Cell Metabolism, Volume *33*

Supplemental information

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Figure S1, related to Figure 1. Characteristics of the plasma-sampled sub-cohorts.

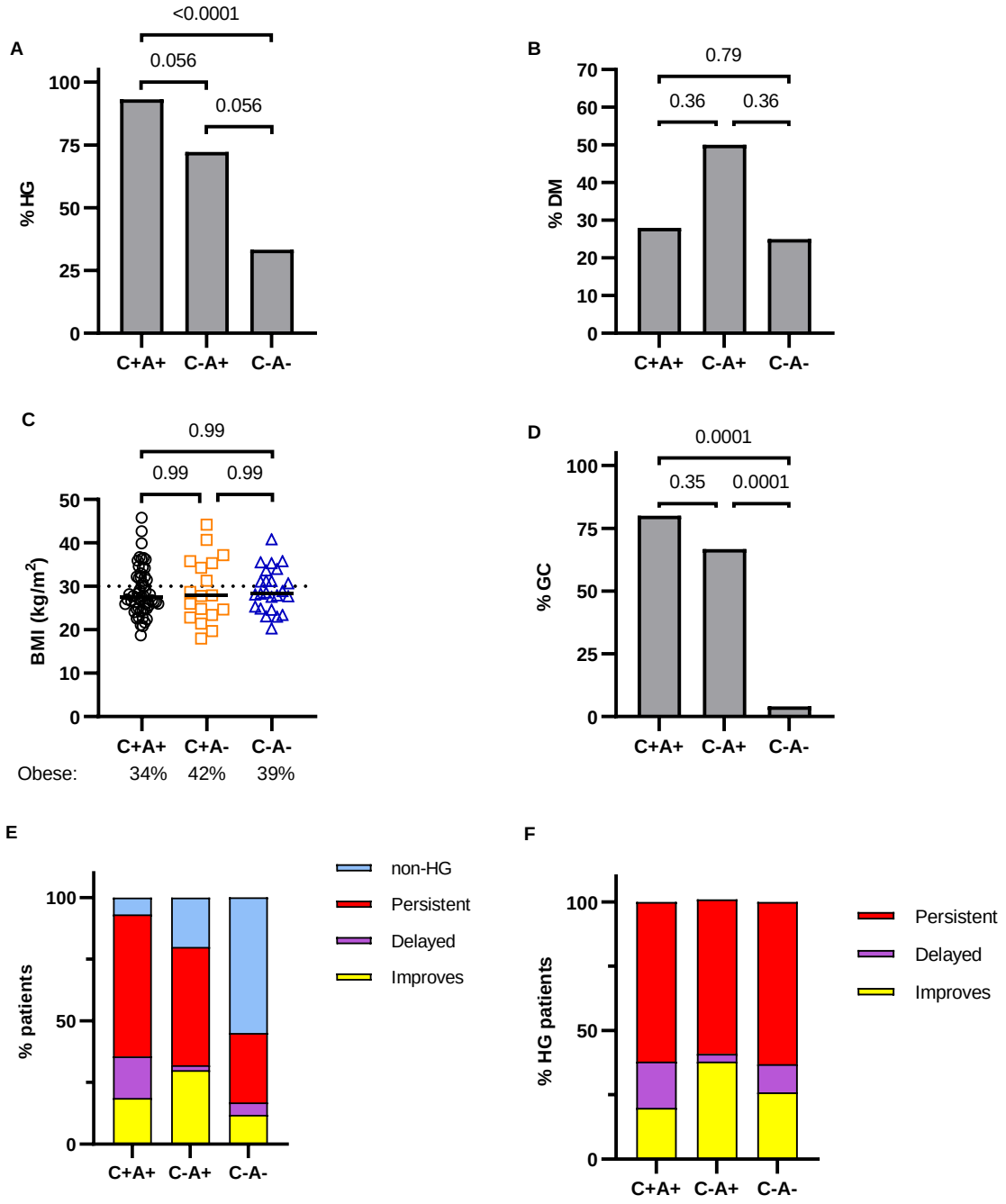

Figure S1, related to Figure 1. Characteristics of the plasma-sampled sub-cohorts.

(A and B) Percentage of patients with hyperglycemia (HG) (**A**) and diabetes (**B**) among plasma sampled patients with COVID-19 and ARDS+ (C+A+, *n* = 59) and ICU controls with (C-A+, *n* = 18) or without ARDS (C-A-, *n* = 24). Data were analyzed by two-sided Fisher's exact test with Bonferroni-Holm's correction for multiple comparisons.

(C) BMI of patients with COVID-19 and ARDS (C+A+, *n* = 59) and ICU controls with (C-A+, *n* = 18) or without ARDS (C-A-, *n* = 24). Data were analyzed by Kruskal-Wallis test with Dunn's test corrected for multiple comparisons (Bonferroni-Holm).

(D) Percentage of patients who received glucocorticoid (GC) treatment among plasma sampled patients with COVID-19 and ARDS (C+A+, *n* = 59) and ICU controls with (C-A+, *n* = 18) or without ARDS (C-A-, *n* = 24). Data were analyzed by two-sided Fisher's Exact Test with Bonferroni-Holm's correction for multiple comparisons.

(E and F) Change in hyperglycemia over time: Percentage of patients who never suffer from HG, display HG throughout their hospital stay ("persistent"), develop HG after at least one week without HG ("delayed"), display HG initially but return to normal glucose levels for at least a week before discharge ("improves") (C+A+ *n* = 59, C-A+ *n* = 50, C-A- *n* = 202 patients). **(F)** Data from **(E)** considering only patients with HG.

Figure S2, related to Figure 2. Distribution of C-peptide and glucose readings.

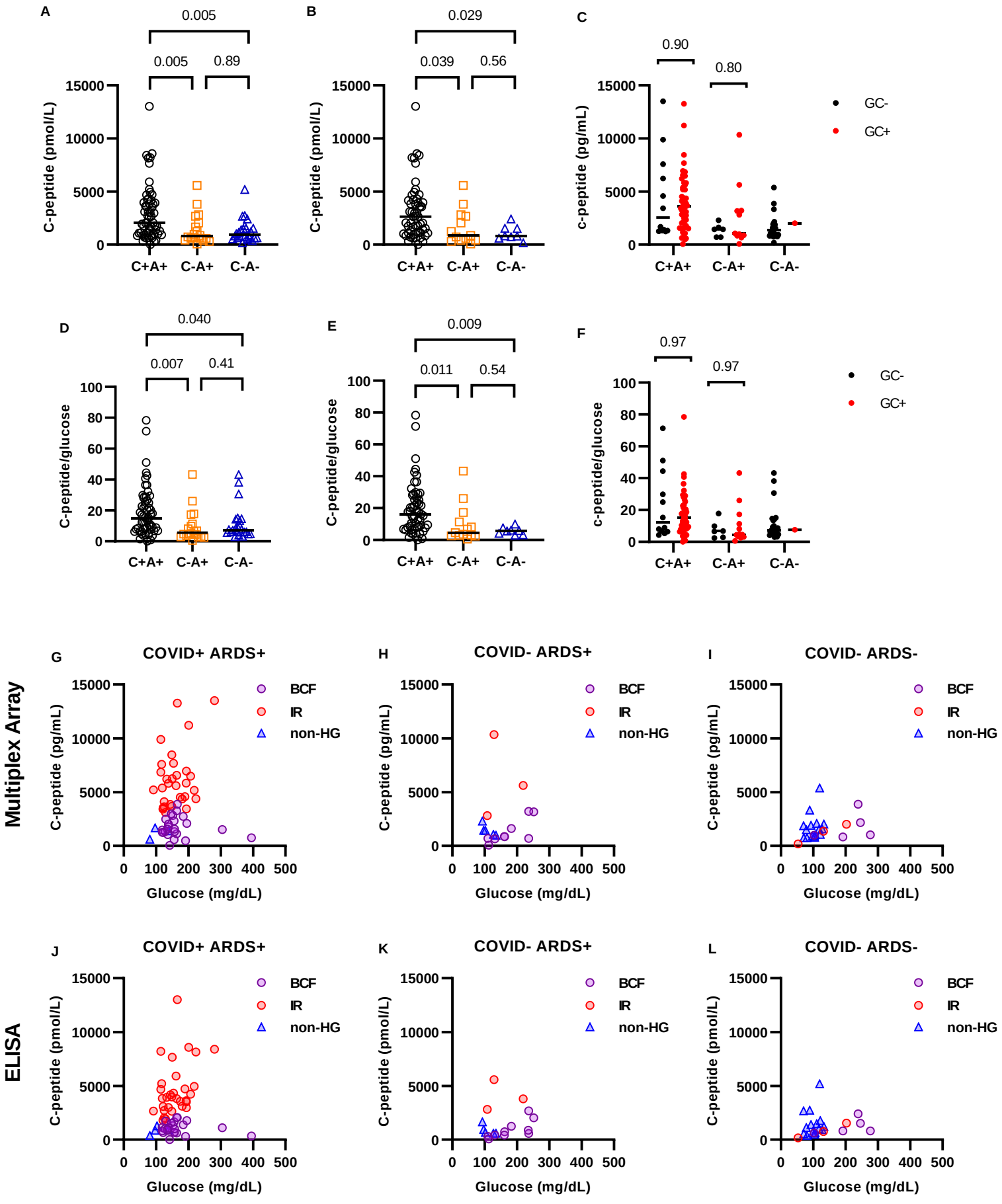

Figure S2, related to Figure 2. Distribution of C-peptide and glucose readings.

(A) C-peptide concentration in the plasma of patients with COVID-19 and ARDS (C+A+, *n* = 59), ICU controls with ARDS (C-A+, *n* = 18), and without ARDS (C-A-, *n* = 24), measured by ELISA. Data were analyzed using Kruskal-Wallis and Dunn's tests with multiple comparison correction (Bonferroni-Holm).

(B), C-peptide concentration in the plasma of patients and controls with hyperglycemia (C+A+ *n* = 55, C-A+ *n* = 13, C-A- *n* = 8), measured by ELISA. Data were analyzed using Kruskal-Wallis and Dunn's tests with multiple comparison correction (Bonferroni-Holm).

(C) C-peptide concentration in the plasma of patients in each of the groups: C+A+ (*n* = 59), C-A+ (*n* = 18), and C-A- (*n* = 24), subdivided according to whether they received glucocortidoids (GC) during their hospital stay, measured by Multiplex Protein Array. C+A+ and C-A+ data were analyzed using Mann-Whitney's tests with Holm-Šídák's multiple comparison correction. Statistical analysis of C-A- was not possible since only 1 patient in this group received GC.

(D and E) C-peptide/glucose ratio of all patients with COVID-19 and ARDS and control groups (**D**) or only those with hyperglycemia (**E**), C-peptide measured by ELISA. Data were analyzed using Kruskal-Wallis and Dunn's tests with multiple comparison correction (Bonferroni-Holm).

(F) C-peptide/glucose ratio of patients in the following groups: C+A+ (*n* = 59), C-A+ (*n* = 18), and C-A- (n=24), subdivided according to whether they received GC during their hospital stay, measured by Multiplex Protein Array. C+A+ and C-A+ data were analyzed using Mann-Whitney's tests with Holm-Šídák's multiple comparison correction. Statistical analysis of C-A- was not possible since only 1 patient in this group received GC.

(G – L) Glucose at plasma collection time was plotted against C-peptide concentration in the plasma, measured by Multiplex Protein Array (**G – I**) or ELISA (**J – L**), for patients in the following groups: C+A+ (**G** and **J**, *n* = 59), C-A+ (**H** and **I**, *n* = 18), and C-A- (**J** and **L**, *n* = 24). Each data point is colored according to their glycemic subgroup: non-hyperglycemic (non-HG), insulin resistant (IR), beta cell failure (BCF).

Figure S3, related to Figure 2. Statistical analysis of insulin resistance and beta cell failure among patients with COVID and ARDS, and ICU controls with or without ARDS

A

	no DM		DM			
	BCF	IR	BCF	IR		p
C+A+	10	28	11	6		0.015
C-A+	2	3	8	0		0.035
C-A-	1	2	5	0		0.11

	non-Ob		Ob			
	BCF	IR	BCF	IR		
C+A+	15	20	6	14		0.4
C-A+	4	2	6	1		0.56
C-A-	3	0	3	2		0.46

	No Gc		Gc			
	BCF	IR	BCF	IR		
C+A+	3	7	18	27		0.72
C-A+	3	0	7	3		0.53
C-A-	5	2	1	0		0.99

B

Model 1: Logistic regression with 3 levels: no hyperglycemia, insulin resistance, and beta cell failure with group 3 (C- A-) as reference.

Outcome – Insulin resistance	OR (95% CI)	P-value
Group 2 (C- A+) vs. Group 3 (C- A-)	1.84 (0.33-10.47)	0.487
Group 1 (C+ A+) vs. Group 3 (C- A-)	15.1 (3.4-81.3)	0.000
Outcome – Beta cell failure	OR (95% CI)	P-value
Group 2 (C- A+) vs. Group 3 (C- A-)	1.24 (0.21-7.22)	0.813
Group 1 (C+ A+) vs. Group 3 (C- A-)	0.61 (0.13-2.94)	0.537
Diagnosed Diabetes	12.6 (4.7-37.7)	0.000
Glucocorticoid Administration	3.6 (1.15-12.32)	0.032

Model 2: Logistic regression with 3 levels: no hyperglycemia, insulin resistance, and beta cell failure with group 2 (C- A+) as reference.

Outcome – Insulin resistance	OR (95% CI)	P-value
Group 3 (C- A-) vs. Group 2 (C- A+)	0.55 (0.10-3.02)	0.487
Group 1 (C+ A+) vs. Group 2 (C- A+)	8.25 (1.73-42.85)	0.009
Outcome – Beta cell failure		
Group 3 (C- A-) vs. Group 2 (C- A+)	0.81 (0.14- 4.75)	0.813
Group 1 (C+ A+) vs. Group 2 (C- A+)	0.49 (0.14- 1.79)	0.279
Diagnosed Diabetes	12.64 (4.72 37.67)	0.000
Glucocorticoid Administration	3.64 (1.15- 12.32)	0.032

Figure S3, related to Figure 2. Statistical analysis of insulin resistance and beta cell failure among patients with COVID and ARDS, and ICU controls with or without ARDS.

(A) Association between insulin resistance (IR)/beta cell failure (BCF) and diabetes (DM), obesity (Ob), and glucocorticoid treatment (Gc). Association was tested using Fisher's exact test for individuals classed as either IR or BCF among patients with COVID-19 and ARDS (C+A+, *n* = 55), ICU controls with ARDS (C-A+, *n* = 13), and without ARDS (C-A-, *n* = 8).

(B) Logistic regression adjusting for diagnosed diabetes and glucocorticoid use. Models with a three level ordinal outcome (0 = no hyperglycemia, 1 = insulin resistance and 2 = beta cell failure). We fitted a partial proportional odds model assuming given nonproportionality only in the group variable and proportionality of odds for all the additional covariates such as Diagnosed Diabetes and Glucocorticoid usage, which were treated as confounders in the model.

Figure S4, related to Figure 3. Glucoregulatory hormone profile in COVID-19.

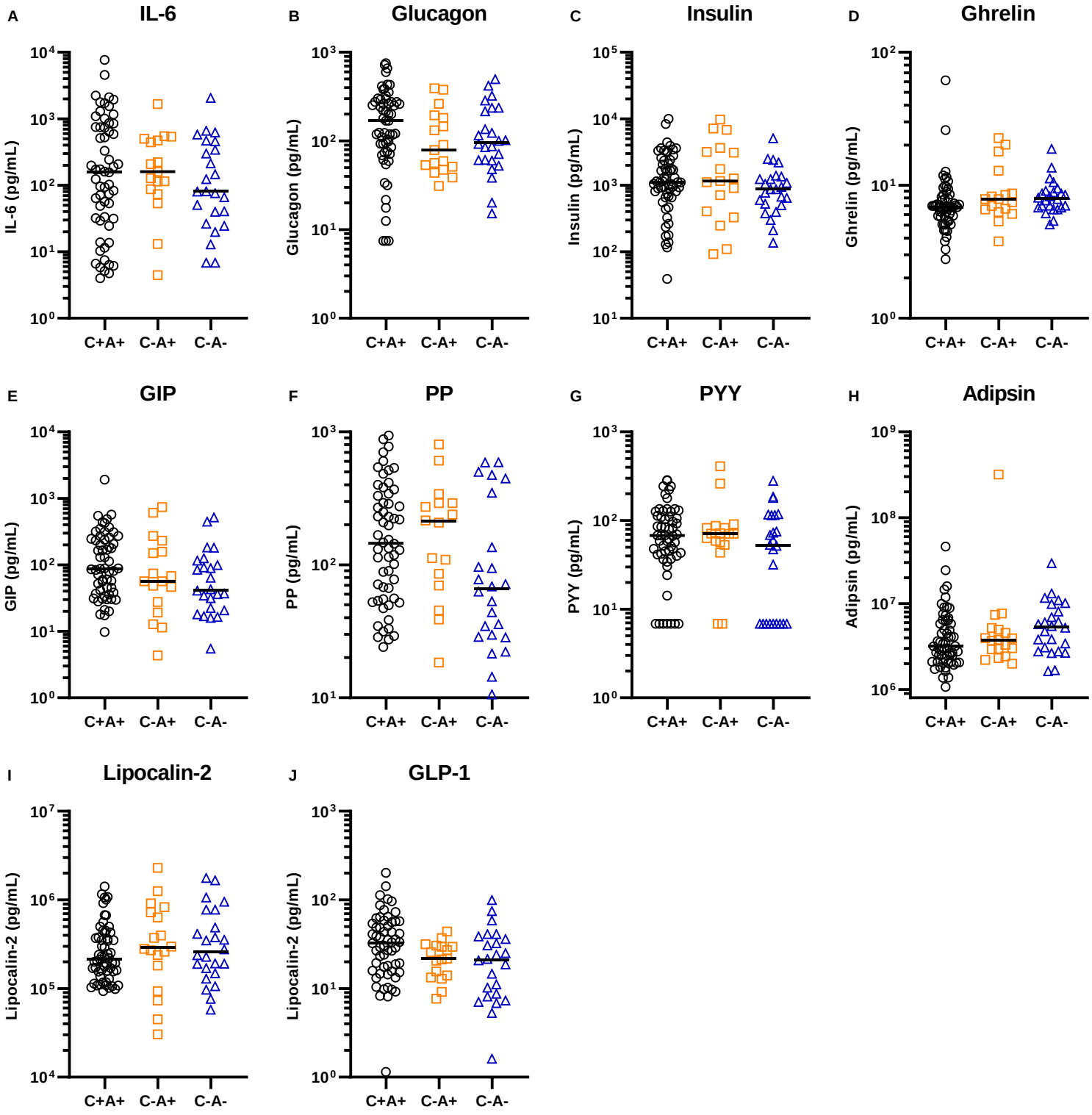

Figure S4, related to Figure 3. Glucoregulatory hormone profile in COVID-19.

(A – J) Plasma from patients with COVID-19 and ARDS (C+A+, *n* = 59) and ICU control with ARDS (C-A+, *n* = 18) and without ARDS (C-A-, *n* = 24) was analyzed by multiplex metabolic protein array, targeting hormones known to modulate blood glucose homeostasis. The data were analyzed using Kruskal-Wallis tests. All targets with $P > 0.05$ in either Kruskal-Wallis or all Dunn's tests are shown here.

Figure S5, related to Figure 3. Metabolic hormone analysis of COVID-19 patients split by glycemic subgroup.

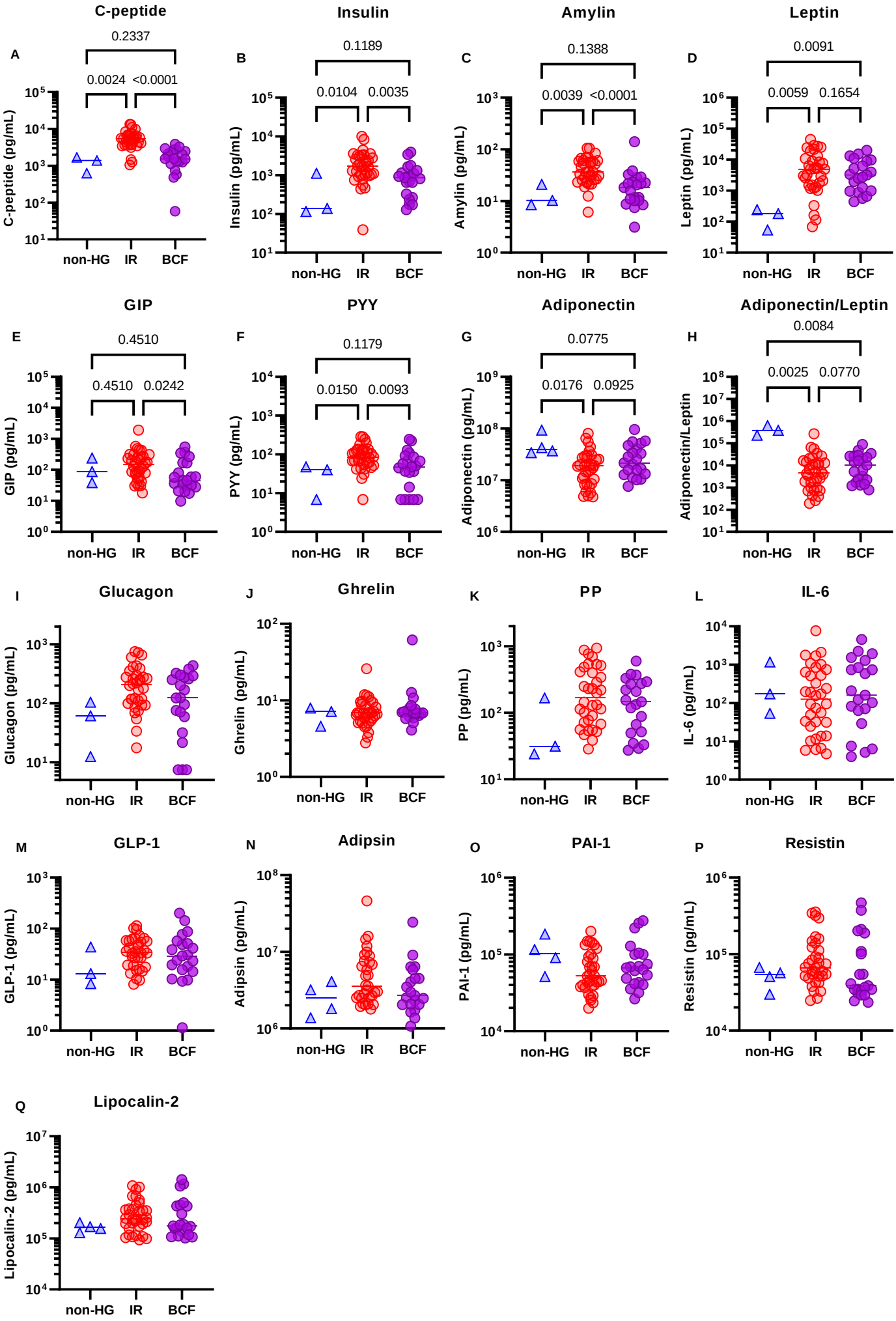

Figure S5, related to Figure 3. Metabolic hormone analysis of COVID-19 patients split by glycemic subgroup.

(A – Q) Metabolic hormone readings of patients with COVID-19 were subdivided according to the glycemic subcategory assigned to each patient: non-hyperglycemic (non-HG), insulin resistant (IR), beta cell failure (BCF). The data were analyzed using Kruskal-Wallis tests. All targets with $P < 0.05$ (**A-H**) were subjected to Dunn's tests with multiple comparison correction (Bonferroni-Holm).

Figure S6, related to Figure 4. Altered gene expression following infection with SARS-CoV-2.

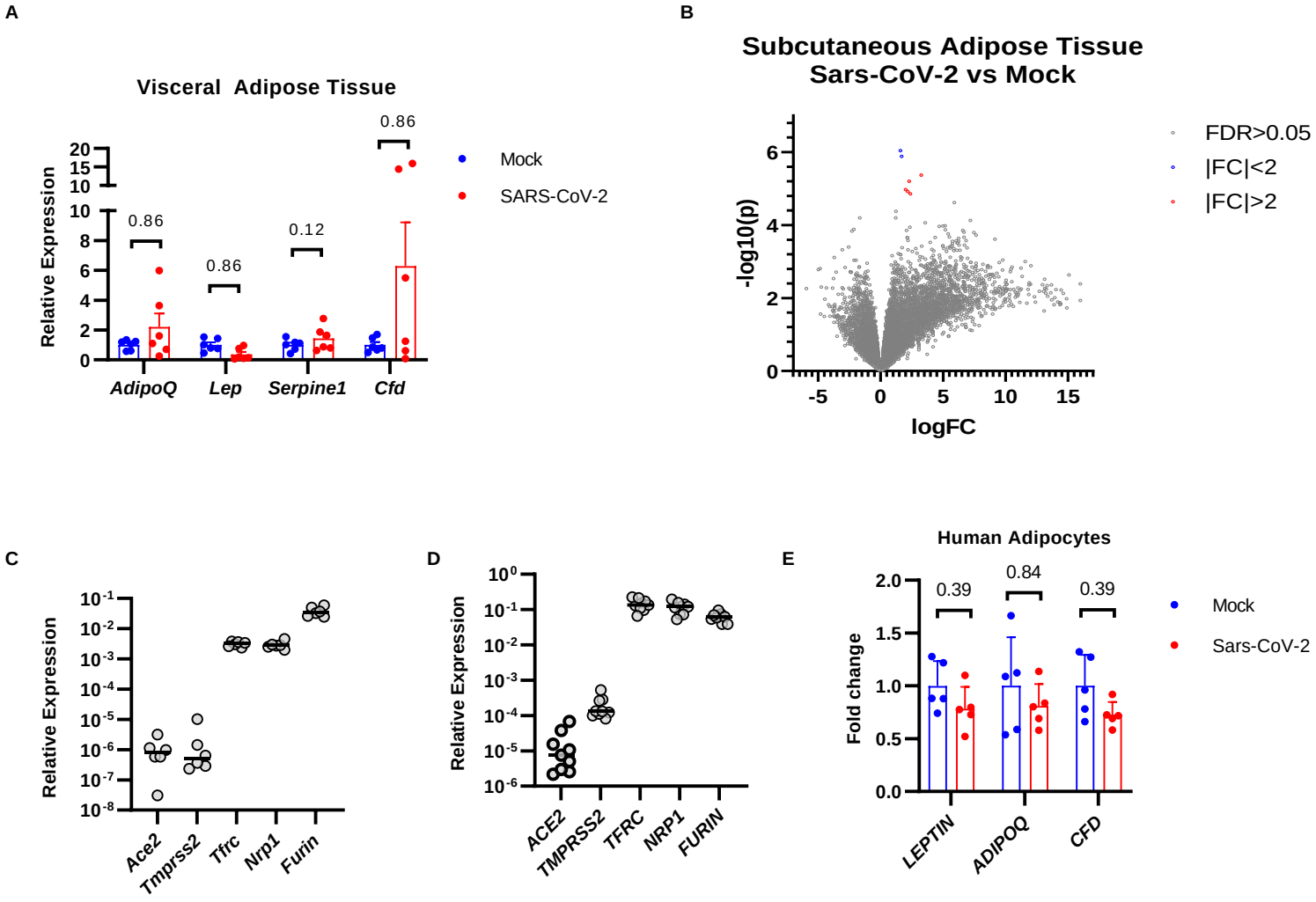

Figure S6, related to Figure 4. Altered gene expression following infection with SARS-CoV-2.

(A) RT-qPCR of mRNA from visceral fat tissue of Syrian hamsters infected with SARS-CoV-2 or mock virus. Data were analyzed using Mann-Whitney tests with Holm-Sidak's multiple comparisons correction (*n* = 6 hamsters per group).

(**B**) Volcano plot comparing gene expression in subcutaneous adipose tissue following SARS-CoV-2 or mock infection (*n* = 6 hamsters per group), no genes were FDR<0.01.

(**C and D**) RT-qPCR for known SARS-CoV-2 entry factors in 3T3-L1 adipocytes (*n* = 6) (**C**) and human adipocytes (*n* = 9) (**D**), expression relative to Rps18 housekeeping gene.

(**E**) RT-qPCR of mRNA from human adipocytes infected with SARS-CoV-2 or mock virus. Data were analyzed using Mann-Whitney tests with Holm-Sidak's multiple comparisons correction (*n* = 5 per group).

Table S1, related to Key Resources Table: Primer oligonucelotide sequences

Hamster:

	Forward	**Reverse**	**Source**
Adipoq	AGGCTAAGCACCCCAAGAATC	AGTTGTGGAGACCAGGGAATG	This paper
Cfd	CGGCTGTACGACGTGCAAA	CACGTAGGGTCCCAGAGACA	This paper
Leptin	AAATGTGCTGGAGACCCCTG	TACCGACTGCGTGTGTGAAA	This paper
Rps18	AAGGGCCATGCGTCACTTC	TGTTGGTGTTGAGGACTCGC	This paper
Serpine1	AAGAAAGTGCCTCTCTCCGC	AGACTTGTGAAGTCGGCCTG	This paper
Gapdh	ACCACAGTCCATGCCATC	CCTGCTTCACCACCTTCT	This paper

Human:

	Forward	**Reverse**	**Source**
36B4	GTGATGTGCAGCTGATCAAGACT	GATGACCAGCCCAAAGGAGA	Magkos *et al.* , 2016
ACE2	GGGATCAGAGATCGGAAGAAGAAA	AGGAGGTCTGAACATCATCAGTG	Wing *et al.* , 2021
ADIPOQ	GGCTGGGCCATCTCCTCCTCA	ACAGCTCCCAGCAACAGCATCC	This paper
CFD	GACACCATCGACCACGACC	GCCACGTCGCAGAGAGTTC	Jovanović *et al.* , 2016
FURIN	GCCACATGACTACTCCGCAGAT	TACGAGGGTGAACTTGGTCAGC	This paper
GAPDH	TTCTTTTGCGTCGCCAGCCGA	GTGACCAGGCGCCCAATAGA	Gucalp *et al.* , 2018
LEPTIN	AGATCCTCACCAGTATGCCTT	CTCTGTGGAGTAGCCTGAAGC	Baranova *et al.* , 2006
NRP1	AACAACGGCTCGGACTGGAAGA	GGTAGATCCTGATGAATCGCGTG	This paper
TFRC	ATCGGTTGGTGCCACTGAATGG	ACAACAGTGGGCTGGCAGAAAC	This paper
TMPRSS2	AATCGGTGTGTTCGCCTCTAC	CGTAGTTCTCGTTCCAGTCGT	Wilson *et al.* , 2005

Mouse:

	Forward	**Reverse**	**Source**
Ace2	GGAGGTGGATGGTCTTTCGG	AACGATCTCCCGCTTCATCTC	This paper
Adipoq	GCACTGGCAAGTTCTACTGCAA	GTAGGTGAAGAGAACGGCCTTGT	This paper
Cfd	CGTACCATGACGGGGTAGTC	ATCCGGTAGGATGACACTCG	Nakamura *et al.* , 2019
Furin	TAGCAGGCAATTATGACCCTGG	TAAGCTACACCTACGCCACAG	This paper
Nrp1	GGCTGTGAAGTGGAAGCACC	AGTGGTGCCTCCTGTGAGC	This paper
Rps18	CATGCAGAACCCACGACAGTA	CCTCACGCAGCTTGTTGTCTA	This paper
Tfrc	GTGGAGTATCACTTCCTGTCGC	CCCCAGAAGATATGTCGGAAAGG	This paper
Tmprss2	TCGTGTACTTGGAGCGGAC	GATTCCTGGAGGTGACCCTGAG	This paper

Other:

SARS-CoV-2-TRS-L	CTCTTGTAGATCTGTTCTCTAAACGAAC	This paper
SARS-CoV-2-TRS-N	GGTCCACCAAACGTAATGCG	