

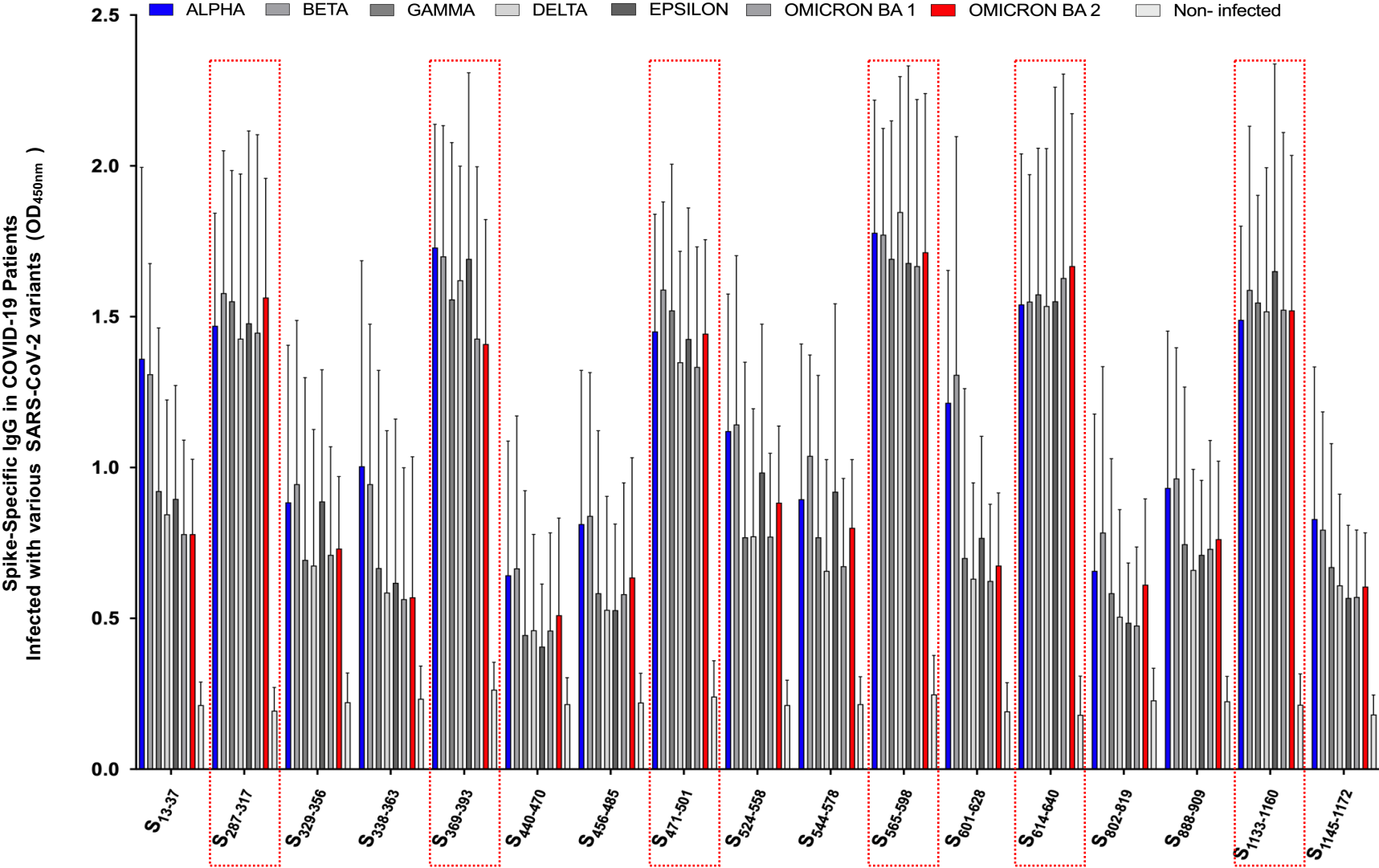
Supplemental Table. S1

| Spike protein position | Start position in sequence | End position in sequence | Sequence                            |
|------------------------|----------------------------|--------------------------|-------------------------------------|
| S <sub>13-37</sub>     | 13                         | 37                       | SQCVNLTTRTQLPPAYTNSFTRGVY           |
| S <sub>287-317</sub>   | 287                        | 317                      | DAVDCALDPLSETKCTLKSFTVEKGIYQTSN     |
| S <sub>329-356</sub>   | 329                        | 356                      | FPNITNLCPFGEVFNATRFASVYAWNRK        |
| S <sub>338-363</sub>   | 338                        | 363                      | FGEVFNATRFASVYAWNRKRISNCVA          |
| S <sub>369-393</sub>   | 369                        | 393                      | YNSASFSTFKCYGVSPTKLNDLCFT           |
| S <sub>440-470</sub>   | 440                        | 470                      | NLDSKVGGNYNLYRLFRKSNLKPFERDIST      |
| S <sub>456-485</sub>   | 456                        | 485                      | FRKSNLKPFERDISTEIYQAGSTPCNGVEG      |
| S <sub>471-501</sub>   | 471                        | 501                      | EIYQAGSTPCNGVEGFNCYFPLQSYGFQPTN     |
| S <sub>524-558</sub>   | 524                        | 558                      | VCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKK |
| S <sub>544-578</sub>   | 544                        | 578                      | NGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRD |
| S <sub>565-598</sub>   | 565                        | 598                      | QFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVI |
| S <sub>601-628</sub>   | 601                        | 628                      | GTNTSNQVAVLYQDVNCTEVPVAIHADQ        |
| S <sub>614-640</sub>   | 613                        | 640                      | QDVNCTEVPVAIHADQLTPTWRVYSTGS        |
| S <sub>802-819</sub>   | 802                        | 819                      | FSQILPDPSKPSKRSFIE                  |
| S <sub>888-909</sub>   | 888                        | 909                      | FGAGAALQIPFAMQMAYRFNGI              |
| S <sub>1133-1160</sub> | 1133                       | 1160                     | VNNTVYDPLQPELDSFKEELDKYFKNHT        |
| S <sub>1145-1172</sub> | 1145                       | 1172                     | LDSFKEELDKYFKNHTSPDVDLGDISGI        |

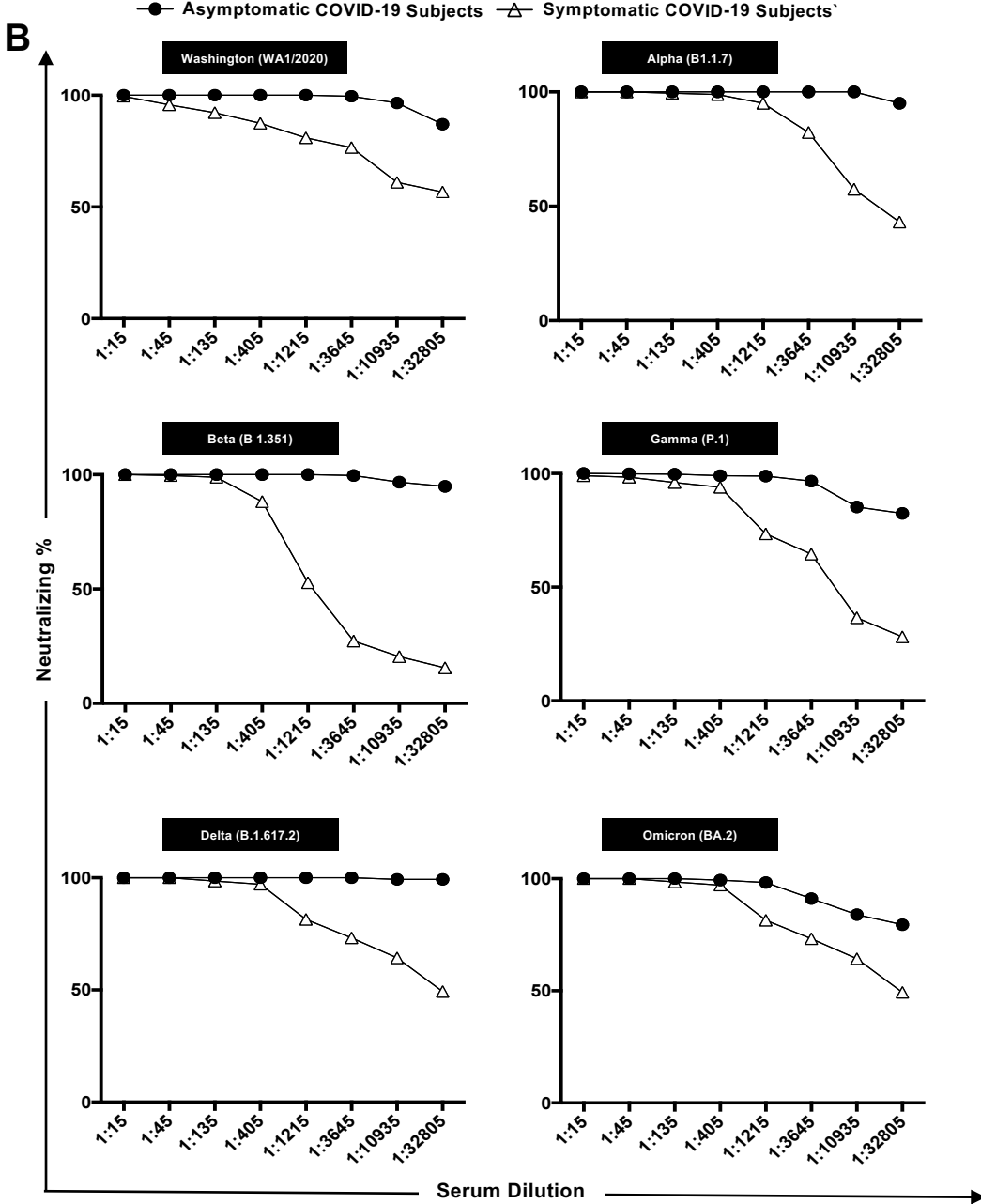
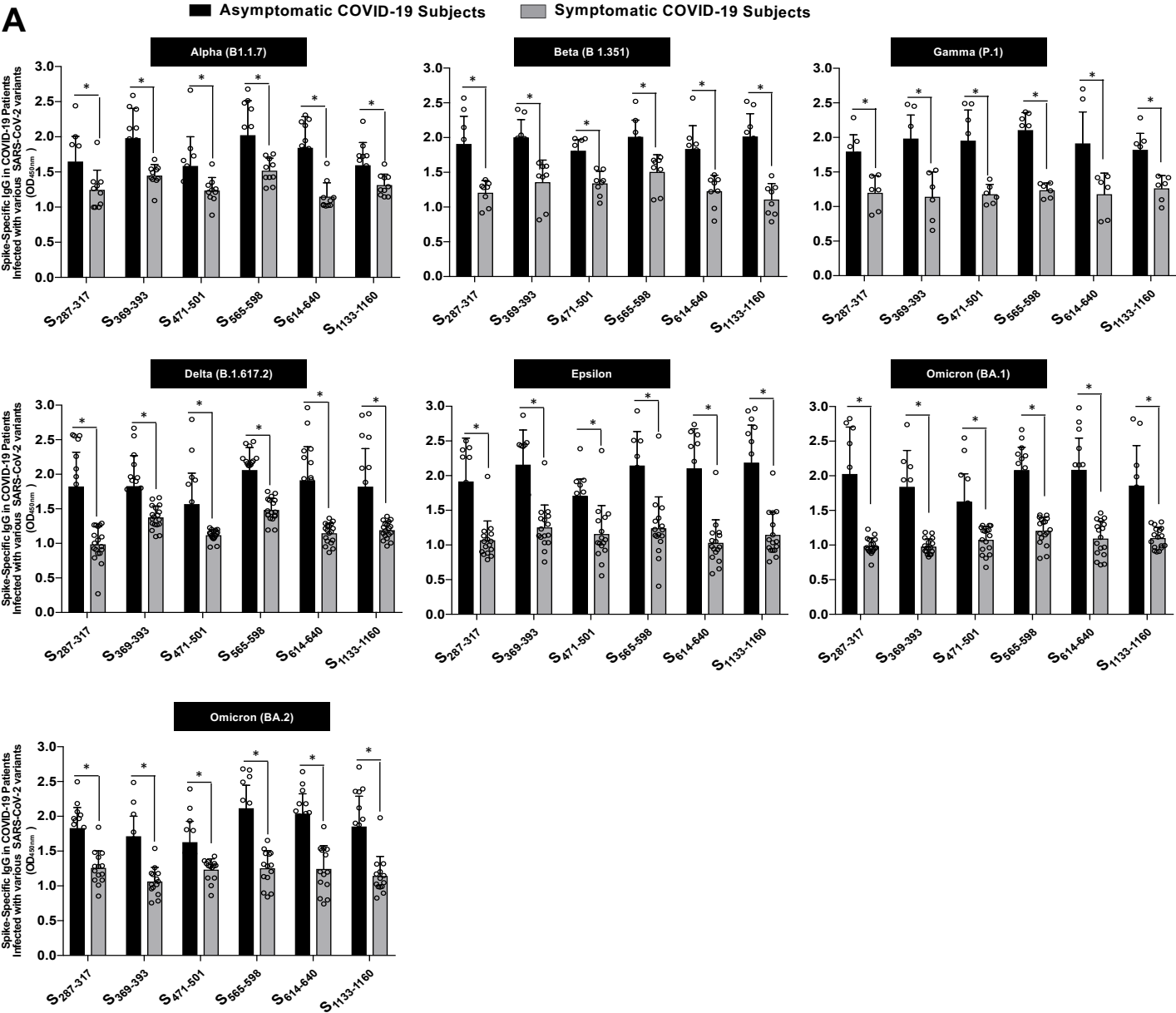
**Supplemental Table S1. The Amino acid sequences and selection criteria of B-cell epitopes from the spike protein of SARS-CoV-2.**

The table presents the amino acid sequences of 17 B-cell epitopes derived from the spike protein of SARS-CoV-2. These epitopes were selected based on their high conservation across various coronaviruses, including SARS-CoV-2, the four major "common cold" coronaviruses (CoV-OC43, CoV-229E, CoV-HKU1, and CoV-NL63), and SARS-like coronaviruses (SL-CoVs) isolated from bats, civet cats, pangolins, and camels. Additionally, epitope selection considered the likelihood of each linear epitope being exposed on the surface of infected target cells.

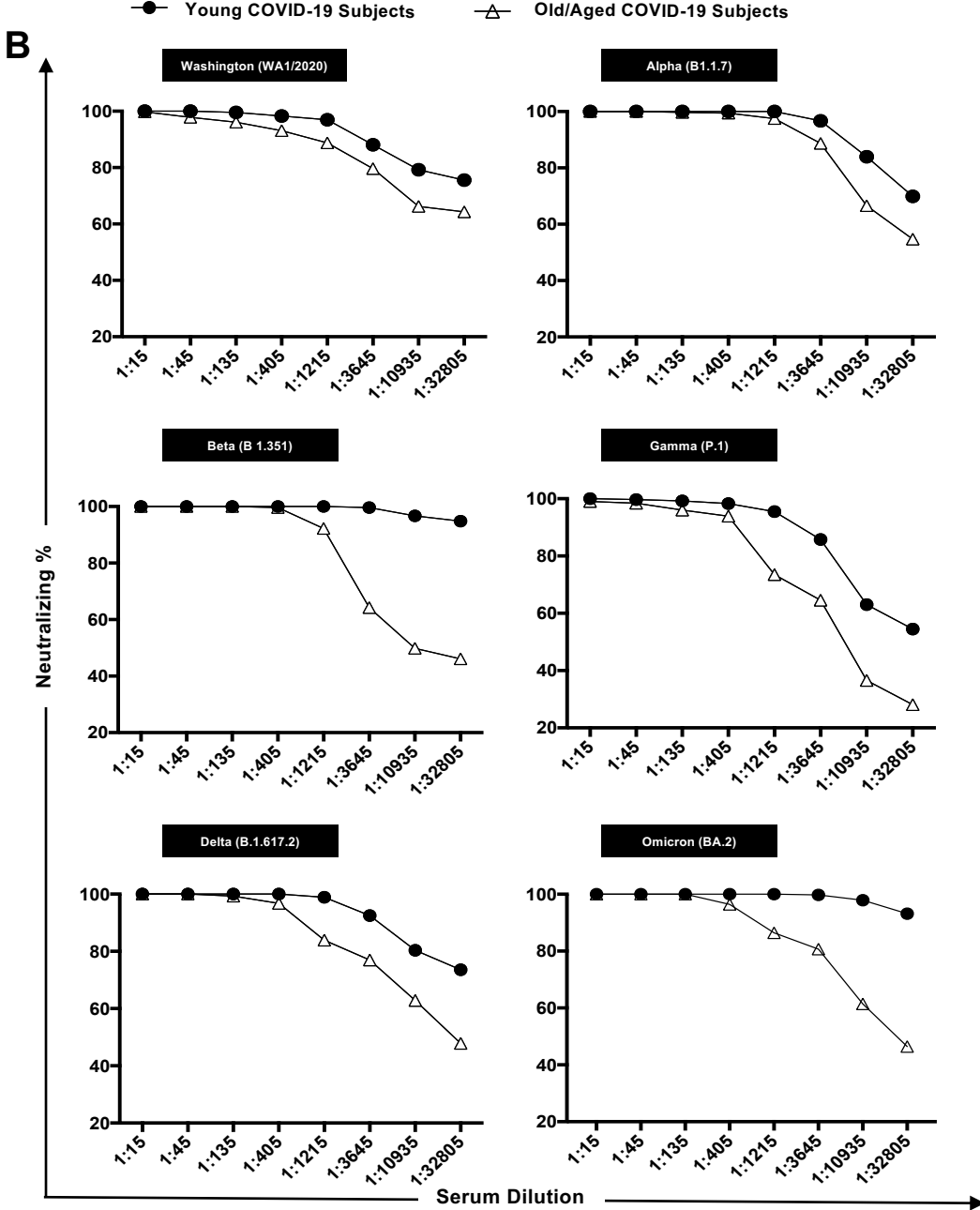
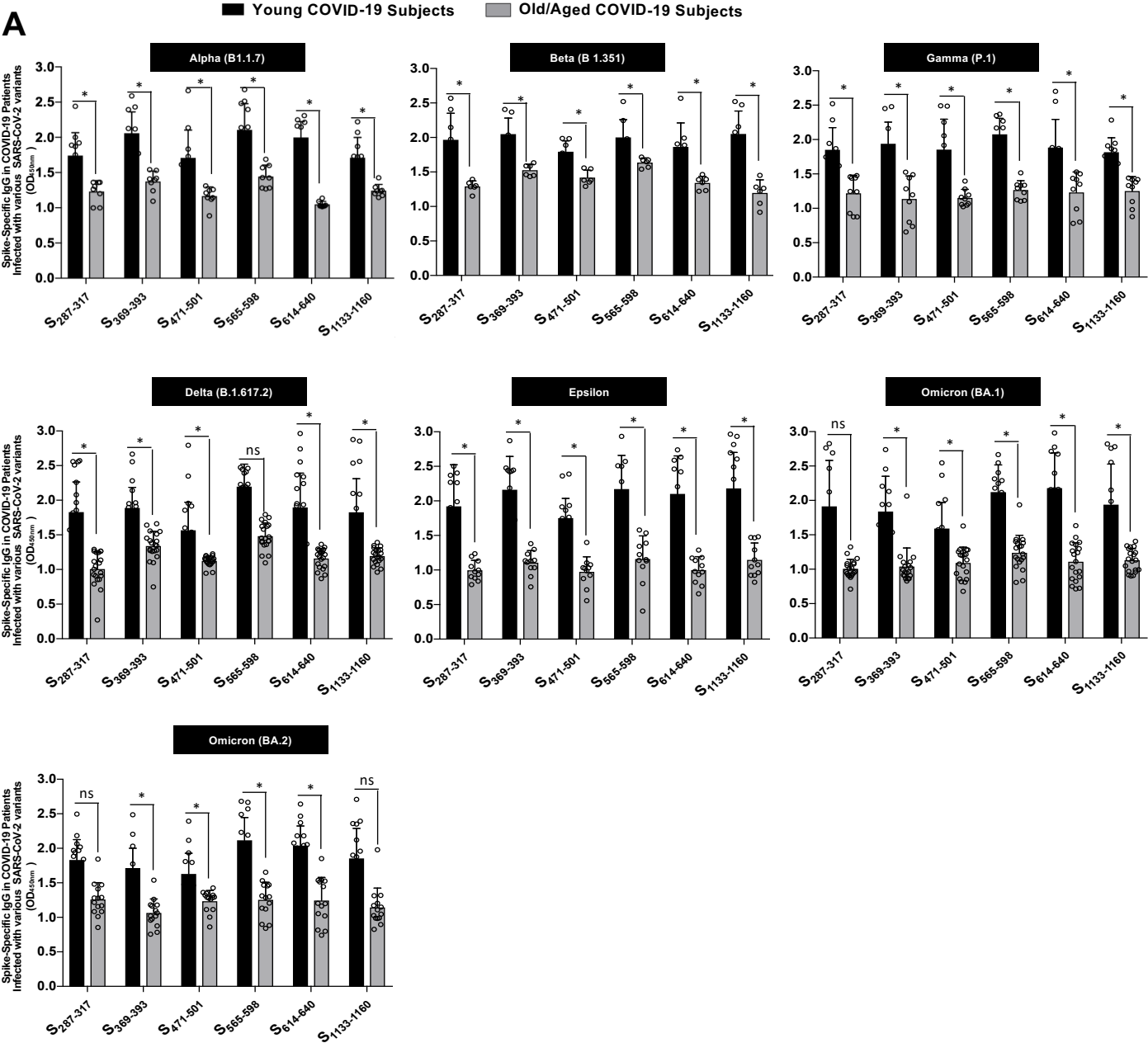
Supplemental Fig. S1



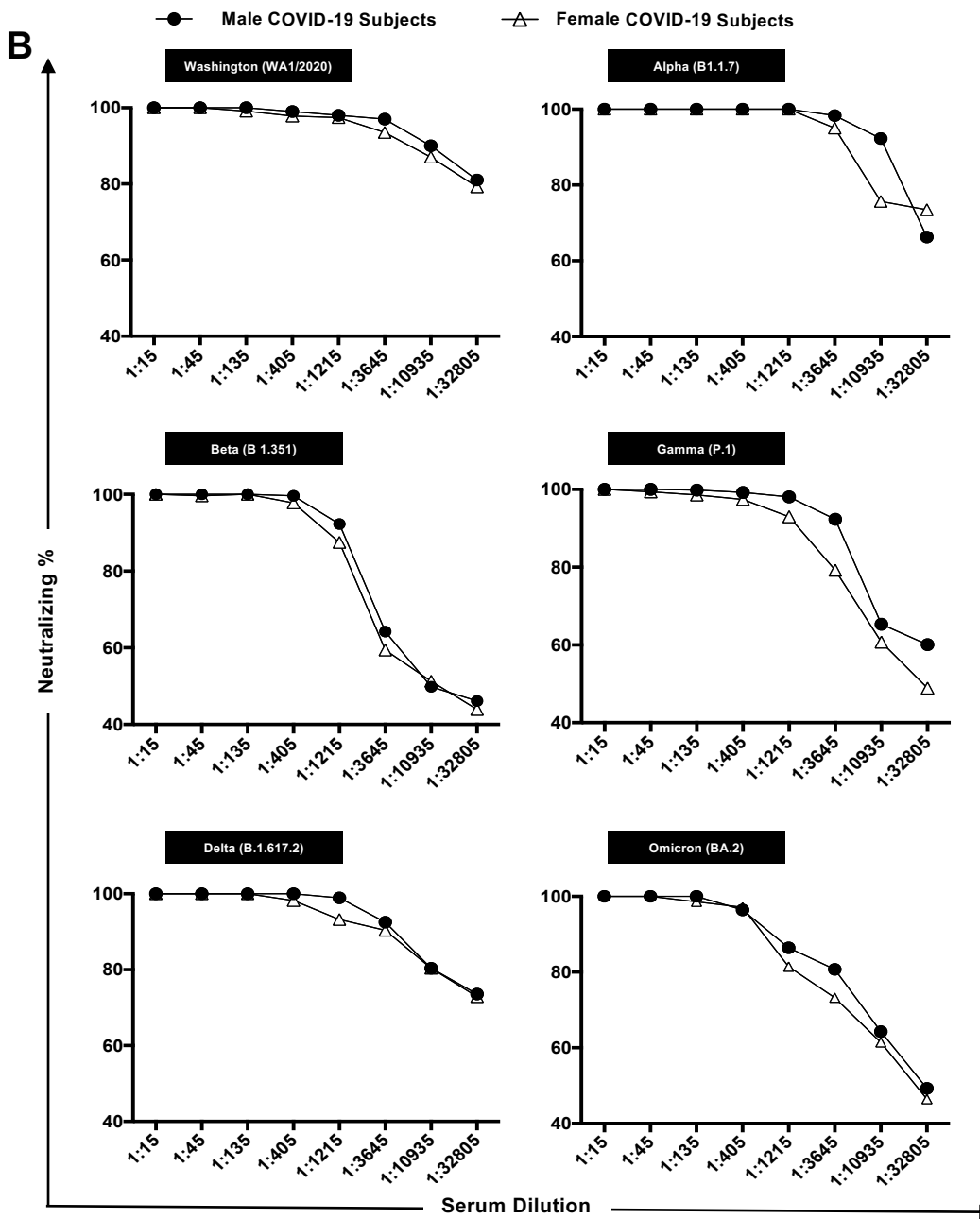
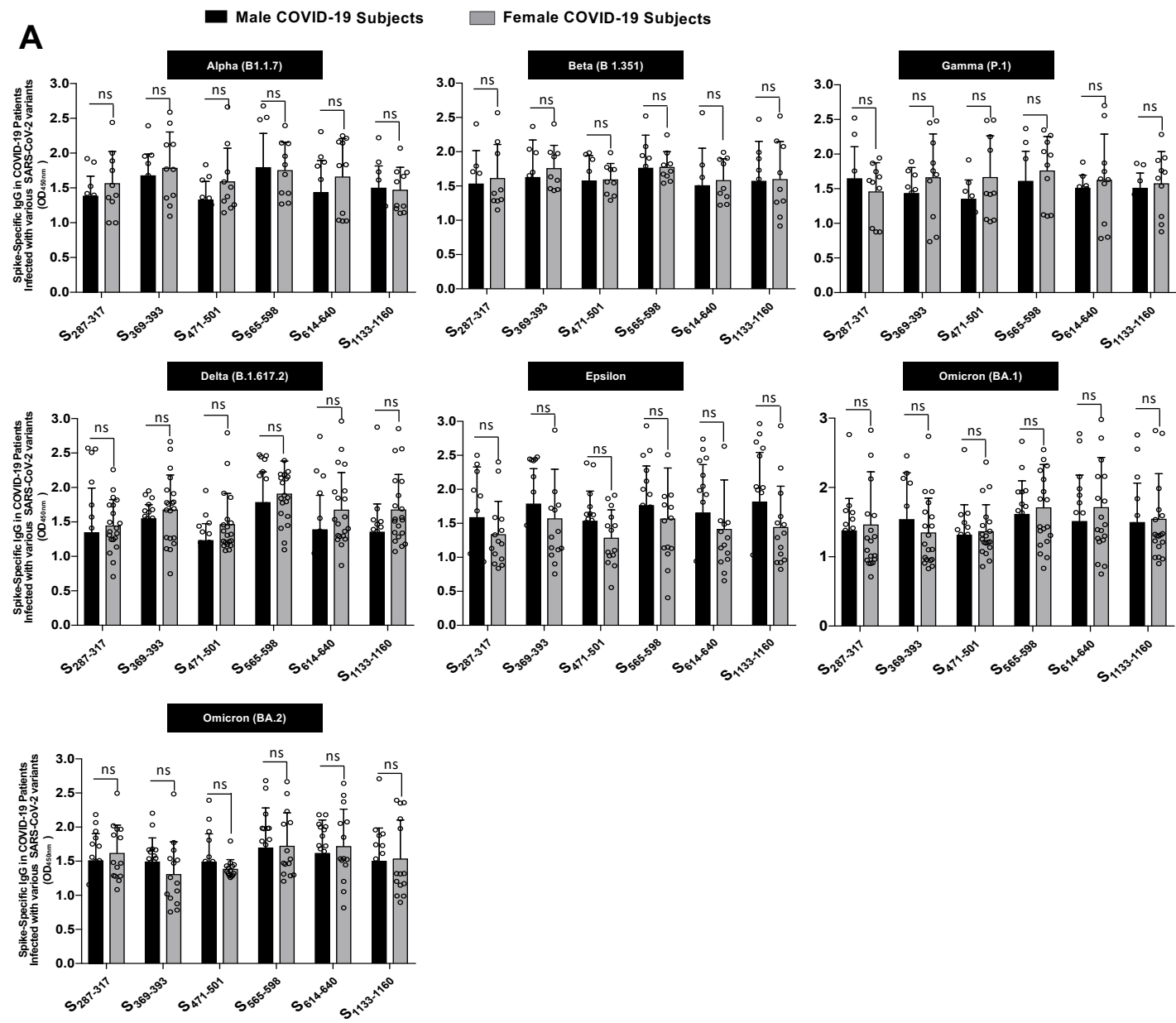
**Supplemental Figure S1: Evaluation of IgG binding to conserved B cell “asymptomatic” epitopes.** Graph shows the optical density for anti SARS-CoV-2 peptide specific IgG measured in sera from different groups of COVID-19 infected with highly pathogenic SARS-CoV-2 variants of concern. Dotted lines indicate selected peptides demonstrating notably high immunogenicity among the 17 immunodominant B cell peptides analyzed.



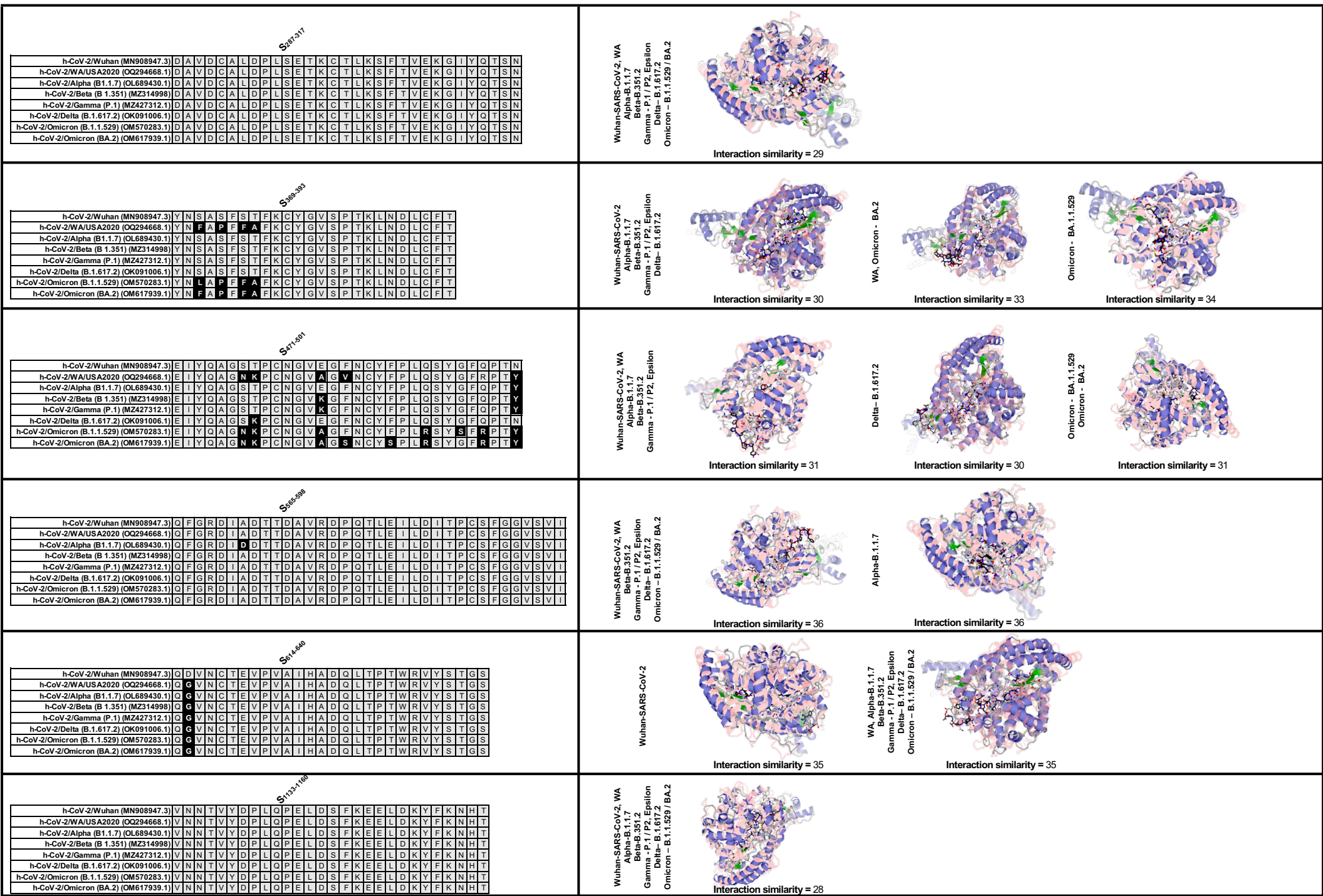
**Supplemental Figure S2. Severity-dependent immune responses against 'universal' B-cell epitopes in COVID-19 patients exposed to different SARS-CoV-2 variants of concern: Highly conserved COVID-19 peptide immunogenicity evaluation.** Bar graphs show the peptide binding IgG level for the 6 “universal” B cell epitopes measured by ELISA as (*panel A*). Serum samples were obtained from COVID-19 patients infected with various SARS-CoV-2 variants of concern (VOC) including Alpha (B.1.1.7), Beta (B.1.351), Epsilon (B.1.427/B.1.429), Delta (B.1.617.2), and Omicron (BA.1 and BA.2), and segregated into two distinct groups based on severity level, categorized as "Asymptomatic" and "Symptomatic". Neutralization (%) by sera from these patients against the different VOCs of SARS-CoV-2: Alpha (B.1.1.7), Beta (B.1.351), Epsilon (B.1.427/B.1.429), Delta (B.1.617.2), and Omicron (BA.2) is presented in (*panel B*). Bars represent means  $\pm$  SEM. Data were analyzed by student's *t*-test and multiple t-tests. Results were considered statistically significant at  $P < 0.05$ . Statistical correction for multiple comparisons was applied using the Holm-Sidak method.



**Supplemental Figure S3. Age-dependent immune responses against 'universal' B-cell epitopes in COVID-19 patients exposed to different SARS-CoV-2 variants of concern: Highly conserved COVID-19 peptide immunogenicity evaluation.** Bar graphs represent the peptide binding IgG level for the 6 “universal” B cell epitopes measured by ELISA as shown in *panel (A)*. Serum was obtained from COVID-19 patients that were infected with one of the following six SARS-CoV-2 different variants of concern (VOC) Alpha (B.1.1.7), Beta (B.1.351), Epsilon (B.1.427/B.1.429), Delta (B.1.617.2), and Omicron (BA.1) and Omicron (BA.2) and then segregated into two distinct age groups, categorized as "Old" and "Young". The **(B)** *panel* represents Neutralization (%) by sera from COVID-19 patients that were infected with one of the six different variants of concern (VOC) of SARS-CoV-2 and then segregated into two distinct age groups; "Old" and "Young" against Alpha (B.1.1.7), Beta (B.1.351), Epsilon (B.1.427/B.1.429), Delta (B.1.617.2), and Omicron (BA.2). Bars represent means  $\pm$  SEM. Data were analyzed by student's *t*-test and multiple *t*-tests. Results were considered statistically significant at  $P < 0.05$ . Statistical correction for multiple comparisons was applied using the Holm-Sidak method.



**Supplemental Figure S4. Gender-dependent immune responses against 'universal' B-cell epitopes in COVID-19 patients exposed to different SARS-CoV-2 variants of concern: Highly conserved COVID-19 peptide immunogenicity evaluation.** Similar to (Fig. 2) and (Fig. 3), bar graphs illustrate the peptide binding IgG level for the 6 “universal” B cell epitopes measured by ELISA (*panel A*). Serum samples were collected from COVID-19 patients infected with various SARS-CoV-2 variants of concern (VOC) and categorized into two distinct groups based on gender. The (**B**) *panel* shows neutralization (%) by sera from these patients against the different SARS-CoV-2 VOCs Alpha (B.1.1.7), Beta (B.1.351), Epsilon (B.1.427/B.1.429), Delta (B.1.617.2), and Omicron (BA.2). Bars represent means  $\pm$  SEM. Data were analyzed using student's t-test and multiple t-tests. Results were considered statistically significant at  $P < 0.05$ , with statistical correction applied using the Holm-Sidak method.



**Supplemental Figure S5. Docking of SARS-CoV-2 Spike glycoprotein-derived B cell epitopes to human ACE2 receptor:** Molecular docking of 6 B-cell epitopes was performed, that were found to be highly immunodominant across all the known SARS-CoV-2 variants of concern. The B-cell epitopes were identified from the SARS-CoV-2 Spike glycoprotein, with ACE2 receptors. B cell epitopes are shown in ball and stick structures whereas the ACE2 receptor protein is shown as a template.  $S_{471-501}$  and  $S_{369-393}$  peptide epitopes possess receptor binding domain region specific amino acid residues. The prediction accuracy is estimated from a linear model as the relationship between the fraction of correctly predicted binding site residues and the template-target similarity measured by the protein structure similarity score and interaction similarity score ( $S_{\text{Inter}}$ ) obtained by linear regression.  $S_{\text{Inter}}$  shows the similarity of amino acids of the B-cell peptides aligned to the contacting residues in the amino acids of the ACE2 template structure. Higher  $S_{\text{Inter}}$  score represents a more significant binding affinity among the ACE2 molecule and B-cell peptides.