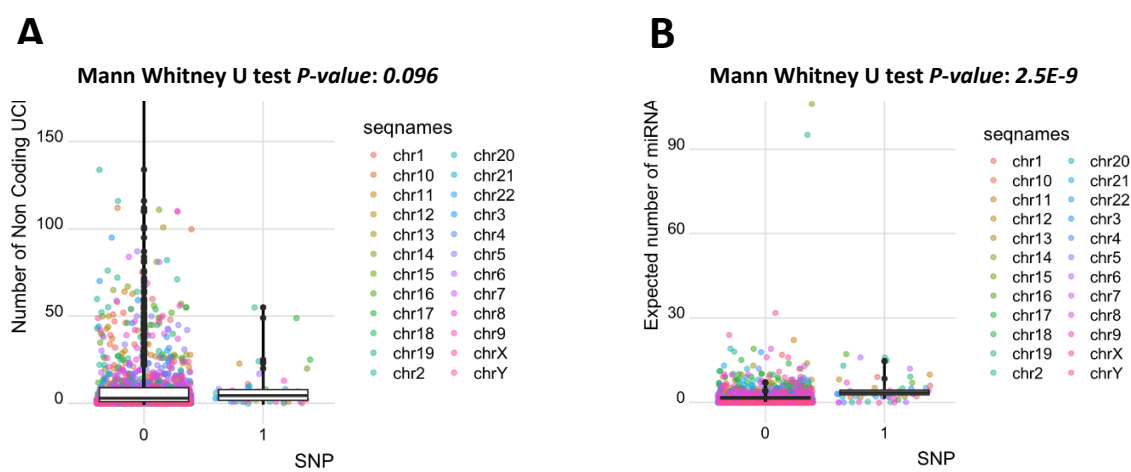
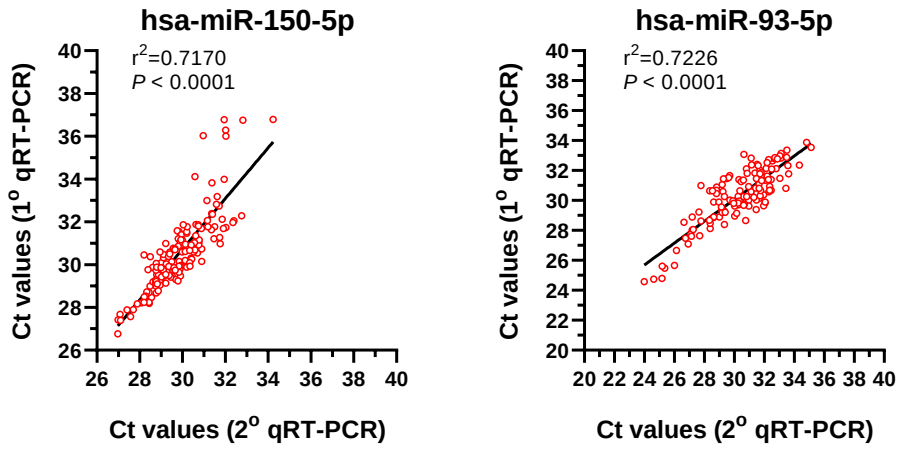


Additional Figure S1



**Additional Figure S1. Association of genomic location between SNPs and UCEs and miRNAs.** A) Boxplots for the regions with and without SNPs versus the number of non-coding ultra-conserved elements (UCEs). The *P* values from the Mann-Whitney U test are shown in the title; B) Boxplots for the regions with and without SNPs versus the expected number of miRNAs by chromosome number.

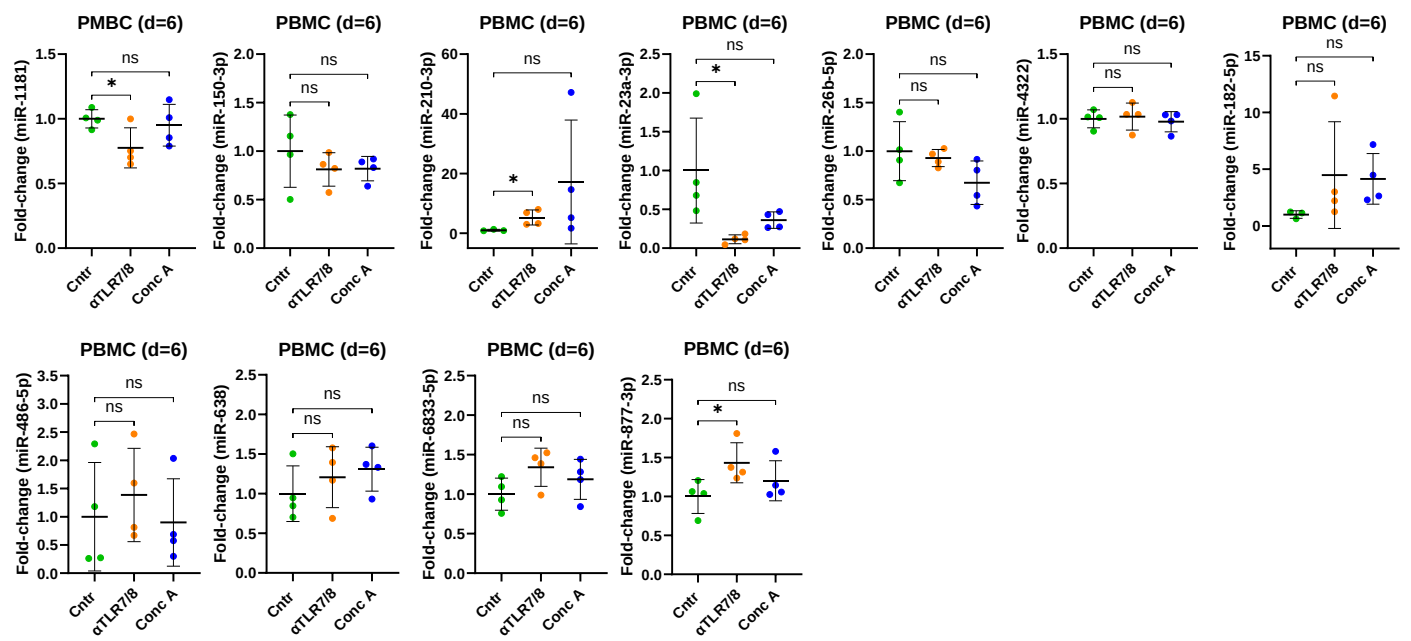
## Additional Figure S2



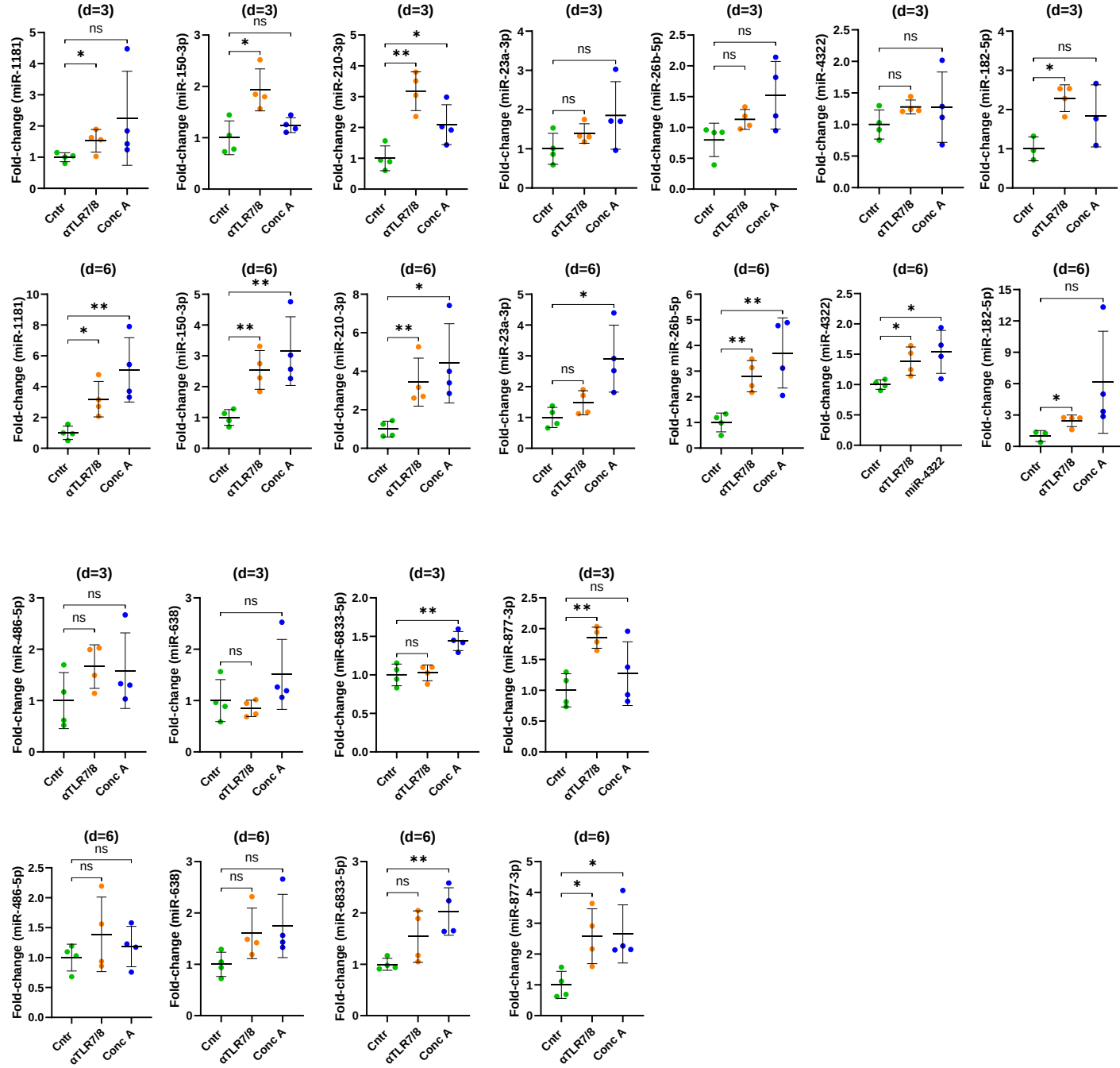
**Additional Figure S2. The reproducibility of qRT-PCR results in two independent experimental replicates.** The qRT-PCR amplification (Ct values) showed high levels of reproducibility in two independent experimental replicates, confirming the excellent quality of the RNA samples and technical procedures (Spearman Correlation for two biological replicate data for hsa-miR-150-5p and hsa-miR-93-5p).

Additional Figure S3

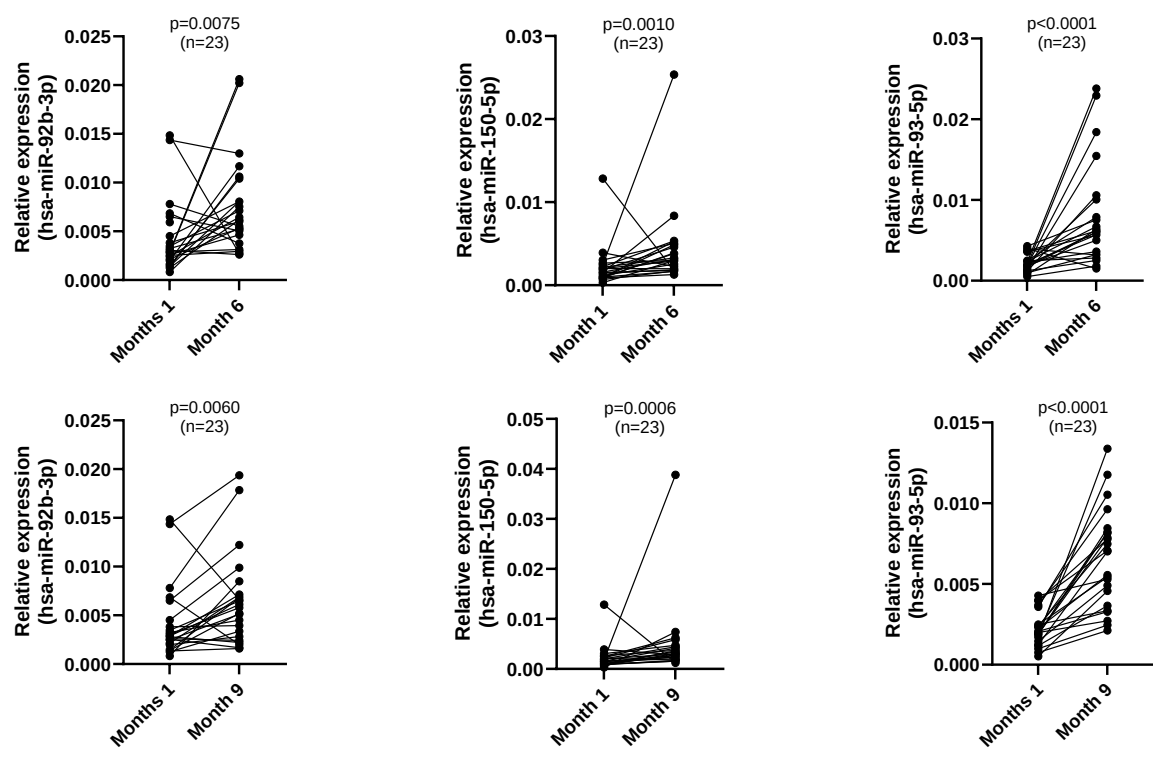
A



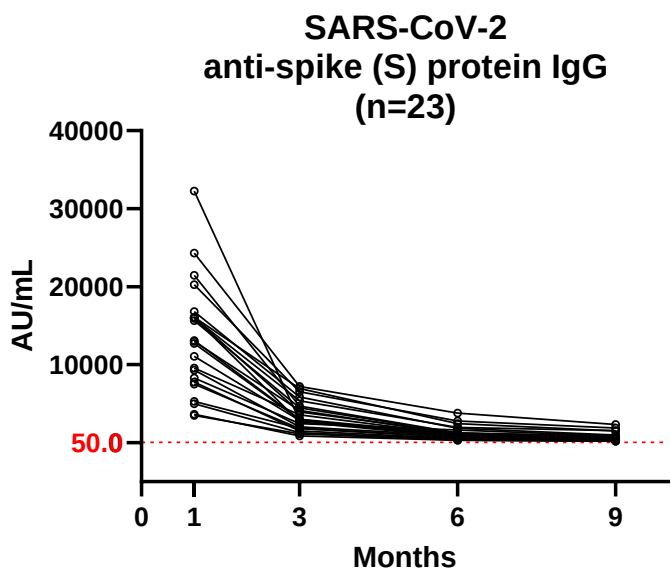
B



C

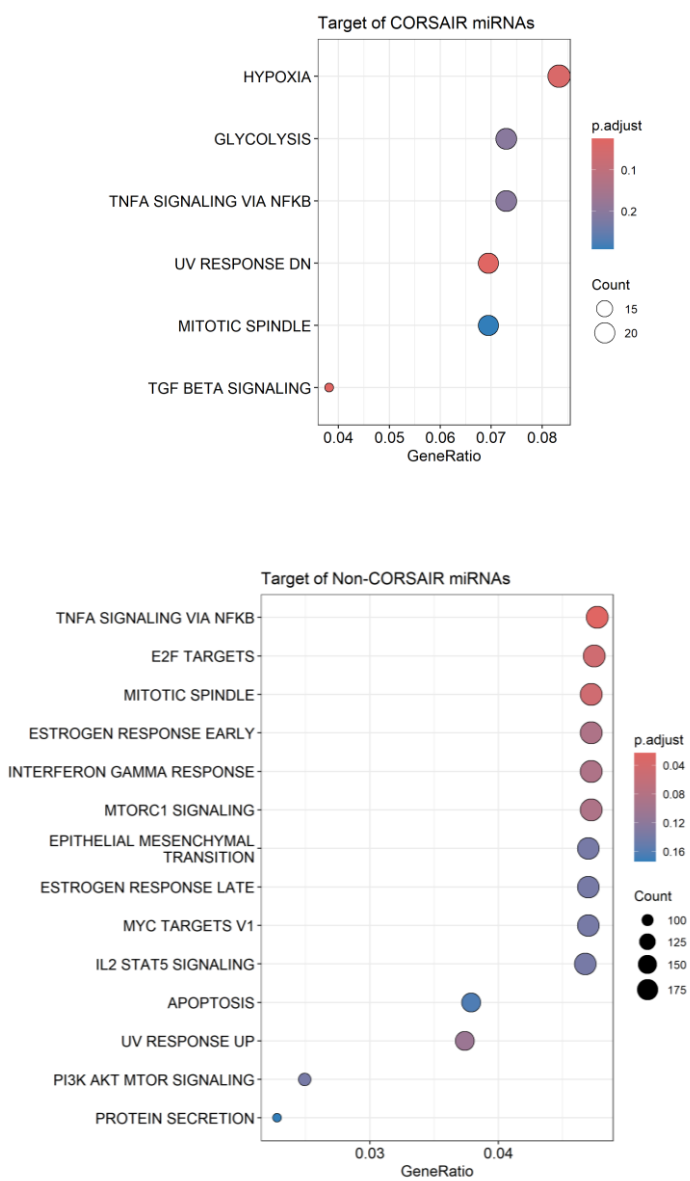


D



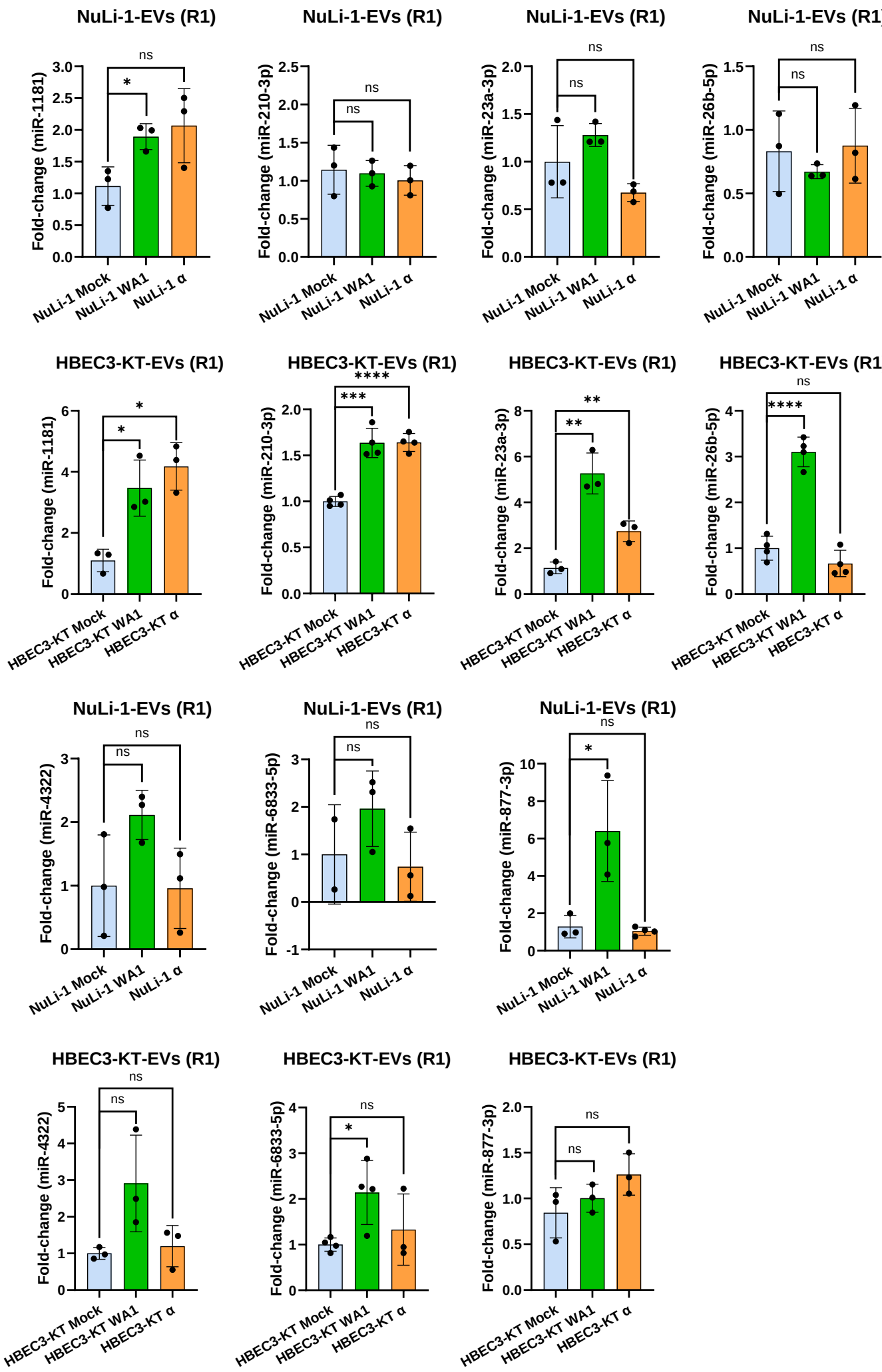
**Additional Figure S3. Levels of miRNAs in activated peripheral blood mononuclear cells (PBMC), their supernatants, and in serum samples of Pfizer-BioNTech vaccinated healthy individuals. A)** Variation of the expression levels of the remaining eleven selected miRNAs in PBMC at six days after activation with TLR-7/8 agonist ( $\alpha$ TLR7/8), T cell mitogen concanavalin A (conc A), compared with unstimulated PBMC; **B)** Variation of the expression levels of the remaining eleven selected miRNAs into the supernatants of PBMC at three and six days after activation with  $\alpha$ TLR7/8, T Conc A, compared with supernatant of unstimulated PBMC; **C)** Variation of the remaining eleven selected miRNAs in the pair-matched serum samples of healthy individuals (n=23) at one, six, and nine months after the administration of the second dose of the Pfizer-BioNTech vaccine; **D)** Variation of the SARS-CoV-2 anti-spike (S) protein IgG in the serum of healthy individuals at different times after the administration of the second dose of the Pfizer-BioNTech vaccine.

Additional Figure S4

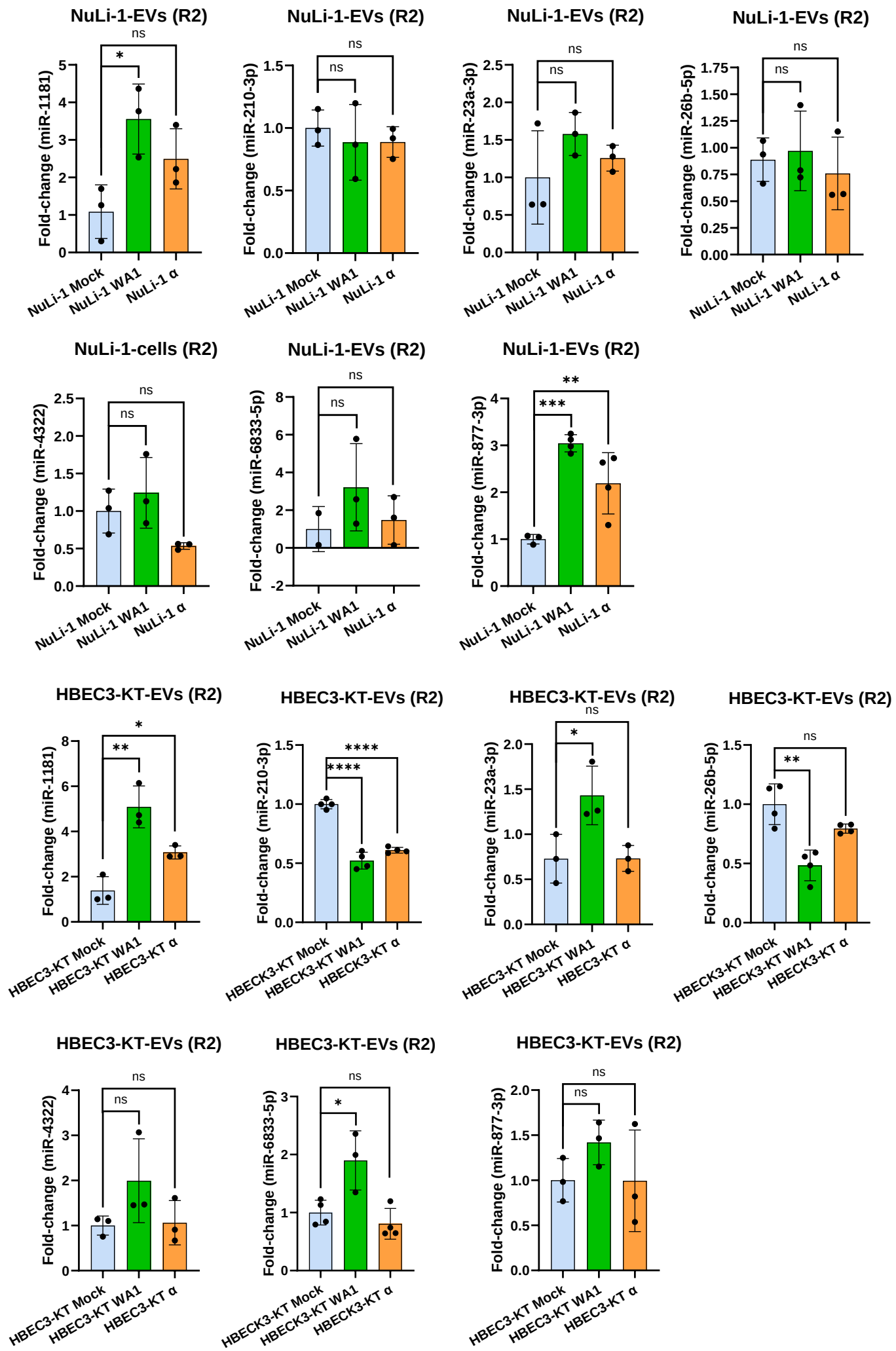


**Additional Figure S4.** Gene set enrichment analysis (GSEA). Hallmark pathway analysis for **A)** CORSAIR and **B)** non-CORSAIR miRNAs with expression higher than one standard deviation (4 CORSAIR and 139 non-CORSAIR miRNAs).

Additional Figure S5

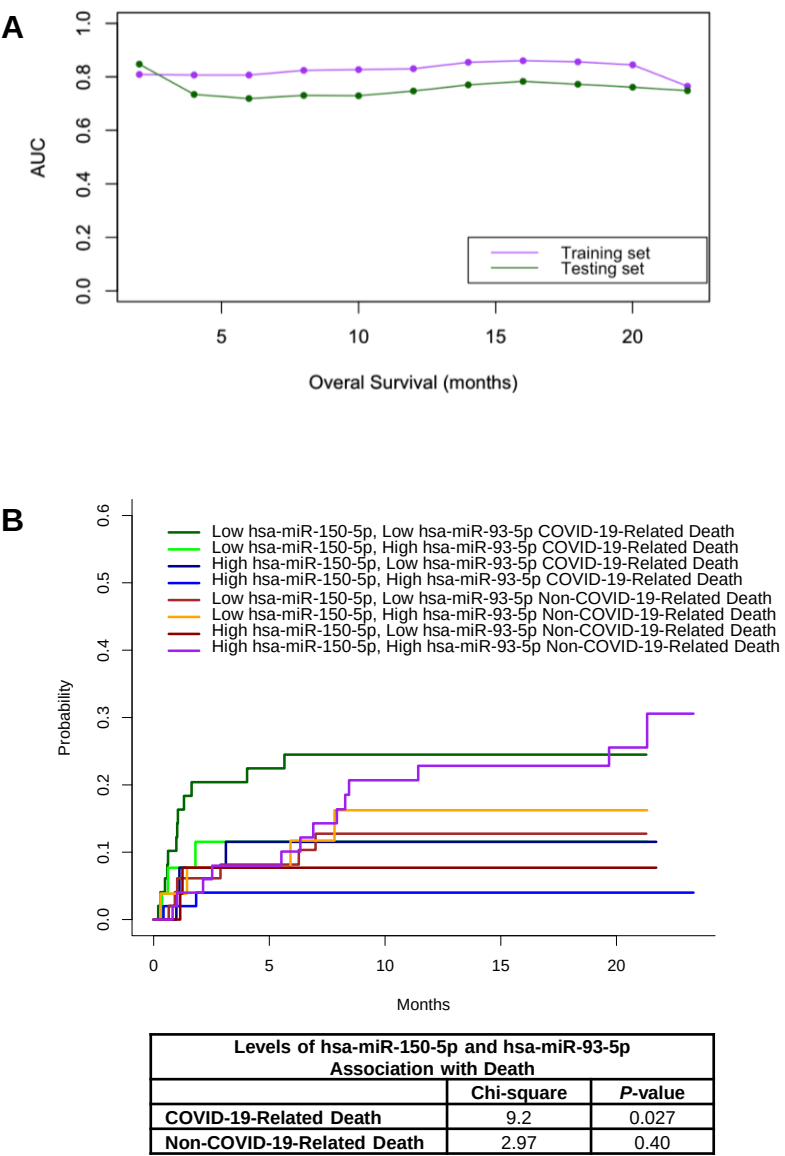


Additional Figure S5 - Continued



**Additional Figure S5. Effect of SARS-CoV-2 infection on miRNA expression levels in the EVs secreted from normal epithelial bronchus epithelial cells.** Variation of the expression levels of the remaining seven selected miRNAs in the secreted EVs from NuLi-1 and HBEC3-KT normal lung epithelial cells after infection with SARS-CoV-2 Washington (USA-WA1/2020) and SARS-CoV-2 UK (Alpha B.1.1.7) (Unpaired t-test. *P* value summary: \* $<0.05$ ; \*\* $<0.01$ ; \*\*\* $<0.001$ ; \*\*\*\* $<0.0001$ ).

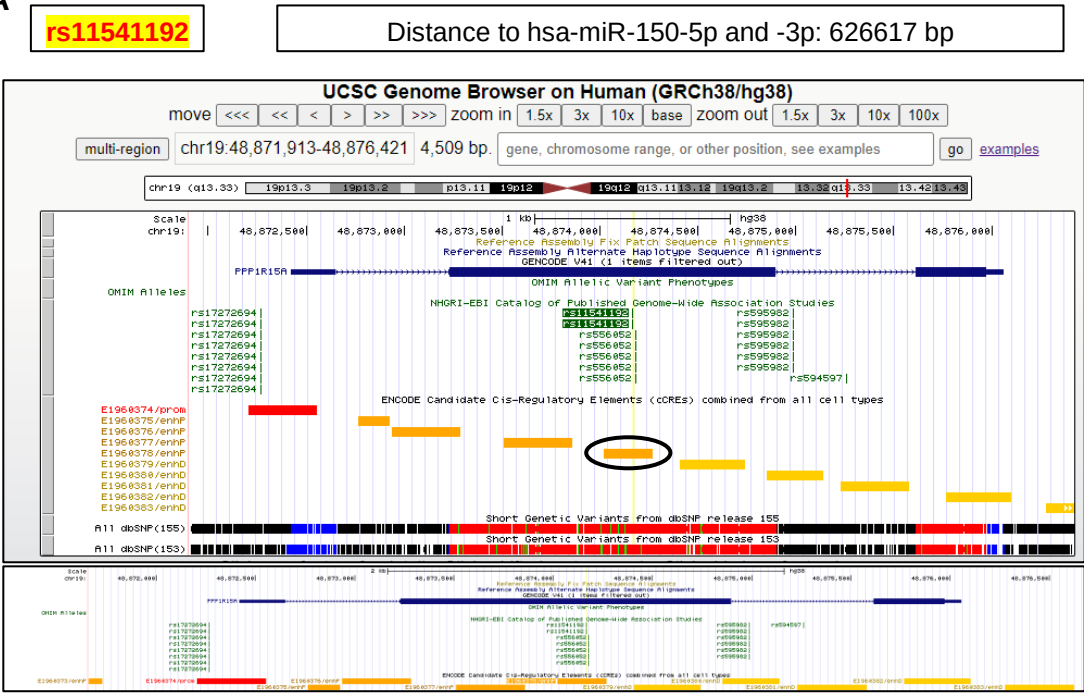
Additional Figure S6



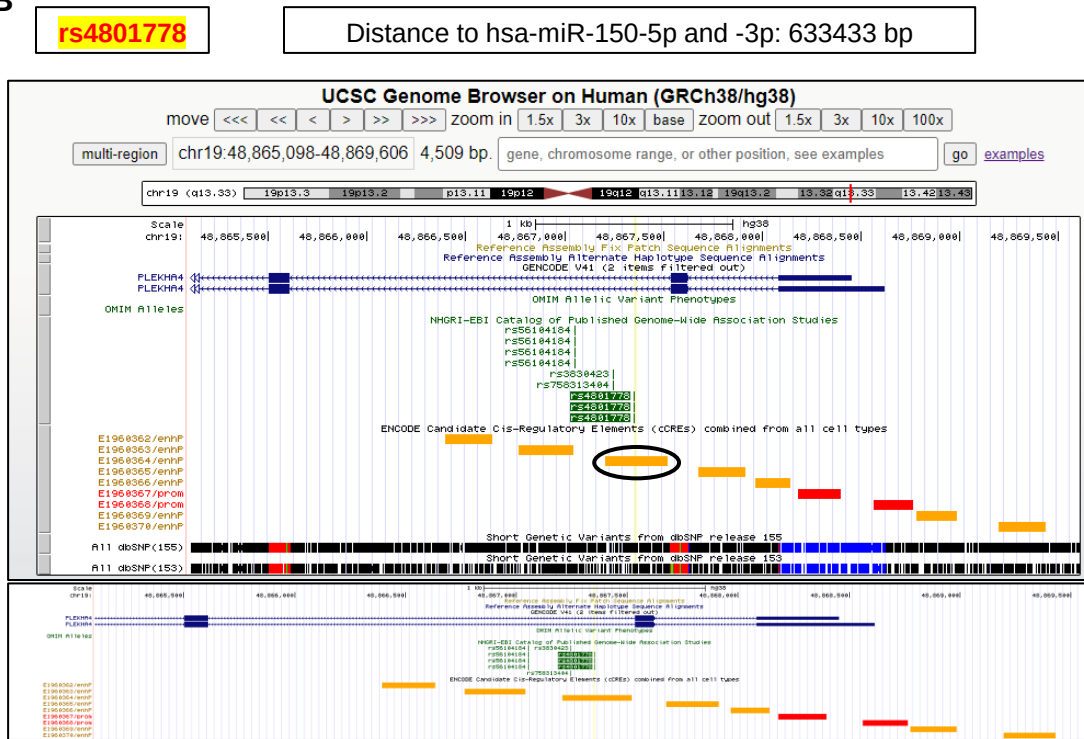
**Additional Figure S6. The probability of COVID-19-related and non-COVID-19-related death across time stratified by high/low expression levels of hsa-miR-150-5p and hsa-miR-93-5p combinations. A)** The AUC is consistently greater than 70% in both training and testing cohorts across time; **B)** The combination of low levels of both hsa-miR-150-5p and hsa-miR-93-5p were associated with increased risk of COVID-19-related death.

Additional Figure S7

A



B



Display Conventions and Configuration

cCREs are colored and labeled according to classification by regulatory signature:

| Color  | UCSC label | ENCODE classification            | ENCODE label  |
|--------|------------|----------------------------------|---------------|
| red    | prom       | promoter-like signature          | PLS           |
| orange | enhP       | proximal enhancer-like signature | pELS          |
| yellow | enhD       | distal enhancer-like signature   | dELS          |
| pink   | K4m3       | DNase-H3K4me3                    | DNase-H3K4me3 |
| blue   | CTCF       | CTCF-only                        | CTCF-only     |

The DNase-H3K4me3 elements are those with promoter-like biochemical signature that are not within 200bp of an annotated TSS.

Classification of cCRE's was performed based on the following criteria:

- cCREs with promoter-like signatures (cCRE-PLS): within 200 bp of an annotated GENCODE TSS and have high DNase and H3K4me3 signals.
- cCREs with enhancer-like signatures (cCRE-ELS): high DNase and H3K27ac with low H3K4me3 max-Z score if they are within 200 bp of an annotated TSS. The subset of cCREs-ELS within 2 kb of a TSS is denoted proximal (cCRE-pELS), while the remaining subset is denoted distal (cCRE-dELS).
- DNase-H3K4me3 cCREs: high H3K4me3 max-Z scores but low H3K27ac max-Z scores and do not fall within 200 bp of a TSS.
- CTCF-only cCREs: high DNase and CTCF and low H3K4me3 and H3K27ac.

**Additional Figure S7. Genomic localization of SNPs associated with the risk of aggressive COVID-19.** The SNPs we studied are generally located in the proximity of candidate Cis-Regulatory Elements (cCREs), such as promoter-like (PLS), proximal enhance-like (pELS), and distal enhancer-like (dELS) signatures, based on UCSC Genome Browser Genome on Human (GRCh38/hg38). In addition, we reported an example of two SNPs: (A) rs11541192 and (B) rs4801778.