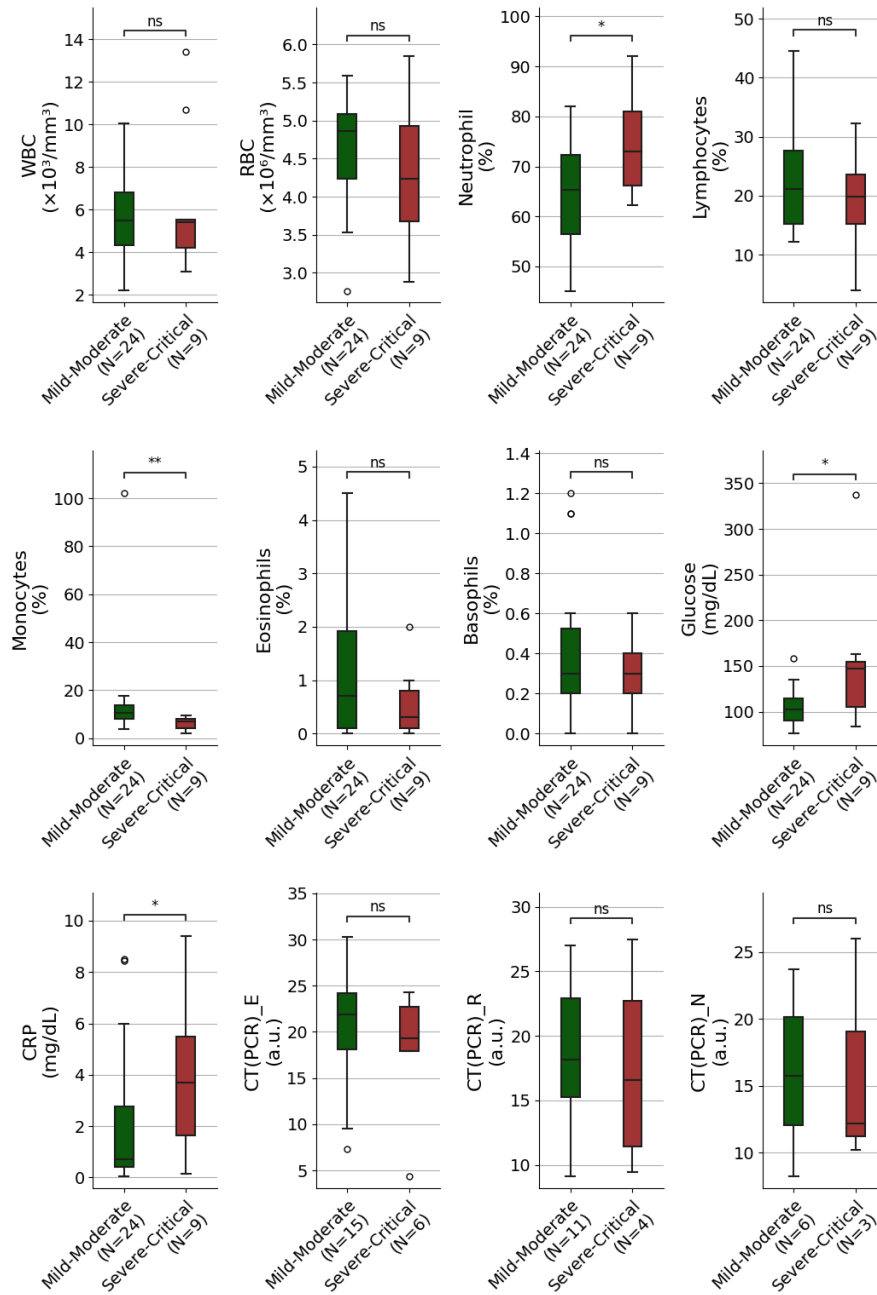
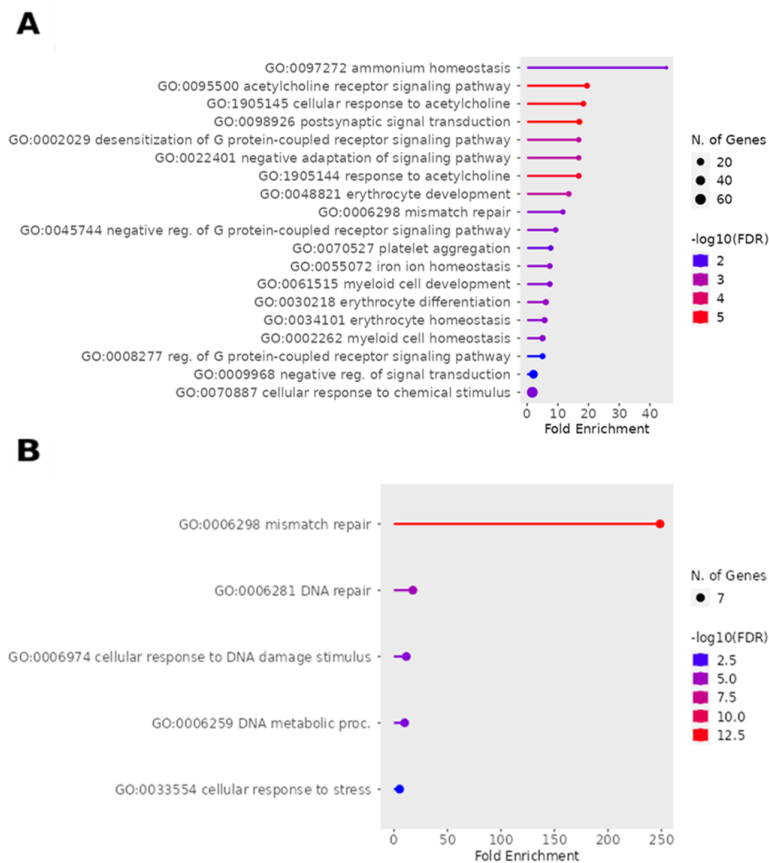


Identification of reactive CpGs and RNA expression in early COVID-19 through *cis*-eQTM analysis reflecting disease severity and recovery

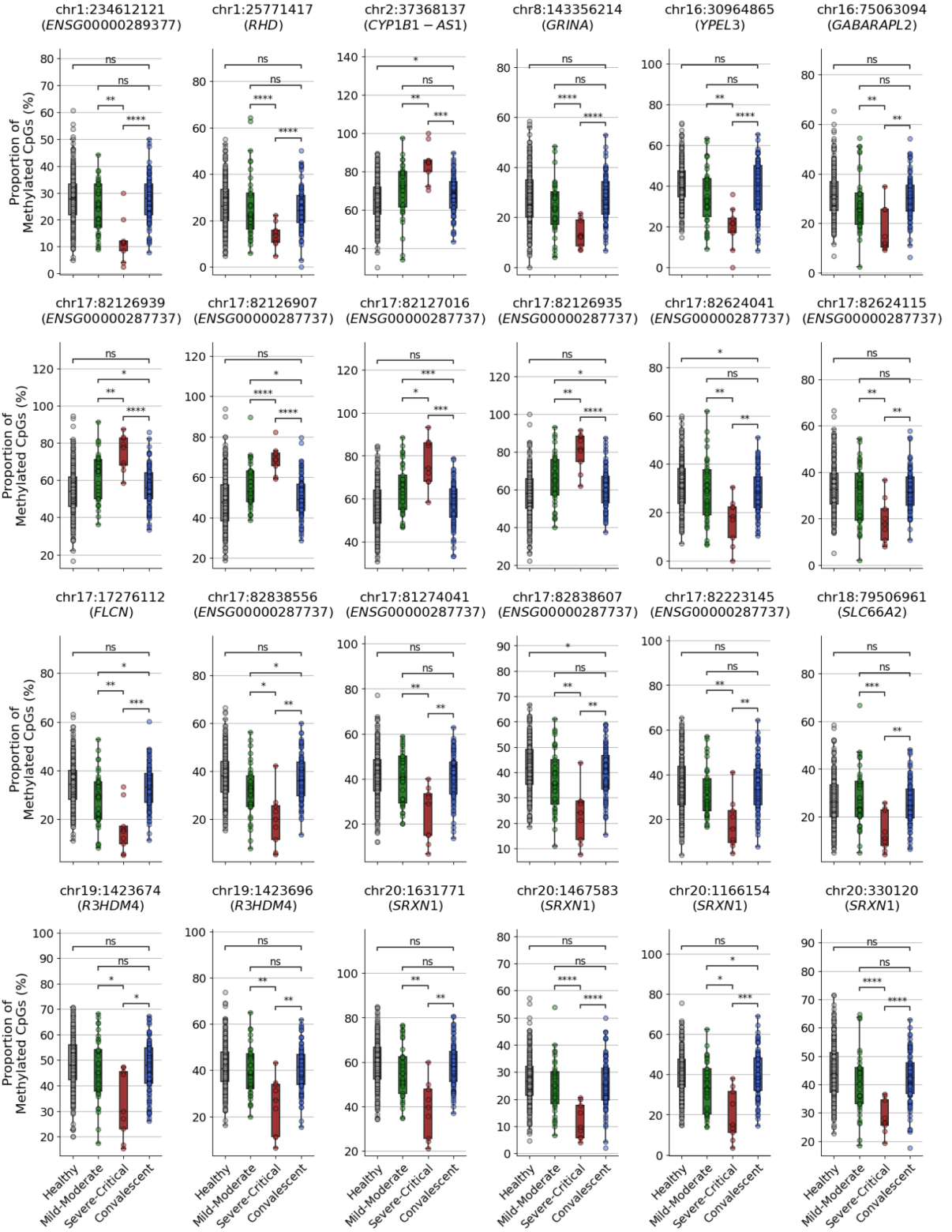
Supplementary Information



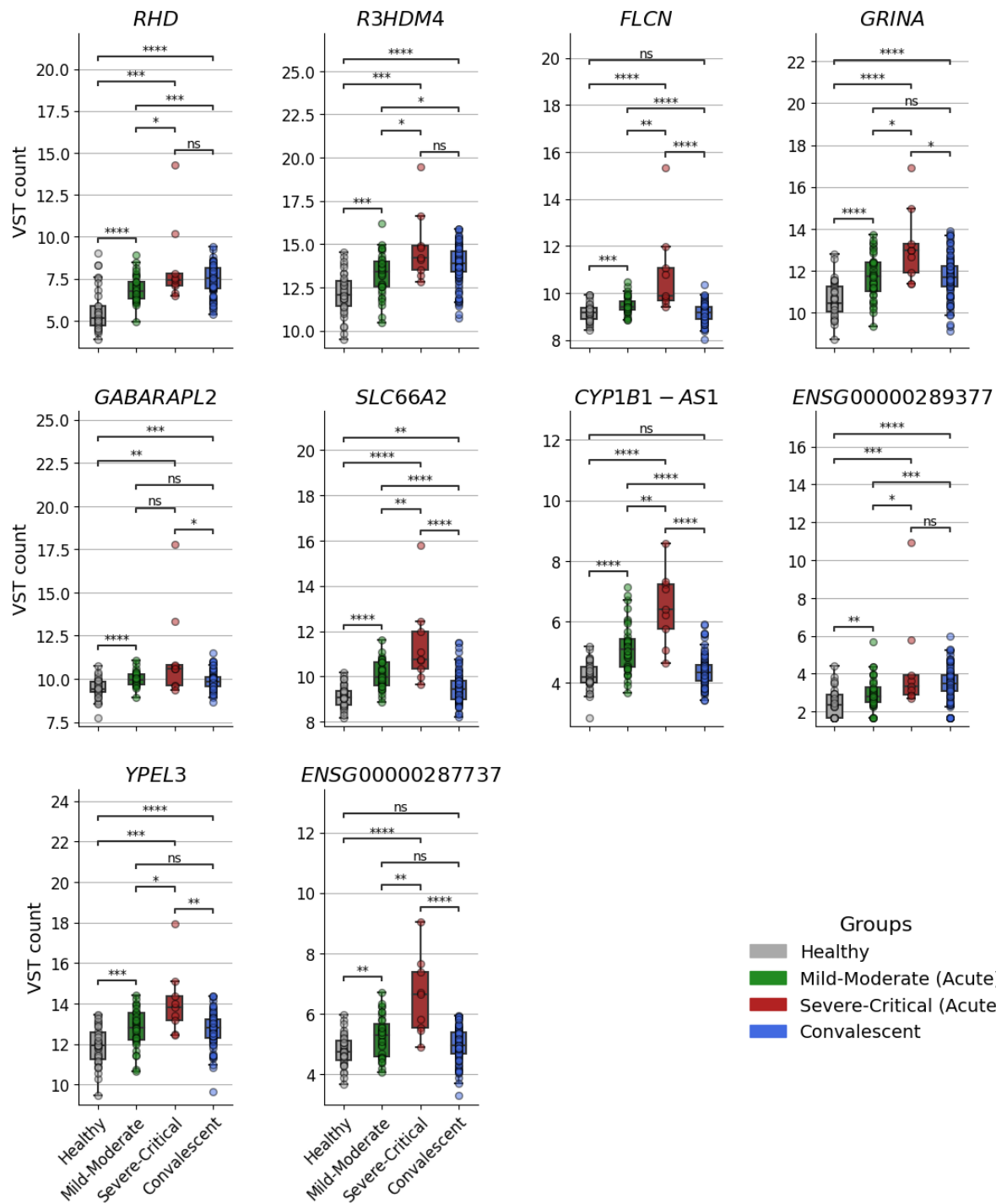
Supplementary Fig 1. Clinical Characteristics of Mild–Moderate and Severe–Critical COVID-19 Patients During the Acute Phase. The x-axis denotes severity groups, with sample sizes indicated in parentheses. The y-axis indicates the clinical parameter measured, with units denoted in parentheses. Boxplots display the median (centre line), interquartile range or IQR (box limits), and 1.5×IQR (whiskers), and outliers (open circles). Significance thresholds are indicated as follows: ns ($P \geq 0.05$), * ($P < 0.05$), ** ($P < 0.01$), *** ($P < 0.001$), **** ($P < 0.0001$). Abbreviations: WBC, White Blood Cell count; RBC, Red Blood Cell count; CRP, C-reactive protein concentration; CT(PCR), Cycle threshold (Ct) values from PCR assays for SARS-CoV-2 targets (*E*, *R*, and *N* genes); a.u., arbitrary units.



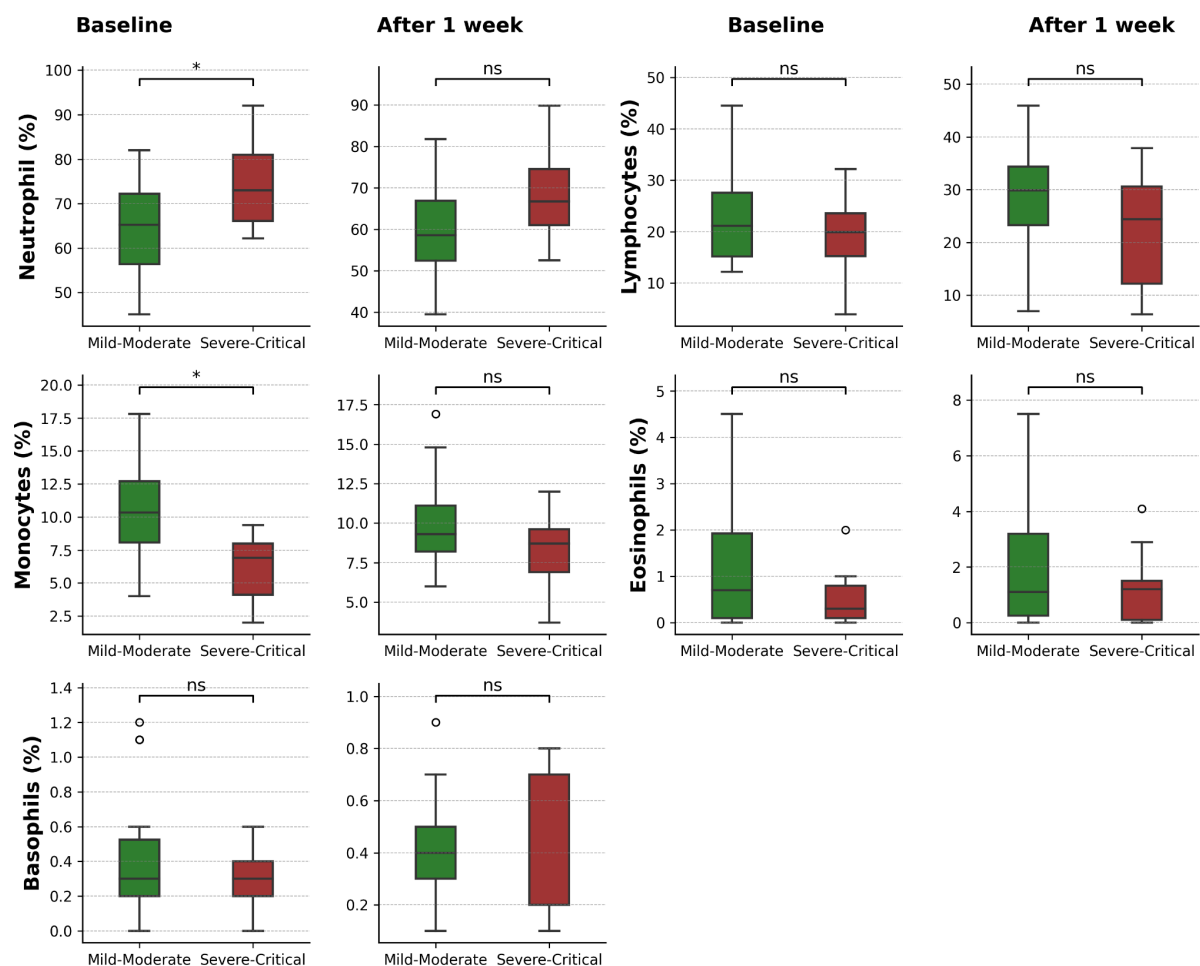
Supplementary Fig 2. Gene Ontology Enrichment of 297 Severity-Associated DEG-LOOs During Acute COVID-19. Lollipop plot illustrating Gene Ontology-Biological Process (GO-BP) enrichment for **A)** 283 up-regulated and **B)** 14 down-regulated genes linked to COVID-19 severity during the acute phase. The x-axis denotes fold enrichment, while the y-axis lists enriched GO terms. Dot size corresponds to the number of genes in each GO term, and color indicates statistical significance as $-\log_{10}(\text{FDR})$. Enrichment was performed using ShinyGO v0.82 based on the hypergeometric test with Benjamini–Hochberg correction, using all RNA-seq expressed genes as the background gene universe. Abbreviations: GO, Gene Ontology; BP, Biological Process; FDR, False Discovery Rate.



Supplementary Fig 3. DNA Methylation Levels of 24 *cis*-eQTM CpGs Associated with COVID-19 Severity During the Acute Phase. DNA methylation levels (% methylated CpGs) are shown for 24 *cis*-eQTM CpGs across four clinical groups: Healthy controls (n = 310), patients with Mild-Moderate (n = 37) or Severe-Critical (n = 9) COVID-19 during the acute phase, and Convalescent individuals (n = 90). The x-axis denotes severity groups. The y-axis represents the proportion of methylation at each CpG site. Boxplots display the median (centre line), IQR (box limits), 1.5×IQR (whiskers), and individual data points (closed circles). Statistical comparisons were conducted using Welch's *t*-test. Statistical significance is indicated as follows: ns ($P \geq 0.05$), * ($P < 0.05$), ** ($P < 0.01$), *** ($P < 0.001$), **** ($P < 0.0001$).

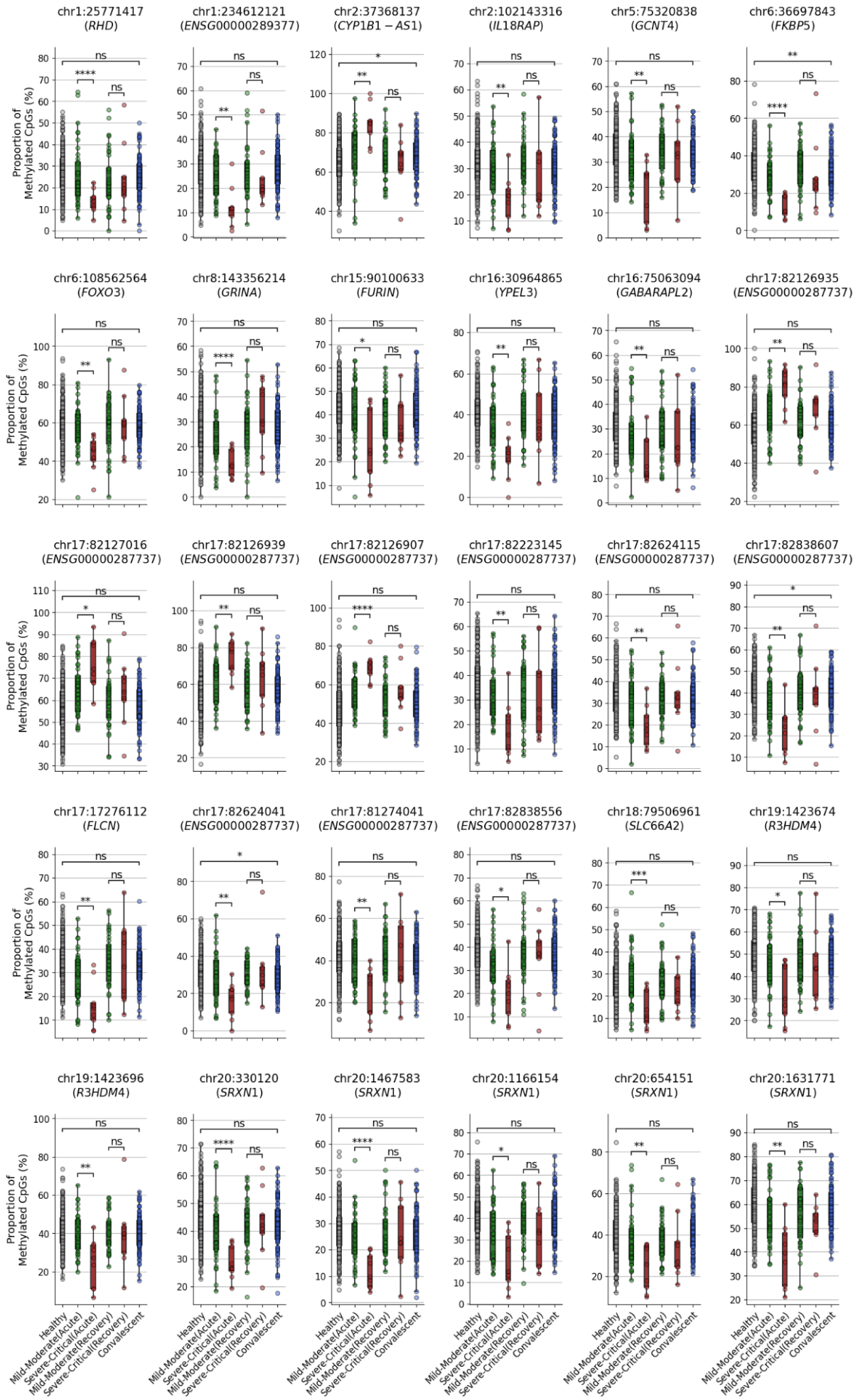


Supplementary Fig 4. Expression Levels of 10 *cis*-eQTM-Regulated Genes Associated with COVID-19 Severity During the Acute Phase. Expression levels of 10 genes regulated by *cis*-eQTM methylation sites are shown across four clinical groups: Healthy controls (n = 35), patients with Mild-Moderate (n = 36) or Severe-Critical (n = 9) COVID-19 during the acute phase, and Convalescent individuals (n = 90). The x-axis represents clinical groups. The y-axis shows gene expression values, represented as variance-stabilizing transformed (VST) counts. Boxplots display the median (centre line), IQR (box limits), 1.5×IQR (whiskers), and individual data points (closed circles). Statistical comparisons were conducted using the Wilcoxon rank-sum test. Statistical significance is denoted as follows: ns ($P \geq 0.05$), * ($P < 0.05$), ** ($P < 0.01$), *** ($P < 0.001$), **** ($P < 0.0001$).

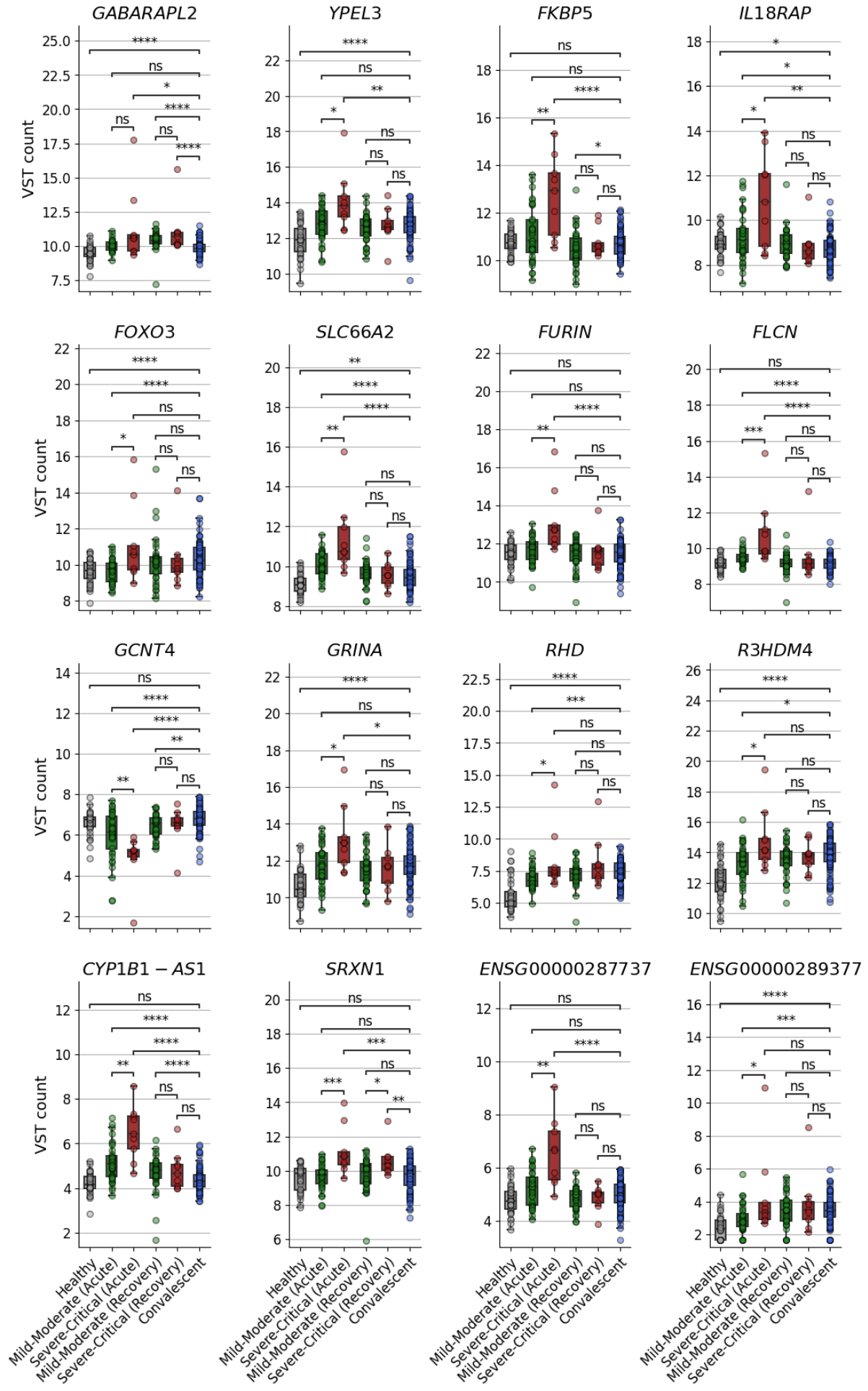


Supplementary Fig 5. Baseline leukocyte proportion and its changes one week later in Mild-Moderate and Severe-Critical groups. Boxplots show the proportions (%) of neutrophils,

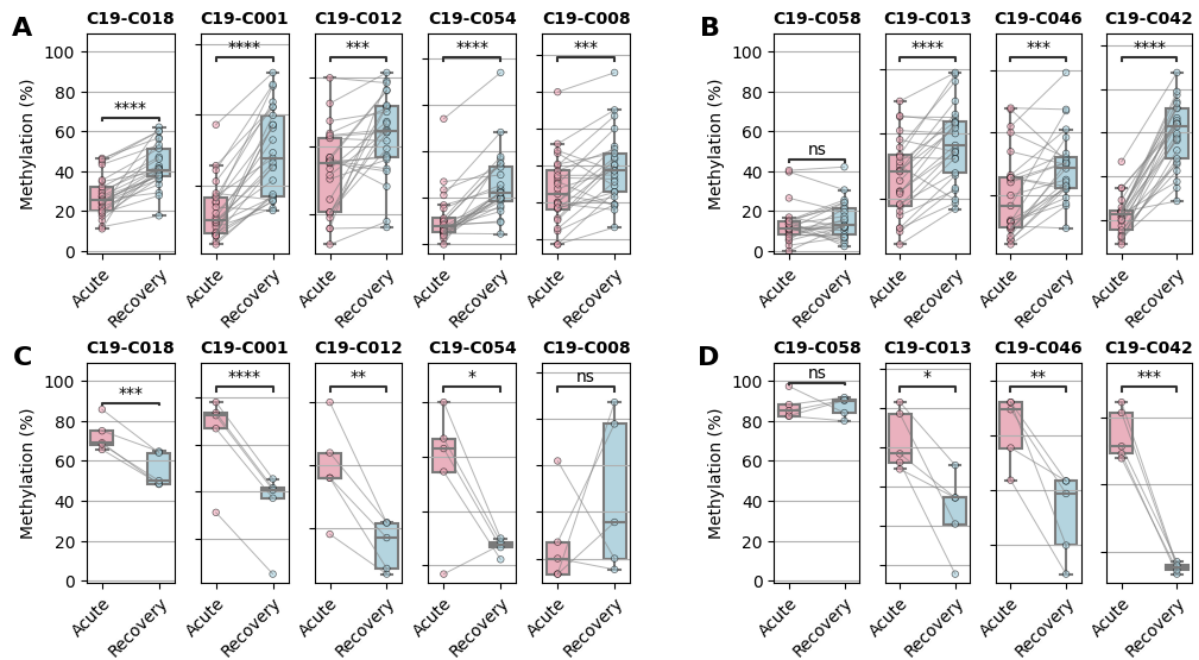
lymphocytes, monocytes, eosinophils, and basophils measured in whole blood at baseline (left panel) and after a week later (right panel) for patients with Mild–Moderate (green) and Severe–Critical (red) disease. Boxplots display the median (centre line), IQR (box limits), and $1.5 \times \text{IQR}$ (whiskers), and outliers (open circles). Statistical comparisons were conducted using the Wilcoxon rank-sum test. Statistical significance is denoted as follows: ns ($P \geq 0.05$), * ($P < 0.05$).



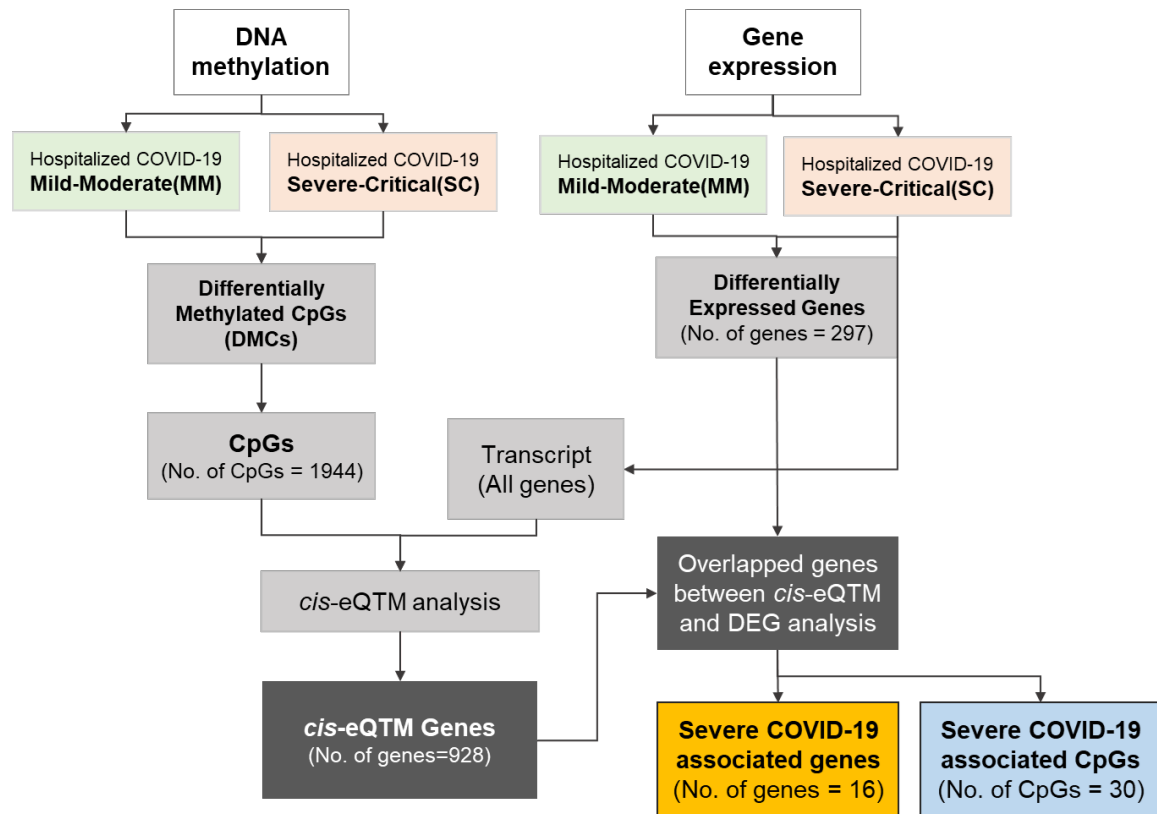
Supplementary Fig 6. DNA Methylation Levels of 30 cis-eQTM CpGs Associated with COVID-19 Severity Across the Acute and Recovery Phases. Methylation levels (% methylated CpGs) are shown for 30 *cis*-eQTM CpGs across clinical groups: Healthy controls (n = 310), patients with Mild-Moderate (n = 37) or Severe-Critical (n = 9) COVID-19 during the acute phase, and Convalescent individuals (n = 90). The x-axis indicates the clinical groups and infection periods. The y-axis represents the proportion of methylation at each CpG site. Boxplots display the median (centre line), IQR (box limits), 1.5×IQR (whiskers), and individual data points (closed circles). Statistical comparisons were performed using Welch's *t*-test. Statistical significance is denoted as follows: ns ($P \geq 0.05$), * ($P < 0.05$), ** ($P < 0.01$), *** ($P < 0.001$), **** ($P < 0.0001$).



Supplementary Fig 7. Expression Levels of 16 *cis*-eQTM-Regulated Genes Associated with COVID-19 Severity Across the Acute and Recovery Phases. Expression levels of 16 genes under *cis*-eQTM regulation are displayed across clinical groups: Healthy controls (n = 35), patients with Mild-Moderate (n = 36) or Severe-Critical (n = 9) COVID-19 during both the acute and recovery phase, and Convalescent individuals (n = 90). The x-axis indicates clinical groups and infection periods. The y-axis represents gene expression values, shown as variance-stabilizing transformed (VST) counts. Boxplots display the median (centre line), IQR (box limits), 1.5×IQR (whiskers), and individual data points (closed circles). Statistical comparisons were performed using the Wilcoxon rank-sum test. Statistical significance is reported as follows: ns ($P \geq 0.05$), * ($P < 0.05$), ** ($P < 0.01$), *** ($P < 0.001$), **** ($P < 0.0001$).



Supplementary Fig 8. Paired longitudinal analysis of DNA methylation changes between acute and recovery phases in COVID-19 patients. DNA methylation levels (β -values, %) at selected CpG sites are shown for matched whole blood samples collected from COVID-19 patients during acute illness and post-recovery. Panels **A** and **B** display CpG sites exhibiting hypomethylation during acute infection, while panels **C** and **D** show sites with hypermethylation, each stratified by clinical severity: **A**, **C**) severely ill and **B**, **D**) critically ill patients. Closed circles represent individual methylation β -values; grey lines denote paired measurements from the same patient across timepoints. Boxplots display the median (centre line), IQR (box limits), $1.5 \times \text{IQR}$ (whiskers), and individual data points within each group. Statistical differences between paired timepoints were evaluated using two-sided paired t -tests. Significance threshold is denoted as follows: ns ($P \geq 0.05$), * ($P < 0.05$), ** ($P < 0.01$), *** ($P < 0.001$), **** ($P < 0.0001$).



Supplementary Fig 9. Overall process of COVID-19 *cis*-eQTM analysis. The figure illustrates the workflow, including the discovery of differentially methylated CpGs and differentially expressed genes. Integration of methylation and gene expression data was achieved through the identification of *cis*-eQTM associations.

Direction of methylation	Position	Gene symbol	Direction of mRNA expression	Correlation methylation with mRNA expression		Median methylation differences(%)	Median gene expression differences (log2FC)
				Spearman's ρ	P-value		
Hyper-methylation	chr17:82126907	<i>ENSG00000287737</i>	Up regulation	0.571	0.006	13.517	1.515
	chr17:82126935	<i>ENSG00000287737</i>	Up regulation	0.615	0.002	14.577	1.515
	chr17:82126939	<i>ENSG00000287737</i>	Up regulation	0.526	0.015	11.995	1.515
	chr17:82127016	<i>ENSG00000287737</i>	Up regulation	0.557	0.008	12.446	1.515
	chr2:37368137	<i>CYP11B1-AS1</i>	Up regulation	0.512	0.020	14.037	1.536
Hypo-methylation	chr1:25771417	<i>RHD</i>	Up regulation	-0.530	0.014	-11.900	2.037
	chr1:234612121	<i>ENSG00000289377</i>	Up regulation	-0.502	0.025	-11.601	2.921
	chr15:90100633	<i>FURIN</i>	Up regulation	-0.602	0.003	-14.306	1.596
	chr16:30964865	<i>YPEL3</i>	Up regulation	-0.544	0.010	-15.843	1.466
	chr16:75063094	<i>GABARAPL2</i>	Up regulation	-0.569	0.006	-10.430	2.249
	chr17:17276112	<i>FLCN</i>	Up regulation	-0.618	0.002	-11.750	1.525
	chr17:81274041	<i>ENSG00000287737</i>	Up regulation	-0.567	0.006	-16.428	1.515
	chr17:82223145	<i>ENSG00000287737</i>	Up regulation	-0.535	0.013	-13.297	1.515
	chr17:82624041	<i>ENSG00000287737</i>	Up regulation	-0.631	0.001	-12.341	1.515
	chr17:82624115	<i>ENSG00000287737</i>	Up regulation	-0.565	0.006	-11.502	1.515
	chr17:82838556	<i>ENSG00000287737</i>	Up regulation	-0.675	0.000	-11.950	1.515
	chr17:82838607	<i>ENSG00000287737</i>	Up regulation	-0.658	0.001	-13.764	1.515
	chr18:79506961	<i>SLC66A2</i>	Up regulation	-0.607	0.002	-13.415	1.562

chr19:1423674	<i>R3HDM4</i>	Up regulation	-0.532	0.013	-12.949	1.819
chr19:1423696	<i>R3HDM4</i>	Up regulation	-0.557	0.008	-14.906	1.819
chr2:102143316	<i>IL18RAP</i>	Up regulation	-0.503	0.024	-11.753	1.774
chr20:330120	<i>SRXNI</i>	Up regulation	-0.582	0.004	-11.078	1.517
chr20:654151	<i>SRXNI</i>	Up regulation	-0.586	0.004	-13.297	1.517
chr20:1166154	<i>SRXNI</i>	Up regulation	-0.547	0.010	-13.335	1.517
chr20:1467583	<i>SRXNI</i>	Up regulation	-0.538	0.012	-12.854	1.517
chr20:1631771	<i>SRXNI</i>	Up regulation	-0.510	0.021	-17.060	1.517
chr5:75320838	<i>GCNT4</i>	Down regulation	0.528	0.015	-14.165	-1.505
chr6:36697843	<i>FKBP5</i>	Up regulation	-0.551	0.009	-15.580	1.875
chr6:108562564	<i>FOXO3</i>	Up regulation	-0.501	0.025	-13.224	1.890
chr8:143356214	<i>GRINA</i>	Up regulation	-0.546	0.010	-10.716	1.490

Supplementary Table 1. COVID-19 severity-associated genes identified through *cis*-eQTM analysis. Columns indicate the direction of DNA methylation change (hypo- or hypermethylation), CpG site genomic position (hg38), associated gene symbol, direction of mRNA expression change (up- or downregulation), direction of correlation between DNA methylation and gene expression, Spearman's correlation coefficient (ρ), and associated *P*-value from *cis*-eQTM analysis adjusted for immune cell proportions.

cis-eQTM CpG Site	Regulated Gene	Case	Control	Mean Difference	Test Statistics	P-value	FDR
chr2:102143316	<i>IL18RAP</i>	Severe-Critical Acute	Healthy	-13.575	-4.425	0.002	0.009
chr2:102143316	<i>IL18RAP</i>	Severe-Critical Acute	Mild-Moderate Acute	-11.566	-3.301	0.005	0.01
chr2:102143316	<i>IL18RAP</i>	Healthy	Convalescent	1.031	0.93	0.354	0.424
chr2:102143316	<i>IL18RAP</i>	Mild-Moderate Acute	Convalescent	-0.978	-0.483	0.631	0.631
chr2:102143316	<i>IL18RAP</i>	Severe-Critical Acute	Convalescent	-12.544	-3.947	0.003	0.009
chr2:102143316	<i>IL18RAP</i>	Mild-Moderate Acute	Healthy	-2.009	-1.088	0.283	0.424
chr5:75320838	<i>GCNT4</i>	Severe-Critical Acute	Convalescent	-15.951	-3.952	0.004	0.011
chr5:75320838	<i>GCNT4</i>	Healthy	Convalescent	0.8	0.865	0.388	0.388
chr5:75320838	<i>GCNT4</i>	Mild-Moderate Acute	Convalescent	-2.561	-1.362	0.179	0.215
chr5:75320838	<i>GCNT4</i>	Severe-Critical Acute	Healthy	-16.751	-4.194	0.003	0.011
chr5:75320838	<i>GCNT4</i>	Mild-Moderate Acute	Healthy	-3.361	-1.881	0.067	0.1
chr5:75320838	<i>GCNT4</i>	Severe-Critical Acute	Mild-Moderate Acute	-13.39	-3.102	0.01	0.02
chr6:36697843	<i>FKBP5</i>	Severe_First	Mild_First	-15.916	-5.915	5.76E-06	1.15E-05
chr6:36697843	<i>FKBP5</i>	Healthy	Convalescent	3.258	2.624	0.01	0.011
chr6:36697843	<i>FKBP5</i>	Mild_First	Convalescent	-2.382	-1.147	0.256	0.256
chr6:36697843	<i>FKBP5</i>	Severe_First	Convalescent	-18.298	-7.987	2.17E-06	6.50E-06
chr6:36697843	<i>FKBP5</i>	Mild_First	Healthy	-5.641	-3	0.004	0.007
chr6:36697843	<i>FKBP5</i>	Severe_First	Healthy	-21.556	-10.198	1.90E-06	6.50E-06
chr6:108562564	<i>FOXO3</i>	Healthy	Convalescent	0.273	0.241	0.81	0.81
chr6:108562564	<i>FOXO3</i>	Severe-Critical Acute	Convalescent	-14.679	-4.665	9.60E-04	0.003
chr6:108562564	<i>FOXO3</i>	Mild-Moderate Acute	Healthy	-1.991	-0.986	0.329	0.494
chr6:108562564	<i>FOXO3</i>	Severe-Critical Acute	Healthy	-14.953	-4.891	9.60E-04	0.003

chr6:108562564	<i>FOXO3</i>	Severe-Critical Acute	Mild-Moderate Acute	-12.962	-3.638	0.002	0.005
chr6:108562564	<i>FOXO3</i>	Mild-Moderate Acute	Convalescent	-1.717	-0.798	0.428	0.514
chr15:90100633	<i>FURIN</i>	Severe-Critical Acute	Healthy	-17.069	-3.256	0.011	0.045
chr15:90100633	<i>FURIN</i>	Healthy	Convalescent	0.954	0.804	0.423	0.507
chr15:90100633	<i>FURIN</i>	Mild-Moderate Acute	Convalescent	-1.574	-0.637	0.527	0.527
chr15:90100633	<i>FURIN</i>	Severe-Critical Acute	Convalescent	-16.115	-3.032	0.015	0.045
chr15:90100633	<i>FURIN</i>	Mild-Moderate Acute	Healthy	-2.529	-1.095	0.28	0.42
chr15:90100633	<i>FURIN</i>	Severe-Critical Acute	Mild-Moderate Acute	-14.541	-2.563	0.026	0.052
chr20:654151	<i>SRXN1</i>	Mild-Moderate Acute	Convalescent	-3.281	-1.337	0.187	0.28
chr20:654151	<i>SRXN1</i>	Severe-Critical Acute	Convalescent	-16.389	-4.305	0.002	0.009
chr20:654151	<i>SRXN1</i>	Mild-Moderate Acute	Healthy	-2.141	-0.93	0.358	0.358
chr20:654151	<i>SRXN1</i>	Severe-Critical Acute	Healthy	-15.249	-4.109	0.003	0.009
chr20:654151	<i>SRXN1</i>	Severe-Critical Acute	Mild-Moderate Acute	-13.108	-3.065	0.008	0.016
chr20:654151	<i>SRXN1</i>	Healthy	Convalescent	-1.139	-0.93	0.354	0.358

Supplementary Table 2. Summary table displaying pairwise comparisons of methylation levels at ten CpG sites identified through *cis*-eQTM analysis. Columns indicate the genomic position of the CpG site (hg38), the regulated gene, the two comparison groups, the mean difference in methylation, test statistic (Welch's *t*-test), nominal *P*-value, and the false discovery rate (FDR).

Gene Symbol	Case	Control	Mean Difference	Test Statistics	P-value	FDR
<i>ENSG00000115607.10_IL18RAP</i>	Severe-Critical Acute	Healthy	-1.966	2.342	0.019	0.038
<i>ENSG00000115607.10_IL18RAP</i>	Severe-Critical Acute	Mild-Moderate Acute	-1.662	2.1	0.036	0.052
<i>ENSG00000115607.10_IL18RAP</i>	Mild-Moderate Acute	Convalescent	-0.521	2.405	0.016	0.038
<i>ENSG00000115607.10_IL18RAP</i>	Healthy	Convalescent	-0.217	2.023	0.043	0.052
<i>ENSG00000115607.10_IL18RAP</i>	Mild-Moderate Acute	Healthy	-0.304	0.782	0.434	0.434
<i>ENSG00000115607.10_IL18RAP</i>	Severe-Critical Acute	Convalescent	-2.183	3.073	0.002	0.013
<i>ENSG00000176928.7_GCNT4</i>	Severe-Critical Acute	Mild-Moderate Acute	1.117	-2.611	0.009	0.014
<i>ENSG00000176928.7_GCNT4</i>	Mild-Moderate Acute	Healthy	0.63	-2.277	0.023	0.027
<i>ENSG00000176928.7_GCNT4</i>	Severe-Critical Acute	Convalescent	1.92	-4.725	2.30E-06	1.38E-05
<i>ENSG00000176928.7_GCNT4</i>	Mild-Moderate Acute	Convalescent	0.803	-3.775	1.60E-04	3.20E-04
<i>ENSG00000176928.7_GCNT4</i>	Healthy	Convalescent	0.174	-1.532	0.126	0.126
<i>ENSG00000176928.7_GCNT4</i>	Severe-Critical Acute	Healthy	1.746	-4.263	2.02E-05	6.06E-05
<i>ENSG00000096060.15_FKBP5</i>	Healthy	Convalescent	-0.035	0.441	0.659	6.59E-01
<i>ENSG00000096060.15_FKBP5</i>	Mild-Moderate Acute	Convalescent	-0.357	1.286	0.198	0.297
<i>ENSG00000096060.15_FKBP5</i>	Severe-Critical Acute	Convalescent	-1.992	3.557	3.75E-04	0.002
<i>ENSG00000096060.15_FKBP5</i>	Mild-Moderate Acute	Healthy	-0.323	0.702	0.483	5.80E-01
<i>ENSG00000096060.15_FKBP5</i>	Severe-Critical Acute	Healthy	-1.958	3.099	0.002	0.006
<i>ENSG00000096060.15_FKBP5</i>	Severe-Critical Acute	Mild-Moderate Acute	-1.635	2.639	0.008	1.70E-02
<i>ENSG00000118689.15_FOXO3</i>	Healthy	Convalescent	0.702	-3.761	1.69E-04	5.08E-04

<i>ENSG00000118689.15_FOXO3</i>	Mild-Moderate Acute	Convalescent	0.664	-3.802	1.44E-04	5.08E-04
<i>ENSG00000118689.15_FOXO3</i>	Severe-Critical Acute	Convalescent	-0.777	0.348	0.728	0.809
<i>ENSG00000118689.15_FOXO3</i>	Mild-Moderate Acute	Healthy	-0.039	0.242	0.809	0.809
<i>ENSG00000118689.15_FOXO3</i>	Severe-Critical Acute	Mild-Moderate Acute	-1.441	1.958	0.05	0.075
<i>ENSG00000118689.15_FOXO3</i>	Severe-Critical Acute	Healthy	-1.479	2.197	0.028	0.056
<i>ENSG00000140564.13_FURIN</i>	Mild-Moderate Acute	Convalescent	-0.21	1.496	0.135	0.202
<i>ENSG00000140564.13_FURIN</i>	Severe-Critical Acute	Mild-Moderate Acute	-1.458	3.121	0.002	0.004
<i>ENSG00000140564.13_FURIN</i>	Severe-Critical Acute	Healthy	-1.627	3.797	1.47E-04	4.39E-04
<i>ENSG00000140564.13_FURIN</i>	Mild-Moderate Acute	Healthy	-0.169	1.093	0.275	0.329
<i>ENSG00000140564.13_FURIN</i>	Severe-Critical Acute	Convalescent	-1.667	3.864	1.12E-04	4.39E-04
<i>ENSG00000140564.13_FURIN</i>	Healthy	Convalescent	-0.041	0.195	0.845	0.845
<i>ENSG00000271303.2_SRXN1</i>	Mild-Moderate Acute	Convalescent	-0.03	-0.026	0.979	0.979
<i>ENSG00000271303.2_SRXN1</i>	Healthy	Convalescent	0.068	-0.441	0.659	0.979
<i>ENSG00000271303.2_SRXN1</i>	Severe-Critical Acute	Convalescent	-1.487	3.333	8.59E-04	0.002
<i>ENSG00000271303.2_SRXN1</i>	Mild-Moderate Acute	Healthy	-0.098	0.23	0.818	0.979
<i>ENSG00000271303.2_SRXN1</i>	Severe-Critical Acute	Healthy	-1.555	3.361	7.78E-04	0.002
<i>ENSG00000271303.2_SRXN1</i>	Severe-Critical Acute	Mild-Moderate Acute	-1.456	3.32	9.01E-04	0.002

Supplementary Table 3. Summary table displaying pairwise comparisons of expression levels at six genes identified through *cis*-eQTM analysis. Columns report the gene symbol, comparison groups, mean difference in expression, test statistic (Wilcoxon rank-sum test), nominal *P*-value, and false discovery rate (FDR).

Direction of methylation	Position	Gene symbol	Direction of mRNA expression	Correlation methylation with mRNA expression	
				Spearman's ρ	<i>P</i> -value
Hypomethylation	chr6:36697843	<i>FKBP5</i>	Up regulation	-0.551	0.00879

Supplementary Table 4. A key gene associated with the severity of COVID-19 in the acute phase after adjustment for leukocyte composition. Columns indicate the direction of DNA methylation change (hypo- or hypermethylation), CpG site genomic position (hg38), associated gene symbol, direction of mRNA expression change (up- or downregulation), direction of correlation between DNA methylation and gene expression, Spearman's correlation coefficient (ρ), and associated *P*-value from *cis*-eQTM analysis adjusted for immune cell proportions.

Severity Level	Criteria
Mild	• Positive testing by virologic test (i.e., a nucleic acid amplification test of an antigen test) • Symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, and loss of taste or smell, without shortness of breath or dyspnea • No clinical signs indicative of Moderate, Severe, or Critical Severity
Moderate	• Positive testing by virologic test (i.e., a nucleic acid amplification test of an antigen test) • Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion • Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥ 20 breaths per minute, heart rate ≥ 90 beats per minute; with saturation of oxygen (SpO₂) $> 93\%$ on room air at sea level • No clinical signs indicative of Severe or Critical Illness Severity
Severe	• Positive testing by standard RT-PCR assay or an equivalent test • Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress • Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO₂ $\leq 93\%$ on room air at sea level or PaO₂/FiO₂ < 300 • No criteria for Critical Severity
Critical	• Positive testing by virologic test (i.e., a nucleic acid amplification test of an antigen test) • Evidence of critical illness, defined by at least one of the following: – Respiratory failure defined based on resource utilization requiring at least one of the following: ▪ Endotracheal intubation and mechanical ventilation, oxygen delivered by high flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation) – Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors) – Multi-organ dysfunction/failure

Supplementary Table 5. COVID-19 Severity Classification According to U.S. FDA Guidance (Feb 2021). The classification of COVID-19 severity used in this study is based on the U.S. FDA’s Guidance for Industry: COVID-19: Developing Drugs and Biological Products for Treatment or Prevention.

CpGs	Healthy	Mild-Moderate	Severe-Critical	Convalescent
chr1:25771417	0.281	0.006	0.965	0.468
chr1:234612121	0.382	0.382	0.382	0.726
chr15:90100633	0.303	0.334	0.303	0.303
chr16:30964865	0.877	0.877	0.877	0.281
chr16:75063094	0.01	0.038	0.038	0.772
chr17:17276112	0.606	0.665	0.606	0.872
chr17:81274041	0.977	0.37	0.511	0.511
chr17:82126907	0.085	0.085	0.653	0.653
chr17:82126935	0.678	0.818	0.678	0.678
chr17:82126939	0.703	0.703	0.703	0.703
chr17:82127016	0.493	0.633	0.633	0.633
chr17:82223145	0.061	0.061	0.572	0.643
chr17:82624041	0.023	0.724	0.724	0.672
chr17:82624115	0.024	0.636	0.636	0.612
chr17:82838556	0.876	0.933	0.876	0.876
chr17:82838607	0.762	0.762	0.762	0.762
chr18:79506961	0.048	0.204	0.204	0.204
chr19:1423674	0.386	0.838	0.357	0.386
chr19:1423696	0.262	0.791	0.791	0.908
chr2:37368137	0.647	0.324	0.647	0.647
chr2:102143316	0.048	0.975	0.846	0.846
chr20:330120	0.056	0.536	0.536	0.776
chr20:654151	0.046	0.009	0.077	0.359
chr20:1166154	0.809	0.646	0.646	0.646
chr20:1467583	0.345	0.712	0.408	0.712
chr20:1631771	0.746	0.746	0.746	0.746
chr5:75320838	0.397	0.397	0.397	0.397
chr6:36697843	0.377	0.961	0.332	0.332
chr6:108562564	0.678	0.678	0.678	0.678
chr8:143356214	0.571	0.849	0.571	0.854

Supplementary Table 6. Summary table displaying significance of Shapiro-Wilk tests for 30 DMC-LOOs. Each value represents an adjusted *P*-value of the normality test after Benjamini-Hochberg correction. Those values that have no evidence of normal distribution have been marked as bold font.

Genes	Healthy	Mild-Moderate	Severe-Critical	Convalescent
ENSG00000287737.3_ENSG00000287737	0.997	0.949	0.949	0.802
ENSG00000232973.14_CYP1B1-AS1	0.556	0.556	0.945	0.002
ENSG00000118689.15_FOXO3	0.559	0.559	0.06	0.019
ENSG00000154803.13_FLCN	0.79	0.309	0.022	0.79
ENSG00000115607.10_IL18RAP	0.853	0.385	0.437	0.385
ENSG00000187010.21_RHD	0.002	0.347	0.003	0.132
ENSG00000090238.12_YPEL3	0.663	0.663	0.138	0.034
ENSG00000140564.13_FURIN	0.608	0.608	0.055	0.364
ENSG00000096060.15_FKBP5	0.634	0.318	0.634	0.318
ENSG00000271303.2_SRXN1	0.059	0.254	0.114	0.059
ENSG00000176928.7_GCNT4	0.028	0.02	0.002	0.02
ENSG00000198858.10_R3HDM4	0.921	0.921	0.136	0.05
ENSG00000122490.19_SLC66A2	0.864	0.864	0.063	0.009
ENSG00000178719.17_GRINA	0.741	0.793	0.524	0.741
ENSG00000034713.8_GABARAPL2	0.539	0.539	0.011	0.032
ENSG00000289377.2_ENSG00000289377	0.004	0.025	0.002	0.037

Supplementary Table 7. Summary table displaying significance of Shapiro-Wilk tests for 16 DEG-LOOs. Each value represents an adjusted *P*-value of the normality test after Benjamini-Hochberg correction. Those values that have no evidence of normal distribution have been marked as bold font.