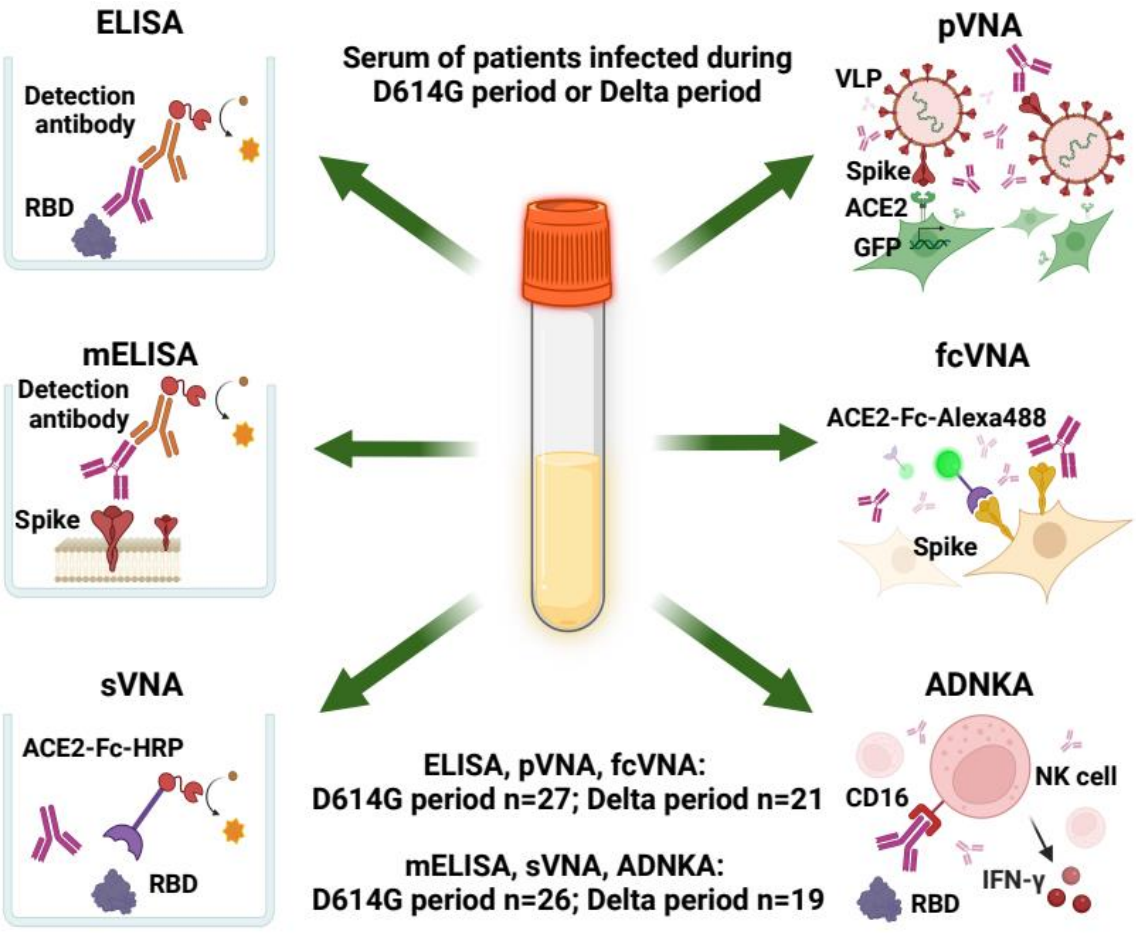
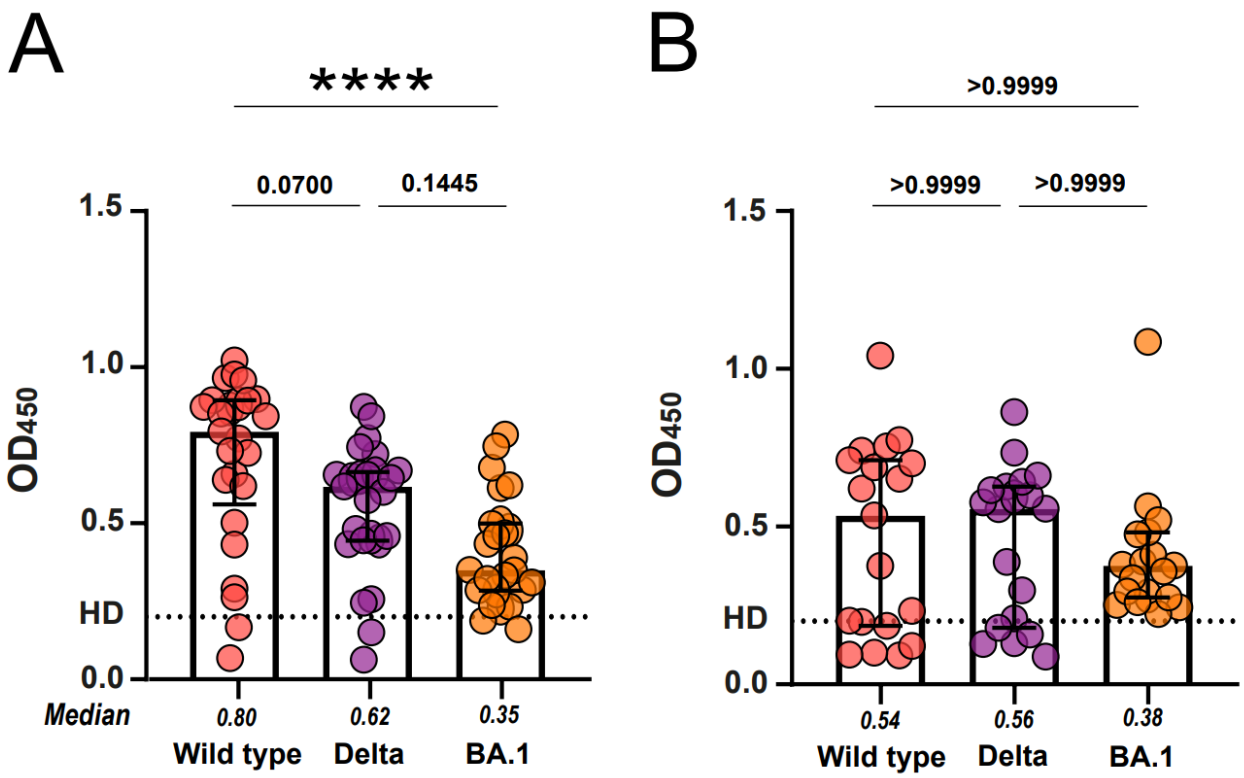
**Supplementary Table 1. Patients' characteristics.**

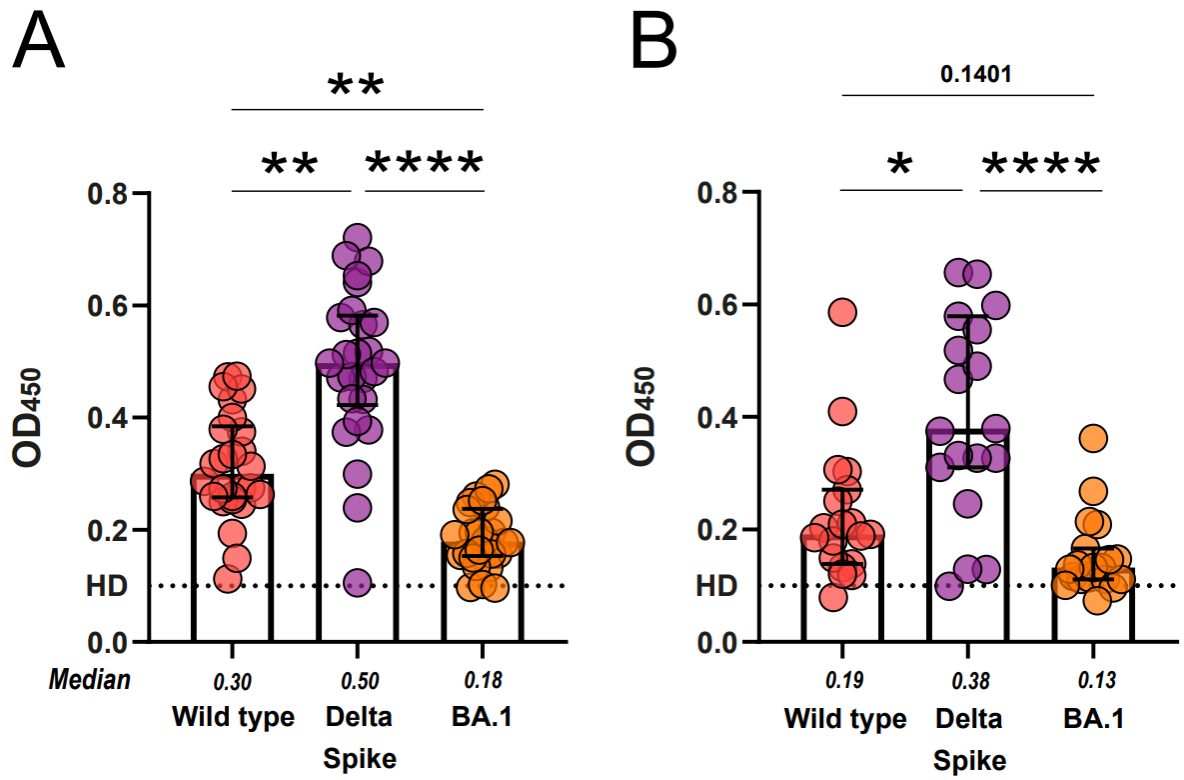
| Characteristics | D614G period | Delta period | Total | *p*-value |
|---|---|---|---|---|
| Females, n (%) | 13 (48.1%) | 13 (61.9%) | 26 (54.2%) | - |
| Age (years), median (IQR) | 68 (IQR 61-72) | 73 (IQR 63-82) | 68 (IQR 62-76) | 0.2127 |
| Days from symptoms' onset to sampling, median (IQR) | 21 (IQR 17-35) | 21 (IQR 18-32) | 21 (IQR 18-33) | 0.5757 |
| COVID-19 severity, n (moderate/severe) | 9/18 | 8/13 | 17/31 | - |
| Vaccine status, Not vaccinated | 100% (27/27) | 100% (21/21) | 100% (48/48) | - |
| Period of infection | May–June 2020 | October–November 2021 | | - |



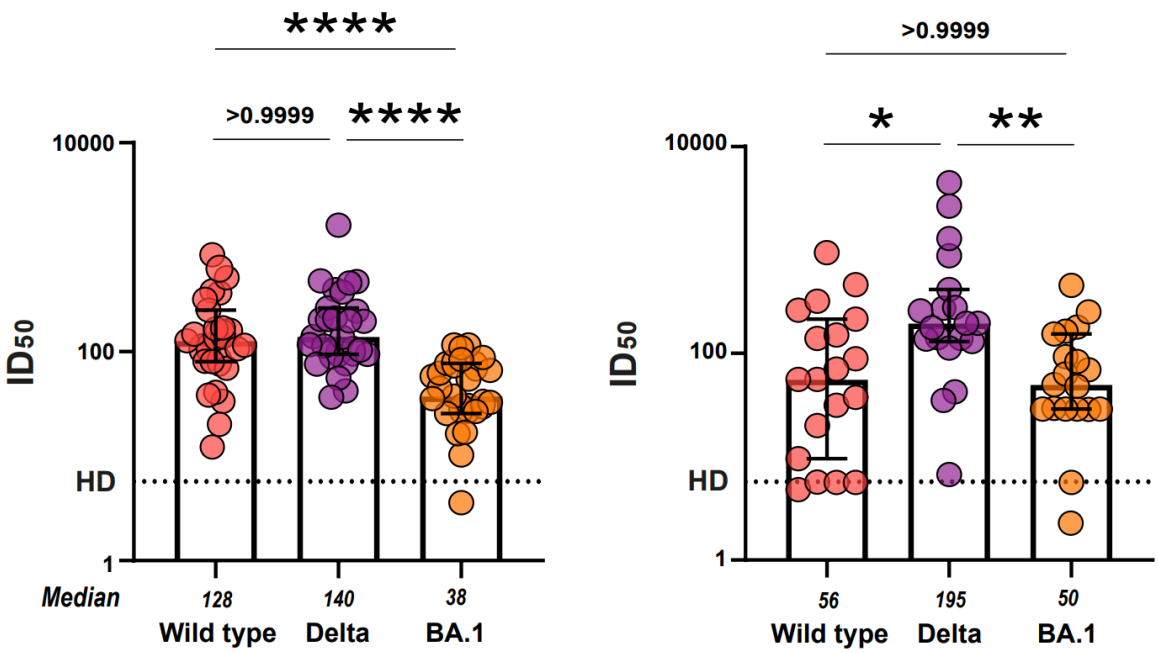

**Supplementary Figure 1. Study design.**
The study included two groups of patients hospitalized for acute COVID-19. Serum samples were collected from patients who had been infected during D614G (n = 27) or Delta (n = 21) periods. Sera were tested for SARS-CoV-2 binding and neutralizing antibodies with six assays based on standard ELISA, cell-membrane-based ELISA (mELISA), surrogate or pseudotyped virus-neutralization assay (sVNA or pVNA), flow-cytometry-based surrogate virus-neutralization assay (fcVNA) and antibody-dependent NK cell activation (ADNKA) with RBD and Spike protein from wild type, Delta and Omicron BA.1 variants as antigen.



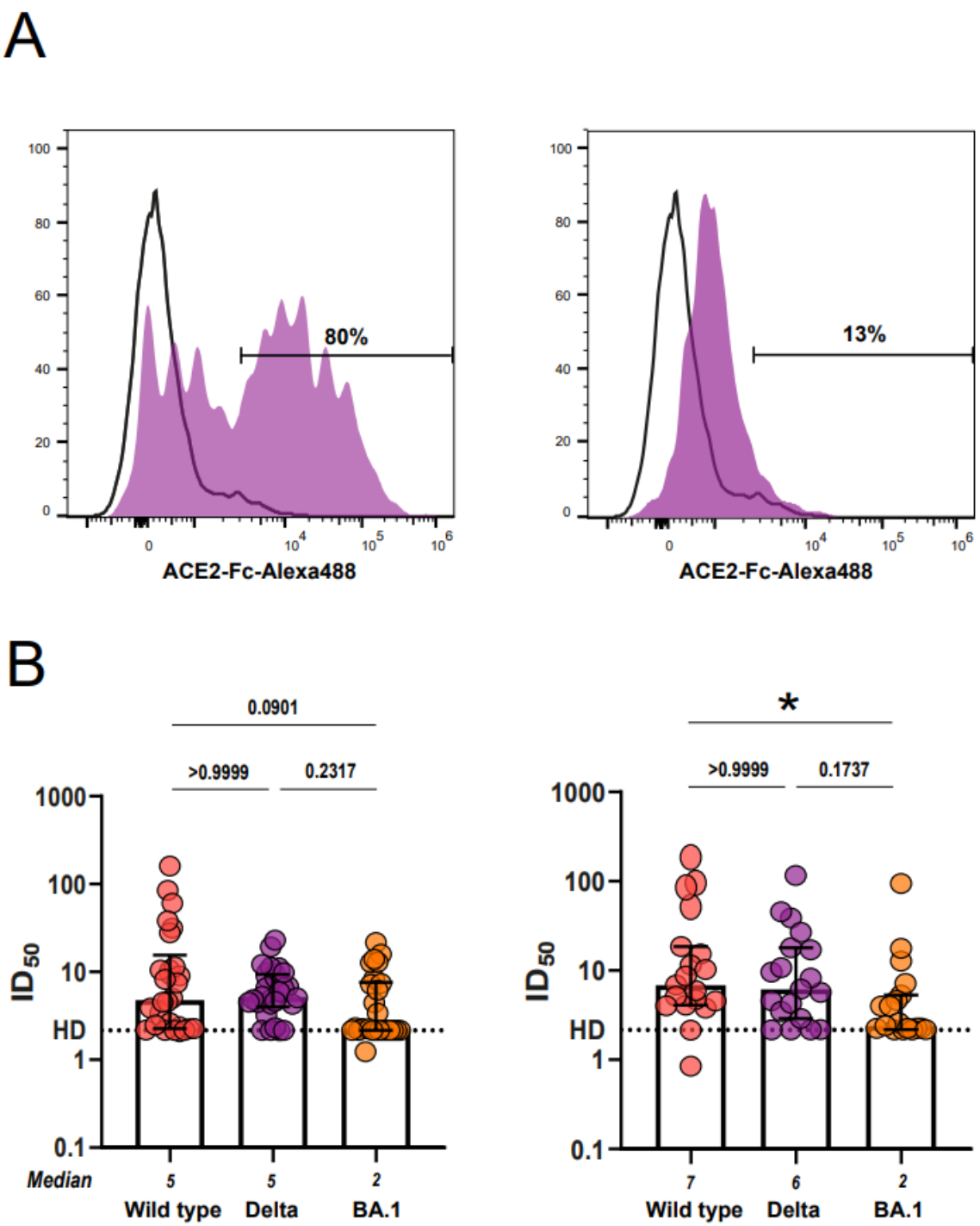

**Supplementary Figure 2.**
Reactivity of D614G (A) and Delta (B) period serum samples with WT, Delta, and BA.1 RBD in ELISA.




**Supplementary Figure 3.**
Reactivity of D614G (A) and Delta (B) period serum samples with WT, Delta, and BA.1 S protein in membrane-based ELISA (mELISA).

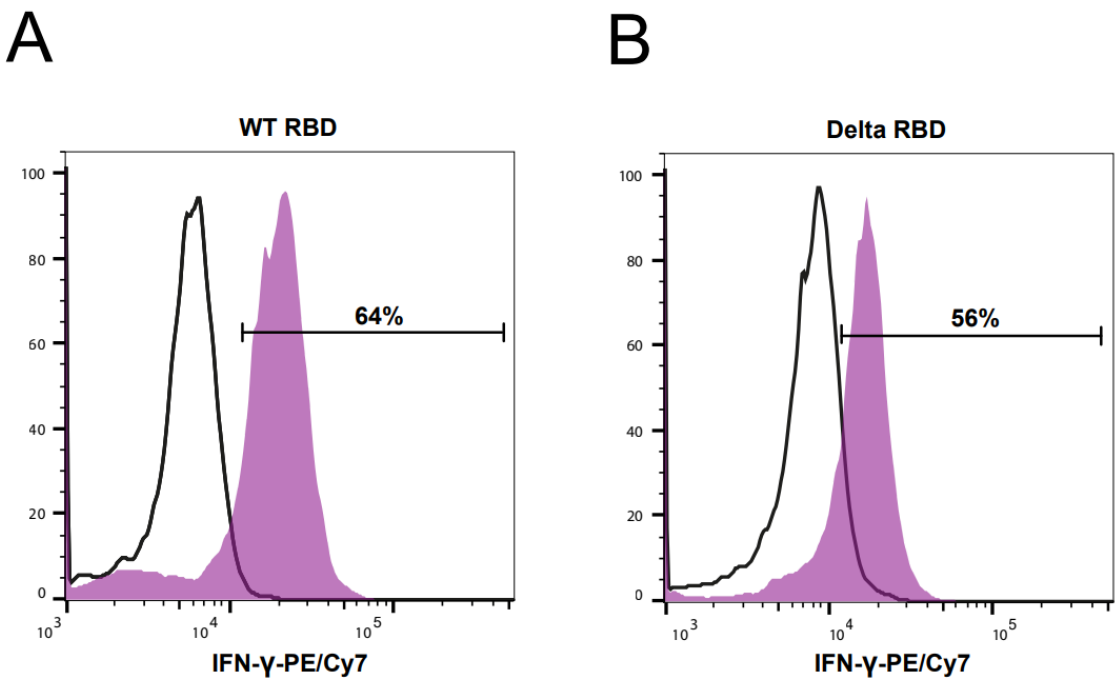



**Supplementary Figure 4.**
Neutralization antibody titers ($ID_{50}$ values) against VLP pseudotyped with WT, Delta, and BA.1 Spike variants in pseudotyped virus-neutralization assay (pVNA).




**Supplementary Figure 5. Flow cytometry based surrogate virus neutralization assay (fcVNA).**

A - representative flow plots for HEK293 cells transiently transfected with WT Spike and stained with ACE2-Fc-Alexa488 without addition of patient serum (left panel) or in the presence of patient serum (right panel)**.** Untransfected cells stained with ACE2-Fc-Alexa488 were used as a control (open plots). B - neutralization antibody titers ($ID_{50}$ values) against WT, Delta, and BA.1 Spike variants in fcVNA.




**Supplementary Figure 6. Representative flow plots of antibody-dependent NK cell activation assay (ADNKA).**

NK cells were incubated in wells coated with WT (A) or Delta (B) RBD, then permeabilized and stained with PE/Cy5-labeled antibody for IFN-γ. Numbers indicate the percentage of positive events. NK cells from uncoated wells stained with for IFN-γ-PE/Cy7 were used as a control (open plots).