 2922–2932 (2011).
12. Patrono, C. & Baigent, C. Role of aspirin in primary prevention of cardiovascular disease. *Nat. Rev. Cardiol.* **16**, 675–686. 10.1038/s41569-019-0225-y (2019).
13. U, H. et al. Aspirin reduces lipopolysaccharide-induced pulmonary inflammation in human models of ARDS. *Thorax* **72** 10.1136/thoraxjnl-2016-208571 (2017).
14. Yu, H., Ni, Y. N., Liang, Z. A., Liang, B. M. & Wang, Y. The effect of aspirin in preventing the acute respiratory distress syndrome/acute lung injury: A meta-analysis. *American J. Emerg. Medicine*, S**0735675718303942** (2018).
15. Wang, G. et al. Aspirin reduces the mortality risk of patients with community-acquired pneumonia: a retrospective propensity-matched analysis of the MIMIC-IV database. **15**, 1402386, (2024). 10.3389/fphar.2024.1402386
16. Kor, D. J. et al. Effect of Aspirin on Development of ARDS in At-Risk Patients Presenting to the Emergency Department: The LIPS-A Randomized Clinical Trial. *Jama* **315**, 2406–2414 (2016).
17. Toner, P. et al. Aspirin as a Treatment for Acute Respiratory Distress Syndrome: a randomised placebo controlled clinical trial. *Chest* (2021).
18. Johnson, A. E. W. et al. MIMIC-IV, a freely accessible electronic health record dataset. *Scientific Data* **10** (2023).

19. Aboonabi, A., Singh, I. J. B. & Pharmacotherapy The effectiveness of antioxidant therapy in aspirin resistance, diabetes population for prevention of thrombosis. **83**, 277–282 (2016).
20. Shen, Y. et al. Impact of chronic respiratory diseases on re-intubation rate in critically ill patients: a cohort study. (2021).
21. Yang, H. M. et al. Chronic Obstructive Pulmonary Disease Exacerbations Increase the Risk of Subsequent Cardiovascular Events: A Longitudinal Analysis of the COPDGene Study. 13 (2024).
22. Zajac, J. D. & Andrikopoulos, S. J. M. J. o. A. Diabetes care for hospital patients in Australia needs repair. 215 (2021).
23. Ludwig, N., Hilger, A., Zarbock, A. & Rossaint, J. Platelets at the Crossroads of Pro-Inflammatory and Resolution Pathways during Inflammation. *Cells* 11, (2022). 10.3390/cells11121957
24. Camprubí-Rimblas, M., Tantinyà, N., Bringué, J., Guillamat-Prats, R. & Artigas, A. Anticoagulant therapy in acute respiratory distress syndrome. *Annals Translational Med.* **6**, 36–36 (2018).
25. Zimmermann, P. & Curtis, N. The effect of aspirin on antibiotic susceptibility. *Expert Opin. Ther. Targets*. **22**, 967–972. 10.1080/14728222.2018.1527314 (2018).
26. Rossaint, J., Thomas, K., Mersmann, S., Skupski, J. & Zarbock, A. Platelets orchestrate the resolution of pulmonary inflammation in mice by T reg cell repositioning and macrophage education. *The J. experimental medicine* **218**, e20201353 .
27. Lu, Z. et al. The impact of aspirin exposure prior to intensive care unit admission on the outcomes for patients with sepsis-associated acute respiratory failure. *Front. Pharmacol.* **14**, 1125611. 10.3389/fphar.2023.1125611 (2023).
28. Sagar, R. C., Naseem, K. M. & Ajjan, R. A. Antiplatelet therapies in diabetes. *Diabetic Medicine* **37** (2020).
29. Cox, R. et al. Enhanced Resolution of Hyperoxic Acute Lung Injury as a result of Aspirin Triggered Resolvin D1 Treatment. *Am. J. Respiratory Cell. Mol. Biology*. **53**, 422 (2015).
30. Boyle, A. et al. Aspirin therapy in patients with acute respiratory distress syndrome (ARDS) is associated with reduced intensive care unit mortality: a prospective analysis. *Crit. Care. (London, England)*. **19**, 109. 10.1186/s13054-015-0846-4 (2015).
31. Ciszewski, W., Woźniak, L. & Sobierajska, K. Diverse roles of SARS-CoV-2 Spike and Nucleocapsid proteins in EndMT stimulation through the TGF-β-MRTF axis inhibited by aspirin. *Cell. communication signaling: CCS*. **22**, 296. 10.1186/s12964-024-01665-z (2024).
32. Spite, M. & Serhan, C. Novel lipid mediators promote resolution of acute inflammation: impact of aspirin and statins. *Circul. Res.* **107**, 1170–1184. 10.1161/circresaha.110.223883 (2010).
33. Damien, P., Cognasse, F., Payrastre, B., Spinelli, S. L. & Hamzeh-Cognasse, H. NF-κB Links TLR2 and PAR1 to Soluble Immunomodulator Factor Secretion in Human Platelets. *Front. Immunol.* **8**, 85 (2017).
34. Zhao, Y. L. et al. Resolvin D1 Protects Lipopolysaccharide-induced Acute Kidney Injury by Down-regulating Nuclear Factor-kappa B Signal and Inhibiting Apoptosis. *Chin. Med. J.* **129**, 1100–1107 (2016).
35. Ornelas, A. et al. Beyond COX-1: the effects of aspirin on platelet biology and potential mechanisms of chemoprevention. *Cancer & Metastasis Reviews* (2017).
36. Blerim, M. et al. Aspirin use is associated with increased risk for incident heart failure: a patient-level pooled analysis. **9**, (2021). 10.1002/ehf2.13688
37. Lennart, W., Lars, W., Arne, B. & Anders, O. J. P. D. S. Aspirin increases mortality in diabetic patients without cardiovascular disease: a Swedish record linkage study. **18**, (2009). 10.1002/pds.1828
38. Delgaudio, J. M., Levy, J. M. & Wise, S. K. Central compartment involvement in aspirin-exacerbated respiratory disease: the role of allergy and previous sinus surgery. *International Forum Allergy Rhinology* **9** (2019).
39. Ahmad, S., Ali, M. S., Alam, M. I., Alam, M. S. & Ali, M. Drug Interactions of OTC Analgesics-Aspirin: A Review. *Res. J. Pharm. Technol.* **8**, 580–586 (2015).
40. Relvas, M. et al. Effects of Aspirin on Kidney Biopsy Bleeding Complications: A Systematic Review and Meta-Analysis (PROSPERO 2021 CRD42021261005). *Kidney360* 4, 700–710 (2023).
41. Stolarek, W., Kasprzak, M., Sikora, J., Sieminska, E. & Grzesk, G. High on-treatment platelet reactivity to aspirin in patients after myocardial infarction. *Biomedicine & pharmacotherapy =: Biomedecine & pharmacotherapie* (2022).
42. Ayonrinde, O. T. et al. Prior oral proton-pump inhibitor use is associated with reduced severity of aspirin-related upper gastrointestinal bleeding in older people. *Internal Med. journal*, 52 (2022).
43. Ogedegbe, O. J. et al. Reye Syndrome: Dangers of Aspirin Use in Children. *International J. Sci. Advances* (2022).
44. Bundhun, P. K., Janoo, G., Teeluck, A. R. & Huang, W. Q. J. B. C. D. Adverse clinical outcomes associated with a low dose and a high dose of aspirin following percutaneous coronary intervention: a systematic review and meta-analysis. **16**, 169 (2016).

Figures

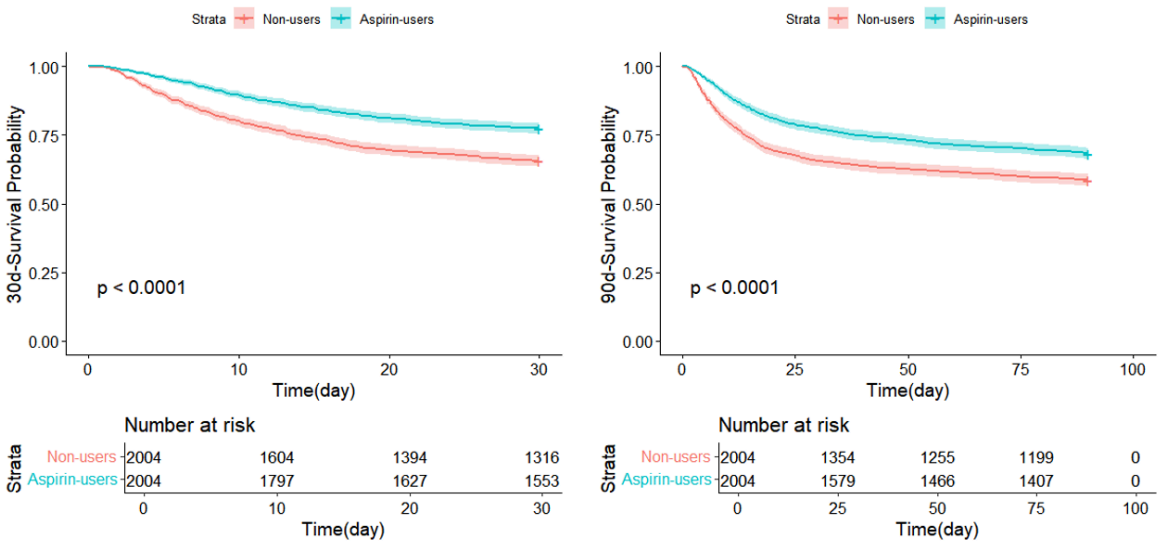


Fig 1. Kaplan-veier survival curves between two groups indicated the 30-day and 90-day mortality risk for the ARF patients

Figure 1

See image above for figure legend.

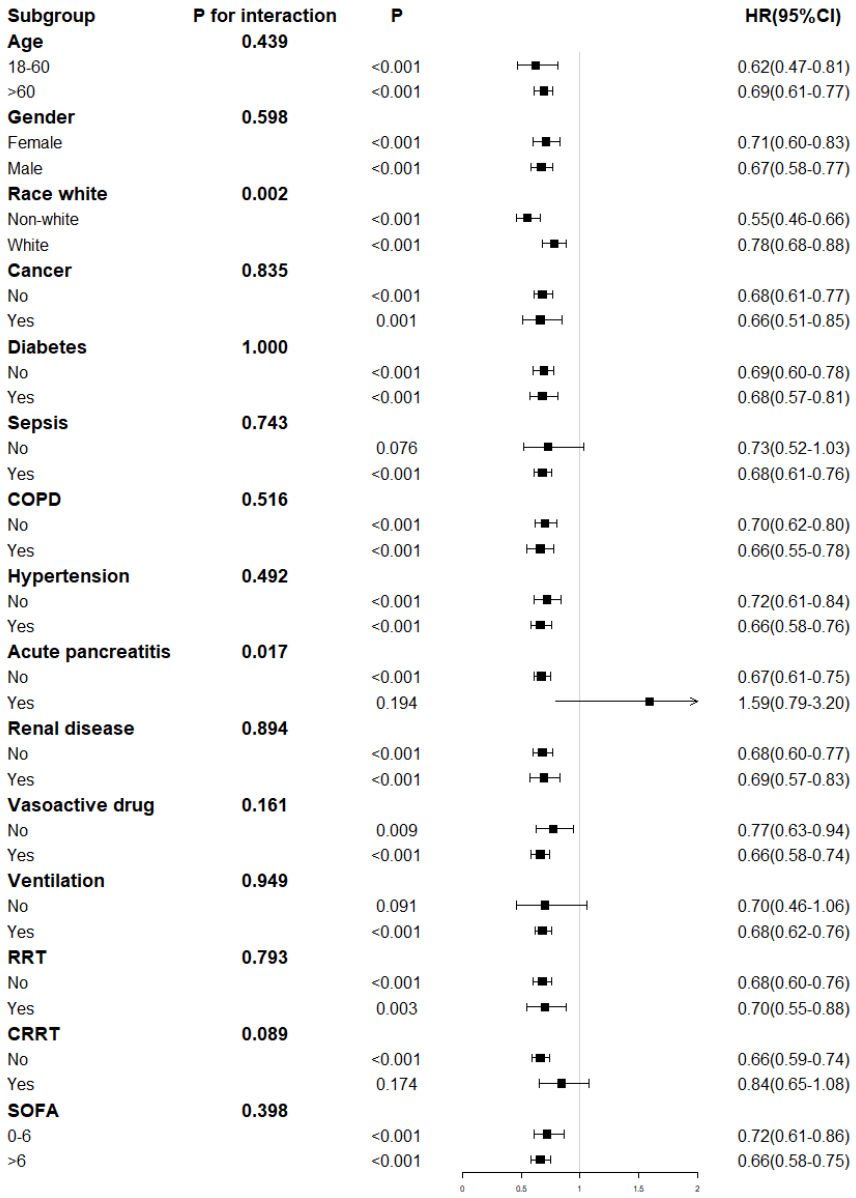


Figure 2

Legend not included with this version.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfigure1.png
- Supplementaryfigure2Loveplotaspirinarf.png
- SupplementaryTable13.xls