

# Supplementary Data

## Significance of Catecholamine biosynthetic/metabolic pathway in SARS-CoV-2 infection and COVID-19 severity

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### Supplementary Tables

**Table S1.** Mean values of the studied genes' expression in nasopharyngeal tissue of SARS-CoV-2 positive or negative subjects.

Characteristics	Negative	SARS-CoV-2	
		Mild- CoV-2	Severe-CoV-2
<i>DDC</i> (2 <sup>ΔΔCt</sup> )	0.004 ± 0.002	0.033 ± 0.019	0.002 ± 0.0015
<i>ACE2</i> (2 <sup>ΔΔCt</sup> )	0.005 ± 0.003	0.008 ± 0.005	0.001 ± 0.002
<i>dACE2</i> (2 <sup>ΔΔCt</sup> )	0.008 ± 0.003	0.023 ± 0.008	0.021 ± 0.008
<i>ISG56</i> (2 <sup>ΔΔCt</sup> )	0.561 ± 0.225	1.414 ± 1.014	0.668 ± 0.318
<i>EPO</i> (2 <sup>ΔΔCt</sup> )	0.011 ± 0.004	0.027 ± 0.011	0.027 ± 0.013

\*The 2<sup>ΔΔCt</sup> mean value for each gene was used to evaluate the fold-differences between the studied groups.

**Table S2.** Demographic data of individuals whose blood samples were used.

Characteristics	Healthy	ICU/CoV-2	ICU/non-CoV-2	p-value
<b>Total number</b>	n=35	n=32	n=30	
<b>Median age in years</b>				
<b>(IQR)</b>	49 (42-55)	57 (62-70)	57 (35 - 73)	0.0024 <sup>a</sup>
<b>Sex</b>				
<b>Male</b>	20 (57.2%)	25 (78.1%)	17 (78.1%)	0.1437 <sup>b</sup>
<b>Female</b>	15 (42.8%)	7 (21.9%)	13 (21.9%)	

<sup>a</sup>: p-value was calculated with Kruskal-Wallis test, followed by Dunn's test.

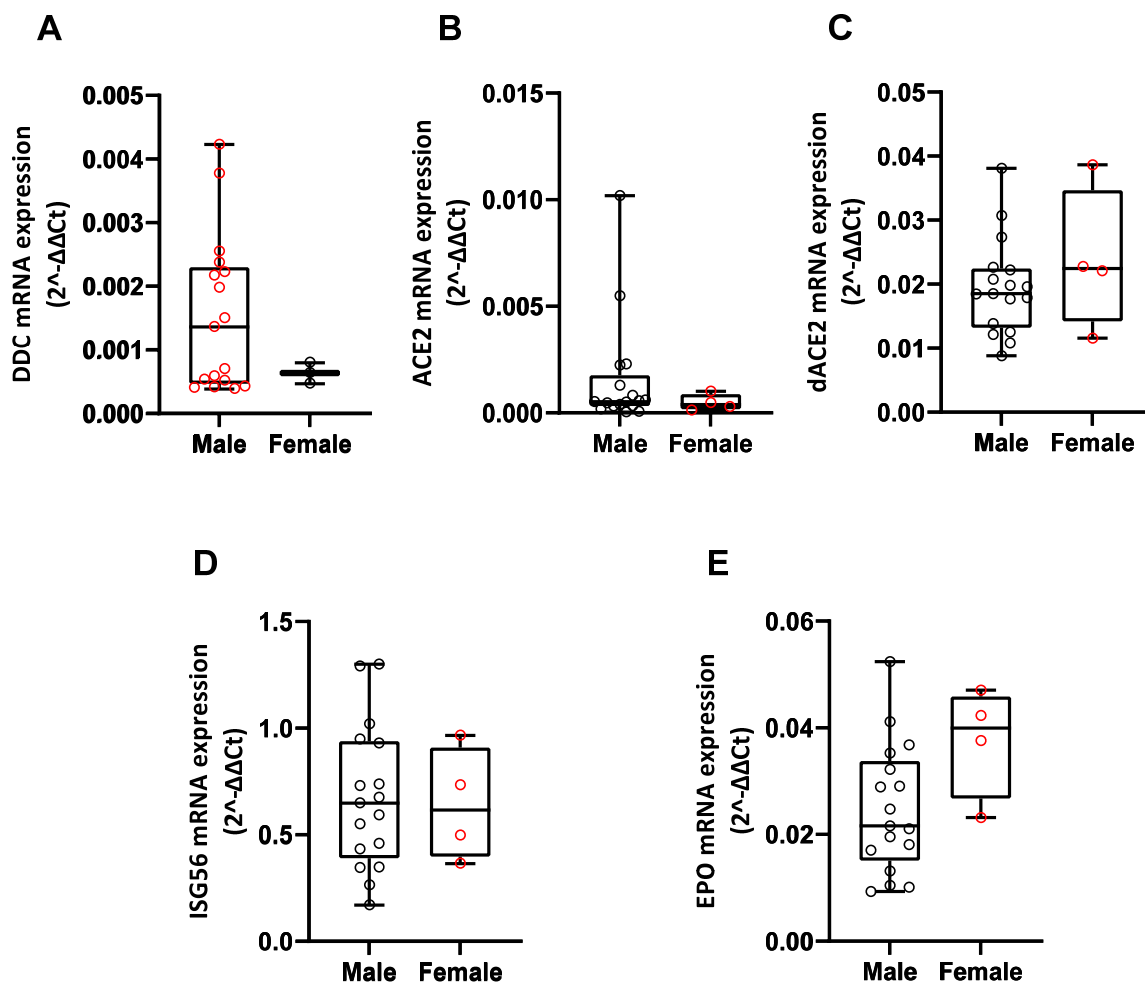
<sup>b</sup>: p-value was calculated with Chi-square test.

**Table S3.** Mean values of the studied genes expression in whole blood samples of SARS-CoV-2 positive or negative subjects.

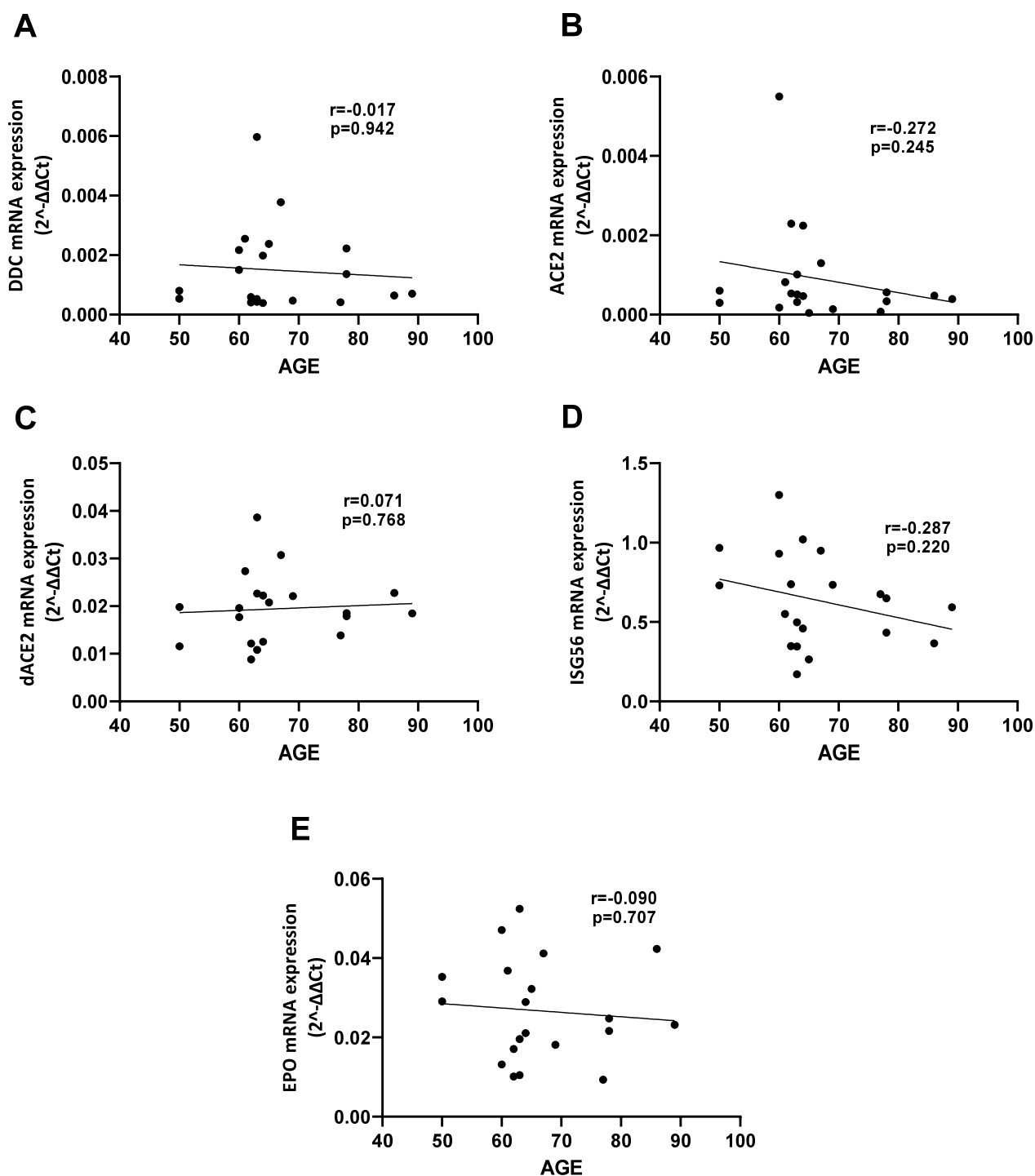
SARS-CoV-2 (Blood samples)				
Characteristics		Healthy	ICU/CoV-2	Ward/CoV-2
<b>Gene expression</b>				
<i>DDC</i> (2 <sup>ΔΔCt</sup> )	Mean ± SD	1.876 ± 0.964	0.538 ± 0.265	0.246 ± 0.243
<i>dACE2</i> (2 <sup>ΔΔCt</sup> )	Mean ± SD	0.134 ± 0.066	0.041 ± 0.0301	0.017 ± 0.02
<i>ISG56</i> (2 <sup>ΔΔCt</sup> )	Mean ± SD	0.704 ± 0.499	0.206 ± 0.127	0.438 ± 0.411
<i>MAOA</i> (2 <sup>ΔΔCt</sup> )	Mean ± SD	0.028 ± 0.026	0.427 ± 0.315	0.102 ± 0.126
<i>MAOB</i> (2 <sup>ΔΔCt</sup> )	Mean ± SD	0.007 ± 0.006	0.072 ± 0.053	0.072 ± 0.049
<i>DBH</i> (2 <sup>ΔΔCt</sup> )	Mean ± SD	0.038 ± 0.025	0.041 ± 0.036	0.049 ± 0.054
<i>EPO</i> (2 <sup>ΔΔCt</sup> )	Mean ± SD	0.688 ± 0.498	0.059 ± 0.053	0.023 ± 0.037

\*The 2<sup>ΔΔCt</sup> mean value for each gene was used to evaluate the fold-differences between the studied groups.

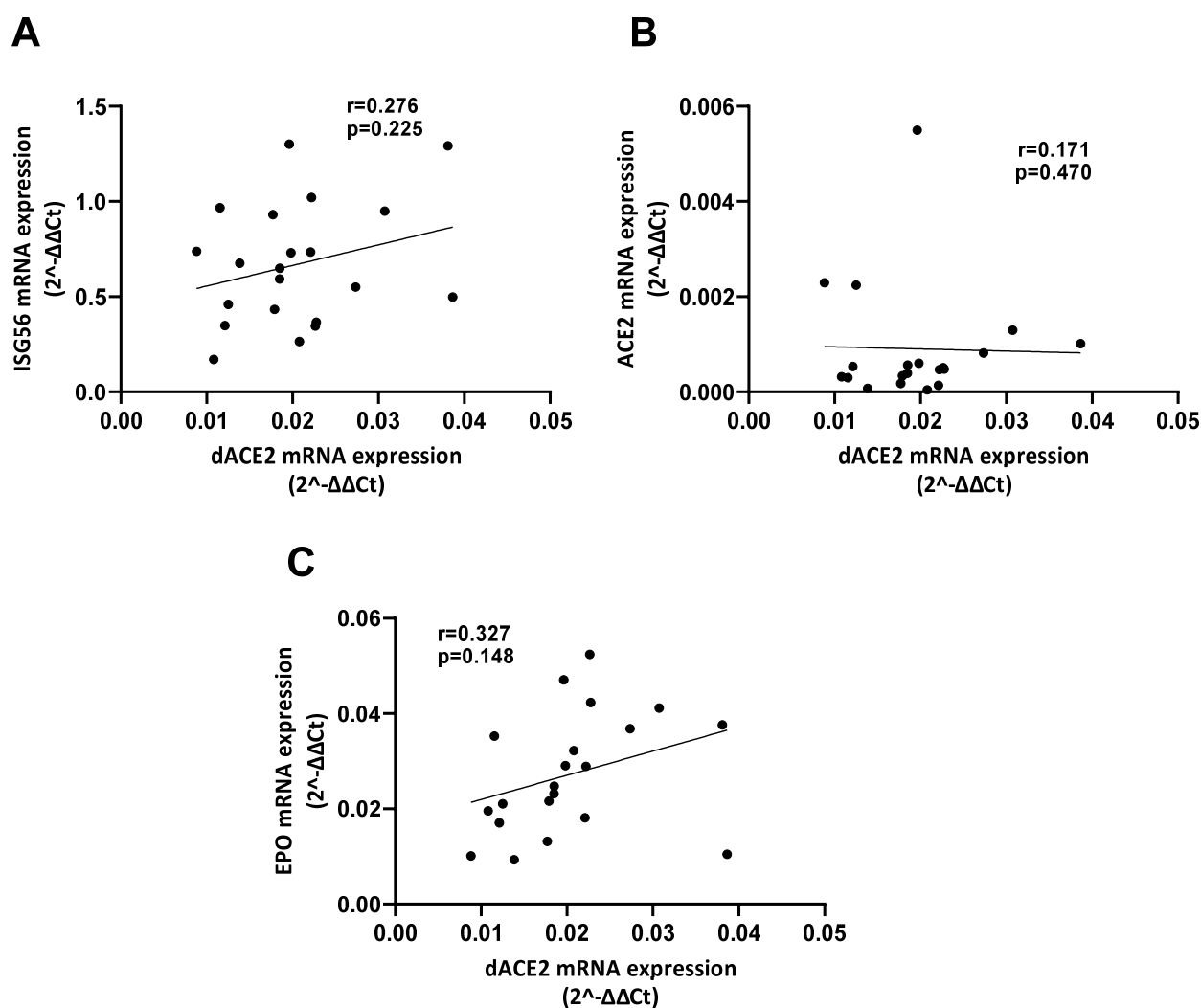
## Supplementary Figures



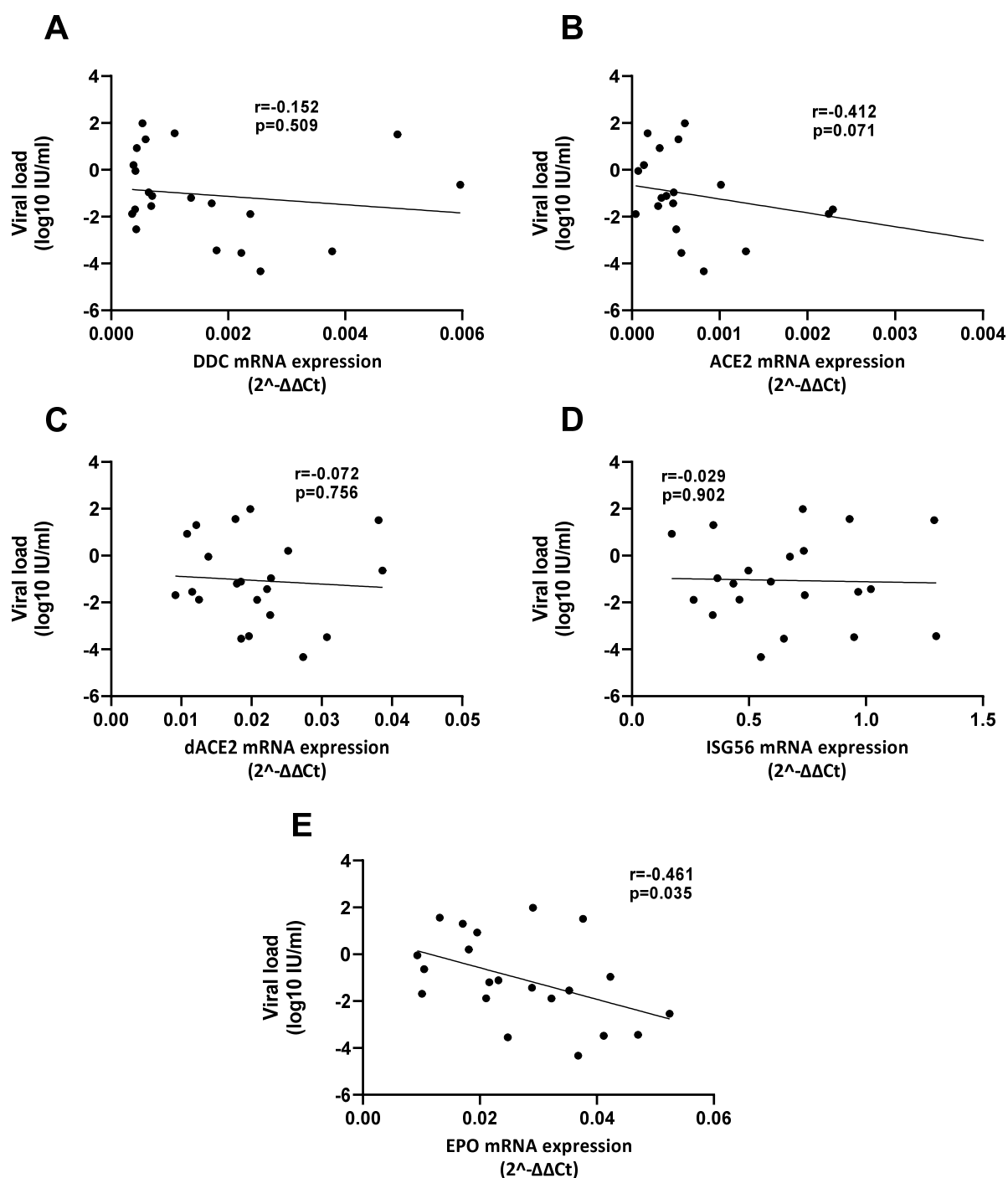
**Figure S1.** Comparison of DDC (A), ACE2 (B), dACE2 (C), ISG56 (D), or EPO (E) expression in the nasopharyngeal swab samples of COVID-19 patients between men and women. Data are displayed as box plots and dots; the line in the middle corresponds to the median value; box edges, 25<sup>th</sup> to 75<sup>th</sup> centiles; whiskers, range of values. p-values were calculated with the Mann-Whitney U test.



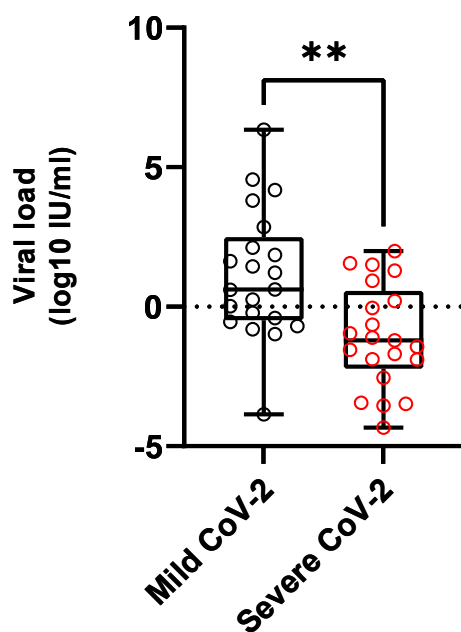
**Figure S2.** Correlation among the expression of *DDC* (A), *ACE2* (B), *dACE2* (C), *ISG56* (D), or *EPO* (E) with patients' age (continuous parameter) in nasopharyngeal swab samples of COVID-19 patients with severe symptoms. Data are presented as XY scatter plot with fitted linear regression lines. Pearson's or Spearman's correlation coefficient (r) and p-values (p) were calculated.



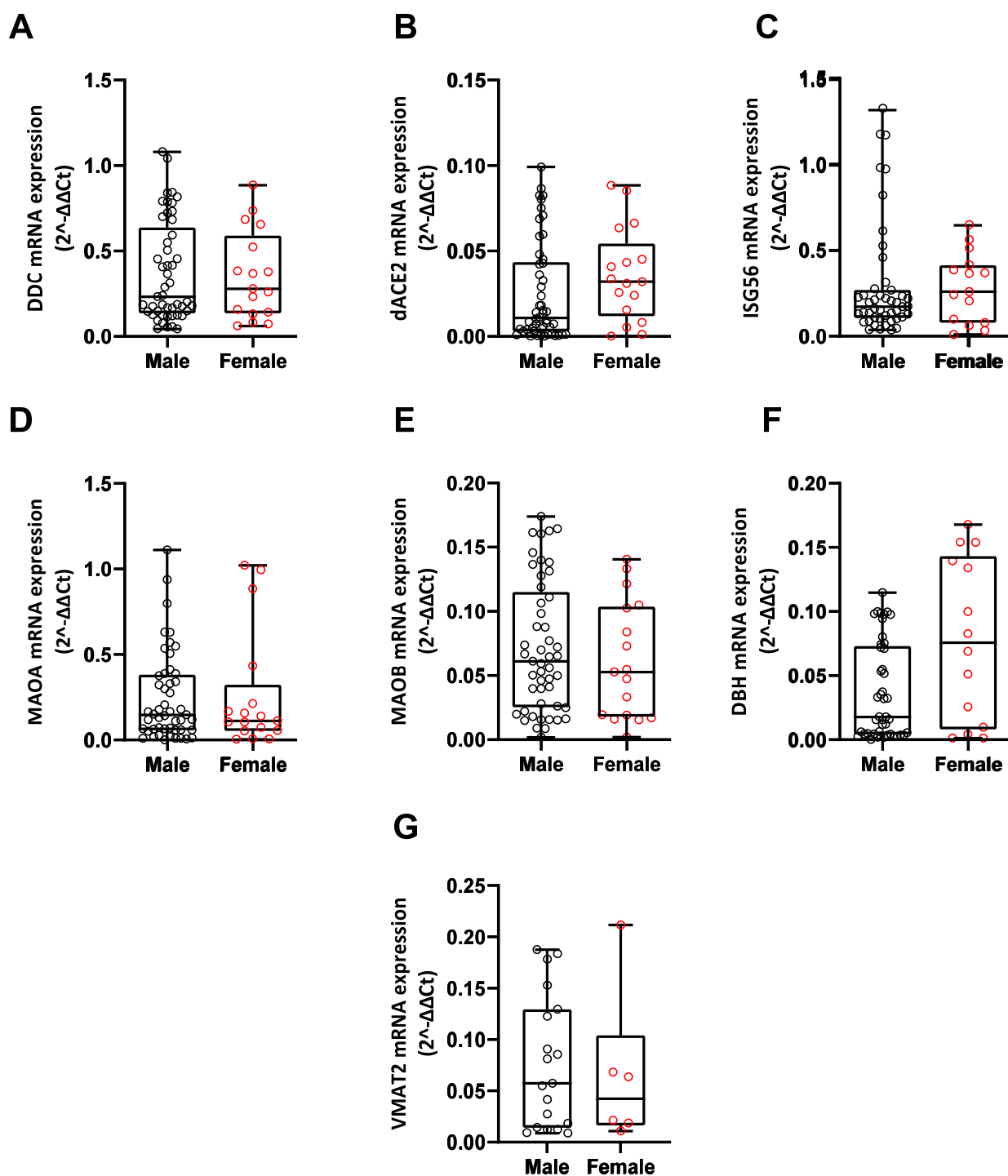
**Figure S3.** Correlation among the expression of *ISG56* (A), *ACE2* (B), or *EPO* (C), with that of *dACE2* in the nasopharyngeal swab samples of COVID-19 patients with severe symptoms. Data are presented as XY scatter plot with fitted linear regression lines. Pearson's or Spearman's correlation coefficient ( $r$ ) and  $p$ -values ( $p$ ) were calculated.



**Figure S4.** Correlation among the expression of *DDC* (A), *ACE2* (B), *dACE2* (C), *ISG56* (D), or *EPO* (E) with SARS-CoV-2 viral titers in the nasopharyngeal tissue of severe COVID-19 cases. Data are presented as XY scatter plot with fitted linear regression lines. Pearson's or Spearman's correlation coefficient ( $r$ ) and  $p$ -values ( $p$ ) were calculated.

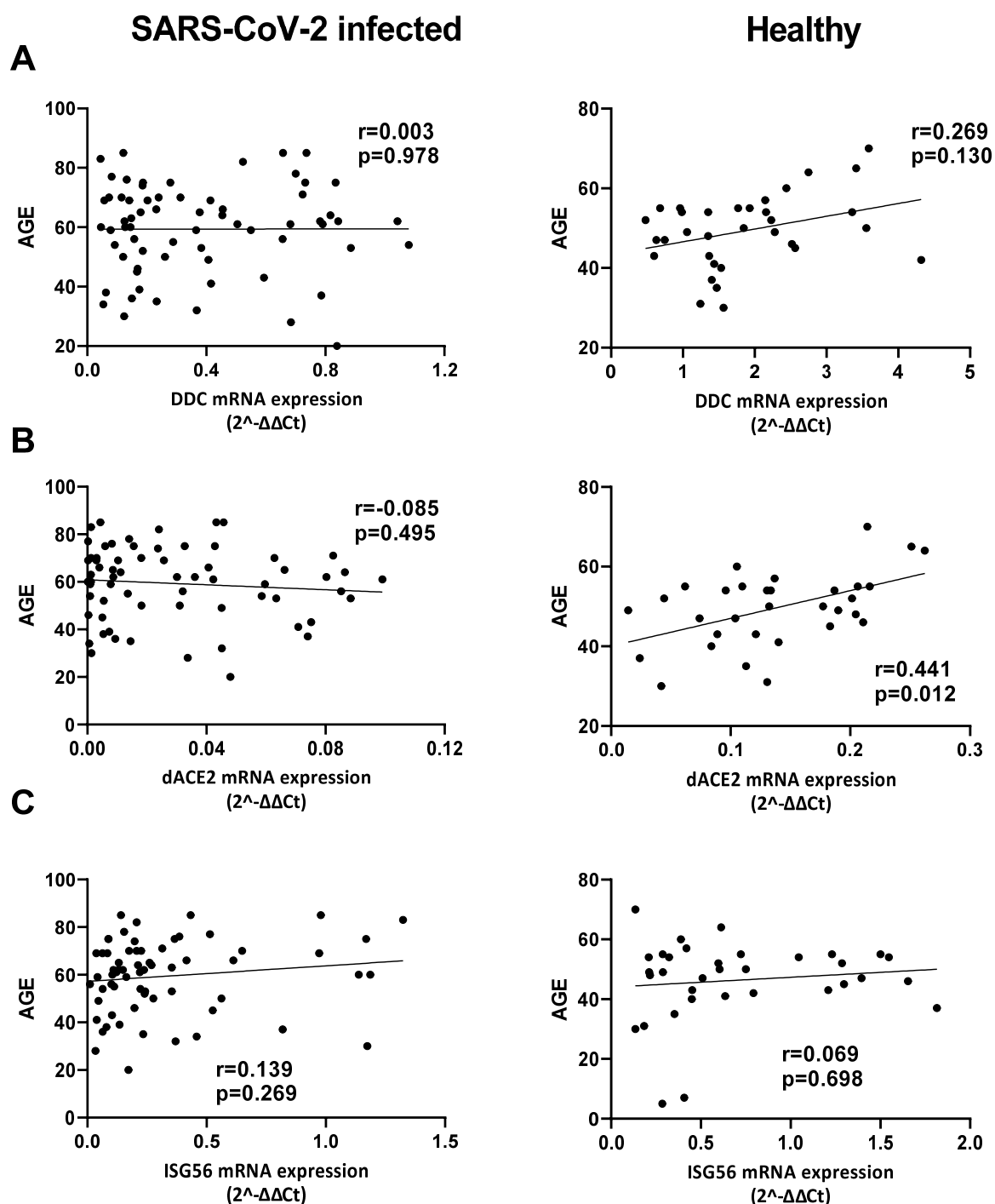


**Figure S5.** Comparison of SARS-CoV-2 viral load levels between COVID-19 patients with mild or no symptoms with more severe cases. Data are displayed as box plots and dots; the line in the middle corresponds to the median value; box edges, 25<sup>th</sup> to 75<sup>th</sup> centiles; whiskers, range of values. p-values were calculated with the unpaired t-test. \*\* p=0.0014.

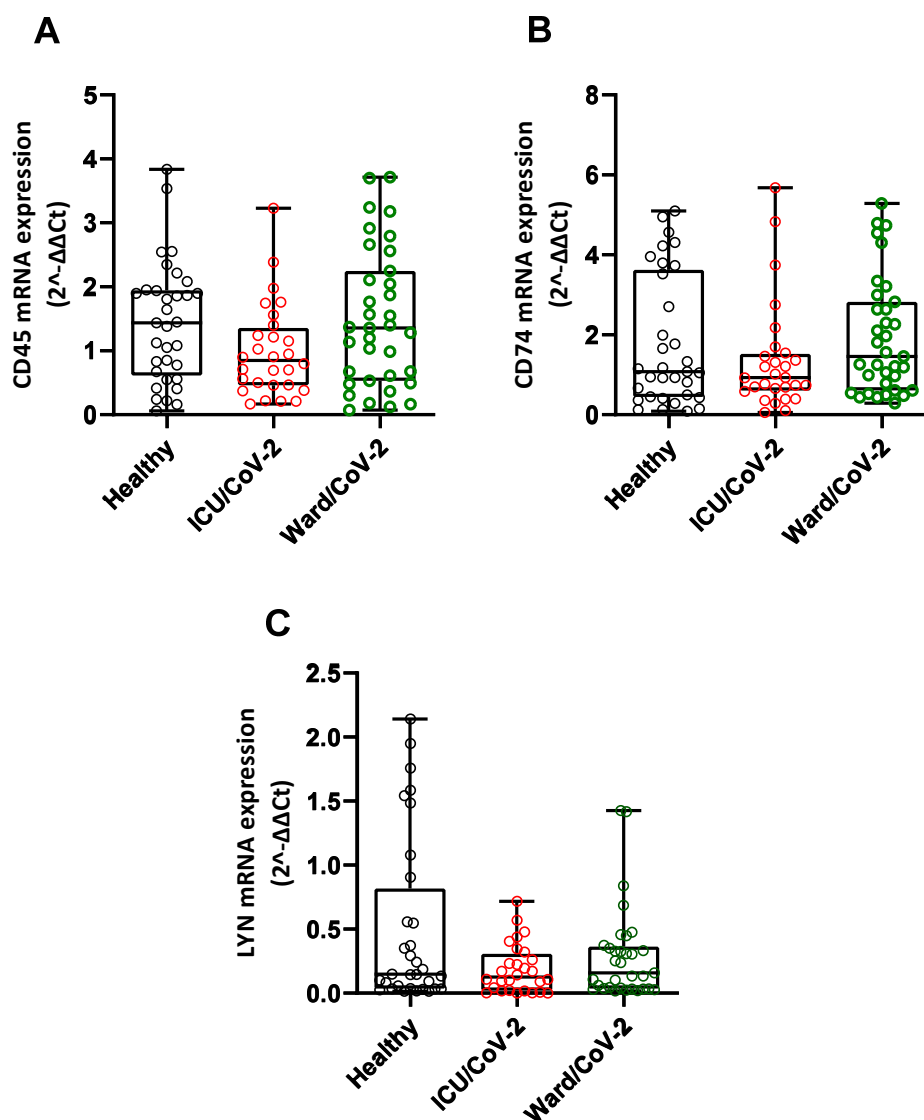


**Figure S6.** Comparison of DDC (A), dACE2 (B), ISG56 (C), MAOA (D), MAOB (E), DBH (F), or VMAT2 (G) expression between men and women, in whole samples of COVID-19 patients with severe symptoms. Data are displayed as box plots and dots; the line in the middle corresponds to the median value; box edges, 25<sup>th</sup> to 75<sup>th</sup> centiles; whiskers, range of values. p-values were calculated with the Mann-Whitney U test.

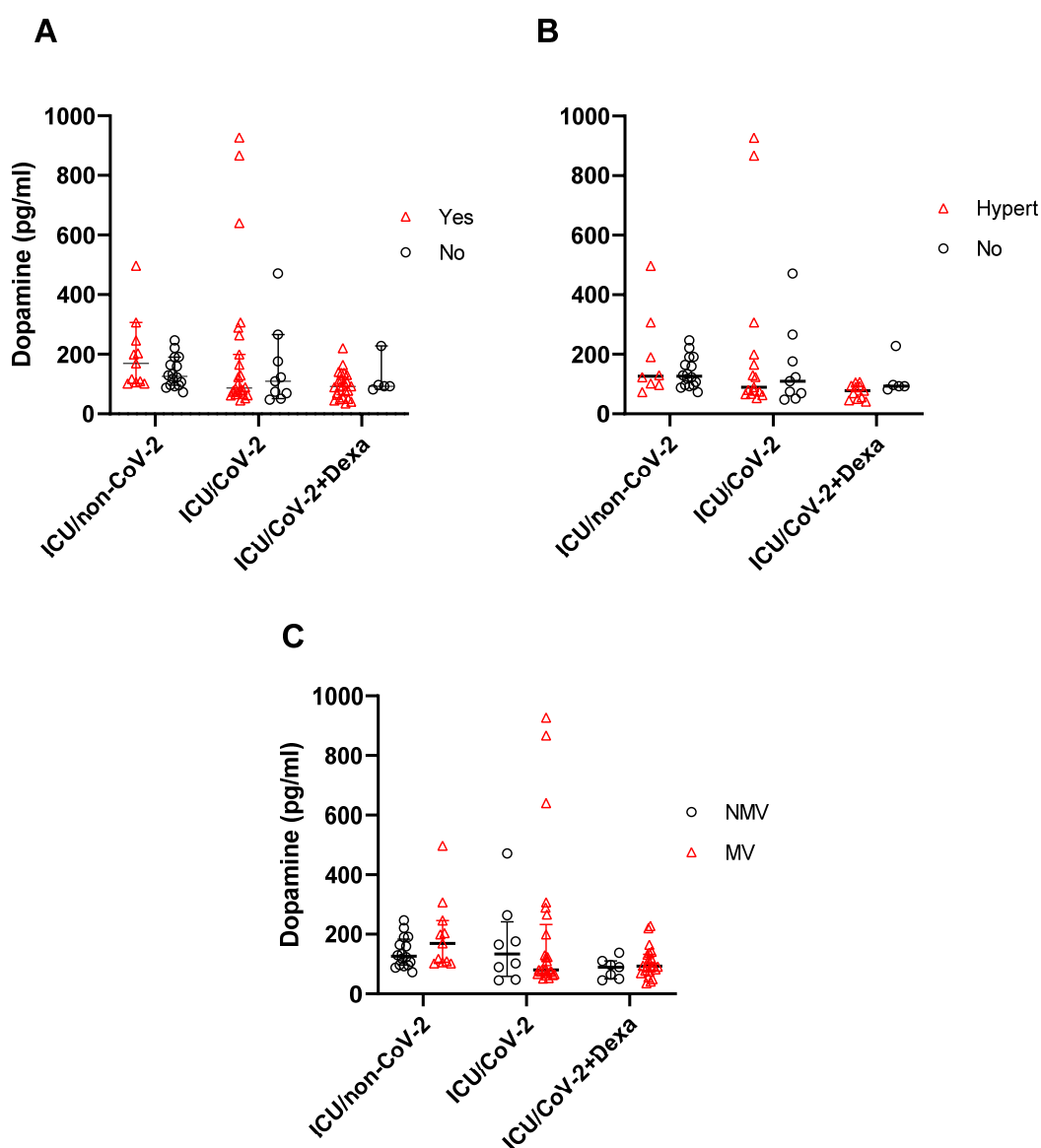




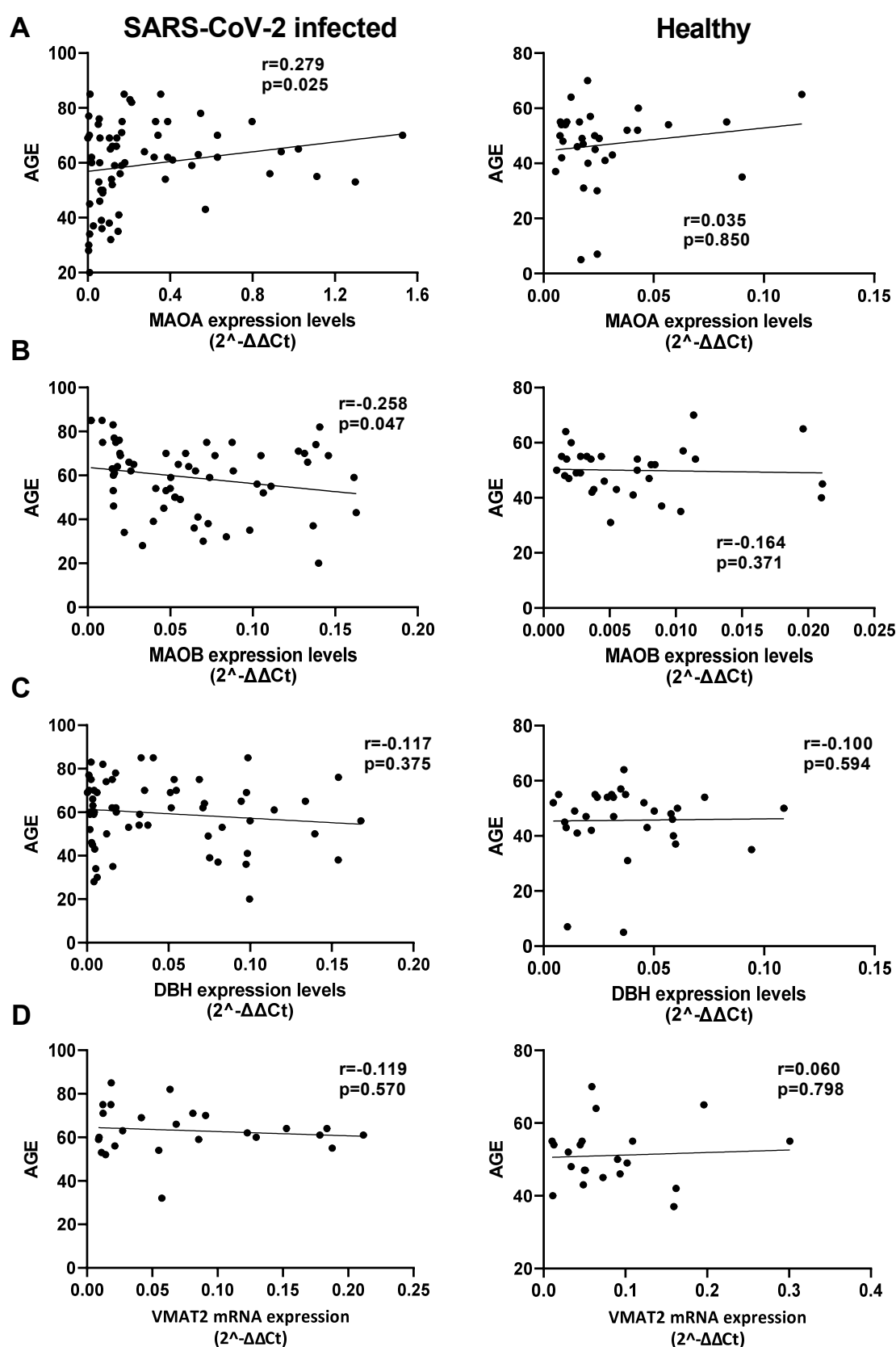
**Figure S7.** XY scatter plot with fitted linear regression lines of DDC (A), dACE2 (B), or ISG56 (C) expression versus age (continuous parameter) in whole blood samples of COVID-19 patients with severe symptoms (Left panels) or healthy individuals (Right panels). Pearson's or Spearman's correlation coefficient (r) and p-values (p) were calculated.



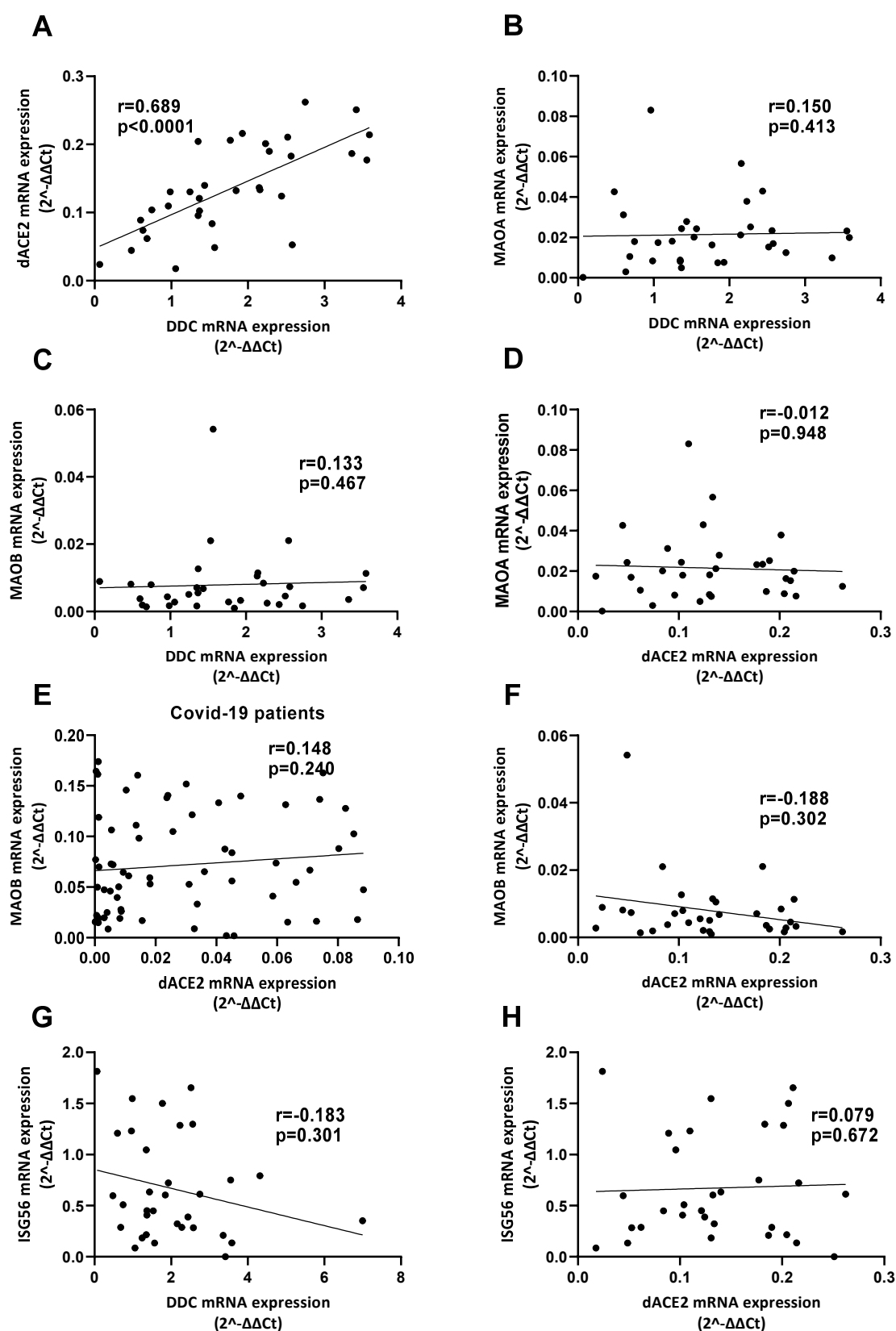
**Figure S8.** Box plot analysis comparing the mRNA expression of *CD45* (A), *CD74* (B) and *LYN* (C) in whole blood samples among Healthy individuals and COVID-19 hospitalized patients (ICU/CoV-2, Ward/CoV-2 groups). Data are presented as box plots and dots, line in the middle corresponds for the median; box edges, 25<sup>th</sup> to 75<sup>th</sup> centiles; whiskers, range of values. p-values were determined with the non-parametric Kruskal-Wallis test. Multiple comparisons among the studied groups were performed with Dunn's test.



**Figure S9.** Serum dopamine levels of SARS-CoV-2 infected subjects in the presence of comorbidities. **(A)** Absolute dopamine levels in the serum of ICU COVID-19 (receiving DEXA or not) or ICU non-COVID-19 patients, with (Yes) or without (No) comorbidities. **(B)** Absolute dopamine levels in the same patient cohorts, with (Hypert) or without (No) hypertension. **(C)** Effect of mechanical ventilation on dopamine levels of the aforementioned patient groups. p-values were determined with Two-Way ANOVA.

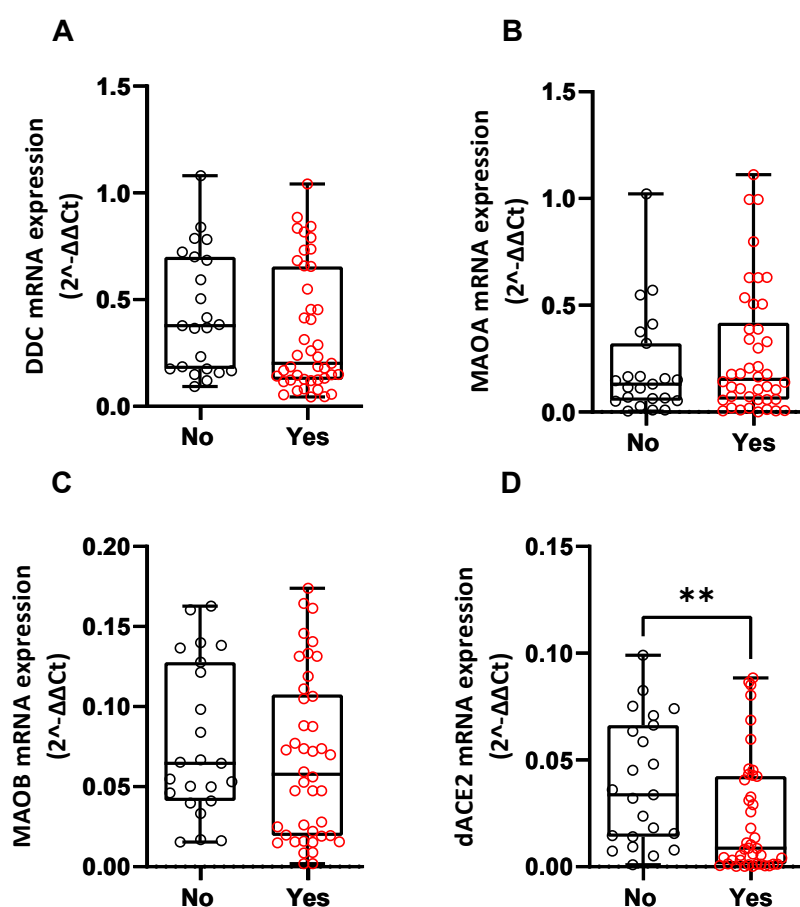


**Figure S10.** XY scatter plot with fitted linear regression lines of MAOA (A), MAOB (B), DBH (C), or VMAT2 (D) expression versus age (continuous parameter) in whole samples of COVID-19 patients with severe symptoms (Left panels) or healthy individuals (Right panels). Pearson's or Spearman's correlation coefficient (r) and p-values (p) were calculated.

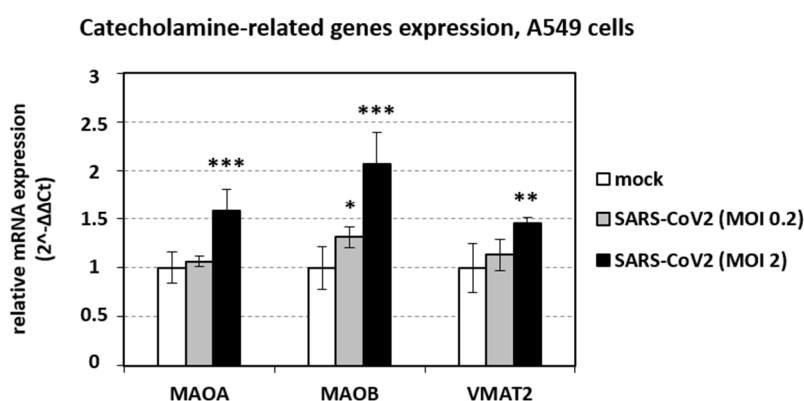


**Figure S11.** Correlation of the expression of all studied genes in the blood of COVID-19 severe cases and healthy individuals. (A–C) Correlation among the expression of *dACE2* (A), *MAOA* (B), or *MAOB* (C), with that of *DDC* in the whole blood samples of healthy individuals. (D–F) Correlation among the expression of *MAOA* and *MAOB* with that of *dACE2* in whole blood samples of COVID-19 patients with severe symptoms (E), or healthy individuals (D,F). (G,H) Correlation among the expression of *DDC* or *dACE2* with that

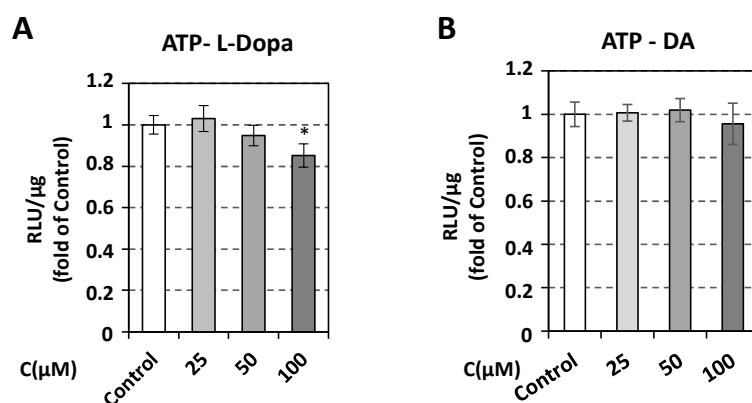
of *ISG56* in the blood of healthy individuals. Data are presented as XY scatter plot with fitted linear regression lines. Pearson's or Spearman's correlation coefficient ( $r$ ) and  $p$ -values ( $p$ ) were calculated.



**Figure S12.** Box plot analysis of the mRNA expression of *DDC* (A), *MAOA* (B), *MAOB* (C) and *dACE2* (D) in whole blood samples among the hospitalized COVID-19 patients, in the presence (Yes) or absence (No) of comorbidities. Each patient's mRNA expression value is represented as a dot; line in the middle, median; box edges, 25<sup>th</sup> to 75<sup>th</sup> centiles; whiskers, range of values.  $p$ -values were calculated using the non-parametric Mann-Whitney U test. \*\* $p$  < 0.01.



**Figure S13.** SARS-CoV-2 infection of A549 cells upregulated the expression of *MAOA*, *MAOB*, and *VMAT2* 24 hours post-infection. Further analysis of data derived from the RNA-sequencing Skyline database ([http://rstats.immgen.org/Skyline\\_COVID-19/skyline.html](http://rstats.immgen.org/Skyline_COVID-19/skyline.html)) [67]. \*  $p$  < 0.05, \*\*  $p$  < 0.01, \*\*\*  $p$  < 0.0001 vs mock.  $p$  values were calculated with Student's  $t$ -test.



**Figure S14.** Effect of DDC substrate (L-Dopa, A) and product (dopamine, B) on intracellular ATP levels. VeroE6 cells were inoculated with the indicated concentrations of (A) L-Dopa, (B) DA, or were mock-treated (Control) for 72 h. A chemiluminescence-based assay was performed to determine the intracellular ATP levels, which were expressed as RLU/μg of total protein amount. Values derived from the Control cells were set to one. Bars represent mean values from three independent experiments in triplicates. Error bars indicate standard deviations. \* $p < 0.05$  vs Control.