Is oxygen therapy beneficial for normoxemic patients with acute heart failure? A propensity score matched study

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Research

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Abstract

Background The clinical efficiency of routine oxygen therapy is uncertain in patients with acute heart failure (AHF) who do not have hypoxemia. The aim of this study was to investigate the association between oxygen therapy and clinical outcomes in normoxemic patients hospitalized with AHF using real-world data.

Methods Normoxemic patients diagnosed with AHF on ICU admission from the electronic ICU (eICU) Collaborative Research Database were included in the current study, in which the study population was divided into the oxygen therapy group and the ambient-air group. Propensity score matching (PSM) was applied to create a balanced covariate distribution between patients receiving supplemental oxygen and those exposed to ambient air. Linear regression and logistic regression models were performed to assess the associations between oxygen therapy and length of stay (LOS), and all-cause in-hospital as well as ICU mortality rates, respectively. A series of sensitivity and subgroup analyses were conducted to further validate the robustness of our findings.

Results A total of 2,922 normoxemic patients with AHF were finally included in the analysis. Overall, 42.1% (1,230/2,922) patients were exposed to oxygen therapy, and 57.9% (1,692/2,922) patients did not receive oxygen therapy (defined as the ambient-air group). After PSM analysis, 1,122 pairs of patients were matched: each patient receiving oxygen therapy was matched with a patient without receiving supplemental oxygen. The multivariable logistic model showed that there was no significant interaction between the ambient air and oxygen group for all-cause in-hospital mortality (odds ratio [OR] 1.30; 95% confidence interval [CI] 0.92–1.82; $P=0.138$) or ICU mortality (OR 1.39; 95% CI 0.83–2.32; $P=0.206$) in the post-PSM cohorts. In addition, linear regression analysis revealed that oxygen therapy was associated with prolonged ICU LOS (OR 1.11; 95% CI 1.06–1.15; $P<0.001$) and hospital LOS (OR 1.06; 95% CI 1.01–1.10; $P=0.009$) after PSM. Furthermore, the absence of an effect of supplemental oxygen on mortality was consistent in all subgroups.

Conclusions Routine use of supplemental oxygen in AHF patients without hypoxemia was not found to reduce all-cause in-hospital mortality or ICU mortality.

Background

Acute heart failure (AHF) is a life-threatening medical condition requiring immediate treatment and leading to urgent hospitalization (1). Supplemental oxygen therapy is a routine treatment modality in the management of AHF patients (2, 3). The underlying rationale behind oxygen therapy for AHF patients is to relieve dyspnea, or improve oxygenation for the threatened myocardial tissue, thereby alleviating myocardial injury and improving cardiac function (4–6). However, above-normal arterial oxygen tension can cause systemic vasoconstriction (7), overproduction of reactive oxygen species (ROS) (8), and, consequently, worsening of heart failure (HF). Currently, most studies have focused solely on AHF patients with refractory and progressive hypoxemia, and oxygen therapy is recommended in patients with

pulse oximetry-derived oxygen saturation (SpO_2) $\geq 90\%$ to correct hypoxemia (2, 9). For normoxemic patients (defined as SpO_2 between 90% and 100%) presenting with AHF, whether supplementary oxygen provides benefit or not remains highly uncertain.

This topic has been studied in other non-AHF clinical settings. For example, several randomized controlled trials (RCTs) have demonstrated that supplemental oxygen had no clinical benefits among patients without hypoxemia presenting with acute myocardial infarction (AMI) and others have suggested possible harm (10–15). Considering the contradictory findings regarding supplemental oxygen therapy, recent HF guidelines diverge from the previous consensus that oxygen should be administered routinely among AHF patients irrespective of oxygen saturation at baseline (16–18). However, this new direction is solely based on expert opinion or low-quality and nonrandomized clinical trials with a small sample size (6, 19, 20). Given the cost of oxygen therapy and the ubiquitous use of oxygen among patients hospitalized with AHF, it is necessary to evaluate the correlation between supplemental oxygen and clinical outcomes (4, 21, 22). Thus, the present study was conducted to investigate the association between routine oxygen therapy and short-term clinical outcomes among normoxemic patients with AHF using real-world data.

Materials And Methods

Data sources and ethical statement

The electronic Intensive Care Unit (eICU) Collaborative Research Database was a multi-center ICU database for more than 200,000 admissions from over 200 hospitals across the USA between 2014 and 2015 (23). The eICU database documents contained comprehensive charted events, including demographic data, diagnosis information via International Classification of Diseases, Ninth Revision (ICD-9) codes, vital sign measurements, laboratory findings and blood gas analyses, hourly physiologic readings from bedside monitors, various scoring systems, treatment information, and clinical outcomes. The establishment of the eICU database was approved by the Institutional Review Boards (IRB) of the Massachusetts Institute of Technology (MIT, Cambridge, MA, USA). All the data were made anonymous prior to research analyses by the eICU programme, and hence the requirement for informed consent was waived. The study was complied with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We finished the “Protecting Human Research Participants” curriculum, and obtained permission to access the dataset (authorization code: 33281932). In addition, we conducted this study in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement (24).

Population selection

We included all ICU patients (aged ≥ 30 years) with a primary diagnosis of AHF using ICD-9 diagnosis codes (ICD-9 codes: 404.91, 415.0, 428.0, 428.1, 428.21, 428.23, 428.31, 428.33, 428.41, and 428.43)

from the eICU database. Patients were excluded who (1) had SpO₂ <90% on admission; (2) presented with cardiac arrest or cardiogenic shock on admission; (3) were at risk of oxygen-induced hypercapnia (chronic obstructive pulmonary disease [COPD], asthma, or pneumonia) on admission; (4) stayed in the ICU for less than 24 hours; (5) required more intensive oxygen therapy including noninvasive ventilation (NIV) or invasive ventilation through endotracheal intubation during hospitalization; (6) received oxygen therapy at a flow rate of 10 L/min or more; and (7) had incomplete or unobtainable documented information about oxygen saturation, oxygen therapy, and clinical outcomes.

Data extraction and data processing

The data were extracted from the database using structured query language (SQL) with PostgreSQL (version 9.6). The code that supported the eICU documentation and website was publicly available (<https://github.com/mit-lcp/eicu-code>). Demographic information included age, gender, and body mass index (BMI). BMI was calculated as weight (kg) divided by height² (m²), using height and weight reported at the time of admission. Comorbidities on admission included sepsis, acute renal injury (AKI), and acute coronary syndrome (ACS). History of disease included atrial fibrillation (AF), coronary artery disease (CAS), hypertension, stroke, diabetes mellitus (DM), chronic kidney disease (CKD), and hyperthyroidism. Vital signs at presentation included systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR), heart rate (HR), SpO₂, and urine output on the first day. Laboratory findings and blood gas analysis data included albumin, creatinine, glucose, blood urea nitrogen (BUN), hematocrit, hemoglobin, blood platelets, white blood cells (WBCs), potassium, and sodium. If vital signs were measured multiple times or patients received a laboratory test more than once during their hospitalization, an initial data on the first day after ICU admission was extracted for subsequent analyses. The severity of illness was assessed by four scoring systems (the Oxford Acute Severity of Illness Score [OASIS], the Sequential Organ Failure Assessment score [SOFA], the Glasgow Coma Scale [GCS], and the Acute Physiology and Chronic Health Evaluation [APACHE] IV). These scoring systems were calculated within the first 24 hours after admission using the values associated with the greatest severity of illness.

For treatment information, each admitted patient was treated independently, although some patients in the dataset might have had multiple admissions. Routine oxygen therapy in this study could refer to oxygen supplementation methods either via face mask or nasal cannula, because the eICU database did not provide detailed information to differentiate these two methods. Patients who received NIV or invasive ventilation during hospitalization were excluded. We took the average value of the SpO₂ measurements during oxygen therapy as a measure of the central tendency of oxygen exposure. To address concerns about the time dependency of oxygen exposure, the duration of oxygen therapy was also recorded for subsequent analyses. Other treatment information included intra-aortic balloon pump, renal replacement treatment (RRT), and in-hospital medication administration (morphine, inotrope,

vasodilator, vasoconstrictor, diuretic, angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers [ACEI/ARB], calcium channel blocker [CCB], beta-blocker, anti-platelet, and anti-coagulant).

As severe data missing might lead to bias, variables with over 20% missing values were not taken into subsequent analysis. Correspondingly, multiple imputation (MI) was used for processing variables with less than 30% missing values (25, 26).

Endpoints

The primary endpoint of our study was all-cause in-hospital mortality, which was defined as survival status at hospital discharge. We selected all-cause ICU mortality and ICU and hospital length of stay (LOS) as secondary endpoints. ICU and hospital LOS were calculated as the total duration spent in the ICU and hospital since hospital admission separately. Patients with missing survival outcome information were excluded from the final cohort.

Statistical analysis

Normoxemic patients with AHF were divided into the oxygen therapy group and the ambient-air group. Baseline characteristics of enrolled participants were presented and compared between two groups by using either Student *t* test, Kruskal Wallis rank test, Pearson's χ^2 test or Fisher's exact test as appropriated. Continuous variables were characterized as mean (standardized differences [SD]) or median (interquartile range [IQR]), while categorical or ranked data were shown as count and proportion.

Given the observational nature of the current study, propensity score matching (PSM) was used to minimize the effect of potential confounders. A logistic regression model was constructed to calculate and assign each patient a propensity score (PS), which was defined as the likelihood of being exposed to an intervention. Next, 1:1 matching (the oxygen therapy group vs. the ambient-air group) without replacement was performed using a nearest neighbor matching algorithm, with a fixed caliper width of 0.05. The standardized mean difference (SMD) was calculated to evaluate the efficiency of PSM in reducing the differences between the two groups.

In the pre-PSM and post-PSM cohorts, logistic regression models were employed to investigate associations between oxygen therapy and clinical outcomes adjusting for confounding variables selected based on $P \leq 0.05$ in the univariate analysis, in which the Akaike information criterion (AIC) was applied as the selection criteria of the optimal model. Linear regression was used to assess the correlation of oxygen therapy with length of stay, and the odds ratios (ORs) were presented using the formula $OR = e^{\beta_i}$. A series of subgroup and sensitivity analyses were performed to further validate the robustness of our findings.

A two-tailed *P* value of less than 0.050 was considered to be statistical significance. All statistical analyses were performed using SPSS software (version 22.0; IBM Corporation, St. Louis, Missouri, USA) and R software (version 3.6.1; The R Project for Statistical Computing, TX, USA; <http://www.r-project.org>).

Results

Basic characteristics

During the study period, 15,187 critically ill patients were admitted with AHF. Consequently, after excluding the patients according to the selection criteria, 2,922 eligible patients were enrolled in the current study (Figure 1). The patients included in the final cohort had a median age of 72 (61-82) years, 54.3% (1,586/2,922) patients were men, and 39.5% (1,155/2,922) patients were identified as having *de novo* AHF (Table 1).

Overall, 42.1% (1,230/2,922) patients were exposed to oxygen therapy, and 57.9% (1,692/2,922) patients did not receive oxygen therapy (defined as the ambient-air group). The median duration of oxygen therapy was 2.5 (1.6-4.1) days. The comparison of baseline characteristics between these two groups was summarized in Table 1. There were significant differences in history of disease (hypertension: 61.5% [1,041/1,692] vs. 67.3% [828/1,230]; *P* = 0.001) and scoring systems (OASIS: 20.0 [15.0-26.0] vs. 19.0 [12.0-25.0]; *P* = 0.001) between the oxygen therapy group and the ambient-air group. Additionally, patients exposed to oxygen therapy were more likely to receive medication administration during hospitalization (inotropes: 4.3% [73/1,692] vs. 8.1% [100/1,230]; *P* = 0.001; diuretic: 4.4% [75/1,692] vs. 8.0% [99/1,230]; *P* = 0.001; ACEI/ARB: 6.6% [111/1,692] vs. 12.8% [158/1,230]; *P* = 0.001; CCB: 4.8% [82/1,692] vs. 7.2% [89/1,230]; *P* = 0.007; and beta-blocker: 17.1% [290/1,692] vs. 32.9% [405/1,230]; *P* = 0.001). No difference was observed in admission SpO₂ level (97.0% [95.0%-99.0%] vs. 97.0% [95.0%-99.0%]; *P* = 0.946) between these two groups. Furthermore, during the intervention, mean SpO₂ level of the oxygen therapy group was higher than that of the ambient-air group (98.7% [97.4%-99.8%] vs. 97.1% [95.5%-97.8%]; *P* = 0.001).

Relationship between oxygen therapy and outcomes

Univariable and multivariable logistic regression models were employed to examine the difference in all-cause in-hospital and ICU mortality rates between these two groups. In the pre-matched cohort, 6.2% (104/1,692) patients in the ambient-air arm and 8.0% (98/1,230) patients in the oxygen therapy arm died in the hospital (OR 1.32; 95% confidence interval [CI] 0.99-1.76; *P* = 0.056) (Table 2; Table S1). 3.5% (43/1,230) patients in the oxygen group died in the ICU in comparison to 2.5% (42/1,692) patients in the ambient-air group (OR 1.42; 95% CI 0.92-2.19; *P* = 0.109) (Table 2; Table S2). By the multivariable analysis, no differences were observed for in-hospital mortality (OR 1.34; 95% CI 0.98-1.84; *P* = 0.067) (Table 2; Table S1) or ICU mortality (OR 1.58; 95% CI 0.97-2.56; *P* = 0.066) after adjusting for possible confounding factors

associated with mortality (Table 2; Table S1; Table S2). Moreover, linear regression was used to evaluate the association between oxygen therapy and ICU as well as hospital LOS. Nevertheless, oxygen therapy was significantly associated with prolonged ICU LOS (OR 1.15; 95% CI 1.11-1.19; $P=0.001$) and hospital LOS (OR 1.07; 95% CI 1.04-1.11; $P=0.001$) (Table 2).

By the PSM analysis, 2,244 patients remained in the post-PSM cohort, and 1,122 patients who received oxygen therapy were matched with 1,122 patients who did not receive oxygen. All the variables listed in Table 1 (except for duration of oxygen therapy and mean SpO₂ during treatment period) were considered in the PSM analysis. The characteristics of matched patients were compared, and the SMDs for all the individual covariates were provided. Differences in all variables between the oxygen therapy group and the ambient-air group were reduced and had no statistical significances measured by SMDs that were less than 10% for all variables (Table 1; Table S3).

Similar to the results in the pre-matched model, the logistic model showed that there was no significant interaction between the ambient air and oxygen groups with regard to all-cause in-hospital mortality (univariable analysis: OR 1.22; 95% CI 0.89-1.68; $P=0.223$; multivariable analysis: OR 1.30; 95% CI 0.92-1.82; $P=0.138$) (Table 2; Table S4) and ICU mortality (univariable analysis: OR 1.18; 95% CI 0.74-1.88; $P=0.479$; multivariable analysis: OR 1.39; 95% CI 0.83-2.32, $P=0.206$) (Table 2; Table S5). Likewise, the results of linear regression analysis revealed that oxygen therapy was associated with prolonged ICU LOS (OR 1.11; 95% CI 1.06-1.15; $P=0.009$) and hospital LOS (OR 1.06; 95% CI 1.01-1.10; $P=0.009$) (Table 2).

Sensitivity analysis

A series of sensitivity analyses were performed to validate the robustness of our findings (Figure 2). When taking the SpO₂ target of oxygen therapy into consideration, we noticed that patients with a high-normal range of 95%–100% SpO₂ were associated with an increased risk of in-hospital mortality when compared with the ambient-air group (OR 1.44; 95% CI 1.03-2.03, $P=0.034$). Oxygen therapy was also associated with deteriorative in-hospital mortality in AHF patients receiving oxygen therapy for ≥ 6 days (OR 3.34; 95% CI 2.15-5.20; $P=0.001$), the etiology of AMI (OR 2.95; 95% CI 1.09-7.99; $P=0.033$), and the history of AF (OR 1.69; 95% CI 1.00-2.87; $P=0.049$). Other subgroups were not found to be significant.

Discussion

This study demonstrated that routine oxygen therapy was not found to reduce the composite endpoints of all-cause in-hospital and ICU mortality rates in normoxemic patients with AHF. The results also suggested that oxygen therapy might be closely correlated to increased LOS in ICU and hospital. In addition, the absence of an effect of supplemental oxygen on mortality was consistent in all subgroups. To our knowledge, this study was the first to investigate the association between supplemental oxygen

and short-term clinical outcomes based on a multi-center and critical care cohort of AHF patients without hypoxia.

Oxygen therapy remains a cornerstone for the treatment of AHF, while guidelines provide various recommendations on its appropriate use, reflecting the lack of robust evidence on such “cornerstone” therapy. The Canadian Cardiovascular Society (CCS) HF guidelines have recommended that supplemental oxygen should be considered for patients who are hypoxemic, and should be used cautiously in normoxemic patients due to concerns of increasing systemic vascular resistance (SVR) and reducing cardiac output (CO) (27). The latest European Society of Cardiology (ESC) and the Taiwan Society of Cardiology (TSOC) guidelines have indicated that oxygen should not be used routinely for AHF patients without hypoxemia (2, 28). Recommendations on oxygen therapy in normoxemic patients with AHF are not mentioned in the latest American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) (1), or the National Institute for Health and Care Excellence (NICE) guidelines (16). However, most of these recommendations appear to be solely based on expert opinion rather than high-quality evidence, and we hope our findings might provide certain evidence for this point of view. In addition, one observational study documented supplemental oxygen to be prescribed among at least half of AHF patients in the emergency department (ED), regardless of SpO₂ level (4). A lack of clinical benefit could mean that by departing from this practice, it might be significant not only for patients to have a lower treatment burden but also to have reduced medical expenses.

Our findings were consistent with the results of studies that evaluated the impacts of supplemental oxygen therapy in other clinical settings. Several RCTs and meta-analyses have demonstrated that oxygen therapy does not significantly reduce all-cause mortality, and can even increase the incidence of early myocardial injury and infarct size among AMI patients with normoxemia (8, 10–13, 29–33). A total of eleven RCTs including 6,366 patients with acute stroke showed a nonsignificant increase in mortality at three, six, and twelve months in patients who received normobaric oxygen compared with those who received ambient air (34). In addition, it was standard to perform neonatal resuscitation with 100% oxygen until multiple RCTs demonstrated that room air resulted in a lower incidence of infant mortality and hypoxic ischemic encephalopathy than 100% oxygen, thereby contributing to a dramatic change in guidelines and practice (35).

Although hypoxic patients can benefit from supplemental oxygen to correct hypoxia, supplementation above normoxia seems to be futile as the hemodynamic response to hyperoxia outbalances the benefit of additionally dissolved oxygen in the blood. The cardiovascular effects of hyperoxia are mainly mediated by following pathways: endothelial production of ROS (36) and hyperoxia-induced vasoconstriction in the coronary (37), retinal (38), and cerebral vascular bed (39). The excessive formation of ROS outweighs the antioxidant capacities of the cells, and results in oxidative stress and a cascade of adverse outcomes including damage to nucleic acids, proteins and lipids, and activation of apoptotic as well as necrotic pathways causing cell death (6, 40, 41). Furthermore, ROS-induced closure of adenosine triphosphate (ATP)-dependent potassium channels and activation of ligand-gated calcium channels in vascular smooth muscle cells lead to the peripheral vasoconstriction and decreased regional blood flow in most

vascular beds (42, 43). A study showed that extreme hyperoxia ($\text{FiO}_2=1.0$; arterial partial pressure of oxygen [PaO_2] ≥ 300 mmHg) was associated with an 8–30% decrease in coronary blood flow, impairment of cardiac relaxation and contractility, and increased left ventricular filling pressures in patients with congestive HF (44). In addition, two studies revealed that hyperoxia caused peripheral vasoconstriction, increased SVR, and did not increase systemic oxygen delivery in HF patients (19, 45). Haque et al. found an increase in pulmonary capillary wedge pressure (PCWP) caused by hyperoxia in AHF patients with this effect starting at an FiO_2 level of 0.24 (46).

The goal of oxygen therapy remains uncertain for AHF patients. In our subgroup analysis, we divided patients by mean SpO_2 level during hospitalization into a low-normal ($90\% \leq \text{SpO}_2 \leq 95\%$) and a high-normal ($95\% \leq \text{SpO}_2 \leq 100\%$) cohort. Among patients with a high-normal range of $95\% \leq \text{SpO}_2 \leq 100\%$, oxygen therapy was associated with worse clinical outcomes compared to the ambient-air group. Although measurement of SpO_2 might be inappropriate tool to quantify the magnitude of hyperoxemia, some researchers reported that the prevalence of arterial hyperoxia increased when SpO_2 was $\geq 95\%$ in a cross-sectional study of one hundred mechanically ventilated patients admitted to the ICU (47). Improving Oxygen Therapy in Acute-illness (IOTA) systematic review and meta-analysis concluded that liberal oxygen therapy (without setting an upper limit of SpO_2) could increase mortality, and SpO_2 should not exceed 96% among acutely ill adults (48). Additionally, the Thoracic Society of Australia and New Zealand (TSANZ) and the British Thoracic Society (BTS) have recommend that oxygen is stopped above an upper limit of SpO_2 in critically ill patients (TSANZ: 96%; BTS: 98%) (49, 50). However, a recent study investigated the effect of oxygen titrated to high ($\text{SpO}_2 \geq 96\%$) vs. low ($90\% \leq \text{SpO}_2 \leq 92\%$) pulse oximetry targets in fifty patients hospitalized with AHF, and implicated that the difference of baseline and 72 hours N-terminal pro-brain-type natriuretic peptide (NT-proBNP) levels were of no obvious significance between groups with high and low SpO_2 targets (51). Nonetheless, limited by the small sample size and few death events, they did not assess the impact of these two groups on clinical endpoints (such as in-hospital mortality).

Notably, the current study must be interpreted in the context of several limitations. First, all patients with an admission SpO_2 level ≥ 90 mmHg were included in our study cohort, yet misclassification could not be ruled out, as SpO_2 was measured by local procedures and therefore subjected to selection bias. Second, some of the AHF patients might develop refractory and progressive hypoxemia during intervention, although we excluded patients receiving more intensive oxygen therapy including endotracheal intubation and NIV during hospitalization. Third, we did not include detailed information with regard to oxygen therapy (oxygen flow rate and oxygen concentration), or some important laboratory variables (such as NT-proBNP) due to more than 30% missing values, which might be related to the efficacy of oxygen therapy. Another limitation was the retrospective nature of the study. Retrospective studies almost always have bias because prognostic factors are unequally distributed between patients exposed or not exposed to an intervention. Although multivariate logistic regression and PSM analysis were applied in the present

study to control the covariate imbalance and selection bias, more high-quality clinical trials are needed to strengthen our results.

Conclusion

Routine use of supplemental oxygen in normoxemic patients with AHF was not found to reduce the composite of all-cause in-hospital or ICU mortality. Thus, our results provided relatively solid evidence for the rationale use of oxygen therapy in the current guidelines.

Abbreviations

AHF: Acute heart failure; ROS: Reactive oxygen species; HF: Heart failure; SpO₂: Pulse oximetry-derived oxygen saturation; RCT: Randomized controlled trial; AMI: Acute myocardial infarction; eICU: Electronic Intensive Care Unit; ICD-9: International Classification of Diseases, Ninth Revision; IRB: Institutional Review Boards; MIT: Massachusetts Institute of Technology; STROBE: STrengthening the Reporting of OBservational studies in Epidemiology; COPD: Chronic obstructive pulmonary disease; NIV: Noninvasive ventilation; SQL: Structured query language; BMI: Body mass index; AKI: Acute renal injury; ACS: Acute coronary syndrome; AF: Atrial fibrillation; CAS: Coronary artery disease; DM: Diabetes mellitus; CKD: Chronic kidney disease; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; RR: Respiratory rate; HR: Heart rate; BUN: Blood urea nitrogen; WBC: White blood cell; OASIS: Oxford Acute Severity of Illness Score; SOFA: Sequential Organ Failure Assessment; GCS: Glasgow Coma Scale; APACHE: Acute Physiology and Chronic Health Evaluation; RRT: Renal replacement treatment; ACEI/ARB: Angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers; CCB: Calcium channel blocker; MI: Multiple imputation; LOS: Length of stay; SD: Standardized difference; IQR: Interquartile range; PSM: Propensity score matching; PS: Propensity score; SMD: Standardized mean difference; AIC: Akaike Information Criterion; OR: Odds ratio; CI: Confidence interval; CCS: Canadian Cardiovascular Society; SVR: Systemic vascular resistance; CO: Cardiac output; ESC: European Society of Cardiology; TSOC: Taiwan Society of Cardiology; ACC: American College of Cardiology; AHA: American Heart Association; HFSA: Heart Failure Society of America; NICE: National Institute for Health and Care Excellence; ED: Emergency department; ATP: Adenosine triphosphate; FiO₂: Fraction of inspired oxygen; PaO₂: Arterial partial pressure of oxygen; PCWP: Pulmonary capillary wedge pressure; IOTA: Improving Oxygen Therapy in Acute-illness; TSANZ: Thoracic Society of Australia and New Zealand; BTS: British Thoracic Society; NT-proBNP: N-terminal pro-brain-type natriuretic peptide.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

YY and RQY designed the study, collected and analyzed data, and drafted the manuscript; YFZ and SYW helped in the statistical analysis and result interpretation; WX, JNW, and XYH prepared the figures and interpret the results; YMY and ZNW were identified as the guarantor of the paper, taking responsibility for the integrity of the work as a whole; All authors contributed to and revised the final manuscript.

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Availability of data and materials

The datasets generated and/ or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study utilized the anonymous data available in the eICU database with pre-existing institutional review board (IRB) approval.

Consent for publication

Not applicable.

Competing interests

The authors have no conflicts of interest to disclose.

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Tables

Table 1. Baseline characteristics of normoxemic patients with AHF between the two groups before matching

Characteristics	Total (N=2922)	Ambient Air (N=1692)	Oxygen Therapy (N=1230)	<i>P</i> value	SMD
Demographics					
Age, years	72.0 (61.0-82.0)	72.0 (61.0-82.0)	72.0 (60.0-82.0)	0.316	0.047
Gender, male	1586 (54.3%)	915 (54.1%)	671 (54.6%)	0.799	0.010
BMI, kg/m ²	28.7 (24.2-34.5)	28.6 (24.3-34.4)	28.8 (24.2-34.7)	0.716	0.004
<i>de novo</i> AHF	1155 (39.5%)	659 (38.9%)	496 (40.3%)	0.452	0.028
Comorbidities on admission					
Sepsis	306 (10.5%)	183 (10.8%)	123 (10.0%)	0.477	0.027
AKI	65 (2.2%)	45 (2.7%)	20 (1.6%)	0.061	0.071
History of disease					
AF	668 (22.9%)	381 (22.5%)	287 (23.3%)	0.604	0.019
CAD					
MI	561 (19.2%)	331 (19.6%)	230 (18.7%)	0.559	0.022
PCI	335 (11.5%)	200 (11.8%)	135 (11.0%)	0.479	0.027
CABG	344 (11.8%)	194 (11.5%)	150 (12.2%)	0.546	0.023
Hypertension	1869 (64.0%)	1041 (61.5%)	828 (67.3%)	0.001	0.121
Stroke	301 (10.3%)	178 (10.5%)	123 (10.0%)	0.648	0.017
DM	1145 (39.2%)	656 (38.8%)	489 (39.8%)	0.590	0.020
CKD	775 (26.5%)	451 (26.7%)	324 (26.3%)	0.850	0.007
Hyperthyroidism	346 (11.8%)	190 (11.2%)	156 (12.7%)	0.230	0.045
Vital signs at presentation					
SBP, mmHg	121.0 (120.0-127.0)	121.0 (120.0-127.0)	121.0 (120.0-127.0)	0.467	0.021
HR, beats/min	86.0 (73.0-101.0)	86.0 (73.0-101.0)	87.0 (74.0-101.0)	0.179	0.043
SpO ₂ , %	97.0 (95.0-99.0)	97.0 (95.0-99.0)	97.0 (95.0-99.0)	0.946	0.013
Laboratory findings and blood gas analysis					

Albumin, mg/dL	3.1 (2.7-3.5)	3.1 (2.7-3.5)	3.1 (2.7-3.5)	0.941	0.007
Creatinine, $\mu\text{mol/L}$	1.3 (0.9-2.2)	1.310 (0.9-2.2)	1.3 (0.9-2.1)	0.195	0.062
Glucose, mg/dL	109.0 (91.0-138.0)	109.0 (91.0-137.3)	110.0 (91.0-139.0)	0.420	0.010
BUN, mg/dL	27.0 (18.0-44.0)	27.0 (18.0-44.0)	27.0 (18.0-43.0)	0.957	0.038
Hematocrit, %	32.1 (6.9)	31.9 (6.9)	32.3 (6.9)	0.110	0.060
Hemoglobin, g/dL	10.5 (8.8-12.1)	10.5 (8.8-12.0)	10.5 (8.9-12.2)	0.137	0.062
Platelet, $10^9/\text{L}$	183.5 (136.0-241.0)	180.0 (134.0-238.0)	186.8 (138.0-244.0)	0.072	0.101
WBC, $10^9/\text{L}$	8.5 (6.3-11.6)	8.4 (6.3-11.4)	8.6 (6.4-11.8)	0.224	0.011
Potassium, mmol/L	3.9 (3.5-4.3)	3.9 (3.5-4.3)	3.9 (3.5-4.3)	0.784	0.018
Sodium, mmol/L	136.0 (133.0-139.0)	137.0 (134.0-140.0)	135.0 (132.0-138.0)	0.002	0.125
Scoring system					
OASIS	19.0 (14.0-25.0)	20.0 (15.0-26.0)	19.0 (12.0-25.0)	<0.001	0.214
SOFA	4.0 (2.0-6.0)	4.0 (2.0-6.0)	4.0 (2.0-6.0)	0.248	0.053
GCS	15.0 (15.0-15.0)	15.0 (15.0-15.0)	15.0 (15.0-15.0)	0.665	0.008
Management of AHF					
Intra-aortic balloon pump	41 (1.4%)	23 (1.4%)	18 (1.5%)	0.813	0.009
RRT	149 (5.1%)	102 (6.0%)	47 (3.8%)	0.007	0.102
In-hospital medication					
Inotrope	173 (15.9%)	73 (14.3%)	100 (18.1%)	0.001	0.158
Diuretic	2221 (76.0%)	1259 (74.4%)	962 (78.2%)	<0.001	0.150
ACEI/ARB	1730 (59.2%)	958 (56.6%)	772 (62.8%)	<0.001	0.214
CCB	171 (5.9%)	82 (4.8%)	89 (7.2%)	0.007	0.100
Beta-blocker	695 (23.8%)	290 (47.1%)	405 (62.9%)	<0.001	0.371
Oxygen therapy					
Duration of oxygen therapy, days	/	/	2.5 (1.6-4.1)	/	/

Median SpO ₂ during treatment period, %	97.9 (96.5-98.8)	97.1 (95.5-97.8)	98.7 (97.4-99.8)	<0.001	/
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Note: Values are n (%), mean ± SD, or median (interquartile range).

Abbreviations: SMD: Standardized mean difference; BMI: Body mass index; AHF: Acute heart failure; AKI: Acute kidney injury; AF: Atrial fibrillation; CAD: Coronary artery disease; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; DM: Diabetes mellitus; CKD: Chronic kidney disease; SBP: Systolic blood pressure; HR: heart rate; SpO₂: Pulse oximetry-derived oxygen saturation; BUN: Blood urea nitrogen; WBC: White blood cell; OASIS: Oxford Acute Severity of Illness Score; SOFA: Sequential Organ Failure Assessment Score; GCS: Glasgow Coma Scale; RRT: Renal replacement treatment; ACEI/ARB: Angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers; CCB: Calcium channel blocker.

Table 2. Association between oxygen therapy and clinical outcomes in normoxemic patients with AHF

Clinical outcomes	Ambient Air	Oxygen Therapy	OR (95% CI)	P value
Pre-matched cohort	N=1692	N=1230		
All-cause in-hospital mortality				
Univariable logistic model	104 (6.1%)	98 (8.0%)	1.32 (0.99, 1.76)	0.056
Multivariable logistic model	104 (6.1%)	98 (8.0%)	1.34 (0.98, 1.84)	0.067
All-cause ICU mortality				
Univariable logistic model	42 (2.5%)	43 (3.5%)	1.42 (0.92, 2.19)	0.109
Multivariable logistic model	42 (2.5%)	43 (3.5%)	1.58 (0.97, 2.56)	0.066
Length of ICU stay, days	2.2 (1.5-3.5)	2.7 (1.8-4.6)	1.15 (1.11, 1.19)	<0.001
Length of hospital stay, days	6.5 (4.0-11.3)	7.8 (4.8-13.1)	1.07 (1.04, 1.11)	<0.001
Post-matched cohort	N=1122	N=1122		
All-cause in-hospital mortality				
Univariable logistic model	74 (6.6%)	89 (7.9%)	1.22 (0.89, 1.68)	0.223
Multivariable logistic model	74 (6.6%)	89 (7.9%)	1.30 (0.92, 1.82)	0.138
All-cause ICU mortality				
Univariable logistic model	34 (3.0%)	40 (3.6%)	1.18 (0.74, 1.88)	0.479
Multivariable logistic model	34 (3.0%)	40 (3.6%)	1.39 (0.83, 2.32)	0.206
Length of ICU stay, days	2.2 (1.5-3.8)	2.7 (1.7-4.4)	1.11 (1.06, 1.15)	<0.001
Length of hospital stay, days	6.8 (4.1-11.2)	7.6 (4.6-12.9)	1.06 (1.01, 1.10)	0.009

Abbreviations: AHF: Acute heart failure; ICU: Intensive care unit; OR: Odds ratio; CI: Confidence interval.

Figures

Figure 1

Case inclusion flowchart. Abbreviations: eICU: Electronic Intensive Care Unit; AHF: Acute heart failure; PSM: Propensity score matching; ICD-9: International Classification of Diseases, Ninth Revision; SpO2: Pulse oximetry-derived oxygen saturation; COPD: Chronic obstructive pulmonary disease; NIV: non-invasive ventilation.

Figure 2

The association between oxygen therapy and all-cause in-hospital mortality in subgroup analysis. Abbreviations: OR: Odds ratio; CI: Confidence interval; SpO₂: Pulse oximetry-derived oxygen saturation; BMI: Body mass index; AF: Atrial fibrillation; MI: Myocardial infarction; CKD: Chronic kidney disease; RRT: Renal replacement treatment.

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