Supplemental Information

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Supplementary Information

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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.

| Metformin vs Non-metformin | Whole cohort | Mild group | Severe group |
|-----------------------------|--------------|------------|--------------|
|                             | chisq        | p Value    | chisq        | p Value    | chisq        | p Value    |
| 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 characteristics in individuals of the Metformin and the Non-metformin groups after PSM, related to Table 2.

| Parameters                          | Total (N=936) | Metformin (n=468) | Non-metformin (n=468) | SD^d |
|-------------------------------------|---------------|-------------------|-----------------------|------|
| **Clinical characteristics on admission** |               |                   |                       |      |
| 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|
| SpO2, median(IQR)                  | 97.0(95.0-98.0) | 97.0(95.0-98.0) | 97.0(95.0-98.0)       | 0.074|
| **Comorbidities on admission**     |               |                   |                       |      |
| 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|
| **Chest CT on admission**          |               |                   |                       |      |
| 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|
| **Laboratory examination on admission** |           |                   |                       |      |
| Leukocyte count > 9.5, 10^9, n/N(%) | 80/902(8.9%) | 36/452(8.0%)    | 44/450(9.8%)          | -0.064|
| Neutrophil count >6.3, 10^9/L, n/N(%) | 128/902(14.2%) | 60/452(13.3%)  | 68/450(15.1%)         | -0.053|
| Lymphocyte count <1.1, 10^9/L, n/N(%) | 366/902(40.6%) | 182/452(40.3%) | 184/450(40.9%)        | -0.013|
| Test                               | Male, n/N (%) | Female, n/N (%) | Median (IQR), mmol/L | p-value |
|------------------------------------|---------------|-----------------|----------------------|---------|
| RBC: Male, <4.5, 10^12/L; Female, <4.0, 10^12/L | 407/902(45.1%) | 216/452(47.8%) | 191/450(42.4%) | 0.108   |
| C-reactive protein > ULN^a, n/N (%) | 246/483(50.9%) | 108/224(48.2%) | 138/259(53.3%) | -0.101  |
| Procalcitonin level > ULN^a, 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^a, 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; SpO2, 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.

^aUpper limit of normal (ULN) was defined according to criteria in each hospital.

^bIndividuals 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.

^cIndividuals with T2D who never took Metformin during hospitalization were enrolled in the Non-metformin cohort.

^dSD, Standardized differences were used to compare the means of baseline covariates between the Metformin and the Mon-metformin groups.
| 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%)                       | 40(9.9%)                         | -0.131        | 0.124               |
| Extracorporeal membrane oxygenation, n(%)      | 1(0.2%)                       | 40(9.9%)                         | -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 χ² test.
Table s4. C Indexes for the mixed effect Cox model after PSM, related to Table 2.

| Metformin vs Non-metformin | Mixed effect Cox model after PSM in the whole cohort | Mixed effect Cox model after PSM in Mild group | Mixed effect Cox model after PSM in Severe group |
|----------------------------|----------------------------------------------------|---------------------------------------------|-----------------------------------------------|
|                            | C Index (95% CI)                                    | C Index (95% CI)                            | C Index (95% CI)                              |
| 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.
| Metformin vs Non-metformin | Cox regression model with time-varying exposure | p Value$^b$ |
|--------------------------|-----------------------------------------------|------------|
| Acidosis                 | Adjusted HR$^a$ (95%CI)                       | 0.129      |
| Lactic Acidosis          | 2.08(0.81,5.36)                              |            |
|                          | 3.01(0.82,11.05)                              | 0.097      |

Abbreviations: HR, Hazard ratio; CI, Confidence interval; $^a$ 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. $^b$ The p values were calculated based on Cox regression model with time-varying exposure.
| Parameters          | Total (N=588) | Metformin<sup>a</sup> (n=326) | Non-metformin<sup>b</sup> (n=262) | p Value |
|---------------------|---------------|-------------------------------|----------------------------------|---------|
| 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.

| Metformin vs Non-metformin | Whole cohort | Mild group | Severe group |
|---------------------------|--------------|------------|--------------|
| Acute heart injury        | 1.14(0.73,1.79) | 2.14(0.91,5.06) | 0.95(0.57,1.60) |
| Acute kidney injury       | 0.71(0.18,2.79) | -          | 0.92(0.24,3.54) |
| DIC                       | 0.44(0.05,4.00) | -          | 0.50(0.04,5.97) |
| Acute extra-pulmonary     | 1.10(0.71,1.70) | 1.91(0.81,4.49) | 0.96(0.59,1.58) |

| Adjusted HR^b (95%CI)     | p Value^c   | Adjusted HR^b (95%CI)     | p Value^c   | Adjusted HR^b (95% CI)     | p Value^c   |
|---------------------------|------------|---------------------------|------------|---------------------------|------------|
| Acute heart injury        | 0.559      | 0.083                     | 0.851      |
| Acute kidney injury       | 0.627      | -                         | 0.902      |
| DIC                       | 0.467      | -                         | 0.581      |
| Acute extra-pulmonary     | 0.670      | 0.139                     | 0.884      |

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

^a Acute injury of extrapulmonary organs include Acute heart injury, Acute kidney injury and DIC.

^b 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.

^c 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                                             | Clinical characteristics on admission | Comorbidities on admission | Chest CT on admission | Lab tests on admission |
|--------------------------------------------------------|---------------------------------------|---------------------------|-----------------------|------------------------|
|                                                        | 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> |
| 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)           | 0.144                 | 133.0(122.0-145.0)       | 132.0(120.0-144.0)        | 0.291                |
| SBP, median(IQR), mmHg                                  | 130.0(122.0-142.0)                    | 135.0(122.3-146.0)        | 0.422                 | 80.0(74.0-91.0)          | 82.0(74.3-90.8)           | 0.348                |
| DBP, median(IQR), mmHg                                  | 80.0(74.0-91.0)                       | 82.0(74.3-90.8)           | 0.147                 | 130.0(122.0-142.0)       | 135.0(122.3-146.0)        | 0.348                |
| 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                |
| Comorbidities on admission                              |                                       |                           |                       |                        |                         |                      |
| 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                 | 6(1.7%)                | 5(1.8%)                   | 1.000                |
| 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                |
| Chest CT on admission                                   |                                       |                           |                       |                        |                         |                      |
| 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%)            | 0.863                 | 301/322(93.5%)         | 235/264(89.0%)           | 0.076                |
| Lab tests on admission                                  |                                       |                           |                       |                        |                         |                      |
| 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                |
| Parameter                          | Value 1 | Value 2 | p-value  | Reference Value 1 | Reference Value 2 | p-value 2 |
|-----------------------------------|---------|---------|----------|-------------------|-------------------|----------|
| Neutrophil count >6.3, 10^9/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, 10^9/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, 10^12/L; Female, <4.0, 10^12/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, 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, 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, n/N(%) | 107/269(39.8%) | 88/217(40.6%) | 0.936 | 202/326(62.0%) | 168/262(64.1%) | 0.651 |
| LDL-c > 3 mmol/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; SpO2, oxygen saturation; RBC, red blood cells; CRP, C-reactive protein; ALT, alanine aminotransferase; cGFR, estimated glomerular filtration rate; LDL-c, low density lipoprotein cholesterol; IQR, interquartile range; SD, standardized difference.

*Upper limit of normal (ULN) was defined according to criteria in each hospital.

*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.

*Individuals with T2D who never took Metformin during hospitalization were enrolled in the Non-metformin cohort.

*P values were calculated by Mann-Whitney U test for non-normally distributed continuous variables and Fisher’s exact test or χ² test for categorical variables.
| 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\(^a\) (95%CI)  | p Value\(^b\)                | Adjusted HR\(^c\) (95%CI)  | p Value\(^d\)                | Adjusted HR\(^a\) (95%CI)  | p Value\(^b\)                | Adjusted HR\(^c\) (95%CI)  | p Value\(^d\)                |
| 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                      | 0.63(0.42,0.96)              | 0.032                      |
| 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                      | 0.47(0.11,2.00)              | 0.303                      |
| 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.

\(^a\) 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.

\(^b\) The p values were calculated based on Cox model-Time varying hazard model.

\(^c\) 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.

\(^d\) 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 (n=213) | Non-metformin (n=213) | SDd | Severe (n=230) | Non-metformin (n=230) | SDd |
|-----------------------------------------|--------------|------------------------|-----|----------------|------------------------|-----|
| **Clinical characteristics on admission** |              |                        |     |                |                        |     |
| 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  |
| **Comorbidities on admission**          |              |                        |     |                |                        |     |
| 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 |
| **Chest CT on admission**               |              |                        |     |                |                        |     |
| 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 |
| **Lab tests on admission**              |              |                        |     |                |                        |     |
| Parameter                        | Value 1 | Value 2 | p-value 1 | Value 3 | Value 4 | p-value 2 |
|---------------------------------|---------|---------|-----------|---------|---------|-----------|
| Leukocyte count > 9.5, 10^9, 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, 10^9/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, 10^9/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, 10^12/L; Female, <4.0, 10^12/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, 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, 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, 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; SpO2, 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.

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

b 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.

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

d 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\(^a\) (n=213) | Non-metformin\(^b\) (n=213) | SD\(^c\) | Metformin\(^a\) (n=230) | Non-metformin\(^b\) (n=230) | SD\(^c\) |
| 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    |
| Immunoglobin, 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    |

\(^a\) 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.

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

c SD, Standardized differences were used to compare the means of baseline covariates between the Metformin and the Non-metformin groups.
| Site    | 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) | 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)     |