

Supplementary Figure and Figure legend

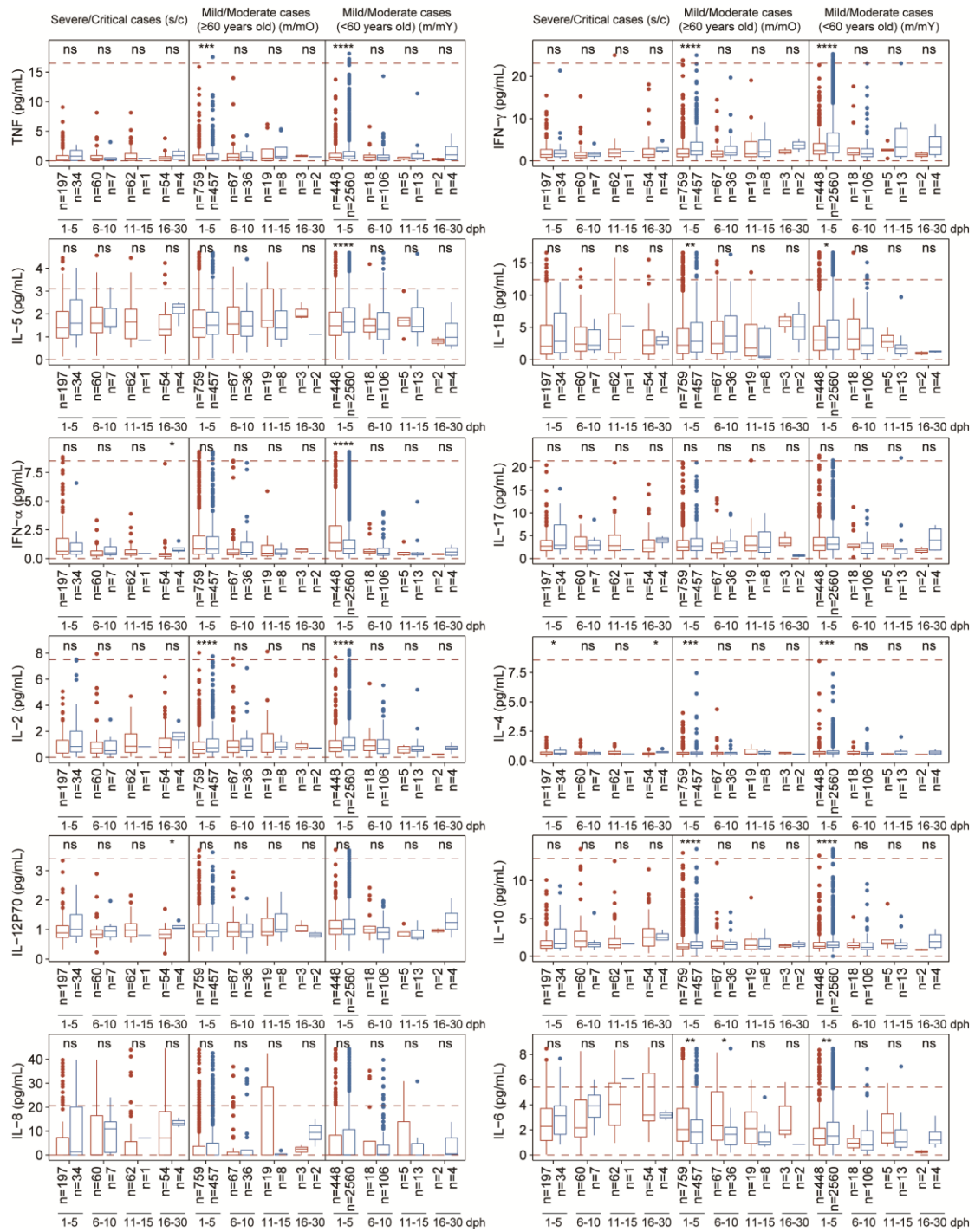


Figure S1. Impact of vaccination on cytokine responses in COVID-19 post BA.2.2 infection.

Longitudinal analysis of a subset of cytokines from 1 to 30 days post hospitalization (dph) in vaccinated and unvaccinated COVID-19 infected by BA.2.2. Results of IFN-

α , IFN- γ , IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17 and TNF are shown.

Wilcox-test ****: $p < 0.001$; ***: $P < 0.01$; **: $P < 0.05$; ns: not significant.

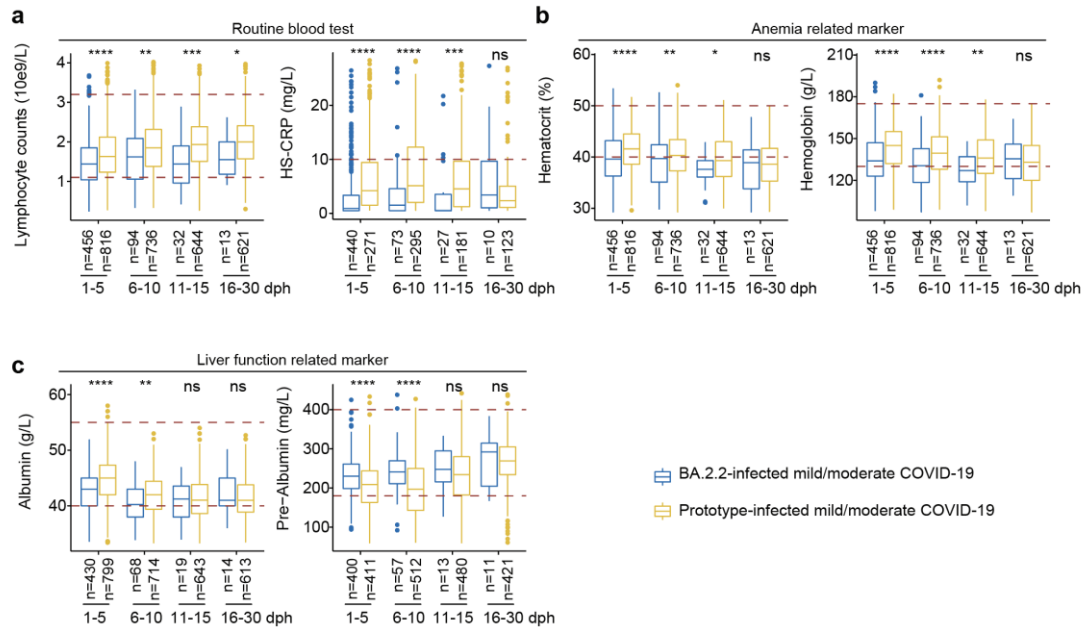


Figure S2. Comparison of markers of immune responses, anemia and liver injury in mild/moderate COVID-19 cases with BA.2.2 or prototype infections.

(a-c) Longitudinal analysis of a subset of routine blood test, cytokines and liver injury, related features from 1 to 30 days post hospitalization (dph) in prototype and BA.2.2 infected mild/moderate COVID-19. Unvaccinated SARS-CoV-2 prototype and BA.2.2-infected mild/moderate COVID-19 cases (10-59 years old) were enrolled for analysis. (a) Lymphocyte counts and HS-CRP in routine blood test. (b) Anemia related features, including levels of hematocrit and hemoglobin. (c) liver function/damage-related markers, including levels of albumin and pre-albumin. Wilcox test. ****: $p < 0.001$; ***: $P < 0.01$; **: $P < 0.05$; ns: not significant.

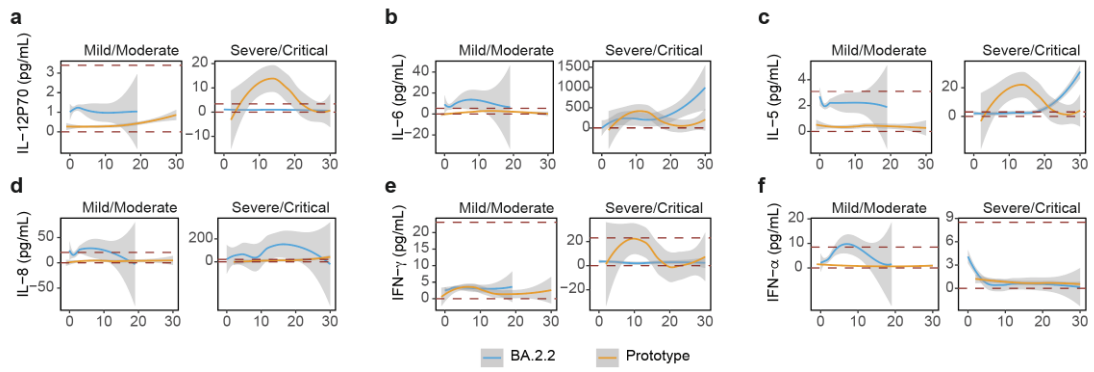


Figure S3. Longitudinal analysis of cytokines in prototype and infected mild/moderate and severe/critical cases. Results of IL-12P70 (a), IL-6 (b), IL-5 (c), IL-8 (d), IFN- γ (e), and IFN- α (f) were shown. Prototype was colored by blue and the BA.2.2 was colored by orange.

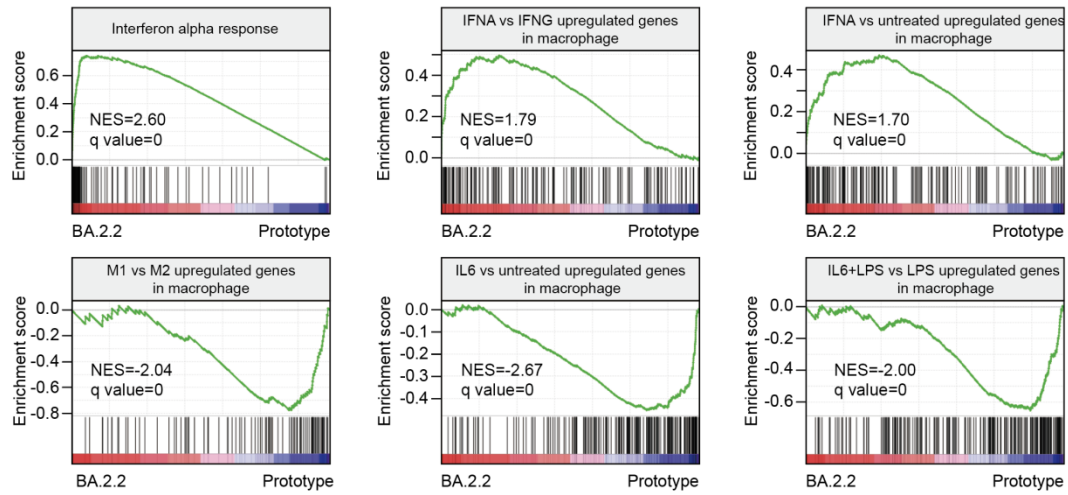


Figure S4. Gene set enrichment analysis of immune signatures in BA.2.2 and prototype infected BALF samples. Genes set enrichment analysis were conducted with the GSEA tools (version 4.1.0) using a rank list of gene expression differences between the BALF of BA.2.2 vs. Prototype. Enrichment of six gene sets are plotted. Normalized enrichment score (NES) and FDR q value are shown.

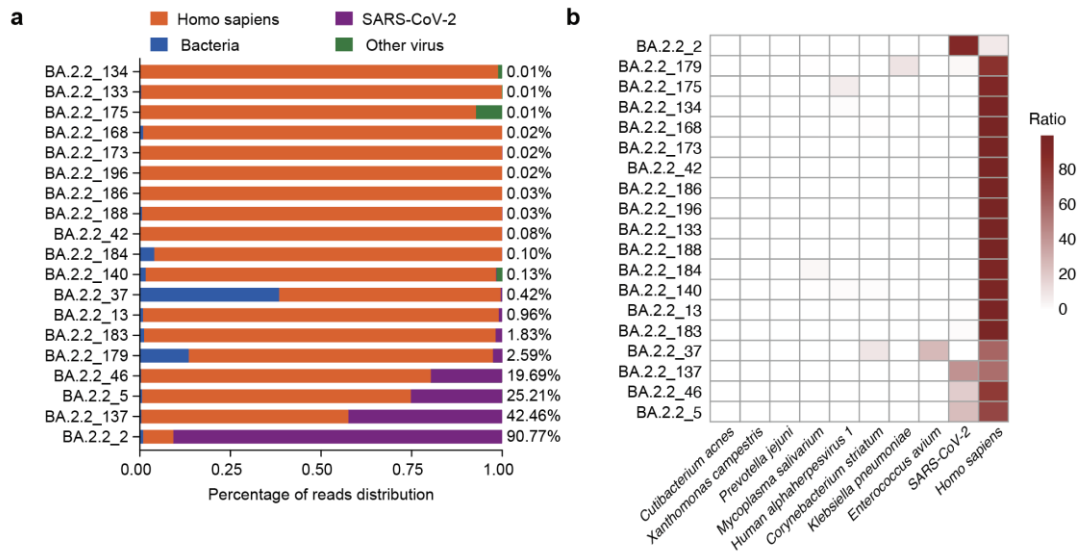


Figure S5. SARS-CoV-2 and co-infection burden in BA.2.2-infected COVID-19.

(a) Distribution of host (Homo sapiens), SARS-CoV-2, bacteria and other virus in BALF samples. Ratio of SARS-CoV-2 were listed in the right panel. (b) Heatmap showing top sequenced species in 19 BA.2.2-infected BALF samples.