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FULL RESEARCH PAPER
Heart failure and cardiomyopathies

Histamine H2 receptor antagonist exposure was related to decreased all-cause mortality in critical ill patients with heart failure: a cohort study

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See the editorial comment for this article 'The role of histamine H2 receptor antagonist in heart failure: a potential game-changer?', by Tomoya Sato and Tadao Aikawa, https://doi.org/10.1093/eurjpc/zwac140.

Aims Previous studies reported that histamine H2 receptor antagonists (H2RAs) had cardioprotective effects. However, the effect of H2RAs on mortality of critical ill patients with heart failure (HF) remains unclear. The aim of this study was to clarify the association between H2RAs and all-cause mortality of critical ill patients with HF based on Medical Information Mart for Intensive Care III database (MIMIC-III).

Methods and results Propensity score matching (PSM) was applied to account for the baseline differences between two groups that were exposed to H2RAs or not. The study primary outcome was all-cause mortality. Kaplan–Meier curves and multivariable Cox regression models were employed to estimate the effects of H2RAs on mortality of critical ill patients with HF. A total of 10 387 patients were included, involving 4440 H2RAs users and 5947 non-H2RAs users. After matching, 3130 pairs of patients were matched between H2RAs users and non-H2RAs users. The results showed significant association between H2RAs exposure and decreased 30-day, 90-day, and 1-year mortality in both univariate analyses and multivariate analyses [hazard ratio (HR) = 0.73, 95% confidence interval (CI): 0.65–0.83 for 30-day; HR = 0.80, 95%CI: 0.72–0.89 for 90-day; and HR = 0.83, 95%CI: 0.76–0.90 for 1-year mortality, respectively] by Cox regression after PSM. Furthermore, stratified analyses revealed that the 30-day, 90-day, and 1-year mortality of ranitidine users were significantly lower than those of famotidine users, respectively.

Conclusion Histamine H2 receptor antagonists exposure was associated with lower mortality in critical ill patients with HF. Furthermore, ranitidine might be superior to famotidine in reducing mortality of critical ill patients with HF.

Keywords Histamine H2 receptor antagonists • Heart failure • Mortality • Medical information mart for intensive care

Introduction

Heart failure (HF) is a global public health problem, accounting for substantial morbidity and mortality worldwide.[1,2] Despite improvements in treatment, the morbidity and mortality of HF continue to increase due to population ageing and the persistent growth of the population with specific risk factors, such as obesity, hypertension, and coronary artery disease.[1–4] As a result, patients with HF may still have poor prognoses especially after admission to the intensive care unit (ICU). Therefore, it is an urgent medical need to determine the exact influence of certain treatments on the mortality of HF patients in ICU.

Histamine H2 receptor antagonists (H2RAs) are widely used in the treatment and prevention of peptic ulcer disease by blocking

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histamine H2 receptor (H2R).[5] However, this histamine receptor subtype also abundantly expresses in cardiovascular system and mediates histamine-induced positive chronotropic and inotropic effects in cardiomyocytes and vasodilatory effects in vascular endothelial cells.[6–8] Since H2R was closely associated with the development of many cardiovascular diseases, such as hypertension,[9] myocardial infarction,[10] and HF,[11] H2RAs might serve as a new potential treatment for various cardiovascular diseases. As for HF, the clinical practice of this kind of treatment has been paid intensive attention to during the last decades. For instance, previous randomized control trials reported that H2RAs were able to reduce heart rate and cardiac output,[12–15] which was further confirmed by a following meta-analysis demonstrating that H2RAs improved the symptoms of patients with chronic HF.[16] Furthermore, famotidine, an effective third-generation H2RAs, was also suggested to improve both symptoms and ventricular remodelling of chronic HF.[17] Besides, following cohort studies further revealed that the application of H2RAs not only decreased the incidence of HF in people without underlying cardiovascular disease,[18] but also significantly associated with decreased mortality of HF patients.[19] On the basis of these findings, the role of H2RAs in HF has gradually been accepted as a theoretically promising treatment strategy for HF.

However, certain limitations in the previous studies still prevent the further clinical practice of H2RAs in HF treatment. For instance, early clinical trials involved limited numbers of patients and merely reflected short-term cardiovascular effects of H2RAs, such as heart rate, cardiac output, and pre-ejection period.[12–15] Furthermore, although following cohort studies regarding medium-term and long-term effects of H2RAs included relatively large-scale populations, they did not consider the effects of different types of H2RAs.[18–21] Additionally, the clinical evidence of H2RAs as a treatment for HF in specifical populations was also missing, particularly for patients admitted to ICU. Since HF is common among ICU patients and characterized by high mortality and poor prognosis, clarifying the treatment effects of different types of H2RAs may provide relatively more direct tools for control of the mortality among HF patients and provide additional evidence regarding the application of H2RAs in clinical practice.

Nevertheless, as the lack of definitive clinical guidelines on the treatment of HF with H2RAs limited the implementations of larger prospective and randomized controlled trials for HF patients in ICU, data mining would be more applicable to clarify the effect of H2RAs on HF mortality. In this regard, we conducted a large retrospective study using the open-source Medical Information Mart for Intensive Care III database version 1.4 (MIMIC-III v1.4) to clarify the relationship of H2RAs and all-cause mortality in HF patients admitted to ICU, hoping to provide further theoretical evidence for the application of H2RAs in critical ill patients with HF.

Methods

Data source

This study was based on the publicly available MIMIC-III v1.4 database that contains information of more than 40 000 patients admitted to critical care units of the Beth Israel Deaconess Medical Center (BIDMC, Boston, MA, USA) between 2001 and 2012,[22] which was in accordance with the Reporting of studies conducted using observational routinely collected data for pharmacoepidemiology (RECORD-PE) reporting guidelines.[23] The database also contains general information (patient demographics, birth and death, ICU admission, and discharge information), vital signs, laboratory data, balance of body fluid, reports, medication, and nursing records. We passed the Protecting Human Research Participant exam and gained the access to MIMIC-III database (Certification Number: 38884075). Informed consent was not required since all the data were deidentified.

Study population

For the present study, the information of all the adult (≥18 years) patients who were diagnosed with HF based on International Classification of Diseases 9th revision (ICD-9) disease code at first ICU admission were included. The ICD-9 disease codes were provided in Supplementary material online, *Table S1*. The patients <18 years were excluded in this study.

Data extraction

Patient information was extracted by Structured Query Language from MIMIC-III database. Histamine H2 receptor antagonists (included famotidine, ranitidine, and cimetidine) exposure was defined as the use of H2RAs during the admission. We collected physical characteristics, vital signs, laboratory parameters, clinical parameters, co-morbidities, medications, and other information, such as admission type, length of stay (LOS), sequential organ failure assessment (SOFA), simplified acute physiology score III (SAPS III), left ventricular ejection fraction (LVEF), use of ventilator, and continuous renal replacement therapy (CRRT). Physical characteristics included age, gender, height, weight, and ethnicity. Vital signs included heart rate, blood pressure, oxygen saturation, and respiratory rate. Laboratory parameters included red blood cell count, white blood cell count, platelet count, glucose, creatinine, blood sodium, magnesium, blood calcium, blood urea nitrogen, and urine output. Co-morbidities included atrial fibrillation, myocardial infarction, coronary atherosclerosis, hypertension, venous thrombosis, anaemia, pneumonia, diabetes, duodenal ulcer, gastritis, gastric ulcer, gastrointestinal bleeding, acute kidney failure, and septic shock. Medications included renin angiotensin aldosterone system (RAAS) inhibitors, diuretics, inotropic agents, adrenaline receptor antagonist, calcium antagonists, proton pump inhibitors (PPIs), anticoagulants, and antiplatelet drugs. Additionally, the daily dose of H2RAs was also extracted for further stratified analyses. The missing data of all variables were <15% (Supplementary material online, *Table S2*).

Primary and secondary endpoints

The primary endpoint in this study was all-cause mortality, including hospital, ICU, 30-day, 90-day, and 1-year all-cause mortality. Hospital mortality was defined as death observed before discharge. Intensive care unit mortality was defined as death that occurred during admission to the ICU. Thirty-day and 90-day mortalities were defined as death observed within 30 days of admission and 90 days of admission, respectively. One-year mortality was defined as death observed

within 1 year after admission. The date of out-of-hospital death was obtained from the Social Security Death Index records. The secondary outcomes were hospital and ICU LOS. The former was calculated from the date of admission and discharge and the latter was extracted directly from the database.

Statistical analysis

According to H2RAs exposure status, the study population was divided into H2RAs group and non-H2RAs group. The missing values of each variable were estimated by multiple imputation method.[24] Continuous variables with normal and non-normal distribution were summarized as mean ± standard deviation (SD) and median with interquartile range, respectively. The Student's *t*-test and the Kruskal–Wallis test were used to assess the significance of differences. Categorical variables were summarized by number and percentages and assessed by χ^2 test. Propensity score matching (PSM) was applied to adjust confounding factors between the two groups.[25] Patients were matched in a 1:1 ratio using a calliper of 0.2 SDs of the logit of the estimated propensity score. Standardized mean difference (SMD) was calculated before and after matching to examine whether the PSM reduced the differences in pretreatment covariates between the two groups. A variable can be considered as a balance between groups when it's SMD < 0.1.[26]

The Kaplan–Meier method and log-rank test were applied to calculate the cumulative mortality of 30-day, 90-day, and 1-year in H2RAs group and non-H2RAs group. The Cox regression model was used to identify the effect of H2RAs on all-cause mortality and the results were summarized as hazard ratios (HRs) with 95% confidence intervals (CIs). Multicollinearity was analyzed in the multivariable analyses via the observation of variance inflation factors and multiple correlation coefficients. After excluding variables with multicollinearity, we selected non-H2RAs group as the reference population and developed three models in the Cox regression analysis: (i) Model 1: unadjusted model; (ii) Model 2: adjusted for gender, age, body mass index (BMI), ethnicity, insurance, and admission type; (iii) Model 3: adjusted for the variables in Model 2 plus heart rate, LVEF, SOFA, SAPS III, CRRT, use of ventilator, urine output, glucose, urea nitrogen, blood creatinine, blood magnesium, blood sodium, blood calcium, white blood cell, red blood cell, platelet, adrenergic receptor antagonists, calcium antagonists, diuretics, RAAS inhibitors, PPIs, inotropic agents, anticoagulants, antiplatelet drugs, pneumonia, duodenal ulcer, gastritis, gastric ulcer, gastrointestinal bleeding, acute kidney failure, septic shock, diabetes, anaemia, hypertension, atrial fibrillation, coronary arteriosclerosis, venous thrombus, and myocardial infarction. The C-statistic was computed to assess model discriminative ability. Subgroup analysis was performed based on LVEF to assess the effects of H2RAs on all-cause mortality in different populations. Heart failure with reduced ejection fraction (HFrEF) is defined as LVEF $< 40\%$, while HF with mid-range ejection fraction (HFmEF) and HF with preserved ejection fraction (HFpEF) is defined as $40\% \leq$ LVEF $< 50\%$ and LVEF $\geq 50\%$, respectively.[27] Furthermore, additional analyses were also performed stratifying patients by types, daily doses of H2RAs, and other factors to estimate differences of all-cause mortality. *P*-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS (version 18.0, IBM Corp, Armonk, NY, USA) and R 3.5.3 software for windows.

Results

Baseline characteristics of the study population

As shown in *Figure 1*, a total of 15 280 records were diagnosed with HF in the database. Multiple admissions were recorded for 4878 patients. Fifteen patients were younger than 18 years of age. Finally, 10 387 records met the inclusion and exclusion criteria and were included, involving 4440 H2RAs users and 5947 non-H2RAs users. Among these patients, 1548 were diagnosed with acute decompensated HF. The baseline characteristics of H2RAs group and non-H2RAs group before matching were summarized in *Table 1*. The mean age of H2RAs group and non-H2RAs group were 71.2 years and 74.2 years, respectively. In general, patients who were exposed to H2RAs during hospitalization differed in most ways from those were not. Briefly, the means of BMI and SOFA were significantly higher in H2RAs group than in non-H2RAs group. In addition, the frequencies of patients who used RAAS inhibitors, diuretics, adrenaline receptor antagonist, calcium antagonists, and PPIs in H2RAs group were lower than those of non-H2RAs group.

In PSM, 3130 patients who were exposed to H2RAs were matched with 3130 patients who did not expose to H2RAs (*Figure 1*). As shown in Supplementary material online, *Table S3*, the baseline characteristics of H2RAs group and non-H2RAs group were almost balanced. Furthermore, the SMDs of variables were all <0.1, indicating the baseline variables in the two groups have similar distributions (*Figure 2* and Supplementary material online, *Table S3*).

Associations between H2RAs use and clinical outcomes of critical ill patients with HF

We first evaluated the differences of all-cause mortalities between H2RAs and non-H2RAs group both before and after PSM. As shown in *Table 2*, each kind of mortality (including ICU, hospital, 30-day, 90-day, and 1-year mortality) of H2RAs users was significantly lower as compared with that of non-H2RAs users before PSM ($P < 0.001$, respectively). Similarly, after PSM, all of the evaluated mortalities of H2RAs users were also lower than those of non-H2RAs users ($P < 0.001$, respectively). However, the hospital and ICU LOS of H2RAs users were significantly longer than those of non-H2RAs users before and after PSM (*Table 2*).

Next, the Kaplan–Meier curves of 30-day, 90-day, and 1-year mortality of two groups before and after PSM were evaluated and respectively reported in Supplementary material online, *Figure S1* and *Figure 3*. In post-matched cohort, the results of survival analyses showed that the 30-day, 90-day, and 1-year mortality of patients in H2RAs group was lower than those in non-H2RAs group (*Figure 3*; log-rank test $P < 0.001$, respectively), which were in accordance with the data from pre-matched cohort (Supplementary material online, *Figure S1*).

We then further performed multivariate analyses using Cox regression models to evaluate the difference in mortality outcomes between the two groups. As shown in *Table 3*, before PSM, significant

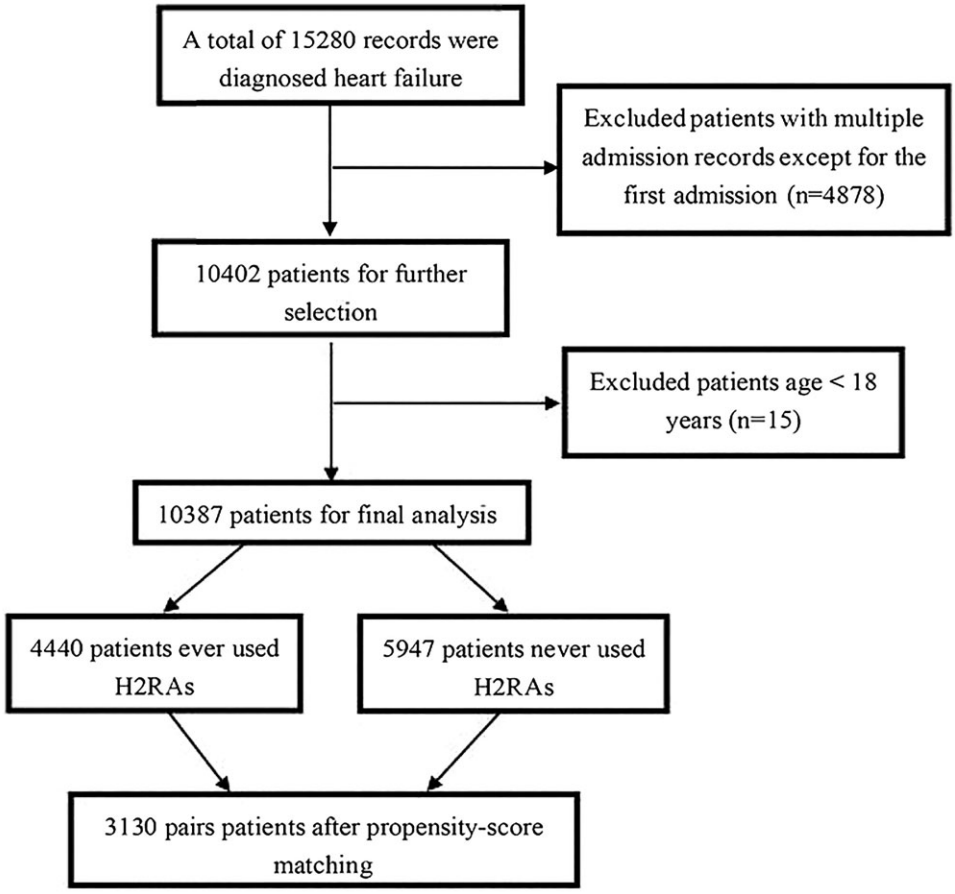

Figure 1 Selection of study population from MIMIC-III database.

Table 1 Baseline characteristics of H2RAs group and non-H2RAs group before matching

	H2RAs ($n = 4440$)	Non-H2RAs ($n = 5947$)	*P*-value	SMD
Acute decompensated heart failure	725	823	—	—
Age, years	71.2 ± 13.8	74.2 ± 14.0	<0.001	0.217
Gender, male, *n* (%)	2446 (55.1)	3073 (51.7)	0.001	0.069
BMI, kg/m^2	28.8 ± 7.0	28.4 ± 6.7	0.004	0.057
SOFA	5.0 ± 3.0	4.6 ± 3.0	<0.001	0.148
SAPS III score	47.1 ± 19.6	49.1 ± 20.4	<0.001	0.100
CRRT, *n* (%)	136 (3.1)	150 (2.5)	0.108	0.033
Use of ventilator, *n* (%)	2841 (64.0)	2405 (40.4)	<0.001	0.485
Vital signs				
Heart rate	81.9 ± 16.5	82.9 ± 17.1	0.001	0.064
SBP, mmHg	125.8 ± 22.1	124.1 ± 23.3	<0.001	0.071
DBP, mmHg	65.9 ± 14.6	64.6 ± 14.7	<0.001	0.086
Oxygen saturation, (%)	96.8 ± 2.6	96.7 ± 2.7	0.002	0.062
Respiratory rate	19.6 ± 4.4	20.0 ± 4.6	<0.001	0.104
Ethnicity				
White, *n* (%)	3296 (74.2)	4310 (72.5)	0.002	0.081
Black, *n* (%)	365 (8.2)	504 (8.5)		
Asian, *n* (%)	125 (2.8)	124 (2.1)		

Continued

Table 1 *Continued*

	H2RAs ($n = 4440$)	Non-H2RAs ($n = 5947$)	*P*-value	SMD
Hispanic, *n* (%)	80 (1.8)	102 (1.7)		
Other, *n* (%)	574 (12.9)	907 (15.3)		
Comorbidity				
Hypertension, *n* (%)	2026 (45.6)	2358 (39.7)	<0.001	0.121
Diabetes, *n* (%)	1643 (37.0)	2133 (35.9)	0.241	0.024
Anaemia, *n* (%)	1414 (31.8)	1995 (33.5)	0.071	0.036
Atrial fibrillation, *n* (%)	2034 (45.8)	2537 (42.7)	0.001	0.063
Coronary arteriosclerosis, *n* (%)	2058 (46.4)	2274 (38.2)	<0.001	0.165
Venous thrombus, *n* (%)	77 (1.7)	112 (1.9)	0.625	0.011
Myocardial infarction, *n* (%)	713 (16.1)	992 (16.7)	0.412	0.017
Gastritis, *n* (%)	61 (1.4)	121 (2.0)	0.014	0.051
Duodenal ulcer, *n* (%)	25 (0.6)	71 (1.2)	0.001	0.068
Gastric ulcer, *n* (%)	20 (0.4)	67 (1.1)	0.000	0.077
Gastrointestinal bleeding, *n* (%)	183 (4.1)	517 (8.7)	0.000	0.188
Acute kidney failure, *n* (%)	1409 (31.7)	2260 (38.0)	0.000	0.132
Septic shock, *n* (%)	262 (5.9)	414 (7.0)	0.033	0.043
Pneumonia, *n* (%)	1331 (22.4)	917 (20.7)	0.036	0.042
Laboratory data				
Urine output, mL	1630 (998–2480)	1585 (920–2445)	0.009	0.043
Urea nitrogen, mg/dL	23 (16–36)	29 (19–45)	<0.001	0.296
Serum creatinine, mg/dL	1.1 (0.8–1.6)	1.3 (0.9–1.9)	<0.001	0.163
Magnesium, mg/dL	2.0 (1.8–2.3)	1.9 (1.7–2.2)	<0.001	0.204
Sodium, mEq/L	139 (136–141)	139 (136–141)	0.3209	0.018
Calcium, mg/dL	8.4 (8–8.8)	8.4 (7.9–8.8)	0.0176	0.058
Glucose, mg/dL	128 (106–159)	130 (105–162)	0.236	0.037
WBC, k/μL	11.4 (8.3–15.2)	10.9 (7.8–14.5)	<0.001	0.082
RBC, m/μL	3.5 (3.0–4.0)	3.5 (3.1–4.0)	<0.001	0.100
Platelet, k/μL	196 (140–261)	211 (154–273)	<0.001	0.121
LVEF, *n* (%)				
10–35%	1359 (30.6)	1938 (32.6)	0.021	0.062
35–55%	2409 (54.2)	3046 (51.2)		
55–70%	500 (11.3)	693 (11.7)		
>70%	174 (3.9)	268 (4.5)		
Medications				
RAAS inhibitors, *n* (%)	2679 (60.3)	2843 (47.8)	<0.001	0.253
Diuretics, *n* (%)	4052 (91.3)	4255 (71.5)	<0.001	0.524
Inotropic agents, *n* (%)	2205 (49.7)	1901 (32.0)	<0.001	0.366
Adrenaline receptor antagonists, *n* (%)	4077 (91.8)	4394 (73.9)	<0.001	0.490
Calcium antagonists, *n* (%)	1710 (38.5)	1737 (29.2)	<0.001	0.198
Anticoagulants, *n* (%)	4082 (91.9)	4778 (80.3)	0.000	0.340
Antiplatelet drugs, *n* (%)	3662 (82.5)	3678 (61.8)	0.000	0.473
PPIs, *n* (%)	2985 (67.2)	4330 (72.8)	<0.001	0.122
Insurance				
Medicare, *n* (%)	3399 (76.6)	4829 (81.2)	<0.001	0.118
Private, *n* (%)	58 (1.3)	80 (1.3)		
Government, *n* (%)	983 (22.1)	1038 (17.5)		
Admission type				
Emergency, *n* (%)	3545 (79.8)	5265 (88.5)	<0.001	0.354
Elective, *n* (%)	795 (17.9)	412 (6.9)		
Urgent, *n* (%)	100 (2.3)	270 (4.5)		

H2RA, histamine H2 receptor antagonist; SMD, standardized mean difference; BMI, body mass index; SOFA, sequential organ failure assessment score; SAPS III, simplified acute physiology score III; CRRT, continuous renal replacement therapy; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; WBC, white blood cell; RBC, red blood cell; RAAS, renin angiotensin aldosterone system; PPIs, proton pump inhibitors.

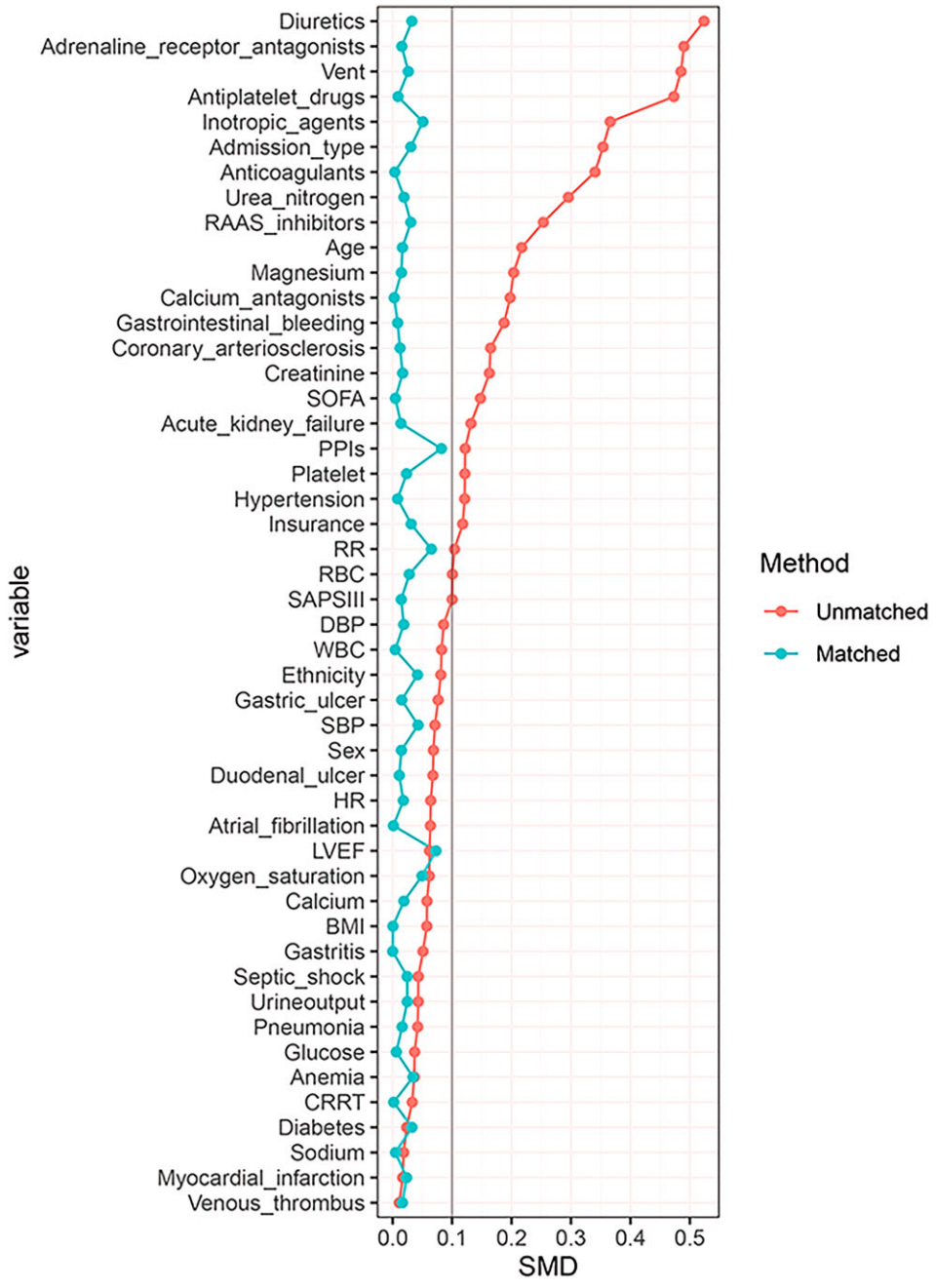

Figure 2 Standardized mean difference of variables before and after propensity score matching.

associations between H2RAs exposure and decreased 30-day, 90-day, and 1-year mortality were observed in each of the three employed models. After PSM, the use of H2RAs was also significantly associated with decreased risks of 30-day, 90-day, and 1-year death of ICU patients with HF in the three models (*Table 3*). Furthermore, the *C*-statistics of Model 3 before and after PSM were 0.804 and 0.800 for 30-day mortality, 0.776 and 0.771 for 90-day mortality, and 0.747 and 0.739 for 1-year mortality, respectively (Supplementary material online, *Table S4*), indicating that the employed model had well discriminative ability and certain reference value for further predictive study in this area.

Additionally, we also performed subgroup analyses based on LVEF levels, which showed significant association between H2RAs use and decreased 30-day, 90-day, and 1-year mortality in both HFrEF group and HFmEF + HFpEF group irrespective of the PSM (Supplementary material online, *Table S5*).

Table 2 Association of H2RAs use and outcomes in heart failure patients

	Before PSM			After PSM		
	H2RA	Non-H2RA	*P*-value	H2RA	Non-H2RA	*P*-value
Mortality, *n* (%)						
ICU mortality	302 (6.8)	712 (12.0)	<0.001	238 (7.6)	354 (11.3)	<0.001
Hospital mortality	468 (10.5)	1033 (17.4)	<0.001	387 (12.4)	500 (16.0)	<0.001
30-day mortality	536 (12.1)	1281 (21.5)	<0.001	451 (14.4)	588 (18.7)	<0.001
90-day mortality	852 (19.2)	1794 (30.2)	<0.001	707 (22.6)	847 (27.1)	<0.001
1-year mortality	1291 (29.1)	2547 (42.8)	<0.001	1074 (34.3)	1236 (39.5)	<0.001
Length of stay (day)						
Hospital LOS	9.9 (6.2–15.9)	7.9 (4.8–13.6)	<0.001	9.9 (6.1–16.5)	8.5 (5.1–14.5)	<0.001
ICU LOS	3.1 (1.8–6.2)	2.6 (1.4–5.0)	<0.001	3.1 (1.8–6.2)	3.0 (1.6–5.8)	0.003

PSM, propensity score matching; ICU, indicates intensive care unit; LOS, length of stay.

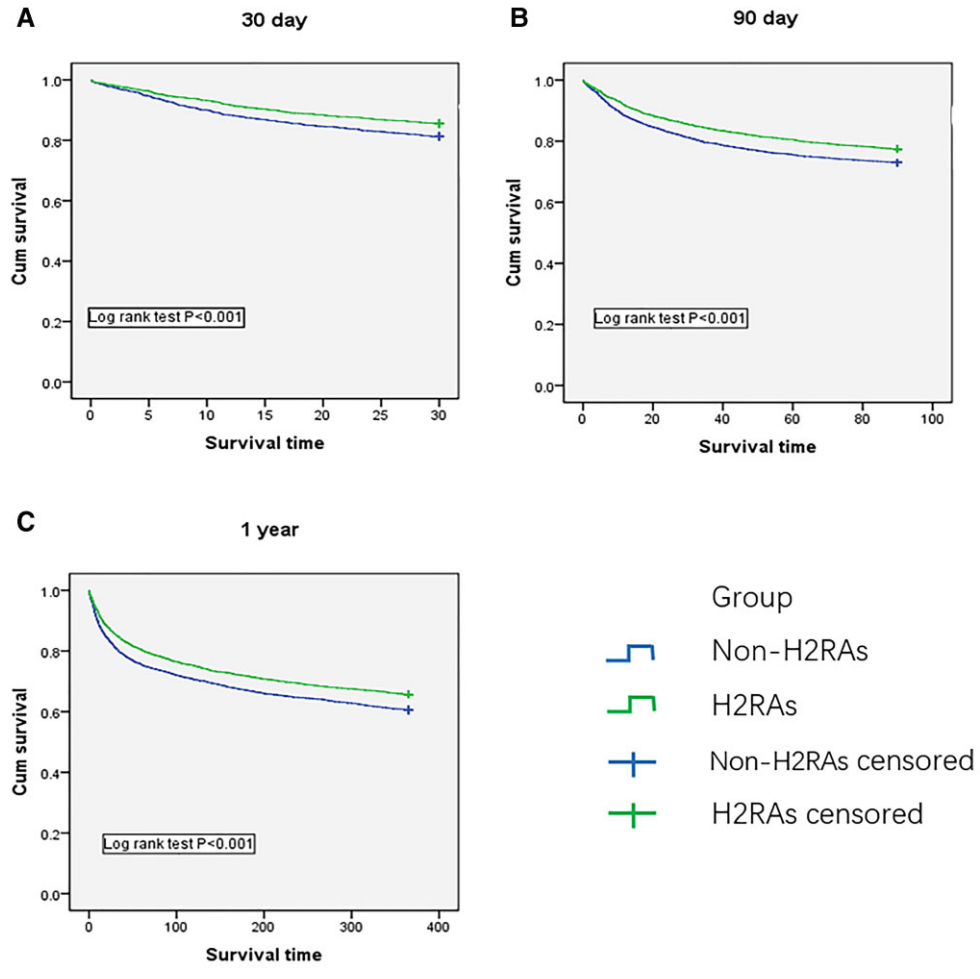

Figure 3 Kaplan–Meier survival curves of histamine H2 receptor antagonists users and non-histamine H2 receptor antagonists users after matching. (*A*) 30-Day mortality; (*B*) 90-day mortality; (*C*) 1-year mortality.

Table 3 The association between H2RAs exposure and all-cause mortality

	Before PSM		After PSM	
	Non-H2RAs ($n = 5947$)	H2RAs ($n = 4440$)	Non-H2RAs ($n = 3130$)	H2RAs ($n = 3130$)
30-day mortality, HR (95%CI)				
Events, *n*	1281	536	588	451
Model 1	Reference	0.52 (0.48, 0.58)	Reference	0.76 (0.66, 0.84)
Model 2	Reference	0.61 (0.55, 0.67)	Reference	0.75 (0.66, 0.84)
Model 3	Reference	0.74 (0.66, 0.83)	Reference	0.73 (0.65, 0.83)
90-day mortality, HR (95%CI)				
Events, *n*	1794	852	847	707
Model 1	Reference	0.58 (0.54, 0.63)	Reference	0.80 (0.73, 0.89)
Model 2	Reference	0.67 (0.62, 0.73)	Reference	0.80 (0.73, 0.89)
Model 3	Reference	0.80 (0.73, 0.88)	Reference	0.80 (0.72, 0.89)
1-Year mortality, HR (95%CI)				
Events, *n*	2547	1291	1236	1074
Model 1	Reference	0.61 (0.58, 0.65)	Reference	0.83 (0.77, 0.90)
Model 2	Reference	0.69 (0.64, 0.74)	Reference	0.83 (0.79, 0.90)
Model 3	Reference	0.82 (0.76, 0.88)	Reference	0.83 (0.76, 0.90)

PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; Model 1, unadjusted; Model 2, adjusted for gender, age, body mass index, ethnicity, insurance and admission type; Model 3, adjusted for variables in Model 2 plus heart rate, left ventricular ejection fraction, SOFA, SAPS III, continuous renal replacement therapy, use of ventilator, urine output, glucose, urea nitrogen, blood creatinine, blood magnesium, blood sodium, blood calcium, white blood cell, red blood cell, platelet, adrenergic receptor antagonists, calcium antagonists, diuretics, renin angiotensin aldosterone system inhibitors, proton pump inhibitors, inotropic agents, anticoagulants, antiplatelet drugs, pneumonia, duodenal ulcer, gastritis, gastric ulcer, gastrointestinal bleeding, acute kidney failure, septic shock, diabetes, anaemia, hypertension, atrial fibrillation, coronary arteriosclerosis, venous thrombus, and myocardial infarction.

Associations between different H2RAs types and all-cause mortality of critical ill patients with HF

According to the application of different H2RAs, we screened patients who used only one type of H2RAs, involving 1830 cases of famotidine, 2083 cases of ranitidine, and 4 cases of cimetidine in pre-matched cohort and 1547 cases of famotidine, 1206 cases of ranitidine and 4 cases of cimetidine in post-matched cohort. Since the sample of cimetidine was limited, the association between cimetidine use and mortality was not estimated. It was shown that ranitidine users had a significantly lower 30-day, 90-day, and 1-year mortality than famotidine users based on the Kaplan–Meier curves before and after PSM (Supplementary material online, *Figure S2* and *Figure 4*; $P < 0.001$, respectively). In addition, comparing with non-H2RAs group, ranitidine significantly reduced 30-day, 90-day, and 1-year mortality of critical ill patients with HF before and after PSM (Supplementary material online, *Figures S3 and S4*; $P < 0.001$, respectively). However, comparing with non-H2RAs group, famotidine only significantly reduced 30-day mortality before PSM (Supplementary material online, *Figure S5A*; $P = 0.023$) but slightly reduced 90-day mortality (Supplementary material online, *Figure S6B*; $P = 0.058$) and significantly reduced 1-year mortality after PSM (Supplementary material online, *Figure S6C*; $P = 0.032$). Moreover, regression analyses also showed that the risks of 30-day, 90-day, and 1-year death of ranitidine users were significantly lower than those of famotidine users among three models before and after PSM (*Table 4*).

Associations between daily dose of H2RAs and all-cause mortality of critical ill patients with HF

Famotidine and ranitidine users were further divided into high-dose (>20 mg/day for famotidine and >150 mg/day for ranitidine) and low-dose (≤20 mg/day for famotidine and ≤150 mg/day for ranitidine) groups, respectively. As shown in Supplementary material online, *Table S6*, no significant association was observed between 30-day mortality and daily doses of famotidine or ranitidine before and after PSM. Moreover, the same trends were also observed for 90-day mortality and 1-year mortality (Supplementary material online, *Table S6*). Although these findings were not statistically significant, the high daily dose of H2RAs still showed a tendency of decreased mortality among critical ill patients with HF. However, due to the accuracy of original data and limitation of sample size, this tendency should still be confirmed in the future investigations.

Stratified analyses according to other factors

To minimize any influence of PPI use or pre-hospital H2RAs use on all-cause mortality of critical ill patients with HF, we also performed the stratified analysis excluding: (i) patients who had received a prescription for H2RAs before their hospitalization and (ii) patients who exposed to PPIs. After PSM, 383 patients who exposed to H2RAs were matched with 383 patients who did not expose to H2RAs. Although the results did not exhibit statistical significance (Supplementary material online, *Table S7*), H2RAs exposure was still,

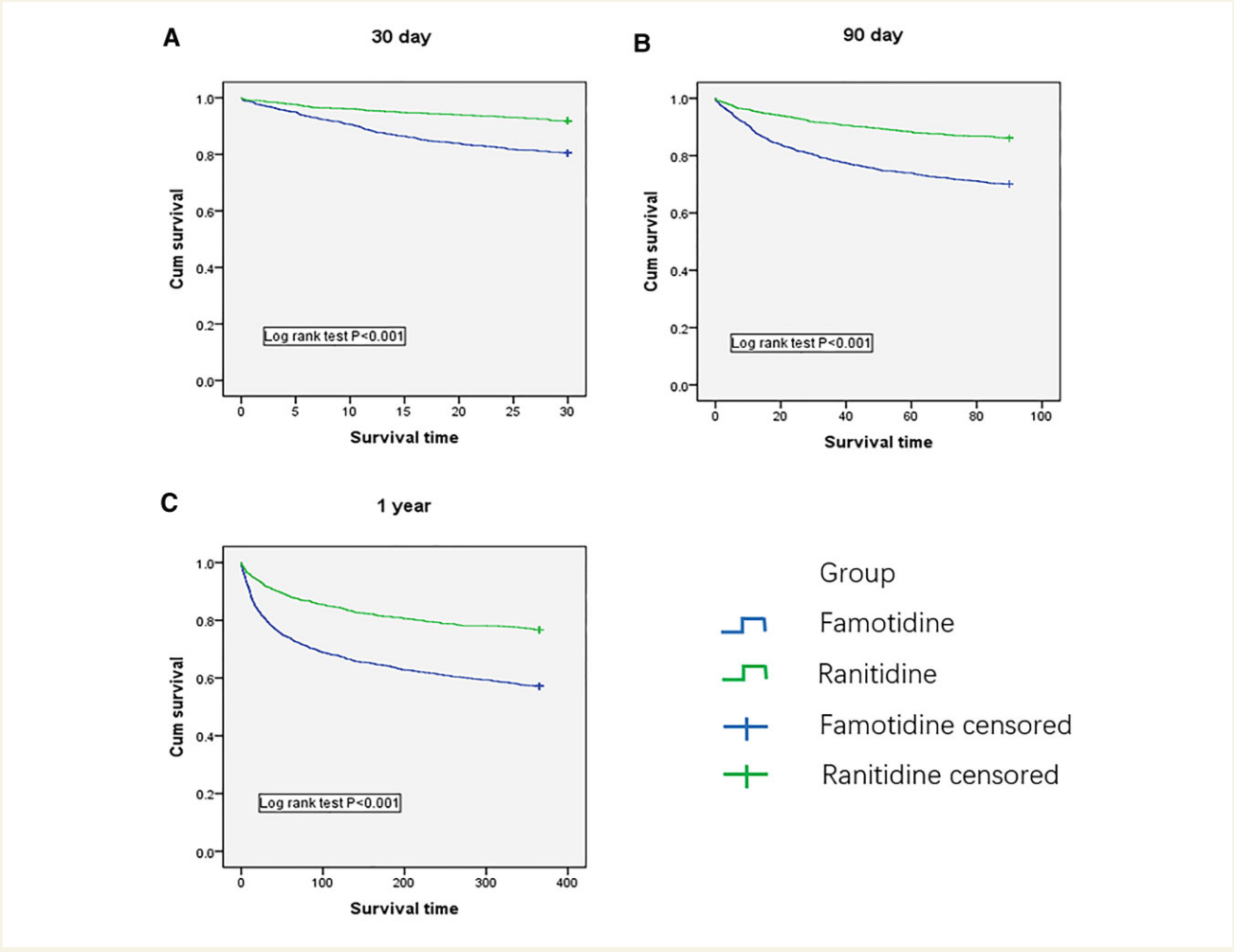

Figure 4 Kaplan–Meier survival curves of ranitidine users and famotidine users after matching. (*A*) 30-Day mortality; (*B*) 90-day mortality; (*C*) 1-year mortality.

respectively, associated with decreased tendencies of 30-day, 90-day, and 1-year mortality. However, as the sample size after PSM was limited, which led to relatively poor statistical efficacy for these stratified analyses, the results should still be interpreted with cautions.

Discussion

To the best of our knowledge, this is the first large cohort study to evaluate the effect of H2RAs on all-cause mortality of critical ill patients with HF based on data mining and MIMIC-III database. The large sample size and database allowed us to adjust a series of potential confounders in our analysis according to PSM analysis and different regression models. It was found that critical ill patients with HF using H2RAs had a lower mortality and a relatively longer LOS as compared with non-H2RAs users, suggesting that the use of H2RAs was a protective factor for HF patients. Additionally, the demographic and clinical characteristics of the present study revealed that population exposed to H2RAs were accompanied with more risk confounding factors such as higher BMI, higher SOFA, and lower frequencies of combination use of classic anti-HF drugs, etc. (*Table 1*), which further highlights the potential effects of H2RAs on reducing mortality in HF patients. These findings provide additional theoretical evidence regarding the clinical application of H2RAs in HF.

Histamine H2 receptor was previously demonstrated to play important pathophysiological roles in various cardiovascular diseases, including HF. During the progress of HF, cardiac mast cells are largely mobilized and degranulated[28,29] and cardiac sympathetic nerves are overactivated,[30,31] both of which would eventually lead to abundant endogenous histamine release and cardiac H2R activation.[17,29] Recent investigations demonstrated that, besides the positive chronotropic and inotropic effects, activation of H2R also produced additional effects on myocardial cells. For instance, H2R activation was found to aggravate myocardial injury through promoting myocardial mitochondrial dysfunction and increasing cardiac vascular endothelial permeability[32,33] and induce myocardial apoptosis through accelerating the up-regulation of the apoptotic signalling molecules Bax and caspase-3.[34] Moreover, it was indicated that H2R was involved in alpha 1 adrenoceptor mediated cardiac hypertrophy and oxidative stress in H9c2 cardiomyoblasts.[35] Additionally, H2R was also involved in histamine-induced decreased release of atrial natriuretic

Table 4 The associations between different type of H2RAs exposure and all-cause mortality

	Before PSM		After PSM	
	Famotidine ($n = 1830$)	Ranitidine ($n = 2083$)	Famotidine ($n = 1547$)	Ranitidine ($n = 1206$)
30-day mortality, HR (95%CI)				
Events, *n*	352	124	303	98
Model 1	Reference	0.29 (0.23, 0.35)	Reference	0.38 (0.31, 0.49)
Model 2	Reference	0.33 (0.27, 0.41)	Reference	0.40 (0.32, 0.50)
Model 3	Reference	0.61 (0.48, 0.78)	Reference	0.68 (0.53, 0.89)
90-day mortality, HR (95%CI)				
Events, *n*	535	214	463	168
Model 1	Reference	0.31 (0.27, 0.37)	Reference	0.42 (0.35, 0.50)
Model 2	Reference	0.36 (0.30, 0.42)	Reference	0.43 (0.36, 0.51)
Model 3	Reference	0.58 (0.48, 0.70)	Reference	0.65 (0.53, 0.79)
1-year mortality, HR (95%CI)				
Events, *n*	762	360	663	281
Model 1	Reference	0.35 (0.31, 0.40)	Reference	0.47 (0.41, 0.54)
Model 2	Reference	0.39 (0.34, 0.44)	Reference	0.47 (0.41, 0.54)
Model 3	Reference	0.57 (0.49, 0.66)	Reference	0.64 (0.54, 0.75)

PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; Model 1, unadjusted; Model 2, adjusted for gender, age, body mass index, ethnicity, insurance and admission type; Model 3, adjusted for variables in Model 2 plus heart rate, left ventricular ejection fraction, SOFA, SAPS III, continuous renal replacement therapy, use of ventilator, urine output, glucose, urea nitrogen, blood creatinine, blood magnesium, blood sodium, blood calcium, white blood cell, red blood cell, platelet, adrenergic receptor antagonists, calcium antagonists, diuretics, renin angiotensin aldosterone system inhibitors, proton pump inhibitors, inotropic agents, anticoagulants, antiplatelet drugs, pneumonia, duodenal ulcer, gastritis, gastric ulcer, gastrointestinal bleeding, acute kidney failure, septic shock, diabetes, anaemia, hypertension, atrial fibrillation, coronary arteriosclerosis, venous thrombus, and myocardial infarction.

peptides (ANP), which further contributed to coronary diastolic dysfunction.[36,37] These lines of evidence further supported the present observation that the application of H2RAs was associated with low mortality of HF patients.

As one of the important traditional anti-HF treatment strategies, beta-blocker was also reported to reduce heart rate, myocardial oxygen consumption, and myocardial fibrosis, to prevent adrenergic overactivation, and, thereby, to inhibit myocardial cell necrosis[38,39] and was acknowledged to exert benefit effects on reducing mortality of severe HF patients.[40,41] In this regard, since H2R shares a common downstream signalling pathway with β1-receptor, H2RAs may have similar effects with beta-blockers. Furthermore, based on the fact that the cardiovascular response to famotidine was reported to be comparable to that of metoprolol,[42] it is reasonable to assume that H2RAs may be a complimentary for the treatment of HF. Moreover, because beta-blockers are known to induce a series of serious side effects (such as ventricular dysfunction, arrhythmia, bronchial asthma, etc.) during the treatment as well, the safety of H2RAs would also be relatively higher than that of beta-blockers.[43] Therefore, these advantages of H2RAs, along with their relatively low market price, are very likely to make H2RAs a novel promising alternative candidate for severe HF patients.

In addition, considering that LVEF is an important indicator for HF patients, we further performed subgroup analyses to evaluate the effects of H2RAs on all-cause mortality according to baseline LVEF. Interestingly, the results showed a decreasing-mortality effect of H2RAs in both HFrEF group and HFmEF + HFpEF group, suggesting that H2RAs might be more widely applicable for critically ill patients with HF irrespective of their LVEF levels.

Actually, a previous cross-sectional observation, included 313 H2RAs users and 6065 non-H2RAs, provided clinical evidence regarding the benefit effect of H2RAs on HF.[18] However, the comparison of the differences among various types of H2RAs was missing in the previous study.[18,21] Therefore, in the present study, further analysis was performed to reveal the effects of different types of H2RAs on mortality in critical ill patients with HF and the results demonstrated that ranitidine was more effective in reducing all-cause mortality in patients with HF as compared with famotidine. One possible explanation for the discrepancy may be that the mean bioavailability of ranitidine is slightly higher than that of famotidine.[44] Additionally, ranitidine has a relatively stronger inhibitory effect on cytochrome P-450 enzymes than famotidine, which would lead to increased activity of certain anti-HF drugs metabolized by these enzymes.[44] In this regard, we further compared the effects of famotidine and non-H2RAs on all-cause mortality in critical ill patients with HF. The results showed that famotidine still reduced 90-day and 1-year mortality compared with non-H2RAs. Since famotidine hardly produced inhibition on cytochrome P-450 enzymes,[44] its H2R blocking effect was further confirmed to have benefit impacts on reducing mortality of critical ill patients with HF.

In stratified analysis, after excluding patients who received prehospital H2RAs, we found no statistical significance between H2RAs use and all-cause mortality of critical ill patients with HF in PSM cohort. This result indicated that the short-term mortality-reducing effects of H2RAs used just during the ICU stay were relatively unsatisfactory while prophylactic administration of H2RAs might be more effective as H2RAs were significantly associated with lower mortality of patients before stratification (*Table 1*). However, as the sample size after PSM

was limited in stratified analyses, the result should still be further verified by future studies.

However, it should be noted that H2RAs relatively increased LOS of ICU patients with HF according to the present results. The possible reason may be due to the fact that H2RAs improved the patients' conditions and lead to relatively longer survival time. Moreover, some patients died as soon as they entered ICU, which may influence the accuracy of the present results. Hence, the effect of H2RAs on LOS of critical ill patients with HF should be interpreted with caution.

As all data of critical HF patients were from MIMIC-III database, several weaknesses related to study design and data extraction still existed in this study. First, the present study is a retrospective study and inherent bias may affect the authenticity of the results. Second, it was challengeable to obtain information stored as text, such as pre-hospital medication information, which may lead to certain bias from study design. As for data extraction, some features that influenced HF mortality were not collected due to the constraints of public database, such as smoking and drinking. Third, HF was identified by searching for ICD-9 disease codes in the 'd_icd_diagnoses' table that listed different diagnoses of HF, making it difficult to determine if patients were admitted for HF. Additionally, the present study did not specifically analyze the associations between H2RAs exposure and cardiovascular mortality or non-cardiovascular mortality due to the lack of a clear cause of death, which might mask the eventual effects of H2RAs on the cardiovascular mortality. Therefore, more multicentre-based prospective trials are still needed to verify the present results in future.

In conclusion, in this large database-based cohort study, we found that H2RAs exposure was associated with low mortality in critical ill patients with HF, which suggested promising potential benefits of treatment with H2RAs for critical ill patients with HF. Furthermore, ranitidine was found to be superior to famotidine in reducing mortality of critical ill patients with HF. Our findings may be helpful for the clinical use of H2RAs in critical ill patients with HF though they should still be further verified by prospective studies or randomized controlled studies.

Authors' contribution

Y.-H.H., W.k.C., S.-J.Y., and G.-H.H. contributed to the conception or design of the work. Y.-H.H., Z.-R.L., Q.Y., P.W., R.M., M.Y., and Y.G. contributed to the acquisition, analysis, or interpretation of data for the work. Y.-H.H., W.k.C., and S.-J.Y. drafted the manuscript. Y.-H.H. and G.-H.H. critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy. All authors read and approved the final manuscript.

Supplementary material

Supplementary material is available at European Journal of Preventive Cardiology.

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Conflict of interest: none declared.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

Ethics approval and consent to participate

MIMIC-III database used in the present study was approved by the Institutional Review Boards (IRB) of the Massachusetts Institute of Technology and does not contain protected health information.

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