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Association of metformin with mortality or ARDS in patients with COVID-19 and type 2 diabetes: A retrospective cohort study

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ABSTRACT

Aims: To determine the association between metformin use and mortality and ARDS incidence in patients with COVID-19 and type 2 diabetes.

Methods: This study was a multi-center retrospective analysis of COVID-19 patients with type 2 diabetes and admitted to four hospitals in Hubei province, China from December 31st, 2019 to March 31st, 2020. Patients were divided into two groups according to their exposure to metformin during hospitalization. The outcomes of interest were 30-day all-cause mortality and incidence of ARDS. We used mixed-effect Cox model and random effect logistic regression to evaluate the associations of metformin use with outcomes, adjusted for baseline characteristics.

Results: Of 328 patients with COVID-19 and type 2 diabetes included in the study cohort, 30.5% (100/328) were in the metformin group. In the mixed-effected model, metformin use was associated with the lower incidence of ARDS. There was no significant association between metformin use and 30-day all-cause mortality. Propensity score-matched analysis

Abbreviations: COVID-19, Coronavirus disease 2019; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; ARDS, acute respiratory distress syndrome; AMPK, AMP-activated protein kinase; RR, respiratory rate; SpO2, pulse oxygen saturation; CHD, coronary heart disease; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; DDI, D-dimer; CRP, C-reaction protein; LDH, lactic dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; IQR, inter-quartile range; MICE, Multivariate Imputation Using Chained Equations; NF-kB, nuclear factor-kB; mTORC1, mechanistic target of rapamycin complex 1; TNF-α, tumor necrosis factor-alpha; DIO, diet induced obesity; IL-10, interleukin-10

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confirmed the results. In the subgroup analysis, metformin use was associated with the lower incidence of ARDS in females.

Conclusions: Metformin may have potential benefits in reducing the incidence of ARDS in patients with COVID-19 and type 2 diabetes. However, this benefit differs significantly by gender.

1. Introduction

As an emerging infectious disease, the Coronavirus disease 2019 (COVID-19) has affected 216 countries and regions worldwide [1], posing a significant threat to human health and economic development. Considering the alarming rate of spread and severity of the disease, the World Health Organization declared the outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) a global pandemic on March 11, 2020 [2]. Diabetes is one of the primary comorbidities of COVID-19 patients [3]. Depending on the global region, 20–50% of patients in the COVID-19 pandemic had diabetes [4].

Diabetes also correlates with a worse outcome for COVID-19 patients [5]. A meta-analysis showed that COVID-19 patients who had diabetes were 1.9 times more likely to die than those without diabetes [6]. A report of 72,314 COVID-19 patients conducted by the Chinese Center for Disease Control and Prevention showed that the mortality of patients with COVID-19 and diabetes was more than three times that of the whole population (7.3% vs 2.3%) [7]. Therefore, it is of great significance to determine the effective therapeutic regimen to improve the prognosis of patients with COVID-19 and diabetes.

Studies have shown that well-controlled blood glucose was associated with improved outcomes in patients with COVID-19 and diabetes [8,9]. Metformin, the most widely used hypoglycemic agent for people with type 2 diabetes, may suppress inflammatory response and reduce the level of the inflammatory factors by activation of AMP-activated protein kinase (AMPK) [10]. Cytokine storm is closely related to the disease aggravation and considered to be one of the major causes of ARDS and multiple organ failure [11]. ARDS is the main death causes of COVID-19 patients [12]. Therefore, it is essential to effective inhibition of the cytokine storm in the treatment of patients with COVID-19. Considering the anti-inflammatory and immunomodulatory of metformin, it has been proposed as a candidate for host-directed therapy of COVID-19 [13]. Metformin may have potential benefits in reducing mortality in COVID-19 patients with diabetes [14], but high-level clinical evidence to prove the efficacy was lacking.

We conducted a multi-center retrospective cohort study to analyze the effect of metformin in patients with COVID-19 and diabetes on the 30-day all-cause mortality and incidence of ARDS, in attempts to provide valuable medication guidance for clinical treatment.

2. Material and methods

2.1. Ethics committee statement

This study was approved by the Medical Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology. The requirement for informed consent was waived by the Ethics Committee. Only pseudonymized data with no risk of identification were used for our analyses.

2.2. Study design and participants

This was a multi-center, retrospective cohort study of 417 patients with COVID-19 and type 2 diabetes admitted to four hospitals in Hubei Province, China from December 31st, 2019 to March 31st, 2020. All four hospitals are general hospitals and are designated for the treatment of COVID-19 patients. The diagnosis of COVID-19 was followed the WHO interim guidance and the Diagnosis and Treatment Protocol for Coronavirus Pneumonia (trial version 7) released by National Health Commission of China [15,16]. According to the definition of the protocol, patients were defined as severe COVID-19 if they met any of the following criteria: respiratory rate (RR) $\geq$ 30 breaths/min; pulse oxygen saturation (SpO2) $\leq$ 93%; more than 50% lesion progression in lung imaging within 24–48 h; shock; acute organ failure; or death. The severity of COVID-19 was assessed on the basis of the condition of patients within 48 h of admission to hospital. Diabetes was diagnosed according the criteria of WHO that fasting plasma glucose $\geq$ 7.0 mmol/L or two hour postprandial glucose $\geq$ 11.1 mmol/L [17]. ARDS was diagnosed according to the Berlin Definition [18].

We used the following inclusion and exclusion criteria to determine the study cohort. The inclusion criteria contained: 1) patients were diagnosed as COVID-19 and admitted to the four hospitals from December 31st, 2019 to March 31st, 2020; 2) diagnosed with diabetes and/or had medical history of diabetes; 3) aged more than 18 years old. The exclusion criteria included type 1 diabetes, pregnancy, greater than stage 4 renal insufficiency, acute heart failure, acute liver failure, and patients without using antidiabetic drugs during hospitalization.

2.3. Data collection

The demographic information (age and gender), clinical symptoms (fever, dyspnea, and asthma), comorbidities (Charlson comorbidity index and coronary heart disease [CHD]), non-antidiabetic therapies (antiviral drugs and glucocorticoids), metformin therapy prior to and during hospitalization, duration of diabetes, weight and clinical outcomes were reviewed and extracted from the electronic medical system. Laboratory data on the routine blood test, fasting blood glucose (FBG), hemoglobin A1c (HbA1c), D-dimer (DDI), C-reaction protein (CRP), lactic dehydrogenase (LDH), ferritin, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine were collected from the laboratory information system. The laboratory findings in this study were collected at the time of admission of patients with COVID-19. Personnel information of patients was anonymous and each patient was given a unique ID to avoid the possibility of identifying individual patients. Any uncertain records were clarified through communication with involved healthcare providers.

2.4. Exposure and outcomes

The exposure of this study was defined as receiving metformin therapy during hospitalization, and the initial treatment dose is at least 500 mg daily (Table S5); patients in this group were classified as metformin group. Patients who receive other antidiabetic drugs other than metformin were classified as the non-metformin group. The primary outcome of the study was 30-day all-cause mortality. For patients with the length of stay less than or equal to 30 days, we determined the patients as survivor or non-survivor based on discharge diagnosis. The secondary outcome was the incidence of ARDS during hospitalization. In the subgroup analysis, we further explored the impact of metformin use on the outcomes disaggregated by gender.

2.5. Statistical analyses

Continuous variables were presented as median and interquartile range (IQR), and categorical variables were expressed as number and percentage (%). Statistical differences between two groups were analyzed using Mann-Whitney *U* test for continuous variables, χ^2 test or Fisher's exact test for categorical variables. To reduce selection bias due to the missing data on weight, duration of diabetes and whether the patient was treated with metformin prior to hospital admission, method of Multivariate Imputation Using Chained Equations (MICE) (Stata, version 15) was used to impute the missing values. The distributions of the variables with missing data did not differ substantially between participants with observed data and those with imputed data (Table S1).

The risk of outcomes was calculated by the Cox proportional hazard model if the proportional hazard assumption was hold (verified using correlation testing based on Schoenfeld residuals) or logistic regression model. The site was modeled as a random effect in the mixed-effect Cox model and random effect logistic regression. Factors were adjusted in the multivariate analysis, including basic demographic characteristics (age and gender), weight, severity of COVID-19, comorbidities (Charlson comorbidity index), treatments (glucocorticoids), metformin therapy prior to hospitalization, duration of diabetes, laboratory findings on admission (FBG, LDH, CRP, and DDI).

Propensity score-matched analysis was used to reduce the selection bias by balancing basic demographic characteristics (age and gender), weight, severity of COVID-19, comorbidities (Charlson comorbidity index and CHD), treatment (glucocorticoids), metformin therapy prior to hospitalization, laboratory findings on admission (FBG and DDI), and site. Two cohorts were matched at a ratio of 1:1 with a caliper width of 0.2. The cumulative probability of death was compared using the Kaplan-Meier method. A two-side α less than 0.05 was considered statistically different. Analyses were performed in SAS 9.4 (by SAS Institute Inc., Cary, NC, USA) and R-3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Clinical characteristics of participants

A total of 417 patients with COVID-19 and type 2 diabetes were initially included in this study. The two individuals with type 1 diabetes, 4 with pregnancy, 14 with greater than stage 4 kidney insufficiency, 1 with acute heart failure, 1 with acute liver failure, and 67 patients without using antidiabetic drugs during hospitalization were excluded. Of the remaining 328 patients with COVID-19 and type 2 diabetes in the study cohort, 100 (30.5%) received metformin therapy were classified as the metformin group, and 228 (69.5%) received other antidiabetic drugs other than metformin were classified as the non-metformin group (Fig. 1). Patients in the non-metformin group were more likely to be older (67.0 [IQR: 60.0–76.0] vs 64.0 [IQR: 56.5–70.0]), be male (54.8% vs 49.0%), have a higher proportion of Charlson comorbidity scores of 3 or greater (68.0% vs 59.0%), and have coronary heart disease (19.1% vs 12.0%). There was no significant difference in severity of COVID-19 between the metformin and the non-metformin group (P = 0.2552). The proportion of patients received metformin therapy prior to hospitalization was higher in the metformin group than in the non-metformin group (36.0% vs 5.8%; $P < 0.0001$). Laboratory findings on admission showed that the median FBG was higher in the metformin group compared to the non-metformin group (9.3 mmol/L [IQR: 6.5, 12.7] vs 9.0 mmol/L [IQR: 6.6, 12.2]; P = 0.6503). The level of albumin was also higher in the metformin group (38.3 g/L [IQR:34.9–41.7] vs 36.0 g/L [IQR: 32.7–39.5]; P = 0.0017). The DDI level was higher in the non-metformin group than that in the metformin group (0.9 mg/L [IQR:0.5–3.0] vs 0.6 mg/L [IQR: 0.3–1.7]; P = 0.0057) (Table 1).

After propensity score matching, the two cohorts were balanced with no significant difference existed (Table 1). The characteristics on admission for male and female were shown in Table S2. The most common in-hospital complication was ARDS (15.55%), followed by heart failure (3.35%) (Tables S3).

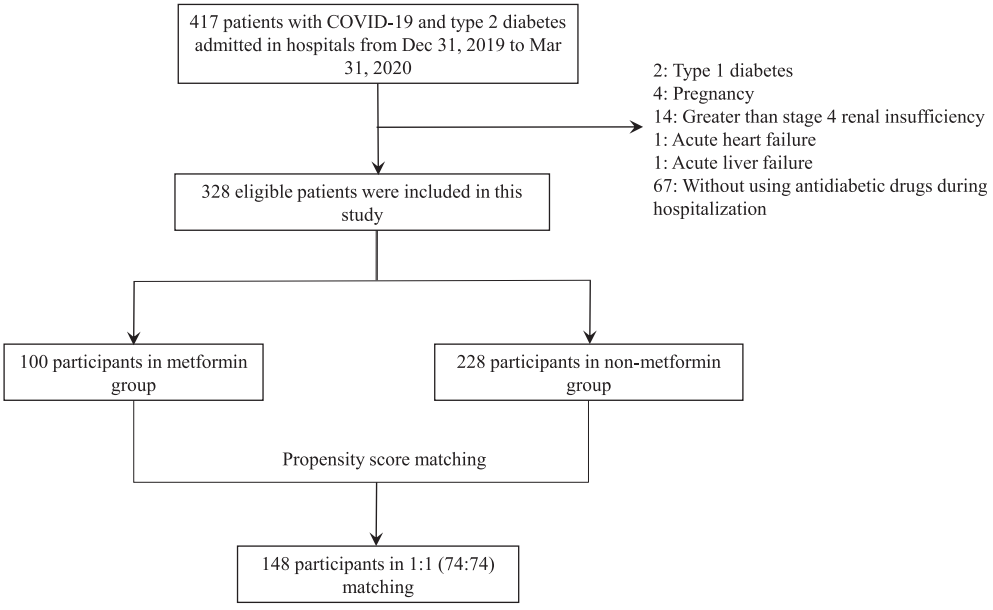

Fig. 1 – The flowchart of patients included in the study.

3.2. *Incidence of ARDS*

The incidence of ARDS in the metformin group was significantly lower than that in the non-metformin group (8.0% [8/100] vs 19.1% [43/228]; P = 0.0175). In the mixed-effect model, patients received metformin during hospitalization was associated with a lower risk of ARDS incidence compared to the non-metformin users (adjusted OR, 0.18; 95%CI, 0.05–0.62; P = 0.0070) (Table 2).

We further performed a propensity score-matched analysis to avoid confounding factors that could have interfered with the association between metformin use and the incidence of ARDS. One hundred and forty-eight patients with diabetes in the metformin and non-metformin groups were succeed matched. The results remained consistent in the propensity score-matched analysis (adjusted OR, 0.16; 95% CI, 0.04–0.72; P = 0.0168) (Table 2).

In the subgroup analysis, we explored the effect of metformin use on the incidence of ARDS by gender. The results showed that metformin use was significantly associated with lower incidence of ARDS in females (adjusted OR, 0.13; 95%CI, 0.02–0.80; P = 0.0276), but not in males (adjusted OR, 0.21; 95% CI, 0.03–1.47; P = 0.1150) (Table 3).

3.3. *The 30-day all-cause mortality*

The 30-day all-cause mortality was 3.0% (3/100) and 11.0% (25/228) in the metformin and non-metformin groups, respectively (P = 0.0175). The main cause of death was ARDS, which accounted for 64.29% of all deaths (Table S4). Kaplan-Meier analyses showed that metformin users had lower mortality than those in the non-metformin group, but there were no significant differences in mortality between metformin and non-metformin groups before and after propensity score matching (Fig. 2).

In the mix-effect Cox model, metformin users was not significantly associated with a lower risk of 30-day all-cause mortality compared with the non-metformin group (adjusted HR, 0.48; 95%CI, 0.13–1.74; P = 0.2635). The result was consistent in the propensity score-matched analysis and in the subgroup analysis (Table 2; Table 3).

4. Discussion

The results of this study showed that the use of metformin while hospitalized significantly reduced the risk of ARDS incidence in patients with COVID-19 and type 2 diabetes, especially in the females. However, there was no significant difference in 30-day all-cause mortality between the metformin and non-metformin groups.

ARDS is one of the most common complications in patients with COVID-19 [17]. It is of great significance to prevent the incidence of ARDS for improving the outcome of patients [19]. We found that metformin treatment was significantly associated with reduced risk of ARDS incidence in COVID-19 patients with type 2 diabetes. Study has shown that the main cause of COVID-19-related ARDS is the injury of alveolar epithelial cells [20]. Metformin has been reported to have anti-inflammation properties and reduced oxidative damage [21]. Piwkowska et al reported that metformin could activate AMPK signaling pathway by inhibiting electron transport chain complex I and reducing intracellular energy [22]. The activation of AMPK inhibits the nuclear factor-kB (NF-kB) pathway, which is an important mediating pathway for acute lung injury [23]. In addition, metformin is able to inhibit mechanistic target of rapamycin complex 1 (mTORC1) pathway in AMPK-dependent or independent manner, and further prevent the immune hyperactivation [24]. Metformin may reduce inflammation and lung injury

Table 1 – Characteristics of COVID-19 patients with type 2 diabetes in the Metformin and Non-metformin groups before and after propensity score matching.

Variables	Unmatched (N = 328)			Matched (N = 148)		
	Metformin group (n = 100)	Non-metformin group (n = 228)	P value	Metformin group (n = 74)	Non-metformin group (n = 74)	P value
Age, years	64.0 [56.5, 70.0]	67.0[60.0, 76.0]	0.0198	65.0 [56.0, 72.0]	65.5 [55.0, 71.0]	0.8436
Weight, kg	64.3 [61.3, 66.7]	65.1 [61.6, 68.5]	0.3327	64.0 [61.2, 66.5]	65.1 [61.5, 67.4]	0.5007
Days from symptoms onset to admission	8.0 [5.0, 14.0]	9.0 [4.0, 15.0]	0.8071	8.0 [6.0, 14.0]	9.5 [5.0, 15.0]	0.5642
Sex						
Male	49 (49.0%)	125 (54.8%)	0.3305	33 (44.6%)	37 (50.0%)	0.5102
Female	51 (51.0%)	103 (45.2%)		41 (55.4%)	37 (50.0%)	
Charlson comorbidity index						
0	8 (8.0%)	5 (2.2%)	0.1477	8 (10.8%)	4 (5.4%)	0.1258
1	12 (12.0%)	21 (9.2%)		6 (8.1%)	10 (13.5%)	
2	21 (21.0%)	47 (20.6%)		15 (20.3%)	14 (18.9%)	
3+	59 (59.0%)	155 (68.0%)		45 (60.8%)	46 (62.2%)	
Coronary heart disease	12 (12.0%)	43 (19.1%)	0.1563	7 (9.5%)	9 (12.2%)	0.7912
Symptoms at admission						
Fever	61 (61.0%)	121 (53.1%)	0.1834	46 (62.2%)	41 (55.4%)	0.4037
Dyspnea	13 (13.0%)	31 (13.6%)	1.0000	8 (10.8%)	9 (12.2%)	0.7966
Asthma	10 (10.0%)	34 (14.9%)	0.3050	6 (8.1%)	7 (9.5%)	1.0000
Severity of COVID-19						
Severe	27 (27.0%)	76 (33.3%)	0.2552	24 (32.4%)	27 (36.5%)	0.6038
Non-severe	73 (73.0%)	152 (66.7%)		50 (67.6%)	47 (63.5%)	
Laboratory findings on admission						
White blood cell count,$\times 10^9$/L	6.0 [4.7, 7.6]	6.0 [4.6, 7.3]	0.7531	6.1 [4.8, 7.8]	5.4 [3.9, 7.2]	0.0524
Lymphocytes,$\times 10^9$/L	1.2 [0.8, 1.6]	1.0 [0.7, 1.5]	0.4415	1.1 [0.8, 1.5]	1.0 [0.7, 1.6]	0.6612
CRP, mg/L	23.1 [3.9, 57.6]	26.4 [3.8, 71.5]	0.5328	27.5 [6.1, 62.8]	20.2 [3.0, 72.5]	0.5120
DDI, mg/L	0.6 [0.3, 1.7]	0.9 [0.5, 3.0]	0.0057	0.7 [0.4, 1.9]	0.7 [0.4, 1.4]	0.8602
LDH, U/L	191.0 [157.0, 245.0]	201.0 [161.9, 267.0]	0.1310	193.0 [172.1, 255.0]	217.0 [174.0, 299.9]	0.2713
Ferritin, μg/L	326.4 [137.6, 966.1]	398.5 [147.0, 649.2]	0.5515	332.0 [146.8, 767.5]	231.4 [147.0, 398.5]	0.8173
Albumin, g/L	38.3 [34.9, 41.7]	36.0 [32.7, 39.5]	0.0017	38.2 [34.4, 42.3]	36.0 [33.6, 40.0]	0.1427
AST, U/L	19.2 [15.1, 29.9]	22.0 [15.5, 34.0]	0.1895	19.6 [14.7, 33.0]	25.2 [15.9, 35.2]	0.2085
ALT, U/L	18.0 [12.9, 36.7]	21.6 [14.1, 29.3]	0.7798	19.8 [14.8, 40.8]	24.7 [20.9, 41.1]	0.3904
Creatinine, mmol/L	0.07 [0.05, 0.08]	0.07 [0.06, 0.09]	0.0612	0.07 [0.05, 0.08]	0.07 [0.05, 0.09]	0.1073
Blood glucose control						
FBG, mmol/L	9.3 [6.5, 12.7]	9.0 [6.6, 12.2]	0.6503	10.0 [7.3, 13.0]	9.3 [6.3, 13.5]	0.6081
HbA1c, %	8.1 [7.5, 10.0]	7.6 [6.8, 9.1]	0.1059	8.1 [7.0,10.0]	7.6 [6.9, 9.2]	0.5095
Non-antidiabetic therapies						
Antivirals drugs	96 (96.0%)	206 (91.7%)	0.2380	71 (96.0%)	69 (93.2%)	0.7162
Glucocorticoids	52 (52.0%)	106 (46.5%)	0.3580	39 (52.7%)	43 (58.1%)	0.5083
Metformin therapy prior to hospitalization	36 (36.0%)	13 (5.8%)	<0.0001	11 (14.9%)	11 (14.9%)	1.0000
Duration of diabetes, years	9.5 [4.0, 17.5]	9.7 [4.3, 19.4]	0.4239	9.7 [5.1, 19.4]	9.4 [3.2, 18.8]	0.4778
Length of hospital stay, days	23.0 [13.5, 30.0]	21.0 [14.0, 30.0]	0.1888	23.5 [14.0, 30.0]	20.0 [15.0, 27.0]	0.0526
ARDS	8 (8.0%)	43 (19.1%)	0.0175	8 (10.8%)	17 (23.0%)	0.0483
Clinical outcome (30 days)						
Survivor	97 (97.0%)	203 (89.0%)	0.0175	71 (96.0%)	64 (86.5%)	0.0814
Non-survivor	3 (3.0%)	25 (11.0%)		3 (4.1%)	10 (13.5%)	

Data are n (%) or median (IQR); CRP, C-reactive protein; DDI, D-dimer; LDH, lactic dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; ARDS, acute respiratory distress syndrome.

Table 2 – Relative risks for outcomes in the Metformin versus Non-metformin groups under mixed-effect model before and after propensity-score matching.

	Unmatched				Matched*			
	Crude		Mixed-effect model†		Crude		Mixed-effect model†	
	HR (95%CI)	P value	Adjusted‡ HR (95%CI)	P value	HR (95%CI)	P value	Adjusted‡ HR (95%CI)	P value
30-day all-cause mortality	0.48 (0.13, 1.74)	0.2635	0.48 (0.13, 1.74)	0.2635	0.54 (0.13, 2.26)	0.3979	0.54 (0.13, 2.26)	0.3979
	OR (95%CI)	P value	Adjusted‡ OR (95%CI)	P value	OR (95%CI)	P value	Adjusted‡ OR (95%CI)	P value
ARDS	0.19 (0.06, 0.64)	0.0077	0.18 (0.05, 0.62)	0.0070	0.24 (0.07, 0.85)	0.0263	0.16 (0.04, 0.72)	0.0168

HR, hazard ratio; OR, odds ratio; ARDS, acute respiratory distress syndrome.

* The propensity score-matched cohort was established on age, gender, weight, FBG, severity of COVID-19, Charlson comorbidity index, CHD, metformin therapy prior to hospitalization, DDI, creatinine and site.

† Site (hospital) was modeled as a random effect in the multivariate analysis.

‡ Adjusted for age, gender, weight, FBG, severity of COVID-19, Charlson comorbidity index, glucocorticoids, DDI, LDH, CRP, duration of diabetes, metformin therapy prior to hospitalization.

Table 3 – Relative risks for outcomes in the Metformin versus Non-metformin group under mixed-effect model by gender.

	Male*				Female†			
	Crude		Mixed-effect model‡		Crude		Mixed-effect model‡	
	HR (95%CI)	*P* value	Adjusted§ HR (95%CI)	*P* value	HR (95%CI)	*P* value	Adjusted§ HR (95%CI)	**P value**
30-day all-cause mortality	0.51 (0.10, 2.51)	0.4059	0.56 (0.11, 2.86)	0.4873	0.15 (0.01, 2.31)	0.1743	0.26 (0.02, 3.88)	0.3267
	OR (95%CI)	***P* value**	**Adjusted§ OR (95%CI)**	***P* value**	**OR (95%CI)**	***P* value**	**Adjusted§ OR (95%CI)**	***P* value**
ARDS	0.31 (0.06, 1.59)	0.1612	0.21 (0.03, 1.47)	0.1150	0.20 (0.05, 0.90)	0.0358	0.13 (0.02, 0.80)	0.0276

HR, hazard ratio; OR, odds ratio; ARDS, acute respiratory distress syndrome.

* There were 49 and 125 participants in metformin group and non-metformin group, respectively.

† There were 51 and 103 participants in metformin group and non-metformin group, respectively.

‡ Site (hospital) was modeled as a random effect in the multivariate analysis.

§ Adjusted for age, gender, weight, FBG, severity of COVID-19, Charlson comorbidity index, glucocorticoids, DDI, LDH, CRP, duration of diabetes, metformin therapy prior to hospitalization.

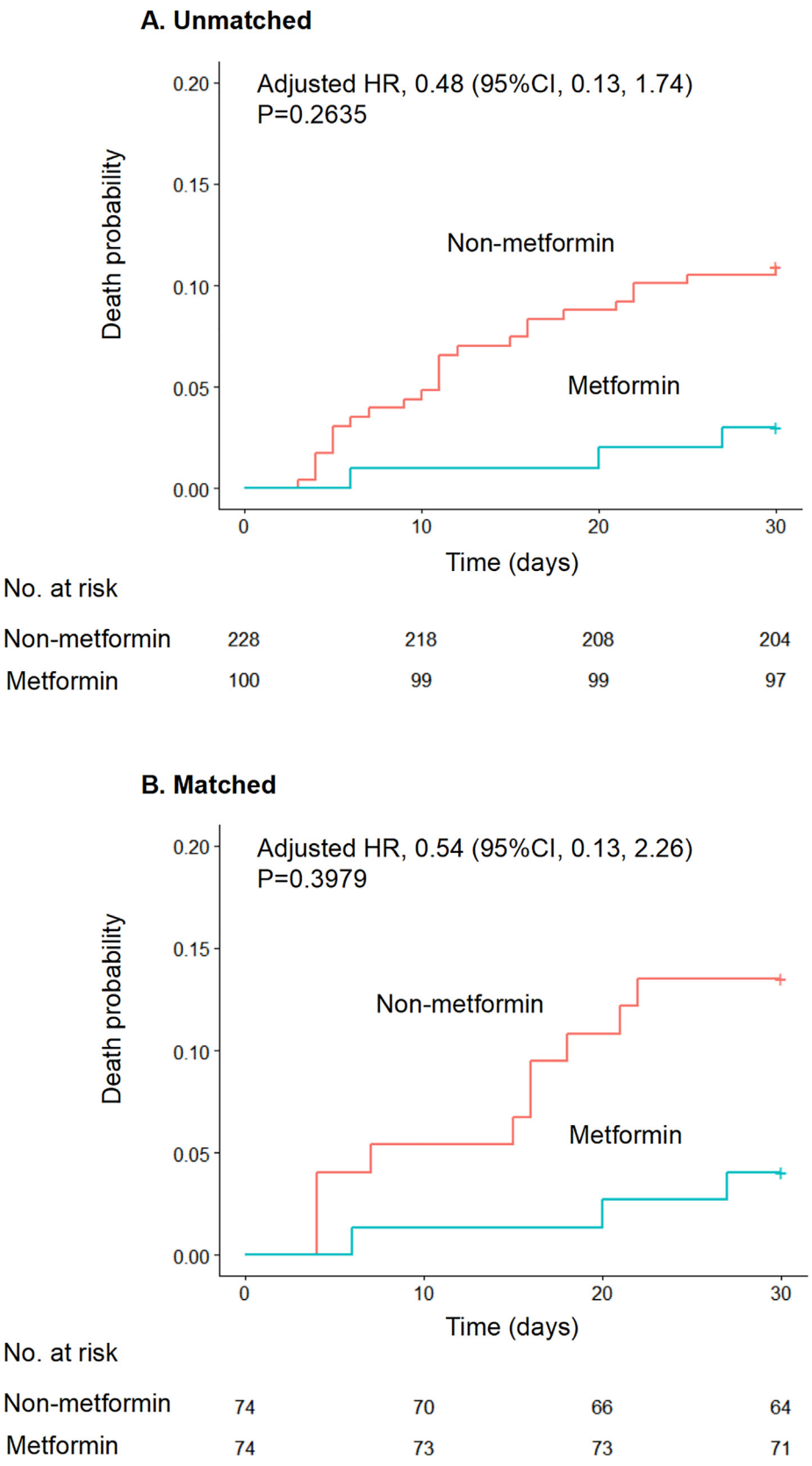

Fig. 2 – Kaplan-Meier Curves for cumulative probability of 30-day all-cause mortality in metformin and non-metformin groups in unmatched and matched model.

through the above mechanism [25], thereby reducing the incidence of ARDS.

Metformin use was not significantly associated with the lower mortality in COVID-19 patients with type 2 diabetes in our study. This was consistent with the results of Cheng et al [26]. A related study in South Korea was also confirmed the findings [27]. However, a meta-analysis showed that metformin use have a favorable association with the mortality in COVID-19 patients with diabetes [28]. The discrepancy of results could be explained in part by the fact that some studies did not exclude patients with contraindications to metformin [14,29], which may cause some biases on the effect of metformin.

We also found that there were differences in the effect of metformin on the disease outcome of COVID-19 patients with type 2 diabetes between male and female. Metformin use was associated with a lower incidence of ARDS in female, but this association has not been observed in male. Studies showed that metformin could inhibit the production of tumor necrosis factor-alpha (TNF-α) in diet induced obesity (DIO) models mice, while low levels of TNF-α can inhibit inflammation response [30]. Interleukin-10 (IL-10) is considered to be the main anti-inflammatory factor. Metformin may up-regulate the protein expression of IL-10 and decrease the level of TNF-α in female more than male [29]. It may be one of the reasons that metformin use was associated with a lower incidence of ARDS in the female of this study.

Our study was based on a multicenter design to explore the association between metformin use and unfavorable outcomes of COVID-19 patients with type 2 diabetes. We further explored the gender difference in the effects of metformin on clinical outcomes. This study also has some limitations. First of all, though data regarding HbA1c was missing in 56.2% of this study, FBG was adjusted in the multivariate analysis. Second, since the nature of the retrospective study, the missing data on metformin treatment prior to hospitalization and duration of diabetes may cause some biases of the research results. But we used multiple imputation to adjust for these missing data and made the best use of the existing information in our analysis. Third, some previous studies used mechanical ventilation [31–33] and ICU admission as outcomes [31,34,35], but due to the large number of missing data for the two variables, we failed to explore the effect of metformin on these outcomes. Finally, the secondary outcome variable ARDS in this study was obtained by discharge diagnosis, it is hard to classify according to the Berlin classification.

5. Conclusion

Patients with COVID-19 and type 2 diabetes in the metformin group had a lower incidence of ARDS than those in the non-metformin group, especially in females. However, the association between metformin use and lower mortality was not significant. Given that patients can benefit from metformin therapy, it is recommended that patients with COVID-19 and type 2 diabetes continue to use metformin in the absence of obvious contraindications.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' Contributions

ZC, NJ, XY, LL, NX, and YG, were responsible for the conception, design, and writing of the manuscript. HY, XT, JW, HL, and MT were responsible for the acquisition of data and literature research. ZC, NJ, XY, LL, ZL were responsible for the analysis and interpretation of data. All authors reviewed and revised the manuscript and approved the final version.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2020.108619.

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