

## Supplemental Information

### **Metformin Is Associated with Higher Incidence of Acidosis, but Not Mortality, in Individuals with COVID-19 and Pre-existing Type 2 Diabetes**

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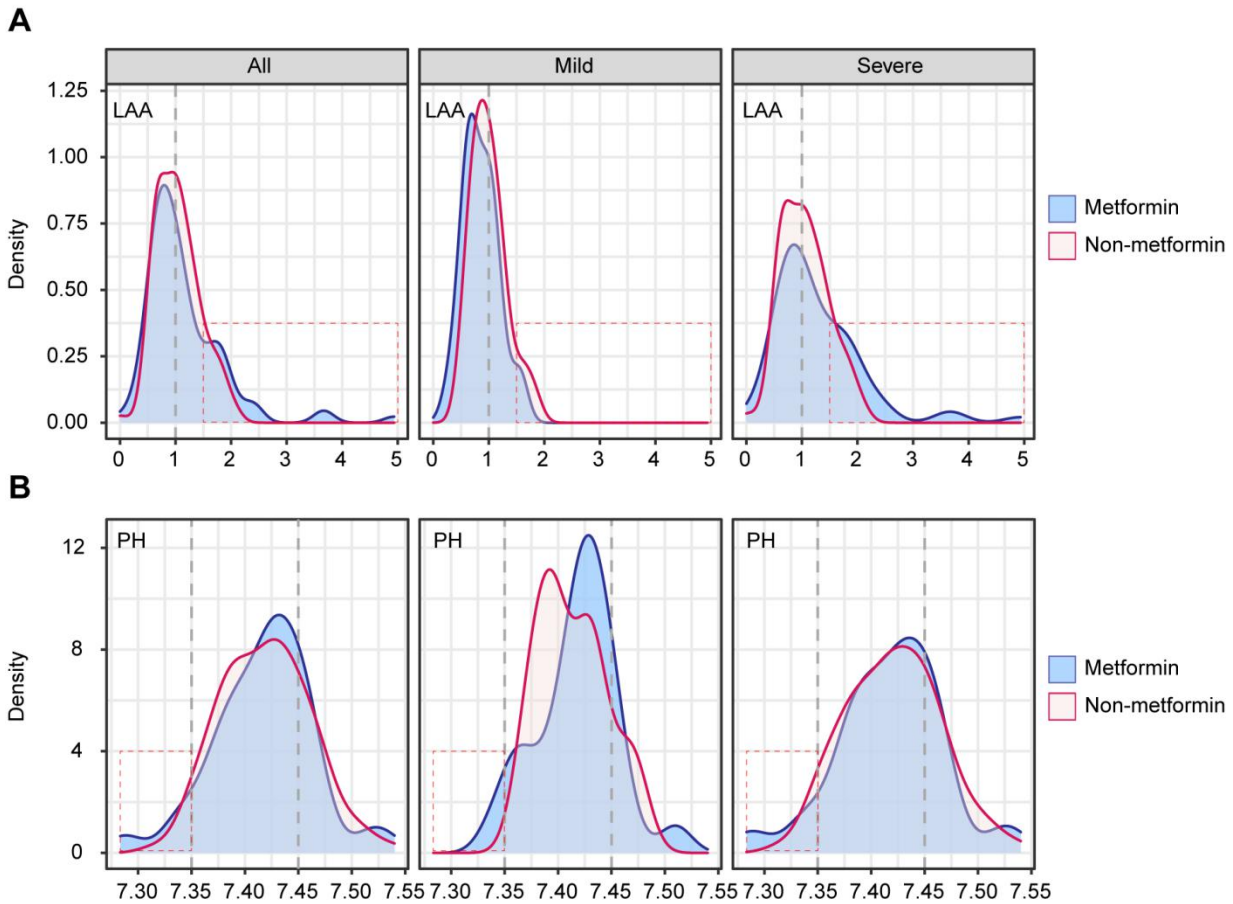
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**Figure s1. Kernel density estimates using Gaussian kernels to display an overlay of lactic acid and PH distributions in the Metformin and the Non-metformin groups, related to Table 2.**

**A.** The overlaid distributions of lactic acid (LAA) between the Metformin and the Non-metformin groups. The x-axis represents the relative levels of LAA to their corresponding ULNs according to the varied criteria in each hospital. **B.** The overlaid distributions of PH in blood gas analysis between the Metformin and the Non-metformin groups. The dotted line represents the upper limit or lower limit of the normal value of the corresponding indicator.

**Table s1. Chisq and p value for mortality, ARDS, DIC, acidosis, lactic acidosis, heart failure, acute heart injury and acute kidney injury between individuals in the entire cohort, mild and severe groups in Cox regression model with time-varying exposure, related to Table 2.**

<b>Metformin vs Non-metformin</b>	<b>Whole cohort</b>		<b>Mild group</b>		<b>Severe group</b>	
	<b>chisq</b>	<b>p Value</b>	<b>chisq</b>	<b>p Value</b>	<b>chisq</b>	<b>p Value</b>
Acidosis	5.081	0.890	-	-	4.938	0.900
Lactic Acidosis	7.015	0.724	-	-	6.775	0.747
Mortality	13.300	0.206	-	-	13.000	0.223
ARDS	16.400	0.088	-	-	16.864	0.077
DIC	14.811	0.139	-	-	14.679	0.144
Heart failure	15.181	0.126	14.680	0.144	10.790	0.374
Acute heart injury	15.300	0.121	5.750	0.840	13.646	0.190
Acute kidney injury	12.212	0.271	-	-	11.795	0.299

Abbreviations: ARDS, acute respiratory distress syndrome; DIC: Disseminated intravascular coagulation.

**Table s2 Baseline characteristic in individuals of the Metformin and the Non-metformin groups after PSM, related to Table 2.**

Parameters	Total (N=936)	Metformin <sup>b</sup> (n=468)	Non-metformin <sup>c</sup> (n=468)	SD <sup>d</sup>
<b>Clinical characteristics on admission</b>				
Age, median(IQR), y	64.0(57.0-69.0)	64.0(57.0-68.3)	64.0(57.0-69.0)	0.001
Male gender, n(%)	476(50.9%)	237(50.6%)	239(51.1%)	-0.009
Heart rate, median(IQR), bpm	83.0(77.0-95.5)	82.0(76.0-96.0)	83.0(78.0-95.0)	-0.025
Respiratory rate, median(IQR), bpm	20.0(19.0-21.0)	20.0(19.0-21.0)	20.0(19.0-21.0)	0.001
SBP, median(IQR), mmHg	133.0(121.0-145.0)	132.0(122.5-145.0)	133.0(120.0-145.0)	0.043
DBP, median(IQR), mmHg	80.0(72.0-89.0)	80.0(73.0-89.0)	80.0(72.0-89.0)	0.011
SpO <sub>2</sub> , median(IQR)	97.0(95.0-98.0)	97.0(95.0-98.0)	97.0(95.0-98.0)	0.074
<b>Comorbidities on admission</b>				
Chronic obstructive pulmonary disease, n(%)	7(0.8%)	3(0.6%)	4(0.9%)	-0.025
Heart failure, n(%)	0(0.0%)	0(0.0%)	0(0.0%)	0.000
Coronary heart disease, n(%)	134(14.3%)	66(14.1%)	68(14.5%)	-0.012
Cerebrovascular diseases, n(%)	25(2.7%)	14(3.0%)	11(2.4%)	0.040
Chronic liver disease, n(%)	14(1.5%)	5(1.1%)	9(1.9%)	-0.070
Chronic renal diseases, n(%)	20(2.1%)	9(1.9%)	11(2.4%)	-0.030
<b>Chest CT on admission</b>				
Unilateral lesion, n/N(%)	48/882(5.4%)	28/433(6.5%)	20/449(4.5%)	0.089
Bilateral lesion, n/N(%)	802/882(90.9%)	395/443(91.2%)	407/449(90.7%)	0.020
<b>Laboratory examination on admission</b>				
Leukocyte count > 9.5, 10 <sup>9</sup> , n/N(%)	80/902(8.9%)	36/452(8.0%)	44/450(9.8%)	-0.064
Neutrophil count >6.3, 10 <sup>9</sup> /L, n/N(%)	128/902(14.2%)	60/452(13.3%)	68/450(15.1%)	-0.053
Lymphocyte count <1.1, 10 <sup>9</sup> /L, n/N(%)	366/902(40.6%)	182/452(40.3%)	184/450(40.9%)	-0.013

RBC:Male,<4.5, 10 <sup>12</sup> /L; Female,<4.0, 10 <sup>12</sup> /L, n/N(%)	407/902(45.1%)	216/452(47.8%)	191/450(42.4%)	0.108
C-reactive protein > ULN <sup>a</sup> , n/N(%)	246/483(50.9%)	108/224(48.2%)	138/259(53.3%)	-0.101
Procalcitonin level > ULN <sup>a</sup> , n/N(%)	325/748(43.5%)	167/390(42.8%)	158/358(44.1%)	-0.027
ALT> 40 U/L, n/N(%)	190/895(21.2%)	94/448(21.0%)	96/447(21.5%)	-0.012
eGFR, median(IQR), mL/min	101.6(85.6-120.1)	101.7(86.6-120.7)	101.4(83.8-120.0)	0.040
D-dimer>ULN <sup>a</sup> , n/N(%)	441/822(53.7%)	222/407(54.6%)	219/415(52.8%)	0.036
LDL-c>3mmol/L, n/N (%)	123/711(17.3%)	64/359(17.8%)	59/352(16.8%)	0.028
Blood glucose, median (IQR), mmol/L	8.4(6.5-12.0)	8.3(6.5-11.9)	8.5(6.5-12.0)	-0.014

Abbreviation: SBP, systolic blood pressure; DBP, Diastolic blood pressure; SpO<sub>2</sub>, oxygen saturation; RBC, red blood cells; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; LDL-c, low density lipoprotein cholesterol; IQR, interquartile range; SD, standardized difference.

<sup>a</sup>Upper limit of normal (ULN) was defined according to criteria in each hospital.

<sup>b</sup>Individuals with T2D taking Metformin during hospitalization were enrolled in the Metformin cohort. Individuals discontinued treatment of diabetes due to inability to take medications or diabetes were not excluded from the cohort.

<sup>c</sup>Individuals with T2D who never took Metformin during hospitalization were enrolled in the Non-metformin cohort.

<sup>d</sup>SD, Standardized differences were used to compare the means of baseline covariates between the Metformin and the Mon-metformin groups.

**Table s3. In-hospital management of the Metformin and the Non-metformin groups after PSM, related to Table 2.**

Treatment	Metformin <sup>a</sup> (n=468)	Non-metformin <sup>b</sup> (n=468)	SD <sup>c</sup>	p Value <sup>d</sup>
Traditional Chinese medicine n(%)	423(90.4%)	413(88.3%)	0.069	0.341
Antiviral drug, n(%)	369(78.9%)	349(74.6%)	0.101	0.142
Antibiotics drug, n(%)	299(63.9%)	313(66.9%)	-0.063	0.372
Antithrombotic or Thrombolysis, n(%)	42(9.0%)	68(14.5%)	-0.173	0.011
Antidiabetic drug, n(%)	468(100.0%)	466(99.6%)	0.093	0.499
Antidiabetic drug, Insulin ,n(%)	245(52.4%)	248(53.0%)	-0.013	0.896
Lipid lowering drug, n (%)	127(27.1%)	110(23.5%)	0.084	0.229
Lipid lowering drug, statin, n(%)	125(26.7%)	108(23.1%)	0.084	0.226
Antiplatelet, n(%)	87(18.6%)	89(19.0%)	-0.011	0.933
Antifungal medications, n(%)	6(1.3%)	16(3.4%)	-0.141	0.052
Vasoactive drug, n(%)	13(2.8%)	24(5.1%)	-0.121	0.093
Immunoglobulin, n(%)	96(20.5%)	105(22.4%)	-0.047	0.524
Systemic corticosteroids, n(%)	63(13.5%)	68(14.5%)	-0.031	0.706
Antihypertensive drugs ACEI, n(%)	17(3.6%)	23(4.9%)	-0.063	0.419
Antihypertensive drugs ARB, n(%)	87(18.6%)	83(17.7%)	0.022	0.799
Noninvasive ventilation, n(%)	33(7.1%)	48(10.3%)	-0.114	0.106
Invasive ventilation, n(%)	6(1.3%)	10(2.1%)	-0.066	0.449
Renal replacement therapy, n(%)	0(0.0%)	4(0.9%)	-0.131	0.124
Extracorporeal membrane oxygenation, n(%)	1(0.2%)	4(0.9%)	-0.087	0.374

<sup>a</sup> Individuals with T2D taking Metformin during hospitalization were enrolled in the Metformin cohort. Individuals discontinued treatment of diabetes due to inability to take medications or diabetes were not excluded from the cohort.

<sup>b</sup> Individuals with T2D who never took Metformin during hospitalization were enrolled in the Non-metformin cohort.

<sup>c</sup> SD, Standardized differences were used to compare the means of baseline covariates between the Metformin and the Non-metformin group.

<sup>d</sup> The p values were calculated by Fisher's exact test or  $\chi^2$  test.



**Table s4. C Indexes for the mixed effect Cox model after PSM, related to Table 2.**

<b>Metformin vs Non-metformin</b>	<b>Mixed effect Cox model after PSM in the whole cohort</b>	<b>Mixed effect Cox model after PSM in Mild group</b>	<b>Mixed effect Cox model after PSM in Severe group</b>
	<b>C Index (95% CI)</b>	<b>C Index (95% CI)</b>	<b>C Index (95% CI)</b>
Acidosis	0.87(0.79,0.96)	-	0.88(0.81,0.95)
Lactic Acidosis	0.92(0.81,1.00)	-	0.91(0.80,1.00)
Mortality	0.90(0.85,0.95)	-	0.87(0.81,0.93)
ARDS	0.68(0.64,0.72)	0.93(0.85,1.00)	0.66(0.62,0.70)
DIC	0.95(0.88,1.00)	-	0.91(0.79,1.00)
Heart failure	0.81(0.78,0.85)	0.86(0.81,0.92)	0.77(0.73,0.82)
Acute heart injury	0.77(0.72,0.83)	0.89(0.82,0.95)	0.76(0.70,0.82)
Acute kidney injury	0.80(0.66,0.93)	-	0.88(0.79,0.98)

Abbreviations: ARDS, acute respiratory distress syndrome; DIC: Disseminated intravascular coagulation.

**Table s5. Hazard ratios for acidosis and lactic acidosis in individuals with GFR >60 ml/min/1.73 m<sup>2</sup>, related to Table s3.**

<b>Metformin vs Non-metformin</b>	<b>Cox regression model with time-varying exposure</b>	
	<b>Adjusted HR<sup>a</sup> (95%CI)</b>	<b>p Value<sup>b</sup></b>
Acidosis	2.08(0.81,5.36)	0.129
Lactic Acidosis	3.01(0.82,11.05)	0.097

Abbreviations: HR, Hazard ratio; CI, Confidence interval;

<sup>a</sup> In the Cox regression model with time-varying exposure, adjusted variables for comparison between the Metformin and the Non-metformin cohorts included age, gender, comorbidities (cerebrovascular diseases, coronary heart disease), blood glucose, C-reactive protein, estimated glomerular filtration rate, alanine aminotransferase and Creatinine.

<sup>b</sup> The p values were calculated based on Cox regression model with time-varying exposure.

<b>Table s6. Association between acidosis and Metformin use in individuals with mild COVID-19, related to Table s3.</b>				
<b>Parameters</b>	<b>Total (N=588)</b>	<b>Metformin<sup>a</sup> (n=326)</b>	<b>Non-metformin<sup>b</sup> (n=262)</b>	<b>p Value</b>
Acidosis	0(0%)	0(0%)	0(0%)	1.000
Lactic Acidosis	0(0%)	0(0%)	0(0%)	1.000

<sup>a</sup> Individuals with T2D taking metformin during hospitalization were enrolled in the Metformin cohort. Individuals discontinued treatment of diabetes due to inability to take medications or diabetes were not excluded from the cohort.

<sup>b</sup> Individuals with T2D who never took metformin during hospitalization were enrolled in the Non-metformin cohort.

**Table s7. Hazard ratios for acute extra-pulmonary organ injury between individuals in the Metformin and the Non-metformin groups in the entire cohort, mild and severe groups in Cox regression model with time-varying exposure, related to Table 4.**

<b>Metformin vs Non-metformin</b>	<b>Whole cohort</b>		<b>Mild group</b>		<b>Severe group</b>	
	<b>Adjusted HR<sup>b</sup> (95%CI)</b>	<b>p Value<sup>c</sup></b>	<b>Adjusted HR<sup>b</sup> (95%CI)</b>	<b>p Value<sup>c</sup></b>	<b>Adjusted HR<sup>b</sup> (95% CI)</b>	<b>p Value<sup>c</sup></b>
Acute heart injury	1.14(0.73,1.79)	0.559	2.14(0.91,5.06)	0.083	0.95(0.57,1.60)	0.851
Acute kidney injury	0.71(0.18,2.79)	0.627	-	-	0.92(0.24,3.54)	0.902
DIC	0.44(0.05,4.00)	0.467	-	-	0.50(0.04,5.97)	0.581
Acute extra-pulmonary organ injury <sup>a</sup>	1.10(0.71,1.70)	0.670	1.91(0.81,4.49)	0.139	0.96(0.59,1.58)	0.884

Abbreviations: HR, Hazard ratio; CI, Confidence interval; DIC: Disseminated intravascular coagulation.

<sup>a</sup> Acute injury of extrapulmonary organs include Acute heart injury, Acute kidney injury and DIC.

<sup>b</sup> In the Cox regression model with time-varying exposure, adjusted variables for comparison between the Metformin and the Non-metformin cohorts included age, gender, comorbidities (cerebrovascular diseases, coronary heart disease), blood glucose, C-reactive protein, estimated glomerular filtration rate, alanine aminotransferase and Creatinine.

<sup>c</sup> The p values were calculated based on Cox regression model with time-varying exposure.

**Table s8. Baseline characteristics in individuals in the Metformin and Non-metformin groups in mild and severe groups before PSM, related to Table 4.**

Parameters	Mild			Severe		
	Metformin <sup>b</sup> (n=326)	Non-metformin <sup>c</sup> (n=262)	p Value <sup>d</sup>	Metformin <sup>b</sup> (n=352)	Non-metformin <sup>c</sup> (n=273)	p Value <sup>d</sup>
<b>Clinical characteristics on admission</b>						
Age, median(IQR), y	61.0(54.0-67.0)	64.0(57.0-70.0)	<0.001	63.0(56.0-69.0)	65.0(59.0-70.0)	0.003
Male gender, n(%)	179(54.9%)	119(45.4%)	0.028	186(52.8%)	148(54.2%)	0.795
Heart rate, median(IQR), bpm	81.0(76.0-90.0)	81.5(76.8-91.0)	0.995	94.0(80.0-108.0)	88.0(79.5-103.5)	0.360
Respiratory rate, median(IQR), bpm	20.0(19.0-20.0)	20.0(18.0-20.0)	0.930	20.0(20.0-22.0)	20.0(20.0-22.0)	0.348
SBP, median(IQR), mmHg	130.0(122.0-142.0)	135.0(122.3-146.0)	0.144	133.0(122.0-145.0)	132.0(120.0-144.0)	0.291
DBP, median(IQR), mmHg	80.0(74.0-91.0)	82.0(74.3-90.8)	0.422	80.0(73.0-87.0)	78.0(71.0-86.0)	0.175
SpO2, median(IQR)	98.0(96.0-98.0)	97.0(96.0-98.0)	0.386	96.0(93.5-98.0)	97.0(94.0-98.0)	0.514
<b>Comorbidities on admission</b>						
Chronic obstructive pulmonary disease, n(%)	2(0.6%)	1(0.4%)	1.000	3(0.9%)	3(1.1%)	1.000
Heart failure, n(%)	0(0.0%)	0(0.0%)	1.000	0(0.0%)	2(0.7%)	0.190
Coronary heart disease, n(%)	33(10.1%)	51(19.5%)	0.002	51(14.5%)	45(16.5%)	0.566
Cerebrovascular diseases, n(%)	6(1.8%)	11(4.2%)	0.147	11(3.1%)	17(6.2%)	0.096
Chronic liver disease, n(%)	7(2.2%)	5(1.9%)	1.000	6(1.7%)	5(1.8%)	1.000
Chronic renal diseases, n(%)	6(1.8%)	6(2.3%)	0.928	10(2.8%)	8(2.9%)	1.000
<b>Chest CT on admission</b>						
Unilateral lesion, n/N(%)	20/305(6.6%)	14/251(5.6%)	0.763	15/322(4.7%)	13/264(4.9%)	1.000
Bilateral lesion, n/N(%)	279/305(91.5%)	226/251(90.0%)	0.663	301/322(93.5%)	235/264(89.0%)	0.076
<b>Lab tests on admission</b>						
Leukocyte count > 9.5, 10 <sup>9</sup> , n/N(%)	18/306(5.9%)	14/246(5.7%)	1.000	40/349(11.5%)	38/270(14.1%)	0.396

Neutrophil count >6.3, 10 <sup>9</sup> /L, n/N(%)	31/306(10.1%)	20/246(8.1%)	0.510	68/349(19.5%)	58/270(21.5%)	0.609
Lymphocyte count <1.1, 10 <sup>9</sup> /L, n/N(%)	81/306(26.5%)	69/246(28.1%)	0.750	175/349(50.1%)	152/270(56.3%)	0.150
RBC:Male,<4.5, 10 <sup>12</sup> /L; Female,<4.0, 10 <sup>12</sup> /L, n/N(%)	133/306(43.5%)	106/246(43.1%)	0.999	153/349(43.8%)	128/270(47.4%)	0.422
CRP increase > ULN <sup>a</sup> , n/N(%)	79/189(41.8%)	75/170(44.1%)	0.737	79/148(53.4%)	92/130(70.8%)	0.004
Procalcitonin increase> ULN <sup>a</sup> , n/N(%)	90/255(35.3%)	60/194(30.9%)	0.384	157/309(50.8%)	126/223(56.5%)	0.226
ALT increase> 40 U/L, n/N(%)	61/307(19.9%)	52/245(21.2%)	0.775	80/334(23.3%)	56/269(20.8%)	0.533
eGFR, median(IQR)	104.4(89.0-121.3)	100.1(86.0-115.7)	0.079	102.1(86.6-120.8)	100.7(79.9-121.7)	0.275
D-dimer> ULN <sup>a</sup> , n/N(%)	107/269(39.8%)	88/217(40.6%)	0.936	202/326(62.0%)	168/262(64.1%)	0.651
LDL-c>3mmol/L n/N (%)	42/245(17.1%)	33/196(16.8%)	1.000	51/273(18.7%)	31/211(14.7%)	0.299
Blood glucose, median (IQR), mmol/L	8.1(6.3-12.2)	7.4(6.0-10.0)	0.008	9.7(7.1-13.7)	9.2(6.6-12.6)	0.044

Abbreviation: SBP, systolic blood pressure; DBP, Diastolic blood pressure; SpO<sub>2</sub>, oxygen saturation; RBC, red blood cells; CRP, C-reactive protein; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; LDL-c, low density lipoprotein cholesterol; IQR, interquartile range; SD, standardized difference.

<sup>a</sup>Upper limit of normal (ULN) was defined according to criteria in each hospital.

<sup>b</sup> Individuals with T2D taking Metformin during hospitalization were enrolled in the Metformin cohort. Individuals discontinued treatment of diabetes due to inability to take medications or diabetes were not excluded from the cohort.

<sup>c</sup> Individuals with T2D who never took Metformin during hospitalization were enrolled in the Non-metformin cohort.

<sup>d</sup> P values were calculated by Mann-Whitney U test for non-normally distributed continuous variables and Fisher's exact test or  $\chi^2$  test for categorical variables.

**Table s9. Hazard ratios for acidosis, lactic acidosis and mortality between individuals of Metformin and Non-metformin in mild and severe group, related to Table 4.**

Metformin vs Non-metformin	Cox model-Time varying exposure in Mild group before PSM		Hazard in Mild group after PSM		Cox model-Time varying exposure in severe group before PSM		Hazard in Severe group after PSM	
	Adjusted HR <sup>a</sup>	p	Adjusted HR <sup>c</sup>	p	Adjusted HR <sup>a</sup>	p	Adjusted HR <sup>c</sup>	p
	(95%CI)	Value <sup>b</sup>	(95% CI)	Value <sup>d</sup>	(95%CI)	Value <sup>b</sup>	(95% CI)	Value <sup>d</sup>
Acidosis	-	-	-	-	2.67(1.20,5.94)	0.016	3.82(1.27,11.50)	0.017
Lactic Acidosis	-	-	-	-	4.97(1.66,14.92)	0.004	5.65(1.06,30.10)	0.042
Mortality	-	-	-	-	1.00(0.41,2.46)	0.995	1.56(0.63,3.85)	0.333
ARDS	-	-	0.43(0.04,4.65)	0.490	0.74(0.51,1.07)	0.106	0.81(0.57,1.16)	0.248
DIC	-	-	-	-	0.50(0.04,5.97)	0.581	0.91(0.10,7.98)	0.932
Heart failure	0.84(0.41,1.70)	0.626	0.57(0.27,1.19)	0.135	0.58(0.39,0.87)	0.009	0.63(0.42,0.96)	0.032
Acute kidney injury	-	-	-	-	0.92(0.24,3.54)	0.902	0.47(0.11,2.00)	0.303
Acute heart injury	2.14(0.91,5.06)	0.083	1.62(0.54,4.91)	0.393	0.95(0.57,1.60)	0.851	0.81(0.48,1.38)	0.444

Abbreviations: HR, Hazard ratio; CI, Confidence interval; ARDS, acute respiratory distress syndrome; DIC: Disseminated intravascular coagulation.

<sup>a</sup> In the Cox model-Time varying, adjusted variables for comparison between the Metformin and the Non-metformin cohorts included age, gender, comorbidities (cerebrovascular disease, coronary heart disease), blood glucose, C-reactive protein, estimated glomerular filtration rate, alanine aminotransferase and Creatinine.

<sup>b</sup> The p values were calculated based on Cox model-Time varying hazard model.

<sup>c</sup> In the Mixed-effect Cox proportional hazard model, adjusted variables for comparison between the Metformin and the Non-metformin cohorts included age, gender, C-reactive protein, aspartate aminotransferase, cerebrovascular diseases, coronary heart disease, eGFR, blood glucose, creatinine and hospital site as a random effect.

<sup>d</sup> The p values were calculated based on Mixed-effect Cox proportional hazard model.

**Table s10. Baseline characteristics in individuals of the Metformin and Non-metformin groups in mild and severe groups after PSM, related to Table 4.**

Parameters	Mild			Severe		
	Metformin <sup>b</sup> (n=213)	Non-metformin <sup>c</sup> (n=213)	SD <sup>d</sup>	Metformin <sup>b</sup> (n=230)	Non-metformin <sup>c</sup> (n=230)	SD <sup>d</sup>
<b>Clinical characteristics on admission</b>						
Age, median(IQR), y	63.0(56.0-68.0)	62.0(55.0-68.0)	0.008	64.0(57.0-70.0)	64.0(58.0-70.0)	-0.039
Male gender, n(%)	107(50.2%)	107(50.2%)	0.000	118(51.3%)	121(52.6%)	-0.026
Heart rate, median(IQR), bpm	80.0(75.0-90.0)	80.0(76.0-90.0)	0.038	96.5(80.0-108.0)	88.5(79.8-104.0)	0.103
Respiratory rate, median(IQR), bpm	20.0(18.0-20.0)	20.0(19.0-21.0)	-0.097	20.0(19.0-22.0)	20.0(20.0-22.0)	-0.000
SBP, median(IQR), mmHg	130.0(121.8-142.0)	135.0(120.0-147.0)	-0.083	134.0(125.0-146.0)	133.0(121.0-144.0)	0.081
DBP, median(IQR), mmHg	80.0(74.0-90.0)	83.0(75.0-91.0)	-0.120	80.0(73.0-87.0)	80.0(72.0-88.0)	0.059
SpO2, median(IQR)	98.0(96.0-98.0)	98.0(96.0-98.0)	0.092	96.5(93.8-98.0)	97.0(93.0-98.0)	0.042
<b>Comorbidities on admission</b>						
Chronic obstructive pulmonary disease, n(%)	1(0.5%)	1(0.5%)	0.000	2(0.9%)	3(1.3%)	-0.042
Heart failure, n(%)	0(0.0%)	0(0.0%)	0.000	0(0.0%)	0(0.0%)	0.000
Coronary heart disease, n(%)	25(11.7%)	29(13.6%)	-0.056	32(13.9%)	36(15.7%)	-0.049
Cerebrovascular diseases, n(%)	6(2.8%)	5(2.4%)	0.030	9(3.9%)	9(3.9%)	0.000
Chronic liver disease, n(%)	3(1.4%)	5(2.4%)	-0.069	6(2.6%)	4(1.7%)	0.060
Chronic renal diseases, n(%)	4(1.9%)	4(1.9%)	0.000	6(2.6%)	7(3.0%)	-0.026
<b>Chest CT on admission</b>						
Unilateral lesion, n(%)	13(6.7%)	9(4.4%)	0.103	11(5.3%)	7(3.1%)	0.109
Bilateral lesion, n(%)	175(90.7%)	189(91.8%)	-0.038	191(92.3%)	207(92.4%)	-0.005
<b>Lab tests on admission</b>						



Leukocyte count > 9.5, 10 <sup>9</sup> , n/N(%)	9/196(4.6%)	11/199(5.5%)	-0.043	33/228(14.5%)	31/227(13.7%)	0.024
Neutrophil count >6.3, 10 <sup>9</sup> /L, n/N(%)	17/196(8.7%)	16/199(8.0%)	0.023	54/228(23.7%)	49/227(21.6%)	0.050
Lymphocyte count <1.1, 10 <sup>9</sup> /L, n/N(%)	50/196(25.5%)	54/199(27.1%)	-0.037	125/228(54.8%)	120/227(52.9%)	0.039
RBC:Male,<4.5, 10 <sup>12</sup> /L; Female,<4.0, 10 <sup>12</sup> /L, n/N(%)	88/196(44.9%)	76/199(38.2%)	0.136	119/228(52.2%)	103/227(45.4%)	0.137
C-reactive protein increase > ULN <sup>a</sup> , n/N(%)	48/118(40.7%)	59/133(44.4%)	-0.075	58/93(62.4%)	78/111(70.3%)	-0.168
Procalcitonin level increase > ULN <sup>a</sup> , n/N(%)	50/162(30.9%)	52/155(33.6%)	-0.057	98/200(49.0%)	110/185(59.5%)	-0.211
ALT increase> 40 U/L, n/N(%)	37/196(18.9%)	39/197(19.8%)	-0.023	50/223(22.4%)	49/226(21.7%)	0.018
eGFR, median(IQR)	102.7(89.1-121.3)	102.1(90.2-117.4)	0.097	103.8(85.9-123.5)	100.3(80.2-119.4)	0.115
D-dimer> ULN <sup>a</sup> , n/N(%)	67/165(40.6%)	66/174(37.9%)	0.055	141/210(67.1%)	137/219(62.6%)	0.096
LDL-c>3mmol/L n/N (%)	22/152(14.5%)	25/153(16.3%)	-0.052	31/171(18.1%)	31/178(17.4%)	0.019
Blood glucose, median (IQR), mmol/L	7.4(6.1-10.8)	7.7(6.1-11.2)	-0.078	9.2(7.1-13.0)	9.2(6.7-13.1)	0.016

Abbreviation: SBP, systolic blood pressure; DBP, Diastolic blood pressure; SpO<sub>2</sub>, oxygen saturation; RBC, red blood cells; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; LDL-c, low density lipoprotein cholesterol; IQR, interquartile range; SD, standardized difference.

<sup>a</sup>Upper limit of normal (ULN) was defined according to criteria in each hospital.

<sup>b</sup> Individuals with T2D taking metformin during hospitalization were enrolled in the Metformin cohort. Individuals discontinued treatment of diabetes due to inability to take medications or diabetes were not excluded from the cohort.

<sup>c</sup> Individuals with T2D who never took Metformin during hospitalization were enrolled in the Non-metformin cohort.

<sup>d</sup>SD, Standardized differences were used to compare the means of baseline covariates between the Metformin and the Non-metformin groups.

**Table s11. In-hospital management of Metformin and Non-metformin in mild and severe groups after PSM, related to Table 4.**

Parameters	Mild			Severe		
	Metformin <sup>a</sup> (n=213)	Non-metformin <sup>b</sup> (n=213)	SD <sup>c</sup>	Metformin <sup>a</sup> (n=230)	Non-metformin <sup>b</sup> (n=230)	SD <sup>c</sup>
Traditional Chinese medicine, n(%)	189(88.7%)	183(85.9%)	0.085	212(92.2%)	207(90.0%)	0.076
Antiviral drug, n(%)	154(72.3%)	145(68.1%)	0.092	190(82.6%)	186(80.9%)	0.045
Antibiotics drug, n (%)	111(52.1%)	120(56.3%)	-0.085	169(73.5%)	172(74.8%)	-0.030
Antithrombotic or Thrombolysis, n(%)	10(4.7%)	15(7.0%)	-0.100	24(10.4%)	53(23.0%)	-0.343
Antidiabetic drug, n(%)	212(99.5%)	213(100.0%)	-0.097	230(100.0%)	228(99.1%)	0.132
Antidiabetic drug Insulin ,n(%)	87(40.9%)	90(42.3%)	-0.029	146(63.5%)	144(62.6%)	0.018
Lipid lowering drug, n(%)	50(23.5%)	48(22.5%)	0.022	59(25.7%)	58(25.2%)	0.010
Lipid lowering drug statin, n(%)	47(22.1%)	47(22.1%)	0.000	57(24.8%)	57(24.8%)	0.000
Antiplatelet, n(%)	25(11.7%)	39(18.3%)	-0.185	48(20.9%)	50(21.7%)	-0.021
Antifungal medications, n(%)	1(0.5%)	3(1.4%)	-0.097	6(2.6%)	11(4.8%)	-0.115
Vasoactive drug, n(%)	0(0.0%)	2(0.9%)	-0.138	16(7.0%)	18(7.8%)	-0.033
Immunoglobulin, n(%)	29(13.6%)	21(9.9%)	0.117	70(30.4%)	79(34.4%)	-0.084
Systemic corticosteroids, n(%)	20(9.4%)	14(6.6%)	0.104	59(25.7%)	45(19.6%)	0.146
Antihypertensive drugs ACEI, n(%)	5(2.4%)	6(2.8%)	-0.030	8(3.5%)	18(7.8%)	-0.189
Antihypertensive drugs ARB, n(%)	29(13.6%)	31(14.6%)	-0.027	46(20.0%)	50(21.7%)	-0.043
Noninvasive ventilation, n(%)	0(0.0%)	0(0.0%)	0.000	28(12.3%)	43(18.9%)	-0.182
Invasive ventilation, n(%)	0(0.0%)	0(0.0%)	0.000	9(3.9%)	11(4.8%)	-0.043
Renal replacement therapy, n(%)	0(0.0%)	0(0.0%)	0.000	1(0.4%)	4(1.7%)	-0.126
Extracorporeal membrane oxygenation, n(%)	0(0.0%)	0(0.0%)	0.000	2(0.9%)	4(1.8%)	-0.074

<sup>a</sup> Individuals with T2D taking Metformin during hospitalization were enrolled in the Metformin cohort. Individuals discontinued treatment of diabetes due to

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inability to take medications or diabetes were not excluded from the cohort.

<sup>b</sup> Individuals with T2D who never took Metformin during hospitalization were enrolled in the Non-metformin cohort.

<sup>c</sup> SD, Standardized differences were used to compare the means of baseline covariates between the Metformin and the Non-metformin groups.

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**Table s12. The normal range of serum CRP, Procalcitonin, Creatinine and D-dimer tests in each hospitals, related to Table 4.**

Site	Normal Range for Serum Test			
	CRP	Procalcitonin	Creatinine	D-dimer
Hospital 1	0-10(mg/L)	0-0.05(ng/mL)	49-90(μmol/L)/64-104(μmol/L)	0-500(ng/mL)
Hospital 2	0-10(mg/L)	0-0.1(ng/mL)	41-73(μmol/L)/ 41-81(μmol/L)/ 57-97(μmol/L)/ 57-111(μmol/L)	0-0.55(μg/mL)
Hospital 3	0-5(mg/L)	0-0.5(ng/mL)	44-97(μmol/L)/ 53-106(μmol/L)	0-0.55(μg/mL)
Hospital 4	0-5(mg/L)	0-0.05(ng/mL)	40-105(μmol/L)	0-0.5(μg/mL)
Hospital 5	0-10(mg/L)	0-0.1(ng/mL)	41-73(μmol/L)/ 41-81(μmol/L)/ 57-97(μmol/L)/ 57-111(μmol/L)	0-0.243(μg/mL)
Hospital 6	0-3(mg/L)	0-0.5(ng/mL)	41-81(μmol/L)/ 57-97(μmol/L)/ 57-111(μmol/L)	0-1(μg/mL)
Hospital 7	0-4(mg/L)	0-0.05(ng/mL)	49-90(μmol/L)/64-104(μmol/L)	0-0.55(μg/mL)
Hospital 8	0-10(mg/L)/0-5(mg/L)	0-0.1(ng/mL)/0-0.5(ng/mL)	38-120(μmol/L)	0-0.243(μg/mL)
Hospital 9	0-10(mg/L)	0-0.5(ng/mL)/0-0.046(ng/mL)	41-81(μmol/L)/ 41-73(μmol/L)/ 57-97(μmol/L)/ 57-111(μmol/L)	0-1(μg/mL)
Hospital 10	0-6(mg/L)	0-0.5(ng/mL)	44-106(μmol/L)/ 53-123(μmol/L)	0-1(μg/mL)
Hospital 11	0-10(mg/L)	0-0.5(ng/mL)	41-73(μmol/L)/ 41-81(μmol/L)/ 57-97(μmol/L)/ 57-111(μmol/L)	0-0.55(μg/mL)
Hospital 12	0-8(mg/L)	0-0.5(ng/mL)	44-106(μmol/L)	0-0.55(μg/mL)
Hospital 13	0-10 (mg/L)	0-0.25(ng/mL)	41-81(μmol/L)/ 57-111(μmol/L)	0-0.5(μg/mL)
Hospital 14	0-10(mg/L)	0-0.5(ng/mL)	41-73(μmol/L)/ 41-81(μmol/L)/ 57-97(μmol/L)/ 57-111(μmol/L)	0-232(ng/mL)
Hospital 15	0-2(mg/L)	0-0.05(ng/mL)	45-84(μmol/L)/ 59-104(μmol/L)	0-0.5(μg/mL)
Hospital 16	0-10(mg/L)/0-8(mg/L)	0-0.05(ng/mL)/0-0.5(ng/mL)	41-81(μmol/L)/57-111(μmol/L)/ 44-106(μmol/L)/ 44-133(μmol/L)/46-92(μmol/L)	0-0.5(μg/mL)