Inhaled Beta2-Agonists Increase In-Hospital Mortality in ICU Patients with Heart Failure
A Real-World Propensity Score-Matched Study

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Summary
The impact of beta-agonists (B2As) on heart failure (HF) remains controversial. This study aimed to investigate whether inhaled B2As increased in-hospital mortality in ICU patients with HF.

The Multiparameter Intelligent Monitoring in Intensive Care III database was initially searched to identify adult patients (≥18 years old) with HF in ICU. Then, patients using or not using inhaled B2As were matched using propensity score matching on a 1:1 basis to control for baseline confounders. In-hospital mortality was compared between the two groups, and logistic regression analysis was performed to assess the association between B2As and in-hospital mortality.

The initial search retrieved 2345 eligible patients with HF from the database. After propensity score matching, 705 pairs of patients were included in the final analysis. Patients using B2As had markedly higher in-hospital mortality than those not using B2As (4.68% versus 2.27%; \(P = 0.013\)). In the multivariate logistic regression analysis, B2A use (odd ratios (OR), 2.471; 95% confidence interval (CI), 1.289-4.734; \(P = 0.006\)), stroke (OR, 4.581; 95% CI, 1.621-12.948; \(P = 0.004\)), and simplified acute physiology score II (SAPS-II) scores (OR, 1.090; 95% CI, 1.064-1.116; \(P < 0.001\)) were significantly associated with increased risk of in-hospital mortality, whereas renin angiotensin system inhibitor use (OR, 0.396; 95% CI, 0.202-0.778; \(P = 0.007\)) was significantly associated with decreased risk of in-hospital mortality. Subgroup analysis further indicated that the association between B2A use and mortality was significant only in patients with HF without chronic pulmonary disease (OR, 2.427; 95% CI, 1.351-4.362; \(P = 0.003\)), but not in those with chronic pulmonary disease (OR, 2.094; 95% CI, 0.582-7.537; \(P = 0.258\)).

In ICU patients with HF but without chronic pulmonary disease, the use of inhaled B2As is associated with increased in-hospital mortality.

Key words: Chronic pulmonary disease, MIMIC III database

Heart failure (HF) is a complex clinical syndrome caused by structural or functional impairment of ventricular filling or ejection of blood, which is responsible for a major part of hospital health expenditure and the third cause of cardiovascular death.1) Because of its significant benefit on prognosis, beta-blockers (BBs) are considered to be one of the cornerstones in the treatment of chronic HF.2) However, sometimes, there is a paradox in the treatment of patients with HF with respiratory comorbidities, such as chronic obstructive pulmonary disease (COPD) and asthma. Beta-agonists (B2As) might be prescribed to these patients to relieve respiratory symptoms. Because of its opposite mechanism to BBs, the impact of B2As on HF is widely discussed but remains controversial. Some studies indicated that B2As might induce myocardial injury and increase the risk of all-cause mortality in patients with HF,3,4) whereas other studies showed that B2As had no relationship with long-term mortality or even had beneficial effects on pulmonary function and cardiovascular hemodynamics.5,6) Researchers considered that the differences in previously reported risk attributed to B2As may be accounted to the clinical characteristics of patients with HF and the type of B2As.7) Besides, most previous studies were conducted in the community. However, the use of B2As, especially the inhaled form, is more common in critically ill patients. Unfortunately, the
impact of B2As on these patients with HF remains unclear. Therefore, this study aimed to investigate whether inhaled B2As would increase in-hospital mortality in ICU patients with HF.

Methods

Study design and variables: The data in this study was extracted from the Multiparameter Intelligent Monitoring in Intensive Care III (MIMIC III) database version 1.4. This database provides deidentified demographic, administrative, and clinical data for more than 50,000 patients with critical illness consecutively admitted between 2001 and 2012 at Beth Israel Deaconess Medical Center (Boston, MA, USA). The database also links to the social security death registry, allowing access to information on mortality. Our access (ID: 32540900) to the database was approved by the institutional review boards of Massachusetts Institute of Technology (Cambridge, MA, USA) and Beth Israel Deaconess Medical Center (Boston, MA, USA), after we completed the National Institutes of Health’s web-based course and passed Protecting Human Research Participants. To protect privacy, the inclusion criteria were hidden. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

We restricted the initial search to patients whose diagnosis included HF using International Classification of Diseases (ICD) 9 code (code = 428.22, 428.23, 428.32, 428.33, 428.42, or 428.43). The exclusion criteria were as follows: (1) patients < 18 years old and (2) patients using other drugs activating adrenergic receptors, such as epinephrine, norepinephrine, phenylephrine, isoprenaline, dopamine, or dobutamine.

Inhaled B2A exposure: The drug history of the included patients was extracted from prescriptions in the MIMIC III database. Exposure to inhaled B2As was defined as the use of any type of inhaled B2As during hospitalization. We identified the use of inhaled B2As using the following keywords: albuterol, terbutaline, clenbuterol, fenoterol, salmeterol, formoterol, indacaterol, olodaterol, or vilanterol. Patients not using any inhaled B2As were defined as non-exposed patients.

Follow-up and outcomes: The primary outcome of our study was in-hospital mortality, and the secondary outcome was ICU stay. Follow-up was started from the date of admission and ended on the date of discharge or death. Events of death were obtained from Social Security Death Index records from the US government.

Propensity score matching: To obtain an unbiased estimate of the treatment effect of B2As, we used propensity score matching to select comparable pairs of patients using or not using inhaled B2As. The following variables were used to construct the propensity score matching model: age, gender, BMI, CAD, cardiac arrhythmias, chronic pulmonary disease, renal failure, liver disease, malignancy, simplified acute physiology score II (SAPS-II) scores, sequential organ failure assessment (SOFA) scores, and ventilation. A propensity score was estimated for each patient from a logistic regression model to fit with the above variables. Then, via the nearest-neighbor matching algorithm without replacement, a 1:1 matching analysis was performed between B2A and non-B2A groups based on the estimated propensity scores. The caliper was set at 0.02.

Statistical analyses: Statistical analysis was performed using STATA 12.0 and SPSS 22.0. Continuous variables were expressed as mean (standard deviation), and categorical variables were expressed as percentage. The differences between the B2A and non-B2A groups were compared using the Mann-Whitney U test for continuous variables and the χ² test for categorical variables. The association between B2As and in-hospital mortality was determined using logistic regression analysis and presented as odd ratios (ORs) with 95% confidence intervals (CIs). Multivariable analyses were performed to control for confounders, which were selected based on factors with a P value < 0.1 in univariate regression analysis. To reduce the impact of comorbidities on the results, subgroup analysis was further performed based on chronic pulmonary disease, CAD, diabetes mellitus, hypertension, and cardiac arrhythmias. A two-tailed P value < 0.05 was considered to indicate statistical significance.

Results

Subject characteristics: A total of 3781 patients with a diagnosis of HF were retrieved in the initial database search. Among them, 1436 patients using other drugs activating adrenergic receptors in hospital were excluded. Then, a total of 2345 patients (73.86 ± 13.90 years old, 50.70% male) meeting the selection criteria were enrolled (Figure 1). According to B2A use in hospital or not, patients were divided into B2A and non-B2A groups. Demographic data, comorbidities, vital signs, laboratorial results, scoring systems, and therapies of the study population were shown in Table I. Patients in the B2A group tended to have a more proportion of cardiac arrhythmias, chronic pulmonary disease, and ventilation and a less proportion of male and CAD than those in the non-B2A group. They also tended to be older, with higher level of BMI, WBC, platelet, sodium, and glucose and SAPS-II and SOFA scores.

Then, propensity score matching was performed to control for baseline confounders. After matching, 705
patients using or not using B2As (74.73 ± 13.40 years old, 47.90% male) were selected (Figure 1). There were no statistically significant differences in baseline characteristics between the B2A and non-B2A groups (Table I).

**Outcomes:** Before propensity score matching, 83 (3.54%) deaths occurred during hospitalization. In-hospital mortality was markedly higher in the B2A group than that in the non-B2A group (5% versus 2.08%, \( P < 0.001 \)). After matching, 49 (3.48%) deaths occurred, and in-hospital mortality remained markedly higher in the B2A group than that in the non-B2A group (4.68% versus 2.27%, \( P = 0.013 \)) (Figure 2).

Before matching, patient ICU stay was longer in the B2A group than that in the non-B2A group (3.41 ± 4.16 days versus 2.65 ± 2.88 days, \( P < 0.001 \)). After matching, however, patient ICU stay was similar between the two groups (3.14 ± 3.56 days versus 2.80 ± 3.21 days, \( P = 0.102 \)) (Figure 3).

**Impact of B2As on in-hospital mortality:** Univariate and multivariate logistic regression analysis was performed after propensity score matching. In the univariate analysis, age, ethnicity, BMI, stroke, SBP, BUN, SAPS-II scores, SOFA scores, RASI use, B2A use, and ventilation were significantly associated with the risk of in-hospital mortality (Table II). In multivariate analysis, B2A use (OR, 2.471; 95% CI, 1.289-4.734; \( P = 0.006 \)), stroke (OR, 4.581; 95% CI, 1.621-12.948; \( P = 0.004 \)), and SAPS-II scores (OR, 1.090; 95% CI, 1.064-1.116; \( P < 0.001 \)) were significantly associated with increased risk of in-hospital mortality, whereas RASI use (OR, 0.396; 95% CI, 0.202-0.778; \( P = 0.007 \)) was significantly associated with decreased risk of in-hospital mortality (Table III).

**Subgroup analysis:** Subgroup analysis was further performed based on chronic pulmonary disease, CAD, diabetes mellitus, hypertension, and cardiac arrhythmias (Table IV). The results showed that B2A use was significantly associated with increased risk of in-hospital mortality only in patients with HF without chronic pulmonary disease, but not in those chronic pulmonary disease. Moreover, other comorbidities seemed not to affect the association between B2A use and mortality.

**Discussion**

Among the 2345 eligible ICU patients with HF retrieved by the initial search of the MIMIC database, the proportion of patients receiving B2As was as high as 48.61%, which is much higher than that of community populations (23.74%-36.04%).\(^{3,11}\) The impact of B2As on
HF has been widely discussed in community populations but remains controversial. ICU patients with HF have more complex conditions and are more likely to receive B2As than community populations. Therefore, it is particularly important to investigate the effect of B2As on the prognosis of ICU patients with HF. The present real-world propensity score-matched study is the first study to confirm that inhaled B2As are associated with significantly increased in-hospital mortality in ICU patients with HF but without chronic pulmonary disease, after adjusting for many covariates, including age, ethnicity, BMI, stroke, SBP, BUN, SAPS-II scores, SOFA scores, RASIs, and ventilation.

In this study, only 47.02% of patients receiving B2As had COPD, asthma, or other chronic pulmonary disease, suggesting that clinicians might not strictly follow the indications for B2A use for ICU patients. ICU patients often have dyspnea, shortness of breath, cough, expectoration, or other symptoms caused by bronchial or pulmonary infection. Clinicians may use bronchodilators, such

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| Table 1. Baseline Characteristics Before and After Propensity Score Matching |
|-----------------------------------|-----------------|-----------------|----------|-----------------|-----------------|----------|-----------------|-----------------|
| Demographics                      | Before matching | After matching  |          | Before matching | After matching  |          | Before matching | After matching  |
|                                  | Non-B2A group   | B2A group       | P        | Non-B2A group   | B2A group       | P        | Non-B2A group   | B2A group       |
| Gender                           | (n = 1205)       | (n = 1140)       |          | (n = 705)       | (n = 705)       |          | (n = 705)       | (n = 705)       |
| Male                             | 659 (54.69)      | 529 (46.40)      | < 0.001  | 333 (47.23)      | 343 (48.65)      | 0.594   |
| Female                           | 546 (45.31)      | 611 (53.60)      |          | 372 (52.77)      | 362 (51.35)      |          |
| Age, years                       | 73.02 ± 14.68    | 74.75 ± 12.96    | 0.025    | 74.75 ± 13.50    | 74.72 ± 13.30    | 0.933   |
| Ethnicity                        | White            | 941 (78.09)      |          | 545 (77.30)      | 542 (76.88)      | 0.960   |
|                                  | Black            | 163 (13.53)      |          | 101 (14.33)      | 101 (14.33)      |          |
|                                  | Other            | 101 (8.38)       |          | 59 (8.37)        | 62 (8.79)        |          |
|                                  | BMI, kg/m²       | 28.24 ± 7.28     |          | 29.91 ± 8.95     | < 0.001          | 28.88 ± 7.96 | 28.82 ± 7.86   | 0.943           |
| Comorbidities                    | Diabetes mellitus| 535 (44.40)      |          | 315 (44.68)      | 318 (45.11)      | 0.872   |
|                                  | Hypertension     | 480 (39.83)      |          | 275 (39.01)      | 289 (40.99)      | 0.447   |
|                                  | Hyperlipidemia   | 346 (28.71)      |          | 160 (22.70)      | 188 (26.67)      | 0.084   |
|                                  | CAD              | 549 (45.56)      |          | 238 (33.76)      | 266 (37.73)      | 0.120   |
|                                  | Cardiac arrhythmias| 325 (26.97)     |          | 229 (32.48)      | 221 (29.93)      | 0.648   |
|                                  | Chronic pulmonary disease| 142 (11.78) |          | 142 (20.14)      | 157 (22.27)      | 0.328   |
|                                  | Renal failure    | 378 (31.37)      |          | 230 (32.62)      | 244 (34.61)      | 0.430   |
|                                  | Liver disease    | 51 (4.23)        |          | 33 (4.68)        | 35 (4.96)        | 0.804   |
|                                  | Stroke           | 38 (3.15)        |          | 27 (3.83)        | 24 (3.40)        | 0.669   |
|                                  | Malignancy       | 219 (18.17)      |          | 146 (20.71)      | 153 (21.70)      | 0.648   |
| Vital signs                      | SBP, mmHg        | 129.44 ± 25.58   |          | 130.76 ± 25.97   | 129.57 ± 24.35   | 0.713   |
|                                  | DBP, mmHg        | 65.71 ± 17.27    |          | 65.31 ± 17.55    | 65.27 ± 17.33    | 0.450   |
| Laboratory results               | WBC, K/µL        | 9.98 ± 5.35      |          | 10.15 ± 5.08     | 10.40 ± 5.02     | 0.275   |
|                                  | Platelet, K/µL   | 232.44 ± 104.93  |          | 237.29 ± 99.51   | 237.88 ± 99.91   | 0.135   |
|                                  | Hemoglobin, g/dL | 10.91 ± 2.03     |          | 10.83 ± 1.94     | 10.79 ± 1.97     | 0.960   |
|                                  | RDW, %           | 15.34 ± 2.03     |          | 15.39 ± 1.96     | 15.38 ± 1.99     | 0.914   |
|                                  | Sodium, mEq/L    | 138.52 ± 5.30    |          | 139.03 ± 4.80    | 138.64 ± 5.69    | 0.312   |
|                                  | Potassium, mEq/L | 4.23 ± 0.78      |          | 4.26 ± 0.73      | 4.27 ± 0.82      | 0.959   |
|                                  | Glucose, mg/dL   | 144.14 ± 76.54   |          | 144.67 ± 64.65   | 143.58 ± 73.87   | 0.332   |
|                                  | BUN, mg/dL       | 34.93 ± 25.50    |          | 33.91 ± 23.96    | 35.55 ± 25.99    | 0.685   |
|                                  | SCr, mg/dL       | 1.78 ± 1.74      |          | 1.64 ± 1.35      | 1.82 ± 1.84      | 0.963   |
| Scoring system                   | SAPS-II scores   | 34.50 ± 11.19    |          | 36.74 ± 10.61    | 35.88 ± 11.30    | 0.740   |
|                                  | SOFA scores      | 3.14 ± 1.97      |          | 3.69 ± 2.09      | 3.43 ± 2.13      | 0.628   |
| Therapy                          | RASIs            | 624 (51.78)      |          | 588 (51.58)      | 361 (51.21)      | 0.831   |
|                                  | MRA              | 8 (0.66)         |          | 3 (0.26)         | 1 (0.14)         | 0.43 (0.31) |
|                                  | BBs              | 928 (77.01)      |          | 892 (78.25)      | 537 (76.17)      | 0.179   |
|                                  | Statin           | 712 (59.09)      |          | 665 (58.33)      | 395 (56.03)      | 0.360   |
|                                  | Ventilation      | 194 (16.10)      |          | 390 (34.21)      | < 0.001          | 176 (24.96) | 178 (25.25)    | 0.902   |

For categorical variables, n (%) is presented. For continuous variables, mean ± standard deviation is presented. BMI indicates body mass index; CAD, coronary artery disease; SBP, systemic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; RDW, red blood cell distribution width; BUN, blood urea nitrogen; SCr, serum creatinine; SAPS-II, simplified acute physiology score II; SOFA, sequential organ failure assessment; RASIs, renin angiotensin system inhibitors; MRA, mineralocorticoid receptor antagonist; and BBs, beta-blockers.
B2As INCREASE MORTALITY IN ICU PATIENTS WITH HF

Table II. Univariate Logistic Regression Analysis After Propensity Score Matching

| Variables          | OR   | 95% CIs Lower | Upper  | P     |
|--------------------|------|--------------|--------|-------|
| Age                | 1.055| 1.024        | 1.086  | < 0.001|
| Ethnicity          |      |              |        |       |
| White              | Ref. | Ref.         | Ref.   |       |
| Black              | 0.124| 0.017        | 0.905  | 0.040 |
| Other              | 1.298| 0.540        | 3.120  | 0.560 |
| BMI                | 0.928| 0.885        | 0.974  | 0.002 |
| Stroke             | 3.249| 1.231        | 8.574  | 0.017 |
| SBP                | 1.097| 1.075        | 1.199  | 0.038 |
| BUN                | 1.012| 1.003        | 1.021  | 0.012 |
| SAPS-II scores     | 1.090| 1.065        | 1.116  | < 0.001|
| SOFA scores        | 1.346| 1.197        | 1.514  | < 0.001|
| RASIs              | 0.336| 0.177        | 0.639  | 0.001 |
| B2As               | 2.115| 1.153        | 3.878  | 0.016 |
| Ventilation        | 1.940| 1.078        | 3.491  | 0.027 |

BMI indicates body mass index; SBP, systemic blood pressure; BUN, blood urea nitrogen; SAPS-II, simplified acute physiology score II; SOFA, sequential organ failure assessment; RASIs, renin angiotensin system inhibitors; and B2As, beta2-agonists.

As B2As, to relieve these symptoms, regardless of their indications. This leads to the abuse of B2As. From baseline data before matching, we found that the patients in the B2A group were more severe, with more proportion of cardiac arrhythmias, chronic pulmonary disease, and ventilation and higher levels of SAPS-II and SOFA scores. This suggests that clinicians are more likely to prescribe B2As in patients with severe disease. In patients with HF, it is hard to distinguish whether dyspnea symptoms were caused by HF or obstructive lung disease.12) Clinicians may prescribe patients with HF with B2As to relieve the symptoms of dyspnea and neglect the cardiac toxicity of B2As.

Except for relieving dyspnea in patients with HF, B2As may not bring more benefits but a series of risks, especially in those without chronic pulmonary disease. As known, the beta2-adrenergic receptors (B2AR) are mainly distributed in airway and vessel smooth muscles, whereas beta1-adrenergic receptors (B1ARs) are mainly distributed in the myocardium.13) Selective B2As, which do not affect the myocardium and lead HF progression, seem to be safe for patients with HF. Elevated catecholamine levels are discovered in patients with HF, which was associated with alterations in both B1AR and B2AR. Some studies14,15) found that B1ARs were downregulated, whereas B2ARs were relatively preserved in the myocardia of patients with HF. This may be the reason why patients with HF are additionally susceptible to inotropic stimulation by B2As. When B2As are administered by inhalation, very little dose of B2As reaches the airways and effectively decreases airway resistance. This greatly reduces plasma concentration and the cardiac toxicity of B2As. However, inhaled B2A residual particles may enter the systemic circulation through the pulmonary vascular bed or gastroin-
testinal tract. In addition, the severe side effects of B2As include cardiac ischemia, arrhythmias, and QT prolongation and may contribute to the increase of mortality.

For different populations, B2As may bring different risks. The present study indicated that the association between B2A use and mortality was significant only in patients with HF and chronic pulmonary disease, but not in those with chronic pulmonary disease. This suggests that the benefit of B2A use for respiratory disease may be more than 50%, the NYHA classification of cardiac function and accurate EF values were not found in the MIMIC database, and we did not put them into analysis. This may affect the reliability of our results. Third, the specific details of B2A use, including the timing, dosage, and course, were not fully recorded in the MIMIC database. This makes it technically difficult to evaluate their effects on the outcomes. Finally, some established risk factors, such as age and blood pressure, were not related to mortality in the multivariate logistic regression analysis. The possible explanations were as follows: 1) In the propensity score matching analysis, the confounding factors, including age, were artificially corrected; therefore, their association with mortality might be weakened. 2) ICU patients often have shock caused by hypovolemia, infection, or ventricular dysfunction. Higher blood pressure may be beneficial for these patients. Besides, this study excluded patients using drugs activating adrenergic receptors, including norepinephrine and dopamine. Therefore, some patients with severe hypotension who were treated with vasopressor drugs might be excluded. The effect of blood pressure on the outcomes might be weakened. To verify the consistency of the results, a large-scale prospective multicenter study is warranted.

Limitations: Our study has some limitations that need to be addressed. First, our study is a single-center retrospective cohort study; selection biases cannot be ignored. Second, because the missing values of BNP and proBNP are more than 50%, the NYHA classification of cardiac function and accurate EF values were not found in the MIMIC database, and we did not put them into analysis. This may affect the reliability of our results. Third, the specific details of B2A use, including the timing, dosage, and course, were not fully recorded in the MIMIC database. This makes it technically difficult to evaluate their effects on the outcomes. Finally, some established risk factors, such as age and blood pressure, were not related to mortality in the multivariate logistic regression analysis. The possible explanations were as follows: 1) In the propensity score matching analysis, the confounding factors, including age, were artificially corrected; therefore, their association with mortality might be weakened. 2) ICU patients often have shock caused by hypovolemia, infection, or ventricular dysfunction. Higher blood pressure may be beneficial for these patients. Besides, this study excluded patients using drugs activating adrenergic receptors, including norepinephrine and dopamine. Therefore, some patients with severe hypotension who were treated with vasopressor drugs might be excluded. The effect of blood pressure on the outcomes might be weakened. To verify the consistency of the results, a large-scale prospective multicenter study is warranted.

Table III. Multivariate Logistic Regression Analysis After Propensity Score Matching

| Variables     | OR   | 95% CIs Lower | 95% CIs Upper | P    |
|---------------|------|---------------|---------------|------|
| Stroke        | 4.581| 1.621         | 12.948        | 0.004|
| SAPS-II       | 1.090| 1.064         | 1.116         | <0.001|
| RASIs         | 0.396| 0.202         | 0.778         | 0.007|
| B2As          | 2.471| 1.289         | 4.734         | 0.006|

Multivariate logistic regression was adjusted for factors with a P value < 0.1 in univariate regression analysis. SAPS-II indicates simplified acute physiology score II; RASIs, renin angiotensin system inhibitors; and B2As, beta2-agonists.

Table IV. Subgroup Analysis of the Associations Between B2As and In-Hospital Mortality

| Subgroups                  | OR   | 95% CIs Lower | 95% CIs Upper | P    |
|----------------------------|------|---------------|---------------|------|
| Chronic pulmonary disease  |      |               |               |      |
| Yes                        | 2.094| 0.582         | 7.537         | 0.258|
| No                         | 2.427| 1.351         | 4.362         | 0.003|
| Coronary artery disease   |      |               |               |      |
| Yes                        | 1.409| 1.014         | 3.236         | 0.019|
| No                         | 3.121| 1.597         | 6.102         | 0.001|
| Diabetes mellitus          |      |               |               |      |
| Yes                        | 2.315| 1.019         | 5.261         | 0.045|
| No                         | 2.518| 1.320         | 4.804         | 0.005|
| Hypertension               |      |               |               |      |
| Yes                        | 4.178| 1.330         | 13.121        | 0.014|
| No                         | 2.083| 1.182         | 3.672         | 0.011|
| Cardiac arrhythmias        |      |               |               |      |
| Yes                        | 2.386| 1.092         | 5.216         | 0.029|
| No                         | 2.243| 1.153         | 4.362         | 0.017|

Logistic regression models were used to calculate odds ratios (ORs) with 95% confidence intervals (CIs).
Conclusion

The use of inhaled B2As is common in ICU patients with HF and may significantly increase in-hospital mortality, especially in those without chronic pulmonary disease. For patients with HF with confirmed or suspicious symptoms of dyspnea, clinicians should carefully weigh the potential risks and benefits of using B2As and consider whether there are other more reasonable alternative treatments for this conflict situation.

Disclosure

Conflicts of interest: All authors have no conflict of interest to disclose.

Ethics approval and consent to participate: The database was approved by the institutional review boards of Massachusetts Institute of Technology (Cambridge, MA, USA) and Beth Israel Deaconess Medical Center (Boston, MA, USA). Therefore, the requirement for written informed consent was waived.

Availability of data and material: The data will be available immediately after the publication, ending two years after the publication. The data will be shared on a request basis for anyone. The data can be applicable for up to 10 years after the publication. The data will be shared on a request basis for anyone. The data can be applicable for up to 10 years after the publication.

Authors’ contributions: Zexiong Li and Yesheng Ling: Conceptualization, Investigation, Data Curation, Writing - Original Draft, and Visualization. Qian Chen and Bingyuan Wu: Software and Methodology. Long Peng and Xixiang Tang: Formal Analysis and Validation. Jinlai Liu and Suhua Li: Resources, Writing - Review and Editing, Supervision, Project Administration, and Funding Acquisition.

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