Supplementary Materials

Anti-infection effects of heparin on SARS-CoV-2 in a diabetic mouse model

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Supplementary Table S1. Characteristics of COVID-19 patients with vs without diabetes at baseline.

Characteristic	Non-diabetes (291)		Diabetes (66)		$t/Z/x^2$	Test	P
	Mean ± SD or median (IQR) or n (%)	Missing Data	Mean ± SD or median (IQR) or n (%)	Missing Data			
Age, year, median (IQR)	64.00 (49.00-70.00)	0	68.00 (59.75–73.25)	0	-2.933	Mann-Whitney test	**0.003**
Sex		0		0	1.120	Chi-Square tests	0.290
Male, n (%)	151 (51.9%)	-	39 (59.1%)	-			
Female, n (%)	140 (48.1%)	-	27 (40.9%)	-			
Smoking, n (%)	16 (7.1%)	65	5 (10.2%)	17	-	Fisher's exact test	0.551
Comorbidities							
Hypertension, n (%)	92 (31.6%)	0	39 (59.1%)	0	17.483	Chi-Square tests	**<0.001**
Hyperlipemia, n (%)	3 (1.0%)	0	3 (4.5%)	0	-	Fisher's exact test	0.079
CHD, n (%)	27 (9.3%)	0	14 (21.2%)	0	7.537	Chi-square tests	**0.006**
COPD, n (%)	18 (6.2%)	0	8 (12.1%)	0	-	Fisher's exact test	0.113
CKD, n (%)	7 (2.4%)	0	5 (7.6%)	0	-	Fisher's exact test	0.051
Cancer, n (%)	10 (3.4%)	0	2 (3.0%)	0	-	Fisher's exact test	1.000
Main symptoms of COVID-19							
Cough, n (%)	234 (80.4%)	0	56 (84.8%)	0	0.694	Chi-square tests	0.405
Fever, n (%)	225 (77.3%)	0	50 (75.8%)	0	0.074	Chi-square tests	0.785
Expectoration, n (%)	153 (52.6%)	0	44 (66.7%)	0	4.318	Chi-square tests	**0.038**
Main laboratory findings							
FBG, mmol/L, median (IQR)	5.45 (4.96–6.67)	27	7.35 (5.89–9.85)	7	-5.659	Mann-Whitney test	**<0.001**
Hemoglobin, g/L, median (IQR)	128.00 (116.00–137.00)	3	126.00 (115.00–139.00)	3	-0.627	Mann-Whitney test	0.531
RBC count, 10^9/L, mean ± SD	4.09 ± 0.61	3	4.08 ± 0.56	3	0.046	*t*-test	0.964

WBC count, 10^9/L, median (IQR)	5.73 (4.45–7.37)	4	6.14 (4.97–7.75)	3	-1.452	Mann-Whitney test	0.146
Lymphocyte count, 10^9/L, mean ± SD	1.27 ± 0.55	3	1.29 ± 0.60	3	-0.217	*t*-test	0.828
Neutrophil count, 10^9/L, median (IQR)	3.68 (2.59–5.20)	3	4.02 (2.86–5.87)	3	-1.469	Mann-Whitney test	0.142
Monocyte count, 10^9/L, median (IQR)	0.47 (0.36-0.63)	3	0.49 (0.37–0.67)	3	-1.069	Mann-Whitney test	0.285
Platelet count, 10^9/L, mean ± SD	248.55 ± 104.45	3	251.39 ± 91.06	4	-0.199	*t*-test	0.843
CRP, mg/L, median (IQR)	12.00 (1.63–59.10)	11	8.60 (2.20–80.65)	1	-0.449	Mann-Whitney test	0.654
Signs at admission							
SpO2, %, median (IQR)	97.00 (95.00–99.00)	27	96.00 (92.00–98.00)	7	-2.366	Mann-Whitney test	**0.018**
RR, bpm, median (IQR)	20.00 (18.00–22.00)	15	20.00 (20.00-22.00)	3	-1.976	Mann-Whitney test	**0.048**
HR, bpm, median (IQR)	86.50 (78.00–96.00)	11	89.50 (76.00–102.00)	2	-0.660	Mann-Whitney test	0.509
BT, °C, median (IQR)	36.70 (36.30–37.00)	19	36.60 (36.30–37.00)	3	-0.923	Mann-Whitney test	0.356
Death, n (%)	47 (16.2%)	0	9 (13.6%)	0	0.257	Chi-square tests	0.612

Note: Bold values represent statistically significant P values.

Abbreviations: CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; FBG, fasting blood glucose; RBC, red blood cell; WBC, white blood cell; CRP, C-reactive protein; SpO$_2$; oxygen saturation; RR, respiratory rate; HR, heart rate; BT, body temperature; IQR, interquartile range; SD, standard deviation.

Supplementary Table S2. Characteristics of COVID-19 patients with vs without diabetes at baseline (other clinical features with no statistically significant difference).

Characteristic	Non diabetes (389) Mean ± SD or median (IQR) or n (%)	Missing data	Diabetes (86) Mean ± SD or median (IQR) or n (%)	Missing Data	$t/Z/x^2$	Test	P
Main symptoms of COVID-19							
Hemoptysis, n (%)	8 (2.7%)	0	0 (0.0%)	0	-	Fisher's exact test	0.360
Shortness of breath, n (%)	106 (36.4%)	0	23 (34.8%)	0	0.058	Chi-square tests	0.810
Pharyngalgia, n (%)	37 (12.7%)	0	9 (13.6%)	0	0.041	Chi-square tests	0.840
Headache, n (%)	43 (14.8%)	0	10 (15.2%)	0	0.006	Chi-square tests	0.938
Dizzy, n (%)	19 (6.5%)	0	3 (4.5%)	0	-	Fisher's exact test	0.777
Muscular soreness, n (%)	62 (21.3%)	0	14 (21.2%)	0	<0.001	Chi-square tests	0.987
Weakness, n (%)	117 (40.2%)	0	24 (36.4%)	0	0.332	Chi-square tests	0.564
Pectoralgia, n (%)	56 (19.2%)	0	10 (15.2%)	0	0.598	Chi-square tests	0.439
Chest stuffiness, n (%)	126 (43.3%)	0	19 (28.8%)	0	4.697	Chi-square tests	0.030
Diarrhea, n (%)	71 (24.4%)	0	15 (22.7%)	0	0.082	Chi-square tests	0.774
Nausea and vomiting, n (%)	41 (14.1%)	0	11 (16.7%)	0	0.287	Chi-square tests	0.592
Palpitation, n (%)	6 (2.1%)	0	2 (3.0%)	0	-	Fisher's exact test	0.644
Main laboratory findings							
PT, s , median (IQR)	13.70 (13.20–14.40)	17	13.75 (13.00–14.50)	6	-0.197	Mann-Whitney test	0.844
PTA, s, median (IQR)	91.50 (82.25–98.00)	19	90.00 (81.00–100.75)	6	-0.166	Mann-Whitney test	0.868
INR, median (IQR)	1.06 (1.01–1.14)	18	1.07 (0.99–1.14)	6	-0.051	Mann-Whitney test	0.959
Fg, g/L, median (IQR)	4.25 (3.40–5.36)	18	4.33 (3.62–5.75)	6	-0.82	Mann-Whitney test	0.412
APTT, s, median (IQR)	37.80 (35.25–41.10)	18	38.40 (36.00–41.05)	6	-0.742	Mann-Whitney test	0.458
TT, s, median (IQR)	16.60 (15.75–17.50)	18	16.70 (15.83–17.70)	6	-0.285	Mann-Whitney test	0.776

D dimer, median (IQR)	0.79 (0.32–2.47)	23	0.58 (0.36–2.95)	10	-0.296	Mann-Whitney test	0.767
FDP, µg/mL, median (IQR)	4.00 (4.00–9.20)	34	4.00 (4.00–9.875)	14	-0.180	Mann-Whitney test	0.857
ATIII, %, median (IQR)	92.00 (81.00–101.00)	37	91.00 (85.00–98.00)	14	-0.355	Mann-Whitney test	0.722
Complications						
RF, n (%)	23 (7.9%)	0	3 (4.5%)	0	-	Fisher's exact test	0.439
ARDS, n (%)	41 (14.1%)	0	10 (15.2%)	0	0.05	Chi-square tests	0.824
AMI, n (%)	54 (18.6%)	0	8 (12.1%)	0	1.553	Chi-Square tests	0.213
ALI, n (%)	63 (21.6%)	0	12 (18.2%)	0	0.39	Chi-Square tests	0.532
AKI, n (%)	29 (10.0%)	0	10 (15.2%)	0	1.487	Chi-Square tests	0.223
Septic shock, n (%)	17 (5.8%)	0	7 (10.6%)	0	-	Fisher's exact test	0.175
MODS, n (%)	3 (1.0%)	0	0 (0.0%)	0	-	Fisher's exact test	1.000

Note: Bold values represent statistically significant P values.

Abbreviations: PT, prothrombin time; PTA, prothrombin activity; INR, international normalized ratio; Fg, fibrinogen; APTT, activated Partial thromboplastin time; TT, thrombin time; FDP, fibrinogen degradation products; AT III, antithrombin III; RF, respiratory failure; ARDS, acute respiratory distress syndrome; AMI, acute myocardial injury; ALI, acute liver injury; AKI, acute kidney injury; MODS, multiple organ dysfunction syndrome; IQR, interquartile range.

Supplementary Table S3. Univariate and multivariate logistic regression analysis between fasting blood glucose and incidence of main symptoms and important complications in COVID-19 patients.

| Characteristic	Crude OR (95% CI)	P	Adjust OR (95% CI)	P
Main symptoms of COVID-19				
Cough	1.04 (0.94–1.15)	0.427	-	-
Fever	1.02 (0.94–1.12)	0.584	-	-
Expectoration	1.04 (0.97–1.12)	0.256	-	-
Hemoptysis	1.03 (0.85–1.26)	0.757	-	-
Shortness of breath	1.01 (0.95–1.09)	0.678	-	-
Pharyngalgia	1.08 (1.00–1.16)	0.051	-	-
Headache	0.99 (0.90–1.09)	0.853	-	-
Dizzy	1.03 (0.92–1.16)	0.574	-	-
Muscular soreness	1.00 (0.92–1.08)	0.928	-	-
Weakness	1.02 (0.96–1.09)	0.502	-	-
Pectoralgia	1.03 (0.95–1.11)	0.531	-	-
Chest stuffiness	1.03 (0.96–1.10)	0.406	-	-
Diarrhea	1.00 (0.92–1.08)	0.955	-	-
Nausea and vomiting	1.02 (0.94–1.11)	0.624	-	-
Palpitation	1.03 (0.86–1.24)	0.724	-	-
Complications				
RF	1.11 (1.03–1.21)	**0.012**	1.10 (1.00–1.20)	**0.041**
ARDS	1.15 (1.06–1.24)	**<0.001**	1.12 (1.04–1.21)	**0.003**
AMI	1.10 (1.02–1.18)	**0.009**	-	-
ALI	1.03 (0.96–1.11)	0.430	-	-
AKI	1.14 (1.06–1.24)	**0.001**	1.11 (1.03–1.20)	**0.006**
Septic shock	1.11 (1.02–1.20)	**0.016**	1.09 (1.00–1.19)	0.055
MODS	0.87 (0.39–1.97)	0.741	-	-
Death	1.18 (1.09–1.29)	**0.001**	1.15 (1.06–1.24)	**0.001**

Note: Bold values represent significant P values.

Abbreviations: RF, respiratory failure; ARDS, acute respiratory distress syndrome; AMI, acute myocardial injury; ALI, acute liver injury; AKI, acute kidney injury; MODS, multiple organ dysfunction syndrome; OR, odds ratio.
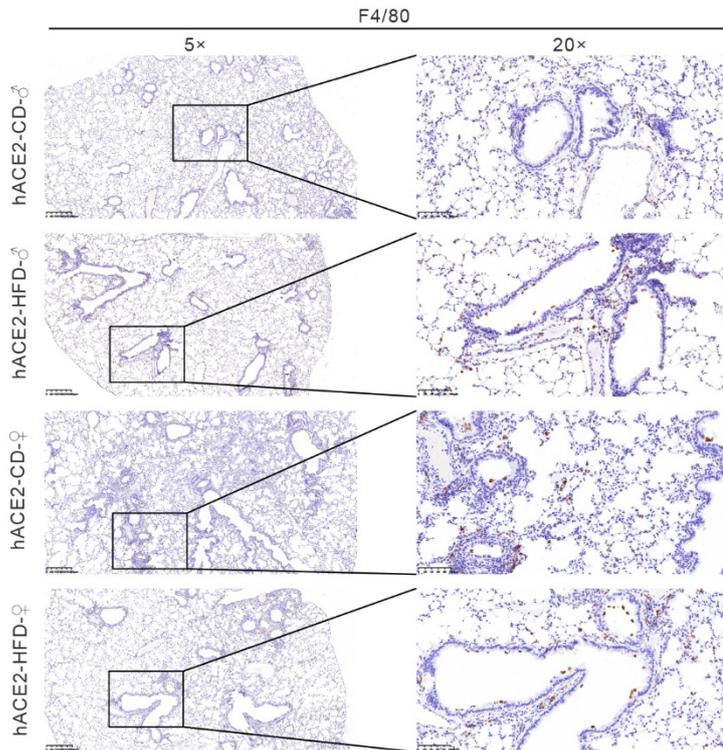
Supplementary Figure S1 hACE2-transgenic mice are sensitive to SARS-CoV-2 infection under a chow diet (CD) and high-fat diet (HFD)

F4/80 in lungs of hACE2-CD and hACE2-HFD mice after infection was detected using immunohistochemistry (IHC). 5×, scale bar represents 300 µm, 20×, scale bar represents 100 µm.
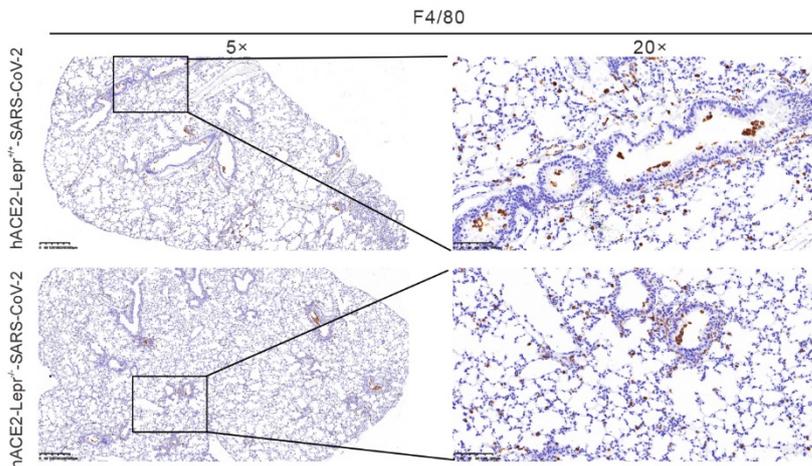
Supplementary Figure S2 Diabetic mice exhibit more severe symptoms after SARS-CoV-2 infection

F4/80 in lungs of hACE2-Lepr$^{-/-}$ and hACE2-Lepr$^{+/+}$ mice after infection was detected using IHC. 5×, scale bar represents 300 µm, 20×, scale bar represents 100 µm.