RESEARCH ARTICLE

Metformin Treatment is Associated with Mortality in Patients with Type 2 Diabetes and Chronic Heart Failure in the Intensive Care Unit: A Retrospective Cohort Study

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Abstract

Objective: Patients receiving intensive care often have diabetes mellitus (DM) together with chronic heart failure (CHF). In these patients, the use of metformin in intensive care is controversial. This study was aimed at assessing the mortality rates of patients with DM and CHF treated with metformin.

Methods: The Medical Information Mart for Intensive Care database was used to identify patients with type 2 diabetes mellitus (T2DM) and CHF. A 90-day mortality comparison was conducted between patients who were and were not administered metformin. Propensity score matching analysis and multivariable Cox proportional hazard regression were used to ensure the robustness of our results.

Results: A total of 2153 patients (180 receiving metformin and 1973 not receiving metformin) with T2DM and CHF were included in the study. The 90-day mortality rates were 30.5% (601/1971) and 5.5% (10/182) in the non-metformin and metformin groups, respectively. In the propensity score matching analyses, metformin use was associated with a 71% lower 90-day mortality (hazard ratio, 0.29; 95% confidence interval, 0.14–0.59; P < 0.001). The results were insensitive to change when sensitivity analyses were performed.

Conclusion: Metformin treatment may decrease the mortality risk in critically ill patients with T2DM and CHF in the intensive care unit.

Keywords: Metformin; type 2 diabetes mellitus; chronic heart failure; propensity score matching; mortality

Significance Statement

Our study demonstrated that metformin reduced mortality risk in patients with T2DM and CHF, adding to the evidence supporting the use of metformin in these patients. In addition, it added to the evidence that metformin can be used to treat patients with T2DM and CHF in intensive care units.

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Abbreviations: CHF, chronic heart failure; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; MAP, mean arterial pressure; MIMIC-IV, Medical Information Mart for Intensive Care (MIMIC)-IV database; PSM, propensity score matching; SAPS II, Simplified Acute Physiology Score; SMD, standardized mean difference; SOFA, organ failure assessment; T2DM, type 2 diabetes mellitus; WBC, white blood cells.

Introduction

Diabetes mellitus (DM) commonly coexists with chronic heart failure (CHF) [1]. A high frequency of patients seen in clinical practice have coexisting T2DM and CHF, and poor prognoses [2].

For patients with T2DM, the preferred first line pharmacological treatment is metformin, an oral antihyperglycemic agent [3]. The multicenter UK Prospective Diabetes Study [4] has demonstrated cardioprotective effects of metformin in patients with T2DM. Metformin decreases all-cause mortality and HF incidence in patients with both DM and cerebrovascular disease [5, 6]. However, the cardioprotective effects of metformin have not been well studied in patients with concomitant T2DM and CHF. Controversy exists regarding whether metformin is associated with lower mortality among patients with DM and advanced HF [7, 8]. Furthermore, no evidence indicates that metformin use decreases the mortality risk in patients with coexisting T2DM and CHF undergoing intensive care unit (ICU) treatment.

This retrospective study was aimed at determining the effect of metformin on overall mortality in patients with concurrent CHF and T2DM in the ICU.

Materials and Methods

Study Population

Patients with coexisting T2DM and CHF who were administered metformin in the ICU according to the Medical Information Mart for Intensive Care (MIMIC)-IV database (version 2.0) were included. MIMIC-IV is an open-access, critical-care database derived from real-life patient records, comprising more than 70,000 ICU admissions at the Beth Israel Deaconess Medical Center between 2008 and 2019 [9]. One author, Qiao Guo, completed the Collaborative Institutional Training Initiative examination (certification number: 10774591) and accessed the database for data extraction. The review boards of the Massachusetts Institute of Technology and the Beth Israel Deaconess Medical Center approved the use of the MIMIC-IV database. Requirements for informed consent were waived because the study was retrospective, and the data were anonymized. The "Strengthening the Reporting of Observational Studies in Epidemiology" guidelines were followed in this study [10].

Definition

Patients with coexisting T2DM and CHF were considered suitable for inclusion this study. DM was diagnosed according to the current recommendations [11]. T2DM was diagnosed according to the World Health Organization's International Classification of Diseases (10th Revision) [12]. The study included patients who were adults (>18 years of age). Patients incapable of taking oral medications were excluded. For patients with repeated ICU admissions, only the first admission was considered.

Metformin Use

Metformin use was defined according to a record of metformin use under the prescribed medications in the ICU in the MIMIC-IV database.

Covariates

The included variables were demographic characteristics, marital status, health insurance status, mean arterial pressure, heart rate, oxygen saturation, white blood cell count, hemoglobin, platelets, albumin, blood urea nitrogen, blood glucose, sequential organ failure assessment (SOFA) score, simplified acute physiology score (SAPS) II, and ventilator use. Details regarding comorbidities, such as cerebrovascular disease, peripheral vascular disease, chronic obstructive lung disease, liver disease, and renal disease, were also recorded. Chronic kidney disease defined as a glomerular filtration rate <60 mL/min/1.73. The marital and health insurance statuses of the included patients were analyzed

because they have the potential to reflect health habits and other factors.

Primary Outcomes

The primary outcome was 90-day mortality during follow-up after ICU admission.

Statistical Analysis

Data for all included patients were subjected to descriptive analysis. Proportions (percentages) were used to express categorical variables. As required, continuous variables are expressed as mean with standard deviation (SD) or median with interquartile range (IQR). Categorical variables were assessed with the chi-square test, and normal and skewed distribution tests were performed with one-way analysis of variance. In contrast to the exclusion of missing values, the use of multiple imputations maximized the statistical power while minimizing bias. The missing values were imputed with chained equations through five-fold multiple imputations [13].

Propensity scores were used to adjust for possible bias introduced by the non-random assignment of patients to different treatments. Our propensity score scale used a caliper width of 0.01 and a 1:1 closest neighbor algorithm. This propensity model consisted of 22 baseline variables: age; sex; marital status; health insurance; race/ethnicity; heart rate; mean arterial pressure; oxygen saturation; hemoglobin; white blood cell count; platelet count; serum albumin; serum blood urea nitrogen; glucose; SAPS II score; SOFA score; ventilator use; and history of cerebrovascular disease, chronic pulmonary disease, peripheral vascular disease, liver disease, and renal disease. Matching efficiency for propensity score matching (PSM) was measured with the standardized mean difference (SMD). An SMD threshold less than 0.1 was considered acceptable [14].

The hazard ratio (HR) was calculated with a univariate Cox proportional hazard regression model with reliable variance estimates. On the basis of the PSM matched patients, multivariable Cox regression analysis was performed to examine whether metformin administration was independent of 90-day mortality. For the various covariate-adjusted models, an extended Cox model technique was used. Analysis of the standardized mortality ratio weighting (SMRW) model was based on weighted cohort generated from propensity scores [15]. The survival curves were plotted with Kaplan–Meier and log-rank analyses.

Statistical analyses were performed in R statistical software version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) and the Free Statistics software version 1.7.1. Statistical significance was defined as a P-value <0.05.

Results

Population

A total of 2170 individuals diagnosed with coexisting T2DM and CHF were identified according to our definition. After exclusion of patients in whom oral medications could not be administered, 2153 patients remained in the final cohort. Figure 1 presents the flowchart of the study patients.

Baseline Characteristics

Table 1 shows a list of the initial characteristics of each included patient. The mean age was 73.1 ± 11.5 years, and 891 patients (41.3%) were women. Furthermore, 1406 (65.3%) patients were white, whereas 747 (34.7%) were non-white. Overall, 180 patients (8%) received metformin (i.e., the metformin group), whereas 1973 patients (92%) did not (i.e., the non-metformin group). In the metformin group, compared with the non-metformin group, fewer individuals had private health insurance (1168 [59.5%] vs. 78 [43.3%], respectively), more patients were white (126 [70%] vs. 1280 [65.2%], respectively), fewer patients had liver disease (168 [8.6%] vs. 9 [5%], respectively), and fewer patients had renal disease (1144 [58.3%] vs. 40 [22.2%], respectively). After PSM, 180 pairs of patients were matched, and the patient characteristics were balanced between groups.

Relationship between Metformin use during ICU stay and 90-day Mortality

The overall 90-day mortality rate was 28.4% (611/2153). In the metformin and non-metformin
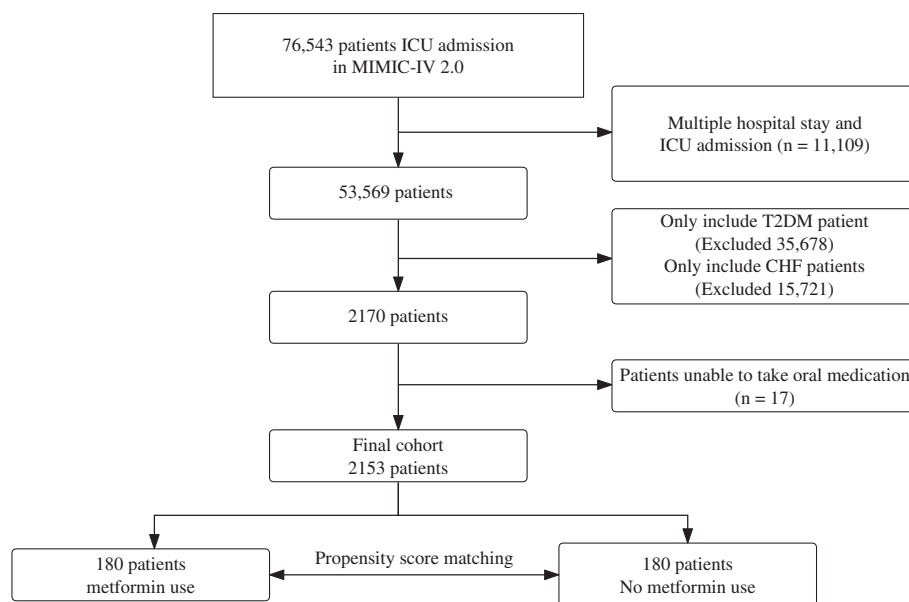
Figure 1 Flowchart Detailing the Selection Process of Patients Included in this Retrospective Analysis.

groups, the 90-day death rates were 30.5% (601/1973) and 5.5% (10/180), respectively (Table 2). After PSM, 180 pairs were well matched between groups (Table 1). No significant differences between matched groups were identified. After PSM, the mortality rates for the non-metformin and metformin groups were 30.5% and 5.6%, respectively. For 90-day mortality, estimated with the univariable Cox proportional hazard regression model, the HR was 0.18 (95% confidence interval [CI], 0.10–0.34; P < 0.001). In the PSM, metformin use was associated with 71% lower 90-day mortality compared with no metformin use (HR, 0.29; 95% CI, 0.14–0.59; P < 0.001). The SMRW demonstrated a significantly lower 90-day mortality rate in the metformin group than the non-metformin group, with an HR of 0.26 (95% CI, 0.14–0.49; P < 0.001); moreover, the Kaplan–Meier curve indicated that the metformin group had lower 90-day mortality rates (log-rank test, P < 0.0001, Figure 2).

Sensitivity Analyses

After adjustment for all confounders in Table 1 in the expanded multivariable Cox models (Table 3), the HRs of the metformin group were consistently significant in all five models (HR range, 0.18–0.28; P < 0.05 for all groups). The metformin group had an 82% decrease in 90-day mortality compared with

no metformin use after adjustment for all variables in Table 1 (HR, 0.28; 95% CI, 0.15–0.53; P < 0.001; Table 2 and Table 3). Furthermore, after adjustment for the propensity score, the HR remained similar (HR, 0.28; 95% CI, 0.15–0.53; P < 0.001; Table 2).

Before exclusion of 17 patients who were unable to take oral medications, the entire cohort comprised 2170 patients, 182 of whom received metformin. The association between metformin use and reduced 90-day mortality persisted (HR, 0.29; 95% CI, 0.15–0.54; P < 0.001; Supplementary Table 1). For comparison purposes, we repeated all analyses with the complete data cohort, using the data before multiple imputations. Metformin treatment and 90-day mortality were closely associated (HR, 0.16; 95% CI, 0.05–0.58; P=0.005; Supplementary Table 2).

Discussion

Patients with coexisting T2DM and CHF who received metformin showed a lower 90-day mortality rate than those who did not receive metformin in this retrospective propensity score-matched cohort study. This relationship was validated in additional models.

The proportion of patients with CHF and coexisting T2DM who received metformin in our study (8.35%; 180/2155) was lower than that in previous studies. In Benes et al., 22.9% of patients with

Table 1 Characteristics of the Studied Patients.

Variables	All patients (N = 2153)	Unmatched patients			All patients (N = 360)	Propensity-score-matched patients		
		No metformin (N = 1973)	Metformin (N = 180)	SMD		No metformin (N = 180)	Metformin (N = 180)	SMD
Age (years)	73.1 ± 11.5	73.4 ± 11.5	69.3 ± 10.6	0.371	69.6 ± 11.5	69.9 ± 12.5	69.3 ± 10.6	0.047
Women, n (%)	891 (41.3)	821 (41.8)	70 (38.9)	0.06	137 (38.1)	67 (37.2)	70 (38.9)	0.034
Marital status, no (%)	946 (44.0)	850 (43.3)	96 (53.3)	0.202	191 (53.1)	95 (52.8)	96 (53.3)	0.011
Insurance, n (%)	1246 (57.9)	1168 (59.5)	78 (43.3)	0.328	156 (43.3)	78 (43.3)	78 (43.3)	<0.001
White, n (%)	1406 (65.3)	1280 (65.2)	126 (70.0)	0.103	257 (71.4)	131 (72.8)	126 (70.0)	0.061
Heart rate (bpm)	83.5 ± 15.8	83.4 ± 16.1	84.5 ± 13.0	0.072	84.5 ± 14.5	84.5 ± 15.8	84.49 ± 13.0	0.003
MAP (mmHg)	78.0 ± 10.8	78.0 ± 10.8	77.3 ± 9.1	0.075	76.9 ± 9.2	76.5 ± 9.3	77.3 ± 9.1	0.086
SPO_2 (%)	96.5 ± 2.5	96.4 ± 2.6	97.1 ± 1.7	0.298	97.0 ± 1.7	97.0 ± 1.7	97.1 ± 1.7	0.083
Hemoglobin (mg/dL)	10.7 ± 2.1	10.63 ± 2.1	10.9 ± 1.7	0.147	11.0 ± 2.0	11.0 ± 2.2	10.9 ± 1.7	0.042
WBC count ($\times 10^9$)	14.5 ± 10.8	14.4 ± 11.1	16.0 ± 6.7	0.172	16.8 ± 18.7	17.7 ± 25.6	16.0 ± 6.7	0.09
Platelet count ($\times 10^{12}$)	184.3 ± 86.6	185.5 ± 87.8	170.2 ± 72.8	0.19	168.3 ± 69.8	166.4 ± 66.8	170.2 ± 72.8	0.054
Albumin (g/dL)	3.2 ± 0.6	3.12 ± 0.6	3.2 ± 0.6	0.12	3.2 ± 0.6	3.3 ± 0.6	3.2 ± 0.6	0.03
BUN (mg/dL)	41.6 ± 29.0	43.4 ± 29.4	22.2 ± 11.5	0.949	22.2 ± 11.5	22.3 ± 11.6	22.2 ± 11.5	0.013
Glucose (mg/dL)	172.1 ± 60.8	172.8 ± 61.9	165.9 ± 45.9	0.126	166.7 ± 50.9	167.4 ± 55.7	165.9 ± 45.9	0.029
SAPS II score	40.6 ± 13.1	41.1 ± 13.3	35.7 ± 10.5	0.451	36.2 ± 11.4	36.7 ± 12.3	35.7 ± 10.5	0.084
SOFA score	5.9 ± 3.8	6.0 ± 3.9	5.14 ± 3.1	0.244	5.1 ± 3.2	5.1 ± 3.3	5.1 ± 3.1	0.026
Ventilator use, n (%)	1777 (82.5)	1617 (82.4)	160 (88.9)	0.187	324 (90.0)	164 (91.1)	160 (88.9)	0.074
CVD, n (%)	346 (16.1)	315 (16.0)	31 (17.2)	0.032	65 (18.1)	34 (18.9)	31 (17.2)	0.043
PVD, n (%)	337 (15.7)	310 (15.8)	27 (15.0)	0.022	50 (13.9)	23 (12.8)	27 (15.0)	0.064
CPD, n (%)	715 (33.2)	645 (32.8)	70 (38.2)	0.111	69.6 ± 11.5	560.1 (28.3)	49.0 (27.2)	0.025
Liver disease, n (%)	177 (8.2)	168 (8.6)	9 (5.0)	0.142	19 (5.3)	10 (5.6)	9 (5.0)	0.025
Renal disease, n (%)	1184 (55.0)	1144 (58.3)	40 (22.2)	0.791	84 (23.3)	44 (24.4)	40 (22.2)	0.053

Bpm, beats per minute; BUN, blood urea nitrogen; MAP, mean arterial pressure; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; WBC, white blood cell; CPD, chronic pulmonary disease; PVD, peripheral vascular disease; and CVD, cerebrovascular disease. Numbers that do not add up to 100% are attributable to missing data.

Table 2 Association between Metformin Use and 90-Day Mortality in Univariate, Multivariate, and PSM Analyses.

| Analysis	90-day mortality (%)	P value
No. of events/no. of patients at risk (%)		
No metformin	601/1973 (30.5)	
Metformin	10/180 (5.6)	
Univariate analysis, HR (95% CI)	0.18 (0.10, 0.34)	<0.001
Multivariate analysis, HR (95% CI)[a]	0.28 (0.15, 0.53)	<0.001
Adjusted for the propensity score[b]	0.28 (0.15, 0.53)	<0.001
PSM[c]	0.29 (0.14, 0.59)	<0.001
SMRW[d]	0.26 (0.14, 0.49)	<0.001

HR, hazard ratio; CI, confidence interval; SMRW, standardized mortality ratio weighting.
[a]Multivariate Cox proportional hazard analysis adjusted for all covariates in Table 1.
[b]Multivariable Cox proportional hazard analysis with additional adjustment for the propensity score.
[c]Multivariable Cox proportional hazard analysis with propensity score matching.
[d]Multivariable Cox proportional hazard model using the same data and covariates, with standardized mortality ratio weighting according to the propensity score.
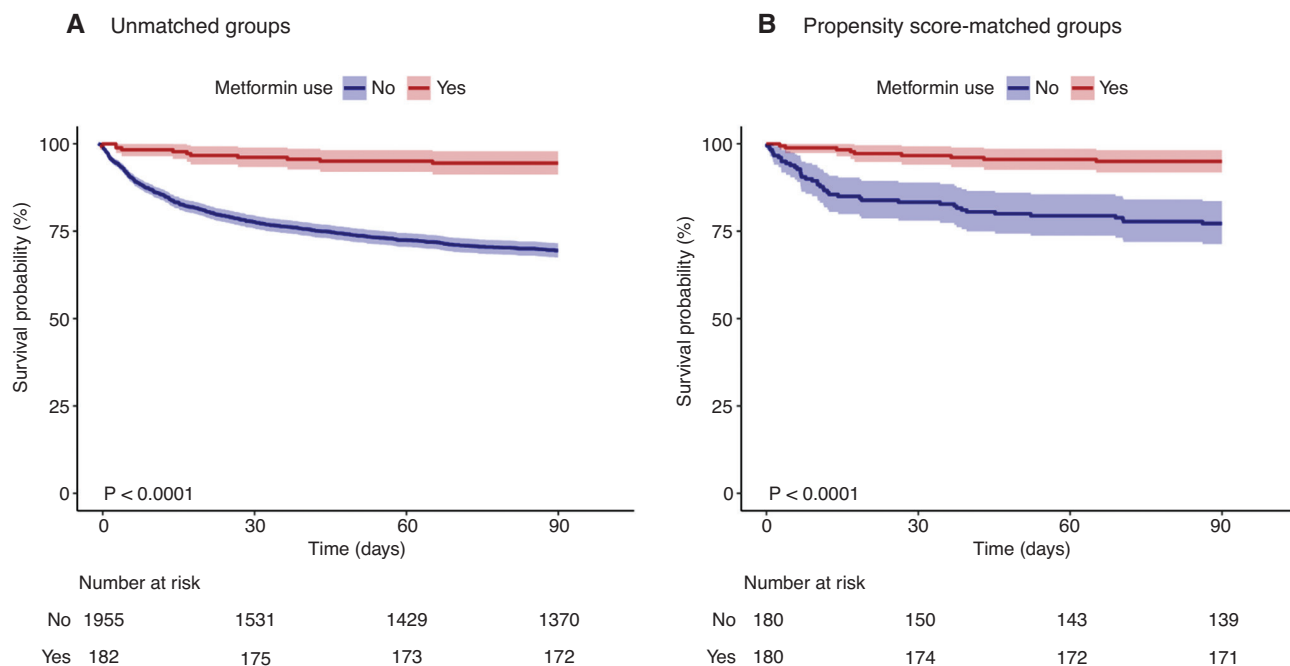
Figure 2 Kaplan–Meier Analyses for Obtaining the Survival Curves for the Study Groups.
(A) Before propensity score matching. (B) After propensity score matching. HR, hazard ratio.

T2DM and advanced HF received metformin [7], whereas in Retwi ski et al., metformin was administered to 38.6% of patients with HF and T2DM [16]. This discrepancy might be attributable to the definition of metformin exposure. These studies included patients at an outpatient clinic, at an inpatient hospital, or discharged from a hospital in the metformin group. In contrast, in our study, metformin exposure was defined as treatment with metformin during an ICU stay.

A large observational study has suggested that metformin may be helpful for patients with coexisting

Table 3 Association between Metformin Use and 90-Day Mortality, According to Multivariable Cox Regression Analysis.

	N	Hazard ratio of metformin use	95% confidence interval	P value
Model 1	180	0.18	0.10–0.34	<0.001
Model 2	180	0.18	0.1–0.33	<0.001
Model 3	180	0.21	0.11–0.40	<0.001
Model 4	180	0.28	0.15–0.53	<0.001
Model 5	180	0.28	0.15–0.52	<0.001

Adjusted covariates:
Model 1: age + sex + race.
Model 2: model 1 + health insurance + marital status + body mass index + heart rate + MAP + respiratory rate + temperature.
Model 3: model 2 + glucose level + platelet count + hemoglobin + blood urea nitrogen level + white blood cell count.
Model 4: model 3 + comorbidity diseases + sequential organ failure assessment score + simplified acute physiology score.
Model 5: model 4 + ventilation.

CHF and DM [17]. A previous meta-analysis [4] of 11 cohort studies with 35,410 patients with both DM and HF, who were followed up for 1–4.7 years, has revealed patients receiving metformin had a 22% reduction in mortality and a 13% reduction in the relative risk of re-hospitalization compared to those not receiving metformin during the follow-up period.

A recent study has indicated that treatment of patients with advanced HF and DM is associated with better outcomes through mechanisms other than improving blood glucose control [7]. In that study, metformin has shown potential benefits in DM and CHF treatment, in agreement with our findings. However, whereas critically ill patients were not included in the prior studies, our study included only patients in the ICU who were diagnosed with both HF and T2DM. Kaplan–Meier curves demonstrated that the death rate had decreased by day 90 in the patients receiving metformin treatment. This study adds to mounting evidence suggesting that metformin can be used to treat patients with coexisting HF and T2DM in the ICU.

This outcome is contrary to that reported Digish et al., who have reported an association between metformin therapy and a non-significant trend toward improved survival over a 1-year follow-up in patients with DM and advanced systolic HF (HR, 0.63; 95% CI, 0.21–1.89; P = 0.40) [8]. However, that study, in contrast to our study, did not include patients with critical illness. Furthermore, several important risk factors, such as the SAPS II score [18], SOFA score, and ventilator use [14], were not effectively adjusted for by Digish et al. [8].

The beneficial effects of metformin on the myocardium in HF are mediated by mechanisms other than glycemic control properties. Insulin resistance, which is responsible for both the onset and development of HF in patients with diabetes, has been found to decrease with metformin treatment [19]. In experimental animal studies, metformin has been demonstrated to improve cardiac function by AMP-activated protein kinase [20, 21]. Metformin decreases inflammation by downregulating proinflammatory cytokines, such as interleukin-6 [22], nuclear factor kappa B [21, 23], and tumor necrosis factor alpha [24, 25]. Moreover, metformin inhibits cytokine signaling in vascular tissue [26]. Some experiments, including human trials, have distinguished between the anti-inflammatory benefits and antihyperglycemic effects of metformin.

Our findings may substantially guide future research, particularly the development of more effective treatment strategies for ICU patients with both T2DM and CHF. However, prospective cohort studies or well-designed observational studies are necessary to evaluate the potential benefits of metformin treatment in this patient population. Our research may markedly influence public health policies, particularly in informing clinical decision-making, improving patient outcomes, and potentially leading to changes in relevant treatment guidelines. By filling knowledge gaps in clinical research in this specific patient population, our study provides potentially valuable insights that may guide policy decisions and improve clinical practice.

Limitations

This study has several limitations. First, its retrospective nature is associated with inherent limitations. Because residual confounding might have been present, we adjusted for many confounders in the propensity score-matched cohorts. Second, the results might not apply to individuals with acute HF and type 1 DM, because our study cohort included only patients with CHF and T2DM. Third, the use of oral medications was difficult to track, because it is uncertain whether the patient is actually taking the medication as prescribed. We excluded some patients for various reasons, such as those whose records indicated that drugs were not given. Fourth, fluctuations in medication status were observed and did not appear specific to an individual patient, because very few patients had good medication compliance. We also excluded participants who had never taken oral medications in the ICU. Fifth, because this was an observational study, we were able to assess only statistical associations but not causal relationships. However, a possibility of misclassification due to such errors exists, thus leading to a potential underestimation of the association between metformin treatment and 90-day mortality.

Future directions

The present study established a strong foundation for future research by providing insights into current understanding of metformin use in patients with both T2DM and CHF in the ICU. Our findings have notable implications for clinical practice and public health policies, particularly in terms of intervention strategies. In the future, we expect that our findings will stimulate further research and advancements in the field, thus leading to new discoveries and improved clinical outcomes for patients with T2DM and CHF.

Conclusion

According to our findings, metformin treatment in patients with coexisting T2DM and CHF in the ICU was associated with diminished risk-adjusted mortality. This study contributes to the evidence suggesting that metformin can be used in the ICU to treat patients with coexisting CHF and T2DM. Large-scale prospective studies should be conducted to further validate the safety of metformin use in critically ill patients.

Data availability statement

The article used data obtained from the MIMIC-IV database (http://mimic.physionet.org/).

Ethics statement

Studies involving human participants were reviewed and approved by the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center.

Conflict of interest

The study was performed without financial or commercial ties that might be viewed as a potential conflict of interest.

Author Contributions

GQ, HH, and DCY conceived the study. CJ and HWL acquired the data. GQ, DCY, and DGY analyzed the data. GQ reviewed the literature and prepared the first draft of this manuscript. HH and DCY critically reviewed and edited the manuscript, and approved the final version. All authors have read and approved the final manuscript.

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Supplementary Material: Supplementary material for this paper can be found at https://osf.io/j3v4u/.