Metformin treatment is associated with mortality in patients with type 2 diabetes and chronic heart failure in intensive care unit: a retrospective cohort study

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Abstract

Objective: Patients undergoing intensive care commonly suffer from diabetes mellitus combined with chronic heart failure (CHF). In these patients, the use of metformin under intensive care is controversial. This study aimed to assess the mortality rates of patients with DM and CHF who are treated with metformin.

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

Results: A total of 2,153 (180 metformin users and 1,973 non-metformin users) patients with T2DM and CHF were included in the study. The 90-day mortality rates were 30.5% (601/1,971) and 5.5% (10/182) for non-metformin and metformin users, 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 reduce the risk-related mortality 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

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

Significance Statement

Our study makes a contribution to the literature because its findings indicate that metformin may reduce the risk-adjusted mortality in critically ill patients with type 2 diabetes mellitus (T2DM) and chronic heart failure. Our study may add to the growing evidence supporting the use of metformin for treating those patients. Further, it adds to the growing evidence that metformin can be used to treat the patients with heart failure and T2DM in the intensive care units.

1 Introduction

Diabetes mellitus (DM) can commonly coexist with chronic heart failure (CHF)[1]. There is a high frequency of the patients with coexisting T2DM and CHF in clinical practice, and they have poor prognoses[2].

For patients with T2DM, metformin, an oral antihyperglycemic agent, is the preferred first line of pharmacological treatment[3]. The UK Prospective Diabetes Study[4] multicenter study demonstrated cardioprotective effects of metformin in the patients with T2DM. Metformin reduces the all-cause mortality and HF incidence in patients with DM combined with cerebrovascular disease[5, 6]. However, the cardioprotective effects of metformin have not been well studied in the patients with concomitant T2DM and CHF. There is controversy regarding the association of metformin with better event-free survival among the patients with DM and advanced HF[7] [8]. Furthermore, there is no evidence that metformin use decreases the mortality risk for patients with coexisting T2DM and CHF in the intensive care unit (ICU).

This retrospective study aimed to determine the effect of metformin on the overall mortality of patients with CHF and T2DM in the ICU.

2 Materials and Methods

2.1 Study population

Patients with coexisting T2DM and CHF who administered metformin in the ICU were enrolled using the Medical Information Mart for Intensive Care (MIMIC)-IV database (version 2.0). MIMIC-IV is an open-access, critical-care database derived from real-life patient records, with 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 usage of the MIMIC-IV database. Obtaining informed consent was 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].

2.2 Definition

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

2.3 Metformin use

Metformin use was defined as a record of metformin usage under prescribed "Medications" in the ICU in the MIMIC-IV database.

2.4 Covariates

The included variables were demographic characteristics, marital status, insurance status, mean arterial pressure, heart rate, oxygen saturation (SPO_2), white blood cell (WBC), hemoglobin, platelet, albumin, blood urea nitrogen (BUN), blood glucose, sequential organ failure assessment

(SOFA) score, simplified acute physiology score (SAPS) II, and ventilator use. Details about comorbidities such as cerebrovascular disease, peripheral vascular disease, chronic obstructive lung disease, liver disease, and renal disease, were also recorded. The renal disease was defined as an abnormal state that occurs in the structure or function of the kidney. The marital and insurance statuses of the included patients were analyzed because they may reflect their health habits and other factors.

2.5 Primary outcomes

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

2.6 Statistical analysis

All subjects were subjected to descriptive analysis. Proportions were used to express the categorical variables (%). As required, continuous variables were expressed as mean with standard deviation (SD) or median with interquartile range (IQR). Categorical variables were tested using the Chi-square test, and normal and skewed distribution tests were performed using a one-way analysis of variance. Unlike excluding missing values, multiple imputations maximized the statistical power while minimizing bias. The missing values were imputed by chained equations using five-fold multiple imputations[13].

Propensity scores were used to adjust for possible bias introduced by the non-random assignment of the 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 the following 22 baseline variables: age; gender; marital status; insurance; ethnicity; heart rate; mean arterial pressure; SPO_2; hemoglobin; WBC count; platelet count; serum albumin; serum blood urea nitrogen; glucose; SAPS II score; SOFA score; ventilator use; history of cerebrovascular disease; chronic

pulmonary disease; peripheral vascular disease; liver disease; and renal disease. Matching efficiency for propensity score matching (PSM) was measured using the standardized mean difference (SMD). The SMD threshold less than 0.1 was considered acceptable[14].

The hazard ratio (HR) was calculated using a univariate Cox proportional hazards regression model with reliable variance estimates. Based on the PSM matched patients, multivariable Cox regression analysis examined whether metformin administration was independent of the 90-day mortality. For the various covariate-adjusted models, an extended Cox model technique was adopted. Analysis of the standardized mortality ratio weighting (SMRW) model was based on weighted cohort generated from propensity scores[15]. The survival curves were plotted using Kaplan–Meier and log-rank analyses[16].

Statistical analyses were carried out using the R statistical software program version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) and the Free Statistics software version 1.7.1. Statistical significance was defined at a p-value <0.05.

3 Results

3.1 Population

A total of 2,170 individuals diagnosed with coexisting T2DM and CHF were identified according to our definition. After excluding the patients who could not administer oral

medications, 2,153 patients comprised the final cohort. Fig. 1 presents the flow chart of the study patients.

3.2 Baseline characteristics

Table 1 represents 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 females. Furthermore, 1,406 (65.3%) patients were Caucasians, while 747 (34.7%) were non-Caucasians. Overall, 180 patients (8%) received metformin (i.e., the metformin group), and 1,973 patients (92%) did not (i.e., the non-metformin group). Compared to those in the non-metformin group, fewer individuals in the metformin group had private insurance (1,168 [59.5%] vs. 78 [43.3%], respectively), more individuals were Caucasians (126 [70%] vs. 1,280 [65.2%], respectively), fewer individuals had liver disease (168 [8.6%] vs. 9 [5%], respectively), and fewer individuals had renal disease (1,144 [58.3%] vs. 40 [22.2%], respectively). Following PSM, 180 pairs of patients were matched, with balanced patient characteristics across the groups.

3.3 Relationship between metformin usage during ICU stay and 90-day mortality

The overall 90-day mortality rate was 28.4% (611/2,153). In the metformin and non-metformin groups, the 90-day death rates were 30.5% (601/1,973) and 5.5% (10/180), respectively (Table 2). After PSM, 180 pairs were well-matched between the groups (Table 1). There were no significant differences between the two matched groups. Following PSM, the mortality rates for the non-metformin and metformin groups were 30.5% and 5.6%, respectively. For the 90-day mortality, estimated using the univariable Cox proportional hazards 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 (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, with an HR of 0.26 (95% CI, 0.14–0.49; P <0.001). The Kaplan–Meier curve revealed that the metformin group had lower 90-day mortality rates (log-rank test, p<0.0001, Fig. 2).

3.4 Sensitivity analyses

After adjusting for all of the confounders in Table 1 in the expanded multivariable Cox models (Table 3), the HRs of the metformin group were consistently significant in all the five models (HR range, 0.18–0.28; p< 0.05 for all the groups). The metformin group had an 82% decreased 90-day mortality after adjusting for all of the variables in Table 1 (HR, 0.28; 95% CI, 0.15–0.53; P< 0.001) (Table 2 and Table 3). Furthermore, after adjusting for the propensity score, the HR was similar (HR, 0.28; 95% CI, 0.15–0.53; P <0.001) (Table 2).

Before excluding 17 patients who were unable to take oral medications, the whole cohort comprised 2,170 patients, with 182 patients using metformin. The association between metformin use and 90-day mortality remained steady (HR, 0.29; 95% CI, 0.15–0.54; P <0.001) (Supplementary Table 1). For comparison, we repeated all the analyses with the complete data cohort using the data before multiple imputations. The metformin treatment and 90-day mortality were closely connected (HR, 0.16; 95% CI, 0.05–0.58; P =0.005) (Supplementary Table 2).

4 Discussion

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

The proportion of patients with CHF and coexisting T2DM who received metformin in our study (8.35%; 180/2,155) was lower than that in previous studies. Benes *et al.* reported that 22.9% of the patients with T2DM and advanced HF used metformin [7], while Retwiński *et al.* revealed that metformin was administered by 38.6% of the patients with HF and T2DM[17]. This discrepancy could be attributed to the definition of metformin exposure. These studies included an outpatient clinic, an inpatient hospital, or patients discharged from a hospital in the metformin group. However, in our study, metformin exposure was considered as being treated with metformin during an ICU stay.

A large observational study suggested that metformin may be helpful for the patients with coexisting CHF and DM[18]. A previous meta-analysis[4] included 11 cohort studies with 35,410 patients with DM combined with HF who were followed up for 1–4.7 years. It revealed a 22% reduction in the mortality risk in the patients administering metformin compared to those not administering metformin and a 13% reduction in the relative risk of the patients being readmitted to the hospital during the follow-up period.

Another finding from a recent study was that treatment for the patients with advanced HF and DM was linked to better outcomes through mechanisms other than improving the blood glucose control[7]. In that study, metformin showed potential benefits against DM and CHF, which is consistent with our findings. Critically-ill patients were not included in these studies; our study, however, included only patients in ICU who were diagnosed with HF and T2DM. Kaplan–Meier curves demonstrated that the death rate had decreased by day 90 in the individuals receiving metformin treatment. This study adds to the mounting evidence that metformin can be used to treat the patients with coexisting HF and T2DM in the ICU.

This outcome is contrary to that obtained in the study by Digish *et al.*, who found that metformin therapy led to a non-significant trend toward improved survival over a 1-year follow-up in the patients with DM and advanced systolic HF (HR, 0.63; 95% CI, 0.21–1.89; p=0.40)[8]. However, unlike our study, the study by Digish *et al.* did not include patients with critical illnesses. Furthermore, several important risk factors, such as the SAPS II score[19], SOFA score, and ventilator use[14], were not effectively adjusted in the study by Digish *et al.*[8].

The beneficial effects of metformin on the myocardium in HF are mediated by mechanisms other than its glycemic control properties. Metformin is associated with reduced insulin resistance[20], which is responsible for both the onset and development of HF in the patients with diabetes. In experimental animal studies, metformin improved the cardiac function by AMP-activating AMP-activated protein[21, 22]. Metformin can decrease inflammation by downregulating proinflammatory cytokines, such as interleukin-6[23], nuclear factor kappa B[22, 24], and tissue necrosis factor alpha[25, 26]. Moreover, metformin inhibits cytokine signaling in vascular tissue[27]. Some experiments, including human trials, distinguished between the anti-inflammatory benefits of metformin and its antihyperglycemic effects.

Our findings could have a significant impact on future research, particularly in the development of more effective treatment strategies for the patients in ICU with both T2DM and CHF. Additionally, prospective cohort studies or well-designed observational studies are needed to evaluate the potential benefits of metformin treatment in this patient population. Our research can have a significant impact on public health policies, particularly in informing clinical decision-making, improving patient outcomes, and potentially leading to changes in the respective treatment guidelines.We have also highlighted the potential impact of our research on public health policies, particularly in informing clinical decision-making and improving patient

outcomes. By filling the gap in clinical research of this specific population, where our study provides valuable insights that can guide policy decisions and improve clinical practice.

Limitations

This study has several limitations. First, its retrospective nature carried inherent limitations. Because residual confounding may exist, we adjusted for many confounders in the propensity score-matched cohorts. Second, the results may not apply to the individuals with acute HF and type 1 DM because the study cohort only included patients with CHF and T2DM. Third, the use of oral medications was difficult to track because of the uncertainty of the administration of the patients as prescribed. We excluded some patients for various reasons, such as those with "not given" drugs in the record. Fourth, there were fluctuations in the medication status and they did not seem specific to an individual patient because very few patients had good medication compliance. We also excluded the participants who had never taken oral medications in the ICU. Fifth, since this was an observational study, we were only able to assess the statistical associations and not causal relationships. However, there is a possibility of misclassification due to such errors, which would underestimate the association between metformin treatment and 90-day mortality.

Future directions

The present study has established a strong foundation for future research by providing insights into the current understanding of metformin use in the patients with T2DM and CHF in ICU. Our findings have significant 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, leading to new discoveries and improved clinical outcomes for the patients with T2DM and CHF.

Conclusion

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

Data availability statement

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

Ethics statement

In the studies that involved human participants, the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center reviewed and approved the studies.

Conflict of Interest

The study was carried out 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 the authors have read and approved the final manuscript.

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Tables

Table 1. Characteristics of the studied patients.

Variables	Unmatched Patients				Propensity-Score-Matched Patients			
	All patients (N= 2,153)	No metformin (N=1,973)	Metformin (N=180)	SMD	All patients (N= 360)	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 (%)	1,246 (57.9)	1,168 (59.5)	78 (43.3)	0.328	156 (43.3)	78 (43.3)	78 (43.3)	<0.001
Caucasian, n (%)	1,406 (65.3)	1,280 (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 (×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 (×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 (%)	1,777 (82.5)	1,617 (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 (%)	1,184 (55.0)	1,144 (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 did 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 analysis.

Analysis	90-day mortality (%)	*P value*
No. of events/ No. of patients at risk (%)		
No metformin	601/1,973 (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 hazards analysis, with additional adjustment for the propensity score.

c. Multivariable Cox proportional hazards analysis with propensity score matching.

d. Multivariable Cox proportional hazards model using the same data and covariates, with standardized mortality ratio weighting according to the propensity score.

Table 3. Connection between metformin use and 90-day mortality using 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 + gender + ethnicity

Model 2: Model 1+ 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

Figure Legends

Fig. 1. Flowchart detailing the selection process of the patients included in this retrospective analysis.

Fig. 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.