

Caption for Supplementary materials

Supplementary Figure S1. Graphical schema representing the population of interest and the screening strategy used to identify epigenetic biomarkers of COVID-19 severity.

Supplementary Figure S2. Manhattan plot from the EWAS performed in the validation cohort.

Supplementary Figure S3. Manhattan plot from the EWAS performed in the entire cohort.

Supplementary Figure S4. Heatmap representing the discovery cohort samples, clustered by methylation beta values of the 44 CpGs defining the EPICOVID signature.

Supplementary Figure S5. ROC curve and AUC value.

Supplementary Figure S6. Heatmap representing the validation cohort samples, clustered by methylation beta values of the 44 CpGs defining the EPICOVID signature.

Supplementary Figure S7. Illustrative examples of CpGs differentially methylated between asymptomatic/paucisymptomatic and severe COVID-19 patients validated by pyrosequencing.

Supplementary Table S1. Description of the 51 CpG sites with a differential DNA methylation status between the asymptomatic/paucisymptomatic (G3, n = 104) and severe (G2 + G1, n = 103) groups in the discovery cohort.

Supplementary Table S2. Description of the 44 CpG sites with a differential DNA methylation status corrected for sex and age between the asymptomatic/paucisymptomatic (G3, n = 104) and severe (G2 + G1, n = 103) groups in the discovery cohort.

Supplementary Table S3. Genomic context of the distinctly methylated 44 CpG sites.

Supplementary Table S4. Description of the 1038 CpG sites in the 40 genes related to COVID-19, based on published studies for differential DNA methylation status between mild and severe cohorts.

Supplementary Table S5. Differentially methylated CpG sites in all the possible comparisons between G1/G2/G3 for the discovery, validation and entire cohort.

Supplementary Table S6. Association of the EPICOVID signature with laboratory parameters linked to COVID-19 severity.

Supplementary Methods. Study protocol, statistical analysis plan and pyrosequencing primers.