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Early acetaminophen administration is associated with lower mortality among ARDS patients after coronary artery bypass grafting: a retrospective study

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Abstract

Background Acetaminophen (APAP) is widely used in the treatment of patients after surgery, but the prognosis of patients with coronary artery bypass grafting (CABG)-related acute respiratory distress syndrome (CABG-ARDS) is still unclear. This study aims to explore the role of APAP in the management of CABG related ARDS.

Methods We collected clinical data on patients with CABG-ARDS from the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database. The primary outcome was early mortality after ARDS, and the secondary outcomes were length of hospital stay and duration of mechanical ventilation (MV). Multivariate logistic regression and Cox regression models were used for statistical analysis, and inverse probability processing weighting (IPTW), overlap weighting (OW) and propensity score matching (PSM) were used to explore the robustness of the outcomes.

Results A total of 5459 patients were enrolled in the analysis. Multivariate logistic regression analysis revealed that the 14-day mortality in APAP group was significantly lower than that in non-APAP group (0.5% vs. 2.7%, OR = 0.301; 95% CI, 0.170–0.531; $P < 0.001$). The APAP group also showed a significant advantage in Cox regression analysis (0.5% vs. 2.7%, HR = 0.329; 95% CI, 0.187–0.577; $P < 0.001$). IPTW, OW, and PSM analyses were conducted between the two groups, and the differences remained significant. These results were consistent in 30-, 60-, and 90-day mortality analyses. Meanwhile, exposure to APAP was associated with a shorter length of hospital stay and a reduced duration of MV ($P < 0.001$).

Conclusion The administration of APAP was associated with reduced early mortality in patients with CABG-ARDS, as well as shorter length of hospital stay and duration of MV.

Keywords Coronary artery bypass grafting, Acute respiratory distress syndrome, Acetaminophen, MIMIC-IV, Mortality

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Introduction

Coronary artery bypass grafting (CABG) is the standard surgical procedure for the treatment of complex coronary artery disease, and its success and safety have significantly improved in the past few decades. However, postoperative complications are still important factors affecting the prognosis of patients, among which acute respiratory distress syndrome (ARDS) has attracted much attention due to its high morbidity and mortality [1, 2]. Patients often develop respiratory distress, refractory hypoxemia, and diffuse infiltrates in both lungs within a short period of time after surgery [3, 4]. The mechanism of CABG-related ARDS (CABG-ARDS) is complex. Its pathophysiological process involves the inflammatory response of the lung, the increase of pulmonary capillary permeability, the decrease of lung compliance, and the imbalance of ventilation/blood flow ratio [5]. Optimization of its management strategy is crucial to improve the prognosis of patients.

The choice of drug therapy is particularly critical in the treatment of CABG-ARDS. Traditionally, analgesics are mainly used to relieve postoperative pain, but in recent years, numerous studies have shown that some analgesics may also have a positive effect on postoperative complications through their non-analgesic mechanisms. Acetaminophen (APAP) is a widely used antipyretic and analgesic drug with definite effects and relatively few side effects. It is worth noting that APAP has antioxidant function, which can neutralize free radicals and reduce tissue damage caused by oxidative stress [6]. A randomized, double-blind, placebo-controlled trial study in patients with severe sepsis found that APAP reduced oxidative damage by lowering plasma F2-isoprostane levels and was more effective than placebo in reducing creatinine [7]. However, the value of APAP in patients with CABG-ARDS has not been fully explored.

We conducted this retrospective cohort study based on a large public database with the aim of exploring the relationship between early APAP use and different outcomes in patients with CABG-ARDS. Our hypothesis was that early use of APAP would reduce mortality and shorten length of hospital stay and mechanical ventilation (MV) in patients with CABG-ARDS. This study may provide a new perspective for the management and new clinical treatment strategies of lung injury after CABG.

Methods

Data sources and study population

This retrospective cohort study was performed by analyzing patient data extracted from the MIMIC-IV v3.0 database, which was developed by the Massachusetts Institute of Technology (MIT), Beth Israel Deaconess Medical Center (BIDMC), and Philips Healthcare. The database includes 94,458 de-identified medical records of patients receiving critical care at BIDMC between 2008 and 2022. The institutional review boards at BIDMC (protocol number 2001-P-001699/14) and MIT (protocol number 040300020206) approved the collection and use of study-related data, including a waiver for obtaining informed consent. In our research team, author HS Cao has completed the training program of collaborative institutions (certification number: 63137030).

Inclusion and exclusion criteria

Eligibility was assessed for all patients in the database who were admitted to the intensive care unit (ICU) after cardiac surgery, and selected patients were at least 18 years of age and underwent their first CABG procedure. Procedure coding for CABG was based on the international code of surgery and operations for disease, ninth edition (ICD-9) and tenth edition (ICD-10), with relevant codes shown in the Supplementary material Table S1. For patients with multiple ICU admissions after CABG, only the record of the first ICU stay was included, and patients with ICU stay less than 24 h and non-ARDS were excluded (Fig. 1). The diagnosis of ARDS was based on the new global definition revised by Kigali [8], which updated the diagnostic criteria established in Berlin in 2012 [9]. This new method utilized pulse oxygen saturation (SpO_2) as an alternative to arterial oxygen pressure (PaO_2), particularly addressing its applicability in non-intubated patients or in resource-limited settings. The severity of ARDS was diagnosed and graded as follows: Mild: $200 < PaO_2/\text{fraction of inspiration oxygen } (FiO_2) \leq 300$ or $235 \leq SpO_2/FiO_2 \leq 315$ (if $SpO_2 \leq 97\%$); Moderate: $100 < PaO_2/FiO_2 \leq 200$ or $148 < SpO_2/FiO_2 \leq 235$ (if $SpO_2 \leq 97\%$); Severe: $PaO_2/FiO_2 \leq 100$ or $SpO_2/FiO_2 \leq 148$ (if $SpO_2 \leq 97\%$). The severity of ARDS was determined by selecting the more severe result obtained from either the PaO_2/FiO_2 or SpO_2/FiO_2 ratio, depending on which method was used and the patient's specific SpO_2 level.

Data collection and processing

Structured query language was used to extract data from MIMIC-IV database. The data collected included: (1) Demographic characteristics: age, sex, race, body mass index (BMI), admission type, surgery type and severity of ARDS; (2) Vital signs: heart rate, mean arterial pressure (MAP), respiratory rate and temperature; (3) Laboratory tests: white blood cell count (WBC), platelet count (PLT), hemoglobin content (Hb), pH, PaO_2 and carbon dioxide pressure ($PaCO_2$); (4) Comorbidities: congestive heart failure, chronic pulmonary disease, diabetes, cerebrovascular disease, peripheral vascular disease and chronic renal disease; (5) Clinical scoring systems: Oxford acute severity of illness score (OASIS), systemic inflammatory response syndrome (SIRS), sequential organ failure

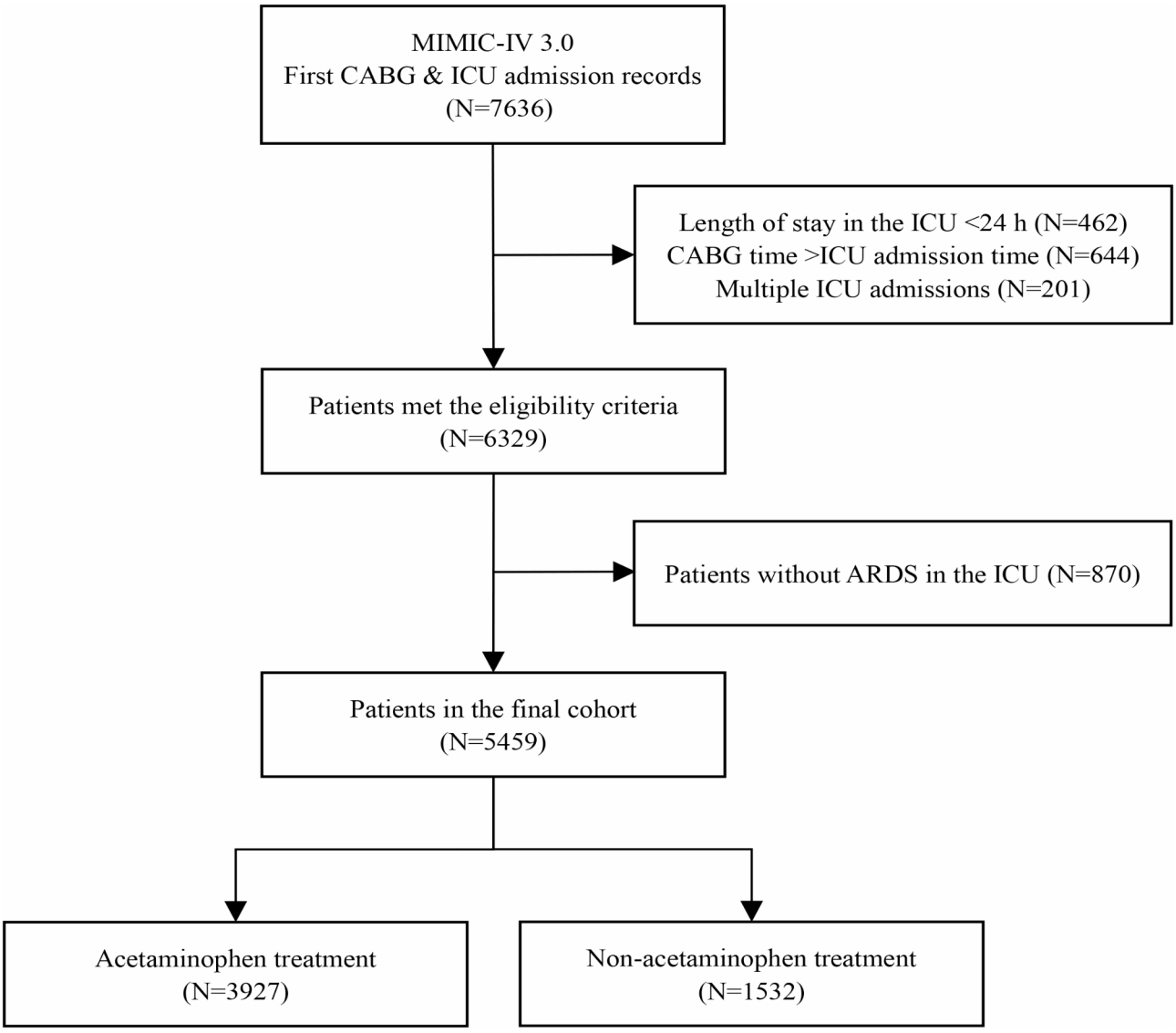

Fig. 1 Study flow chart
MIMIC-IV, medical information mart for intensive care-IV; CABG, coronary artery bypass grafting; ICU, intensive care unit; ARDS, acute respiratory distress syndrome

assessment (SOFA), etc. Variables in the database that were missing by more than 20% were removed, while those missing less than 20% were imputed with the use of multiple imputation. The multiple imputation method was based on the random forest method in the mice package of R language and details of missing covariates are shown in Supplementary material Figure S1. Multiple collinearity between variables was tested by variance inflation factor (VIF), and any variable with VIF greater than 3 was excluded (Supplementary material Table S2). APAP exposure was defined as at least 1 dose of any form of APAP given within 48 h of the ARDS diagnosis based on the above, whereas patients given APAP after 48 h were considered unexposed.

Outcomes

The study focused on four primary outcomes of mortality at 14-, 30-, 60-and 90-day after diagnosis of the most severe type of ARDS while in the ICU. Additionally, the length of hospital stay and the duration of MV between the exposed and non-exposed groups were analyzed as secondary outcomes in the study results.

Statistical analysis

R language (version 4.2.3) were used for data analysis and visualization. Normally distributed continuous variables were compared between groups using *t*-tests, and the results were listed as mean ± standard deviation. Non-normally distributed continuous variables were tested using Mann-Whitney *U* tests, and the results were

expressed as median [interquartile range, IQR]. Categorical variables were compared between groups using χ^2 or Fisher's exact tests, and results are presented as percentages. $P<0.05$ was considered a statistically significant difference.

Kaplan-Meier (K-M) survival curves were used to analyze the difference in survival between the two groups, and a Log-rank test of $P<0.05$ was used to consider the difference statistically significant. Then we performed sensitivity analysis. First, we used multivariate logistic regression analyses to describe the association between APAP exposure after CABG-ARDS and postoperative mortality at multiple time points. Second, multivariate Cox regression analysis was used to further explore the relationship between exposure and the primary outcome after adjusting for the differences in baseline data between patients who were and were not given APAP after surgery. Before constructing Cox regression models, we used collinearity diagnostics and proportional-hazards hypothesis testing to assess the feasibility of modeling. Finally, we calculated the propensity score (PS) based on the values of covariates to estimate the likelihood of APAP treatment after surgery. We used inverse probability of treatment weighting (IPTW), overlap weighting (OW) and 1:1 propensity score matching (PSM) to reduce the bias between the two groups to varying degrees. The standardized mean difference (SMD) between the two groups was calculated to judge the balance of each covariate, with SMD > 0.1 indicating imbalance in baseline data.

The robustness of the relationship between exposure and primary outcomes was explored by analyzing all covariates from different dimensions in a multi-model strategy based on Cox regression analysis. Five nested models were constructed by progressively incorporating demographic characteristics, vital signs, laboratory tests, comorbidities, and clinical scoring systems based on crude models. In addition, we performed separate complementary analyses for admission type, medication use, intraoperative cardiopulmonary bypass (CBP) use (based on ICD-9), and absence of missing covariates to further explore the relationship between APAP use and outcomes.

In the subgroup analysis, the subgroups were divided according to age, sex, race, BMI, surgery type, ARDS grade, presence of chronic pulmonary disease, and SOFA score. Multivariate Cox regression analyses were used to simultaneously adjust for all of the above variables and to assess potential interactions between APAP use and subgroup-specific variables. Significant interactions were considered if the *P*-value for the interaction was less than 0.05.

We also explored possible unmeasured confounding between exposure and 14-, 30-, 60-, and 90-day mortality by calculating E-values [10, 11], which quantify the magnitude required for an unmeasured confounding factor that could negate the observed association between APAP and mortality at different times.

Results

Study population

We searched for records of 7636 ICU admissions after CABG, and a total of 5459 patients were ultimately eligible for the study. The APAP group comprised 3927 individuals with a median age of 69 years (IQR, 62–76), while the non-APAP group consisted of 1532 patients with a median age of 70 years (IQR, 63–77). The majority of patients in both groups were male. Concomitant valve surgery was performed in 862 patients (22%) in the APAP group, a slightly lower rate than in the non-APAP group (424, 27.7%). The prevalence of mild and moderate ARDS was significantly higher in the APAP group, while severe ARDS was more frequent in the non-APAP group (35.2% vs. 22.4%). In the APAP group, the values for MAP (median [IQR], 75 [71,79] mmHg), temperature (median [IQR], 36.6 [36.4,36.8] °C), Hb (median [IQR], 10.4 [9.4,11.5] g/dL), pH (median [IQR], 7.37 [7.35,7.40]), and PaO_2 (mean ± standard deviation, 241.6 ± 50.8 mmHg) were higher than those in the non-APAP group. However, OASIS (median [IQR], 33 [28, 37]), SOFA (median [IQR], 6 [4, 7]) scores, and the incidence of comorbidities were higher in the APAP group, the remaining baseline data are shown in Table 1.

Outcomes

The K-M survival curve showed that the survival difference between the two groups was statistically significant (Log-rank $P<0.05$) (Fig. 2). In the traditional multivariate logistic regression analysis, the 14-day mortality of ARDS patients in the APAP group was considerably lower compared to those not receiving APAP (0.5% vs. 2.7%, OR = 0.301; 95% CI, 0.170–0.531; $P<0.001$). The K-M curves for the four primary outcomes were between the APAP and non-APAP groups and did not cross each other, which was consistent with the proportional-hazards assumption. In multivariate Cox regression analysis, the APAP group also exhibited a lower 14-day mortality (0.5% vs. 2.7%, HR = 0.329; 95% CI, 0.187–0.577; $P<0.001$). After calculating PS by weighting and matching, IPTW, OW and PSM analyses were performed between the two groups, and the SMDs of each covariate obtained in all three ways were less than 0.1 (Supplementary material Figure S2), and the difference in mortality at 14-day after ARDS between the two groups was still significant, with IPTW (HR = 0.320; 95% CI, 0.182–0.563; $P<0.001$), OW (HR = 0.312; 95% CI, 0.176–0.554; $P<0.001$), and PSM (HR = 0.277; 95% CI, 0.137–0.560; $P<0.001$) (Fig. 3). The baseline data of the APAP group

Table 1 Baseline characteristics of the original cohort

Variables	Total (*n* = 5459)	Non-APAP group (*n* = 1532)	APAP group (*n* = 3927)	*P* value
Demographic characteristics				
Age, years	69 [62, 76]	70 [63, 77]	69 [62, 76]	< 0.001
Sex, male, *n*(%)	4272 (78.3)	1177 (76.8)	3095 (78.8)	0.110
Race (%)				0.104
White	3882 (71.1)	1065 (69.5)	2817 (71.7)	
Others	1577 (28.9)	467 (30.5)	1110 (28.3)	
BMI, kg/m^2	28.9 [25.7, 32.7]	29.0 [25.7, 33.0]	28.9 [25.8, 32.5]	0.355
Admission type (%)				0.023
Elective	472 (8.7)	111 (7.3)	361 (9.2)	
Urgent	1749 (32.0)	521 (34.0)	1228 (31.3)	
Others	3238 (59.3)	900 (58.8)	2338 (59.5)	
Surgery type (%)				< 0.001
CABG	4173 (76.4)	1108 (72.3)	3065 (78.1)	
CABG + Valve	1286 (23.6)	424 (27.7)	862 (22.0)	
ARDS (%)				< 0.001
Mild	1664 (30.5)	371 (24.2)	1293 (32.9)	
Moderate	2378 (43.6)	622 (40.6)	1756 (44.7)	
Severe	1417 (26.0)	539 (35.2)	878 (22.4)	
Vital signs				
Heart rate, bpm	81 [76, 87]	81 [77, 87]	81 [76, 87]	0.543
MAP, mmHg	75 [71, 79]	74 [70, 78]	75 [71, 79]	< 0.001
Respiratory rate, bpm	17 [16, 19]	17 [16, 19]	17 [16, 18]	0.002
Temperature, ℃	36.6 [36.3, 36.8]	36.5 [36.3, 36.8]	36.6 [36.4, 36.8]	0.006
Laboratory tests				
WBC, 10^9/L	13.2 [10.4, 16.9]	13.3 [10.4, 17.0]	13.2 [10.4, 16.8]	0.486
PLT, 10^9/L	156 [128, 190]	154 [126, 190]	157 [130, 190]	0.091
Hb, g/dL	10.3 [9.3, 11.4]	10.1 [9.1, 11.2]	10.4 [9.4, 11.5]	< 0.001
pH	7.37 [7.35, 7.40]	7.37 [7.34, 7.39]	7.37 [7.35, 7.40]	< 0.001
PaO_2, mmHg	240.3 ± 50.6	236.9 ± 50.1	241.6 ± 50.8	0.002
$PaCO_2$, mmHg	41 [39, 44]	41 [39, 44]	41 [39, 44]	0.141
Comorbidities				
Congestive heart failure, *n* (%)	1477 (27.1)	512 (33.4)	965 (24.6)	< 0.001
Chronic pulmonary disease, *n* (%)	580 (10.6)	184 (12.0)	396 (10.1)	0.038
Diabetes, *n* (%)	2399 (44.0)	737 (48.1)	1662 (42.3)	< 0.001
Cerebrovascular disease, *n* (%)	584 (10.7)	191 (12.5)	393 (10.0)	0.008
Peripheral vascular disease, *n* (%)	740 (13.6)	256 (16.7)	484 (12.3)	< 0.001
Chronic renal disease, *n* (%)	1082 (19.8)	363 (23.7)	719 (18.3)	< 0.001
Clinical scoring systems				
OASIS	33 [29, 38]	33 [29, 38]	33 [28, 37]	< 0.001
SIRS	3 [2, 3]	3 [2, 3]	3 [2, 3]	0.214
SOFA	5 [4, 7]	6 [4, 7]	5 [4, 7]	< 0.001
Clinical outcomes				
14-day mortality (%)	62 (1.1)	42 (2.7)	20 (0.5)	< 0.001
30-day mortality (%)	87 (1.6)	56 (3.7)	31 (0.8)	< 0.001
60-day mortality (%)	125 (2.3)	71 (4.6)	54 (1.4)	< 0.001
90-day mortality (%)	150 (2.8)	81 (5.3)	69 (1.8)	< 0.001
Hospital stay, days	5.0 [4.1, 6.9]	5.5 [4.3, 8.0]	4.9 [4.0, 6.2]	< 0.001
Duration of MV, days[a]	0.4 [0.2, 0.8]	0.6 [0.3, 1.0]	0.3 [0.2, 0.7]	< 0.001

APAP, acetaminophen; BMI, body mass index; CABG, coronary artery bypass grafting; ARDS, acute respiratory distress syndrome; MAP, mean arterial pressure; WBC, white blood cell; PLT, platelet; Hb, hemoglobin; PaO_2, arterial oxygen pressure; $PaCO_2$, carbon dioxide pressure; OASIS, Oxford acute severity of illness score; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment; MV, mechanical ventilation

[a] Among the 5459 patients, MV records were available for 4481 patients, with 3233 in the APAP group and 1248 in the Non-APAP group

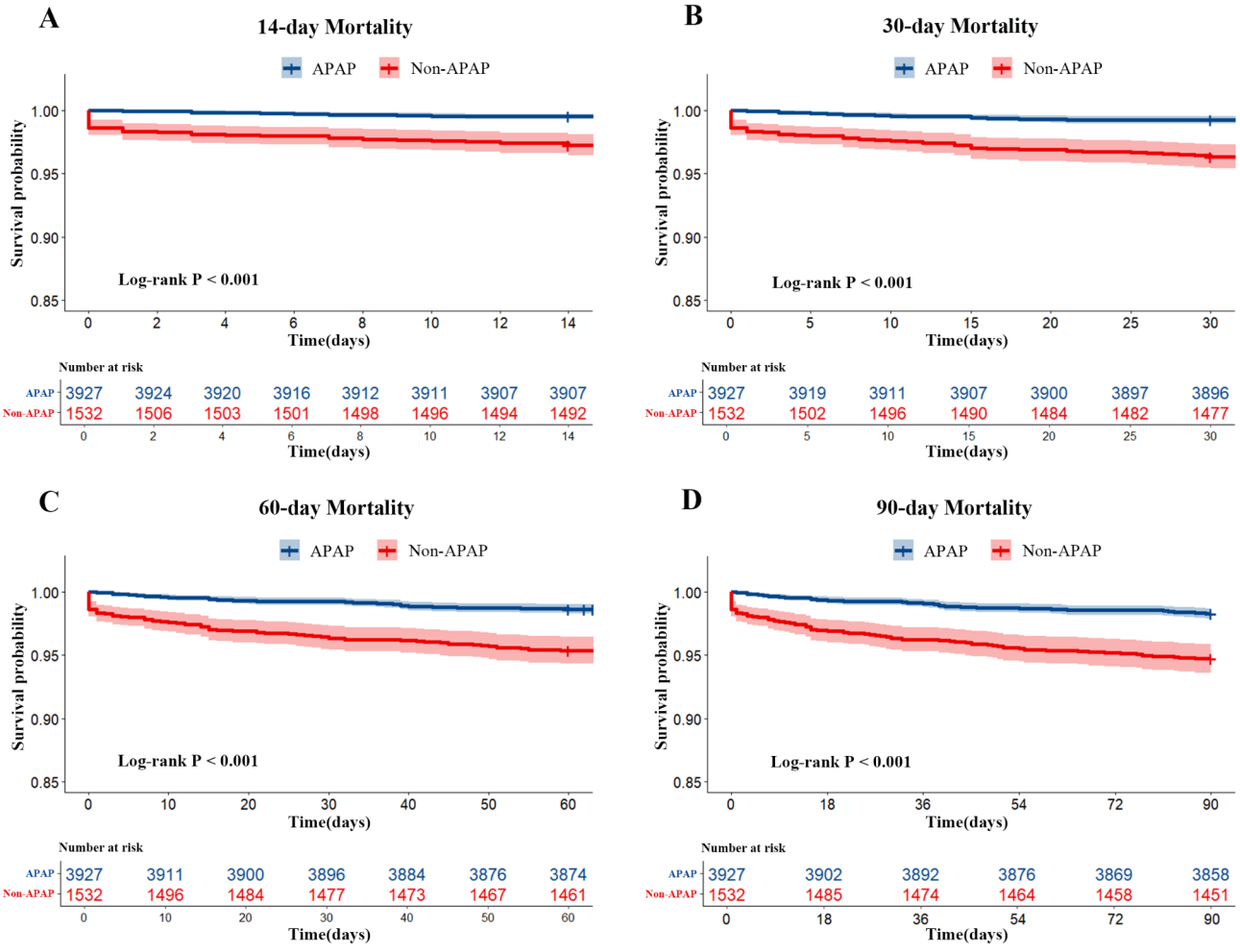

Fig. 2 Kaplan-Meier (K-M) survival analysis curve. (**A**) 14-day K-M survival curves; (**B**) 30-day K-M survival curves; (**C**) 60-day K-M survival curves; (**D**) 90-day K-M survival curves
APAP, acetaminophen

and the non-APAP group before and after weighting and matching are compared in Supplementary material Table S3-5. Multivariate Cox regression was used to examine the association between APAP and primary outcomes. In a crude model of univariate Cox regression analysis, APAP administration was strongly associated with an 81.6% lower probability of mortality at 14-day after ARDS (HR = 0.184; 95% CI, 0.108–0.313; $P < 0.001$). Models I to V were adjusted for demographic characteristics, vital signs, laboratory tests, comorbidities, and clinical scoring systems on the basis of the crude model. Although the effect size HR and 95% CI were higher in the crude model, the difference was still statistically significant ($P < 0.001$). The administration of APAP demonstrated a significant positive impact on reducing the risk of mortality within 14 days (HR = 0.329; 95% CI, 0.187–0.577; $P < 0.001$). The same analysis also validated the significance and robustness of the differences in 30-, 60-, and 90-day mortality between the two groups (Table 2).

In the supplementary analysis, separate evaluations of admission type, medication use, intraoperative CPB use (based on ICD-9), and the absence of missing covariates showed results consistent with those of the primary analysis (Supplementary material Table S6-9).

In the statistical analysis of secondary outcomes, the length of hospital stay (median [IQR], 4.9 [4.0,6.2] days) and duration of MV (median [IQR], 0.3 [0.2,0.7] days) were lower in the APAP group compared with the non-APAP group, and the difference in secondary outcomes between the two groups was statistically significant ($P < 0.001$) (Table 1).

We explored potential unmeasured confounding between exposure and mortality by calculating E-values. The observed association between APAP and 14-, 30-, 60-, and 90-day mortality required HR greater than 5.529, 4.760, 3.439, and 3.059, respectively, to be explained by an unmeasured confounding factor (Fig. 4 and Supplementary material Table S10). This suggests that other

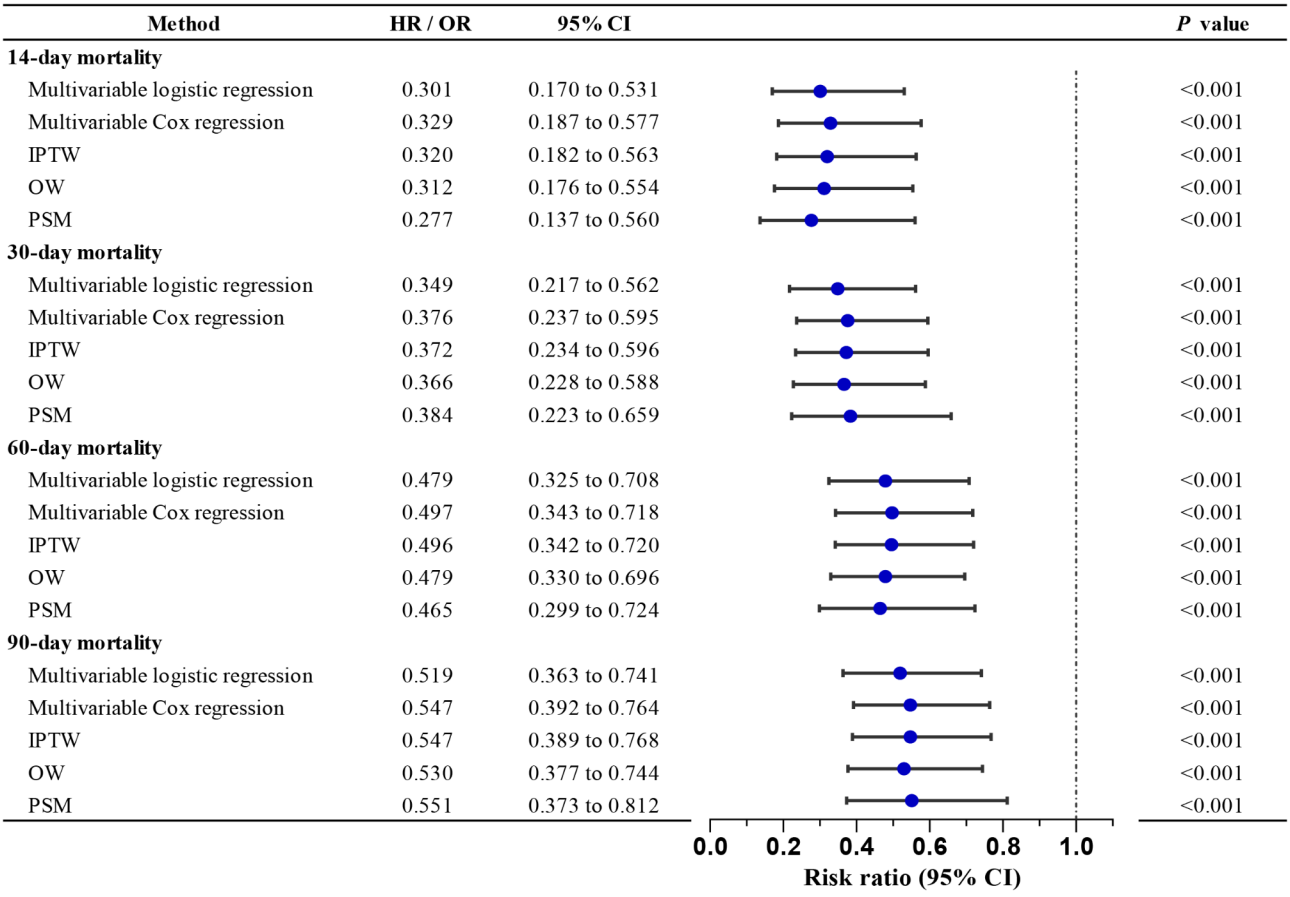

Fig. 3 Comparative analysis of mortality in CABG-ARDS patients across five statistical models. Comparison of 14-, 30-, 60-, and 90-day mortality in the APAP and non-APAP groups of CABG-ARDS patients by five statistical methods, multivariate logistic regression, multivariate Cox regression, IPTW, OW and PSM

HR, hazard ratio; OR, odds ratio; CI, confidence interval; IPTW, inverse probability of treatment weighting; OW, overlap weighting; PSM, propensity score matching; APAP, acetaminophen; CABG, coronary artery bypass grafting; ARDS, acute respiratory distress syndrome

unknown or unmeasured factors have a relatively small effect on mortality.

Subgroup analysis

The results of subgroup analyses were consistent and robust with the main results, and no interaction was found between subgroups (P interaction > 0.05). The association between APAP exposure and the severity of ARDS was more pronounced in the three ARDS subgroups (Fig. 5).

Discussion

In this study, we performed a retrospective analysis using the large publicly available MIMIC-IV database. Among patients with ARDS after CABG, the use of APAP was associated with significantly lower mortality, shorter length of hospital stay, and shorter duration of MV. After adjusting for potential confounding factors by various statistical methods, the use of APAP remained associated with significantly lower mortality and shorter duration of MV. This provides clinicians with new therapeutic ideas in the treatment of CABG-ARDS patients and brings valuable insights into the development of more effective treatment strategies.

ARDS is a life-threatening respiratory failure characterized by acute hypoxemia and bilateral imaging infiltrates [12] with a mortality rate of approximately 15% [13]. The pathogenesis of CABG-ARDS is multifaceted and includes an inflammatory response, lung injury, systemic reactions, and various risk factors during the perioperative period. Patients undergoing CABG surgery are affected by multiple cardiovascular comorbidities. In addition, ARDS is more common after cardiac surgery, and treatment regimens used for patients with traditional ARDS (e.g., prone position) may not be appropriate for cardiac surgery, which poses a challenge for their management [14]. Current ARDS management remains largely supportive, with a focus on strategies aimed at limiting further lung injury.

Table 2 Correlation of early APAP use with 14-day, 30-day, 60-day, and 90-day mortality in CABG-ARDS cohort

Category	Models	HR	95%CI	*P* value
14-day mortality	Crude Model	0.184	0.108–0.313	< 0.001
	Model I	0.249	0.145–0.427	< 0.001
	Model II	0.281	0.162–0.485	< 0.001
	Model III	0.317	0.182–0.552	< 0.001
	Model IV	0.307	0.176–0.535	< 0.001
	Model V	0.329	0.187–0.577	< 0.001
30-day mortality	Crude Model	0.213	0.137–0.330	< 0.001
	Model I	0.293	0.188–0.458	< 0.001
	Model II	0.335	0.214–0.527	< 0.001
	Model III	0.373	0.236–0.587	< 0.001
	Model IV	0.363	0.230–0.573	< 0.001
	Model V	0.376	0.237–0.595	< 0.001
60-day mortality	Crude Model	0.291	0.204–0.415	< 0.001
	Model I	0.396	0.276–0.567	< 0.001
	Model II	0.441	0.307–0.634	< 0.001
	Model III	0.477	0.331–0.687	< 0.001
	Model IV	0.480	0.333–0.691	< 0.001
	Model V	0.497	0.343–0.718	< 0.001
90-day mortality	Crude Model	0.325	0.236–0.448	< 0.001
	Model I	0.437	0.315–0.605	< 0.001
	Model II	0.487	0.350–0.678	< 0.001
	Model III	0.526	0.377–0.732	< 0.001
	Model IV	0.535	0.384–0.746	< 0.001
	Model V	0.547	0.392–0.764	< 0.001

APAP, acetaminophen; CABG, coronary artery bypass grafting; ARDS, acute respiratory distress syndrome; HR, hazard ratio; CI, confidence interval

Adjusted covariates: Model I: ARDS, age, sex, race, admission type, surgery type, BMI. Model II: Model I + vital signs (heart rate, MAP, respiratory rate, temperature). Model III: Model II + laboratory tests (WBC, PLT, Hb, PH, PaO_2, $PaCO_2$). Model IV: Model III + comorbidities (congestive heart failure, diabetes, cerebrovascular disease, peripheral vascular disease, chronic pulmonary disease, chronic renal disease). Model V: Model IV + clinical scoring systems (OASIS, SIRS, SOFA)

Activation of the inflammatory cascade during CABG is a prominent event that may affect all organs and systems, including the lungs and lung function. Abnormal gas exchange and poor pulmonary mechanism due to increased pulmonary permeability, pulmonary vascular resistance and changes in surfactant content after CPB [15]. On the other hand, chemicals released by damaged lung tissue (such as 7 S protein and procalcitonin after breakdown of type IV collagen) and activation of the inflammatory cascade [16], including polymorphonucleocyte activation and cytokine activation, can lead to severe lung injury [17, 18]. The histological changes after CPB, including alveolar edema, alveolar capillary congestion, accumulation of red blood cells and neutrophils, also aggravate lung injury to a certain extent. At present, much attention has been paid to the new global definition of ARDS revised by Kigali in clinical practice [8]. SaO_2/FiO_2 is used as an alternative to PaO_2/FiO_2 to more easily evaluate the timing of MV treatment. The definition of postoperative ARDS in our study was also based on this, and the most severe indicators were used as the judgment criteria of mild, moderate, and severe ARDS, which also reduced the missing data to a certain extent. Riviello et al. [19] found that among 1046 hospitalized patients, 42 (4%) met the Kigali's modified definition of ARDS, and 30.9% of ARDS patients were admitted to the ICU with a mortality rate of 50%, whereas no patient met the criteria for ARDS according to the traditional Berlin definition. This also demonstrates the rationality and higher sensitivity of Kigali's revised diagnosis.

APAP is a commonly used clinical antipyretic and analgesic, which achieves its cooling and analgesic effects by affecting the hypothalamic thermoregulatory center and inhibiting prostaglandin synthesis [20], as well as having weak anti-inflammatory effects. In sepsis, erythrocytes are damaged and die at an abnormally high rate, releasing cell-free hemoglobin (CFH) into the bloodstream, and overloaded CFH may lead to damage in a variety of organs [21–23]. CFH has been detected in plasma in a variety of disease states such as those undergoing hemodialysis [24], malaria [25], and CABG surgeries [26, 27] etc. APAP may provide protection by minimizing CFH-induced oxidative damage by binding to divalent iron (Fe^{2+}) in CFH and converting it to less reactive trivalent iron (Fe^{3+}) at clinically relevant doses [28–31]. For APAP exposure we based on a multicenter retrospective observational study [32] where 64% of patients admitted to the ICU received APAP therapy, 90% of these critically ill

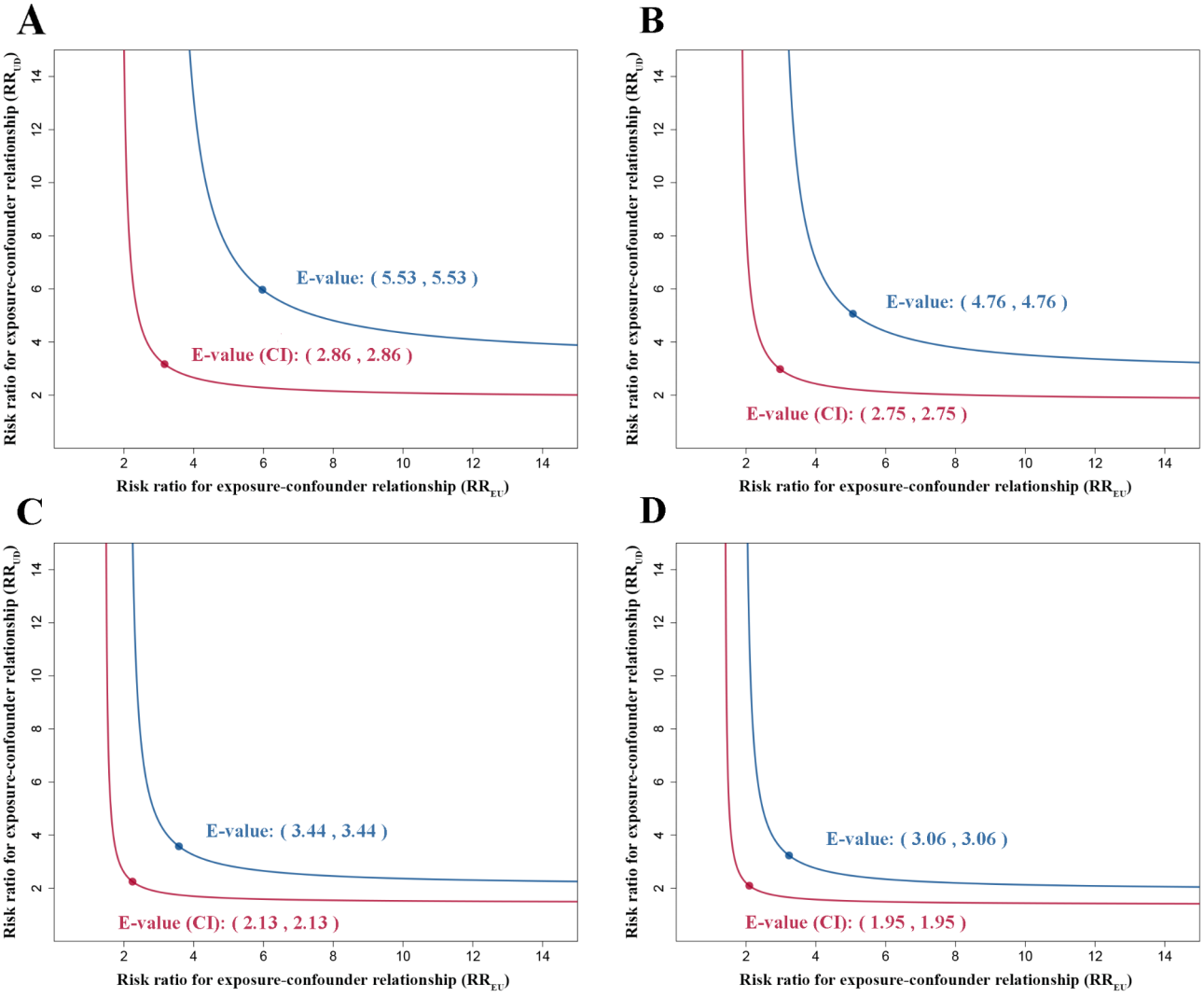

Fig. 4 E-value for mortality association in APAP-treated CABG-ARDS patients. E-value for the lower 95% CI and point estimation in 14-day mortality (**A**), 30-day mortality (**B**), 60-day mortality (**C**), and 90-day mortality (**D**) of CABG-ARDS patients
CI, confidence interval; CABG, coronary artery bypass grafting; ARDS, acute respiratory distress syndrome

patients received the first dose of APAP in the first 2 days and APAP therapy was independently associated with a reduction in in-hospital mortality. 71.9% of patients in this study received APAP therapy that met the exposure criteria, and the utilization of APAP as a commonly used medication in the ICU is similar to other findings reported in the literature, which reported that 58–70% of patients received antipyretic and analgesic therapy [33–35].

APAP exposure reduced short-term mortality in CABG-ARDS patients, and this correlation was found to be strong after correcting for confounders such as demographic characteristics, vital signs, laboratory tests, comorbidities, and clinical scoring systems. After adjusting for covariates by IPTW and PSM, the findings still confirmed the protective effect of APAP exposure. CABG-ARDS usually has a rapid onset, and APAP usually begins to exert pharmacological function within 15 min to 1 h. Dynamic studies have found a linear association between HR and increased mortality endpoints, which weakens with time, thus emphasizing that earlier intervention is important for patient outcomes. Although the classical PS methods can adjust for differences in measured characteristics, these methods have potential limitations. We attempted to use OW to mimic the important attributes of randomized clinical trials [36, 37], to maximize adjustment for balance and maintain precision when the initial balance between the APAP and non-APAP groups differed significantly, and the APAP group in this study maintained the results after OW with traditional logistic regression and Cox regression analyses after adjusting for confounding factors of consistency. This is similar to the Suzuki et al. [32] study, where 9994 surgical patients had better survival improvement after

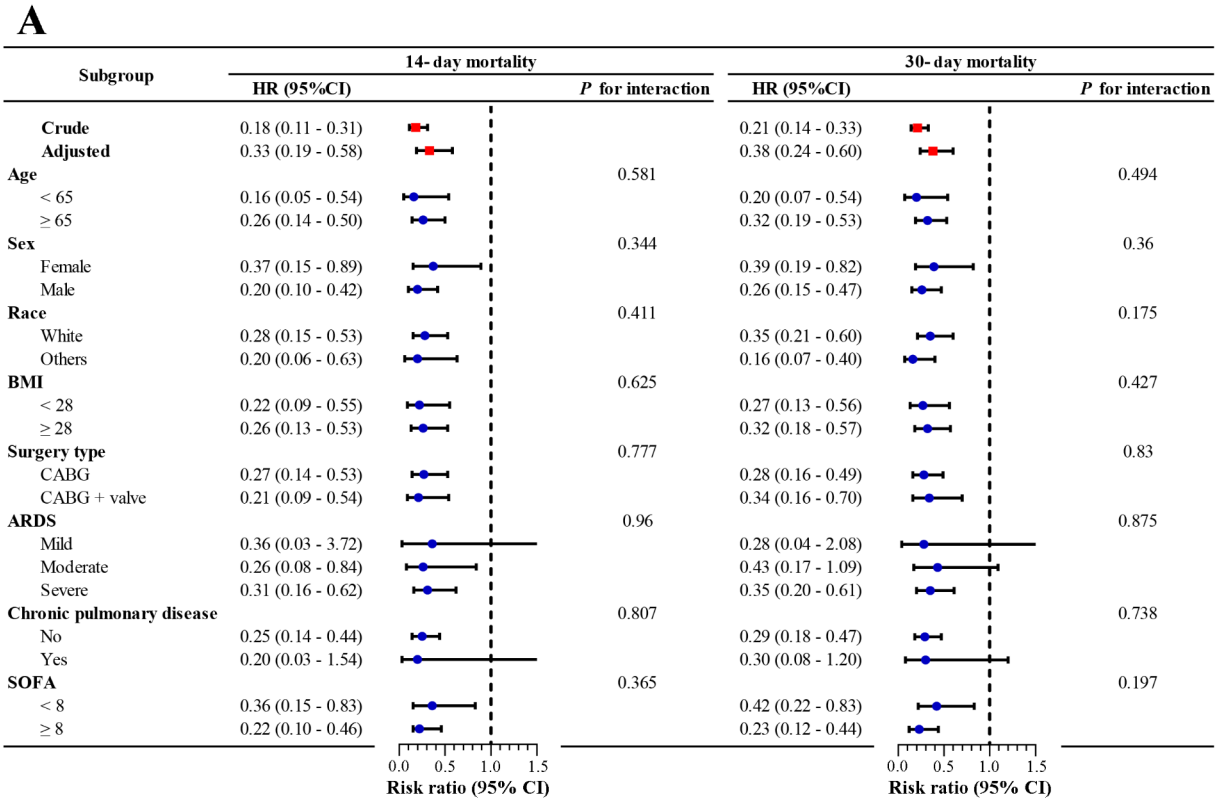

Fig. 5 Subgroup analyses. Early use of APAP was associated with 14-, 30-day mortality (**A**) and 60-, 90-day mortality (**B**) in CABG-ARDS patients
HR, hazard ratio; CI, confidence interval; BMI, body mass index; ARDS, acute respiratory distress syndrome; SOFA, sequential organ failure assessment; APAP, acetaminophen; CABG, coronary artery bypass grafting

APAP administration (HR = 0.64; 95% CI, 0.53–0.77; $P < 0.001$), and the association persisted after using propensity analysis, adjusting for baseline variables. However, the PS models have the inherent limitation of not being able to correct for unmeasured and unincorporated patient characteristics. We attempted to compensate for this limitation by calculating the E-value. The associations between APAP use and 14-, 30-, 60-, and 90-day mortality rates required a HR of at least greater than 3.059 in order to be explained by unmeasured confounders. Thus, it is unlikely that the presence of an unmeasured measured confounder to overcome the effect of the included variables on APAP treatment in this study.

Among secondary outcomes, the length of hospital stay and duration of MV were significantly different between the two groups, however we only found this difference in 4481 patients with a complete record of ventilator use ($P < 0.001$), which is different from previously reported results. In a clinical randomized trial conducted by Ware et al. [6], the number of days survived within 28 days of sepsis and freedom from organ support therapy (dialysis, assisted ventilation, and vasopressor medication) was found to be not significantly different between the APAP and placebo groups, with an all-cause mortality rate of 17% in the APAP group compared with 22% in the placebo group ($P = 0.19$). This discrepancy may be related to the severity of disease in the study population, as the incidence of sepsis after CAGB is low and there are differences in ARDS severity. APAP not only has a mild anti-inflammatory effect, but also can reduce postoperative inflammatory response and stress response through analgesic and antioxidant mechanisms, promote early ambulation and deep breathing, and reduce postoperative pulmonary infection, which highlights the significant advantages of APAP group in terms of secondary outcomes. In addition, acute brain injury (such as stroke, hemorrhage, ischemic brain injury) is one of the serious complications after CABG. Studies have shown that different pulse pressure and oxygen delivery are associated with poor neurological outcomes in ECMO patients [38, 39]. Whether APAP can have a positive effect on brain edema and secondary injury by inhibiting the activity of prostaglandin synthetase needs to be further explored.

There are some limitations of this study. First, we were unable to retrieve a complete record from the database on whether CPB was used during CABG (ICD-10). Given that pathophysiologic changes, inflammatory responses, and ischemia-reperfusion injury during CPB have been associated with patient prognosis [40], this limited our comprehensive assessment of patient prognosis. Second, the dose effect of APAP was not explored in depth in this study, and the adverse reactions that may be triggered during APAP treatment, such as acute liver injury and allergic reactions, were also not analyzed exhaustively. These adverse reactions are incompletely documented in the existing database, and although serious adverse prognosis caused by the drug is relatively rare in clinical practice, its potential risk should not be ignored. Finally, as a retrospective study based on database, this study has some selection bias in the representativeness of the sample, the completeness of the data and the accuracy of ICD entry. Future multi-center studies will be more conducive to verify the universality and reliability of the results of this study.

Conclusion

The use of APAP at 48 h after CABG-ARDS was associated with lower early postoperative mortality, while shortening the length of hospital stay and MV. These studies highlight the potential of APAP as a key component of ARDS management, providing a new perspective and strategy for clinical management.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13019-025-03421-x.

Supplementary Material 1

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Not applicable.

Author contributions

MC, CN contributed to the conception and design of the study; LG, HC contributed to manuscript drafting, software, and data analysis. MZ, YP data acquisition and review; All the authors participated in critical revisions of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study protocol adhered the ethical guidelines of the Declaration of Helsinki. MIMIC-IV is an anonymized public database. The project was approved by the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. As all personal data in the database are de-identified, informed consent was waived.

Competing interests

The authors declare no competing interests.

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