

Supplementary Materials for
**Severe COVID-19 induces autoantibodies against angiotensin II that
correlate with blood pressure dysregulation and disease severity**

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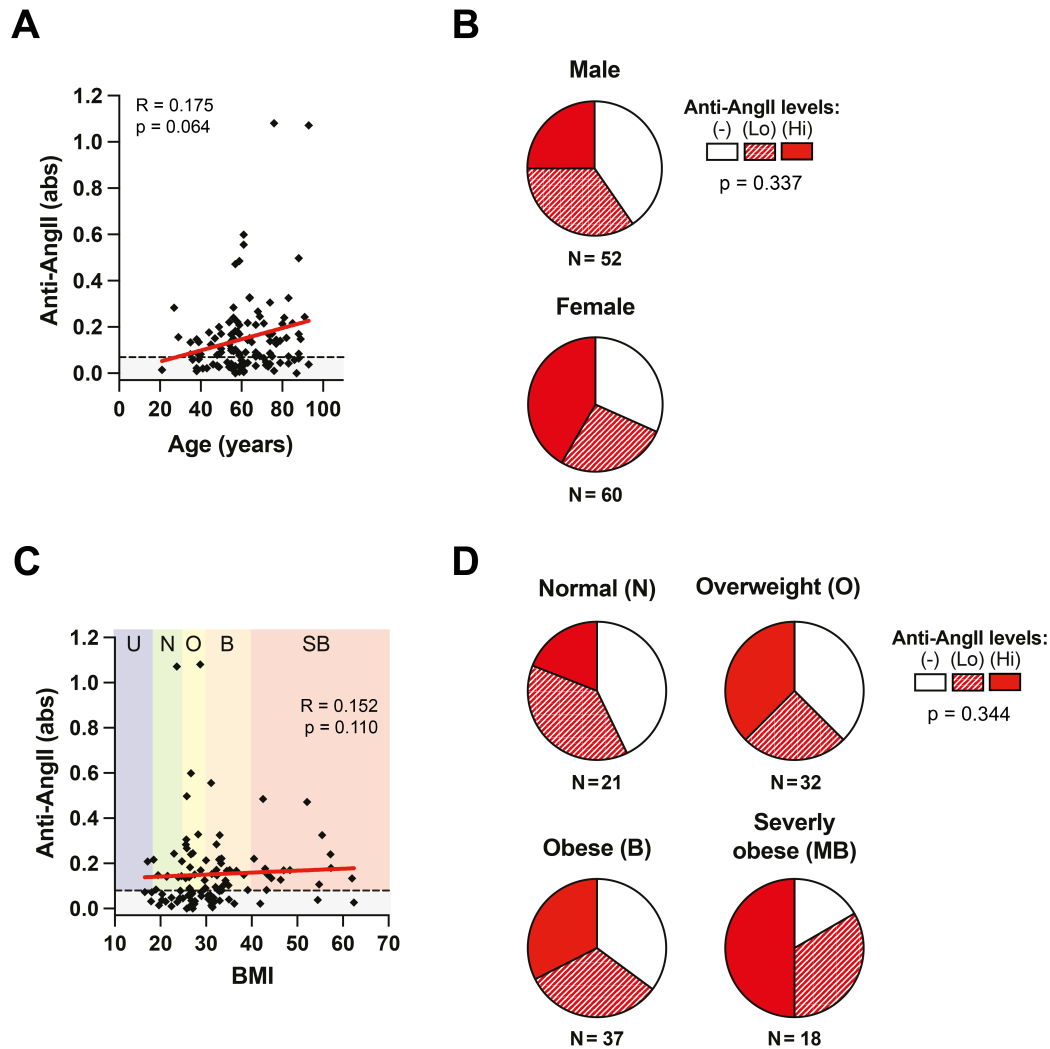
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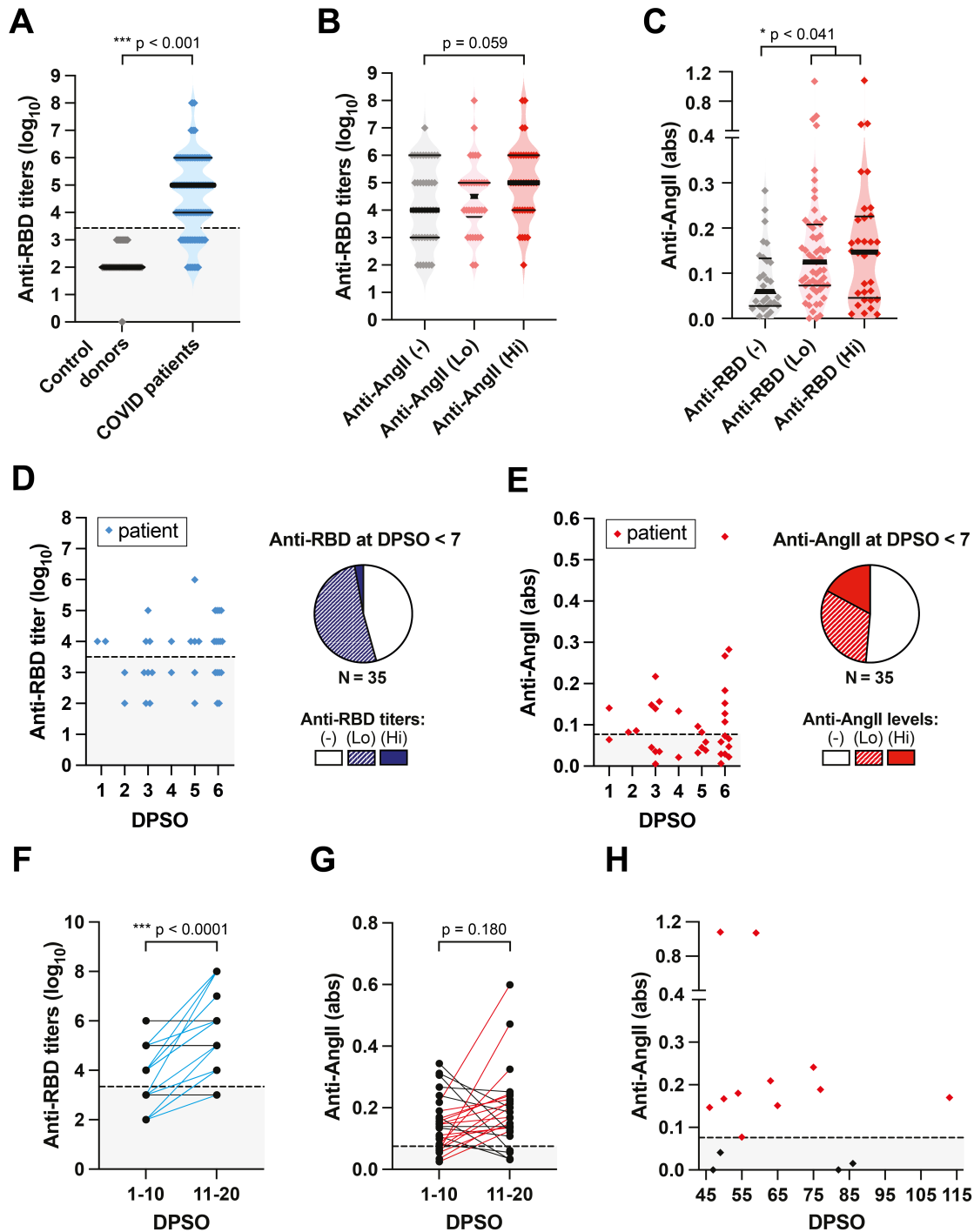
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Supplementary Figures



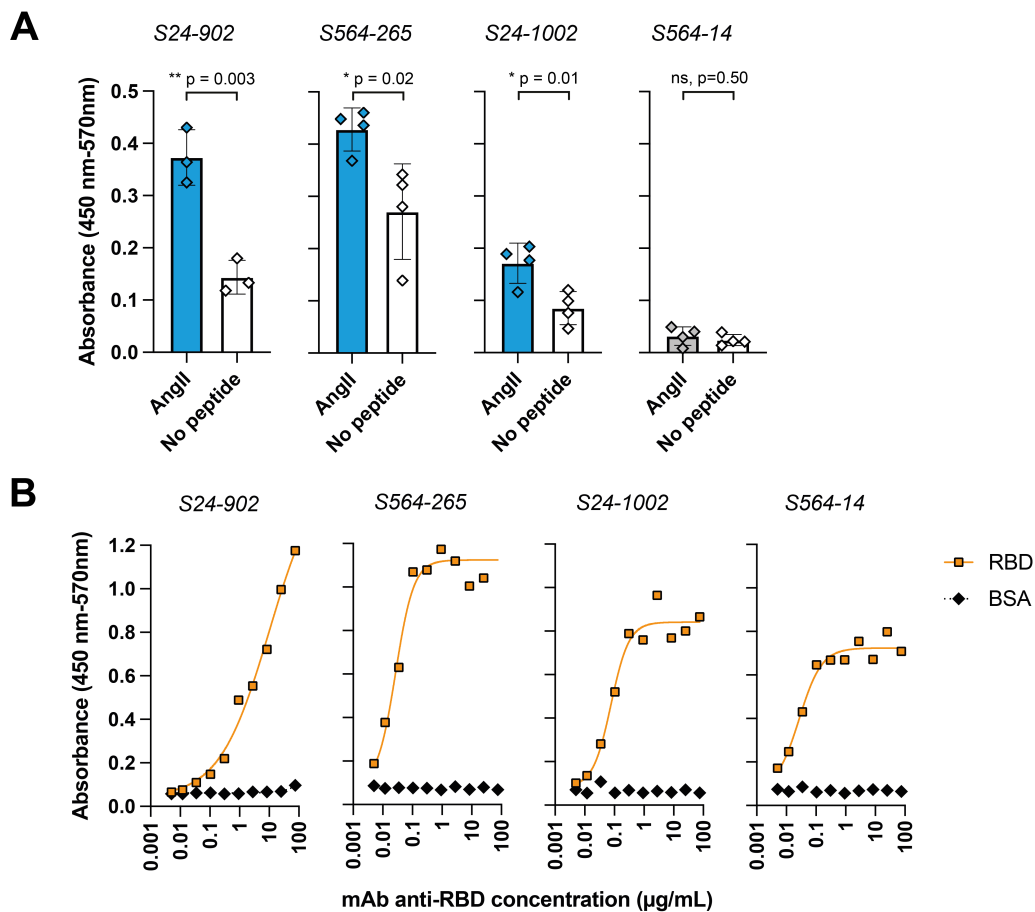
Supplementary Figure 1. Anti-AngII does not correlate with sex, age and body mass index (BMI) in hospitalized COVID patients (N=112). Grey threshold = limit for anti-AngII positivity. **(A)** Correlation between the level of anti-AngII antibodies and the age of patients (Spearman correlation; linear regression in red). **(B)** Proportion of male or female patients with high (Hi), low (Lo) or negative (-) levels of anti-AngII (χ^2 test). **(C)** Correlation between the level of anti-AngII antibodies and the BMI of patients (Spearman correlation; linear regression in red). **(D)** Correlation of the age of the patients with their level of anti-AngII (Spearman correlation; linear regression in black). U = underweight, N = normal weight, O = overweight, B = obese, SB = severely obese. **(E)** Proportion of patients of different weight categories that had no (-), low (Lo) or high (Hi) anti-AngII levels (χ^2 test).



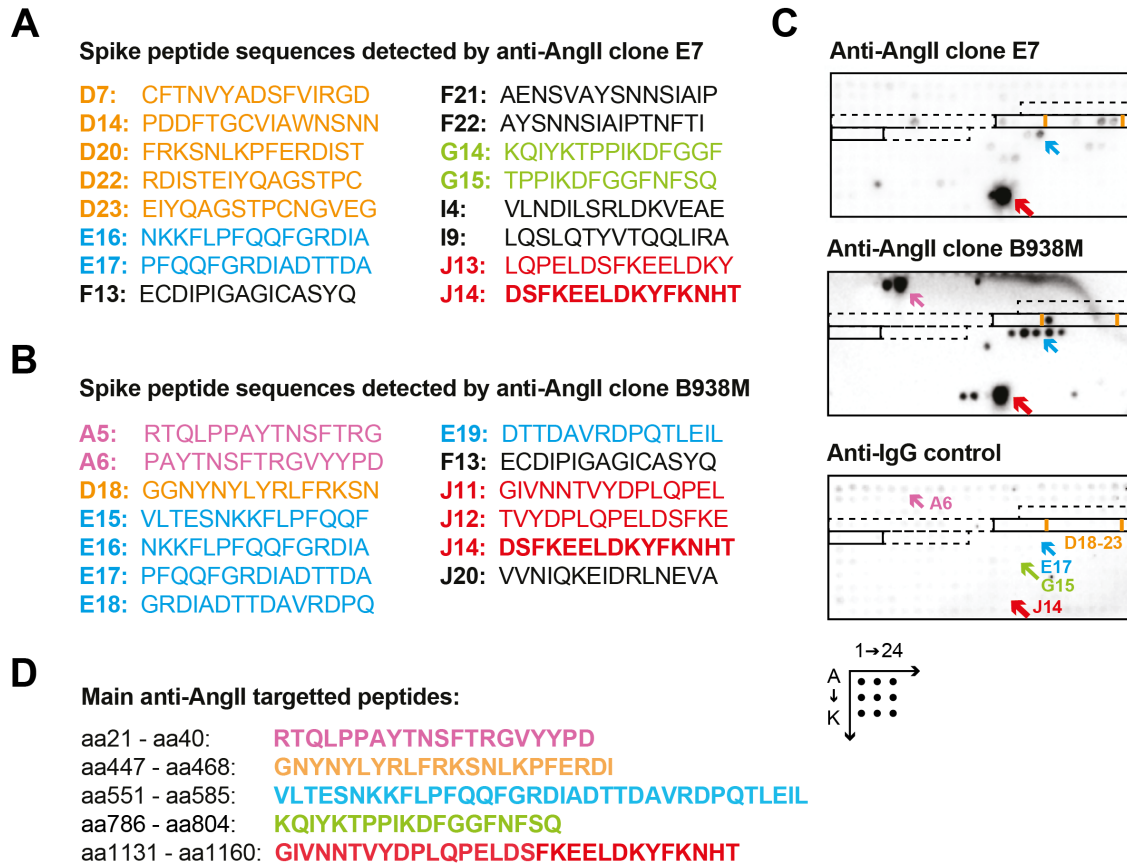
Supplementary Figure 2. Analysis of anti-AngII vs. anti-RBD titers in COVID patients (N=115).

(A) Anti-RBD titers (\log_{10}) in hospitalized COVID patients as compared to control donors (sampled prior to the COVID pandemic; Mann-Whitney test). (B) Anti-RBD titers in COVID patients with negative (-), low (Lo) or high (Hi) levels of anti-AngII (Kruskal-Wallis test with Dunn's post-test). (C)

Level of anti-AngII in COVID patients with negative (-), low (Lo) or high (Hi) titers of anti-RBD (Kruskall-Wallis test with Dunn's post-test). **(D)** Presence of anti-RBD in COVID patients at early times post-symptom (DPSO <7). **(E)** Presence of anti-AngII in COVID patients at early times post-symptom (DPSO <7). **(F)** Increase in anti-RBD titers in COVID patients between 1-10 and 11-20 days post-symptoms onset (DPSO) (N=25; Wilcoxon matched pairs signed rank test). **(G)** Increase in anti-AngII levels in COVID patients between 1-10 and 11-20 DPSO (N=25; Wilcoxon matched pairs signed rank test). **(H)** Levels of anti-AngII at late time (>45 DPSO) after symptoms onset (N=15 patients).

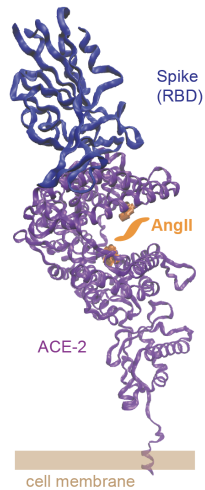


Supplementary Figure 3. Binding of monoclonal anti-RBD to AngII and RBD. **(A)** Monoclonal anti-RBD (at a concentration of 100 μg/mL) binding to AngII as compared to no peptide (nonspecific binding control). **(B)** Specific binding of monoclonal anti-RBD to RBD at various concentrations, as compared to BSA, used as a control for nonspecific binding.

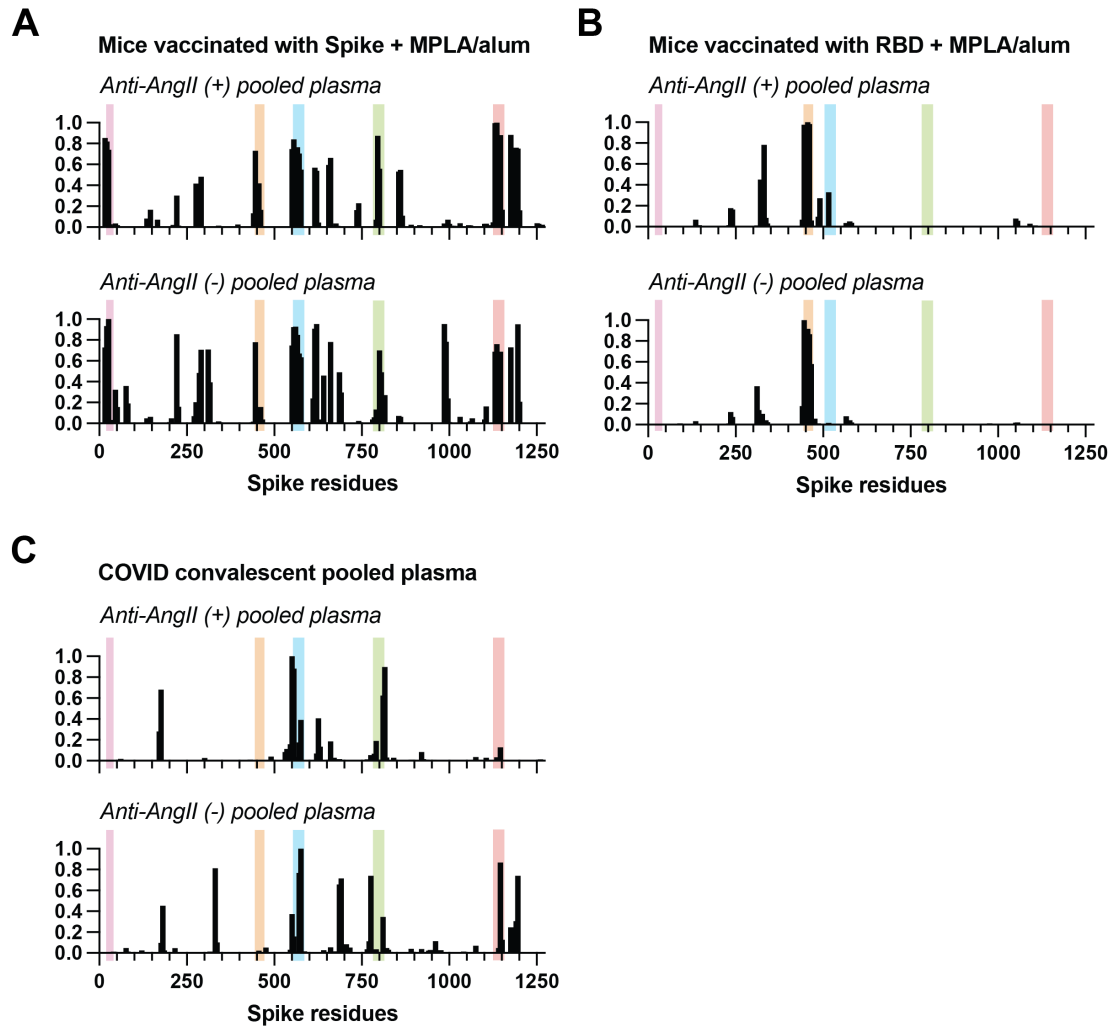


Supplementary Figure 4. Epitopes targeted by the monoclonal anti-AngII clone E7 and B938M.

Monoclonal anti-AngII were added onto a peptide array containing the full-length of Spike with 15-mers peptide with a 5 amino-acids overlap. **(A)** Sequences of the Spike linear epitopes targeted by the anti-AngII clone E7. **(B)** Sequences of the Spike linear epitopes targeted by the anti-AngII clone B938M. **(C)** Representative images of the positive spots on the Spike peptide arrays probed with the anti-AngII clone E7 or B938M, or the anti-IgG secondary control only. The spot J14 is the primary target of both anti-AngII monoclonal antibodies. **(D)** Sequences of the main targeted domains by the anti-AngII monoclonal antibodies that are highlighted in the 3D structure of Spike in Fig. 4F, with the corresponding amino-acid positions (aa#). All domains are targeted by both anti-AngII clones except the aa21-aa40 domain, which is a strong target of the clone B938M only, and aa786-804 which is targeted by clone E7 only.



Supplementary Figure 5. Binding sites of SARS-CoV-2 RBD and AngII on the human Angiotensin Converting Enzyme (ACE)-2. The binding of RBD on ACE-2 seems to occur at a different location than the catalytic site of AngII (PDB: 6M17 (12) by and AngII binding residues were determined from Guy *et al.* (13)).



Supplementary Figure 6. The Spike linear epitopes targeted by anti-AngII monoclonal antibodies are the same as the ones targeted by the plasma IgG of mice vaccinated with recombinant Spike or RBD proteins or of COVID convalescent patients. Highlighted colored regions are the main domains targeted by at least one anti-AngII monoclonal antibody. X-axes represent the position of linear epitopes covering the full-length of Spike. **(A, B)** Linear epitopes of Spike targeted by IgG antibodies in plasma of mice positive (+) or negative (-) for anti-AngII, upon immunization with recombinant Spike (A) or RBD (B) adjuvanted with MPLA/alum (plasma pooled from N=5 mice). **(C)** Linear epitopes of Spike targeted by IgG antibodies in plasma of COVID patients positive (+) or negative (-) for anti-AngII (plasma pooled from N=5 patients).