# Severe COVID-19 induces autoantibodies against angiotensin II that correlate with blood pressure dysregulation and disease severity

PRISCILLA S. BRIQUEZ, SHERIN J. ROUHANI, [...] MELODY A. SWARTZ +11 authors

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## Abstract

Patients infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can experience life-threatening respiratory distress, blood pressure dysregulation, and thrombosis. This is thought to be associated with an impaired activity of angiotensin-converting enzyme 2 (ACE2), which is the main entry receptor of SARS-CoV-2 and which also tightly regulates blood pressure by converting the vasoconstrictive peptide angiotensin II (AngII) to a vasopressor peptide. Here, we show that a significant proportion of hospitalized patients with COVID-19 developed autoantibodies against AngII, whose presence correlates with lower blood oxygenation, blood pressure dysregulation, and overall higher disease severity. Anti-AngII antibodies can develop upon specific immune reaction to the SARS-CoV-2 proteins Spike or receptor-binding domain (RBD), to which they can cross-bind, suggesting some epitope mimicry between AngII and Spike/RBD. These results provide important insights on how an immune reaction against SARS-CoV-2 can impair blood pressure regulation.

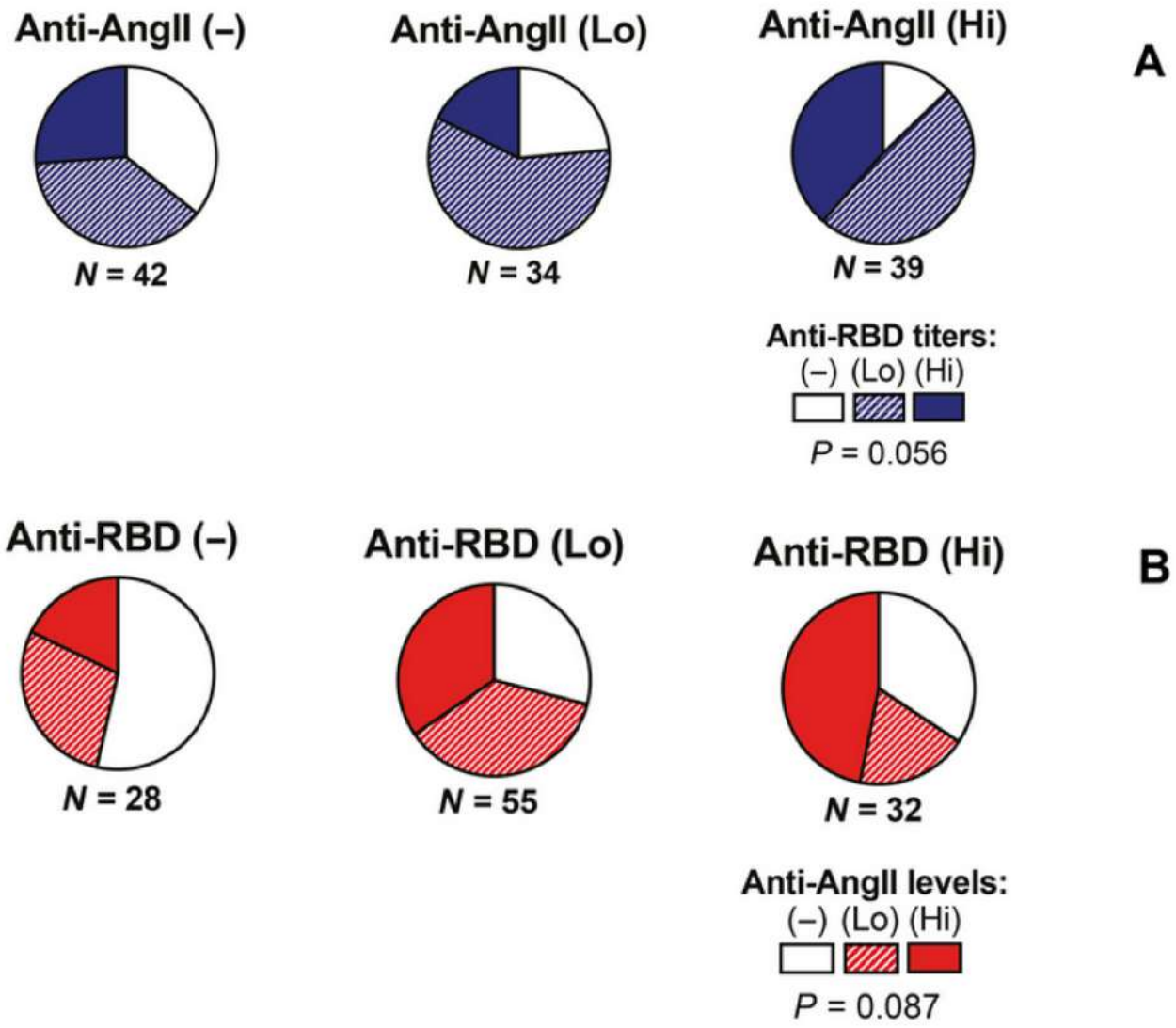


**Fig. 2. Relationship between anti-AngII and anti-RBD antibodies in COVID-hospitalized patients.**

Anti-RBD antibodies were tittered in the plasma of SARS-CoV-2 convalescent hospitalized patients (COVID, *N* = 115), in addition to anti-AngII autoantibodies. Anti-RBD titers are displayed as $\log_{10}$ values [Hi = high (titers 6 to 8); Lo = low (titers 4 to 5); and (−) = negative (titer <4); gray thresholds = limits for anti-AngII or anti-RBD positivity]. Gray threshold indicates positivity of anti-AngII and anti-RBD. (**A**) Proportion of patients with high, low, or no titers of anti-RBD among patients having high, low, or negative levels of anti-AngII ($\chi^2$ test). (**B**) Proportion of patients with high, low, or negative levels of anti-AngII among patients having high, low, or no titers of anti-RBD ($\chi^2$ test). (**C**) Correlation between anti-AngII levels and anti-RBD titers in patients with COVID (Spearman correlation). (**D**) Covariations of anti-AngII and anti-RBD levels between 1 to 10 DPSO (tail of the arrow) and 11 to 20 DPSO (tip of the arrow) matched per patient (arrow, *N* = 25).

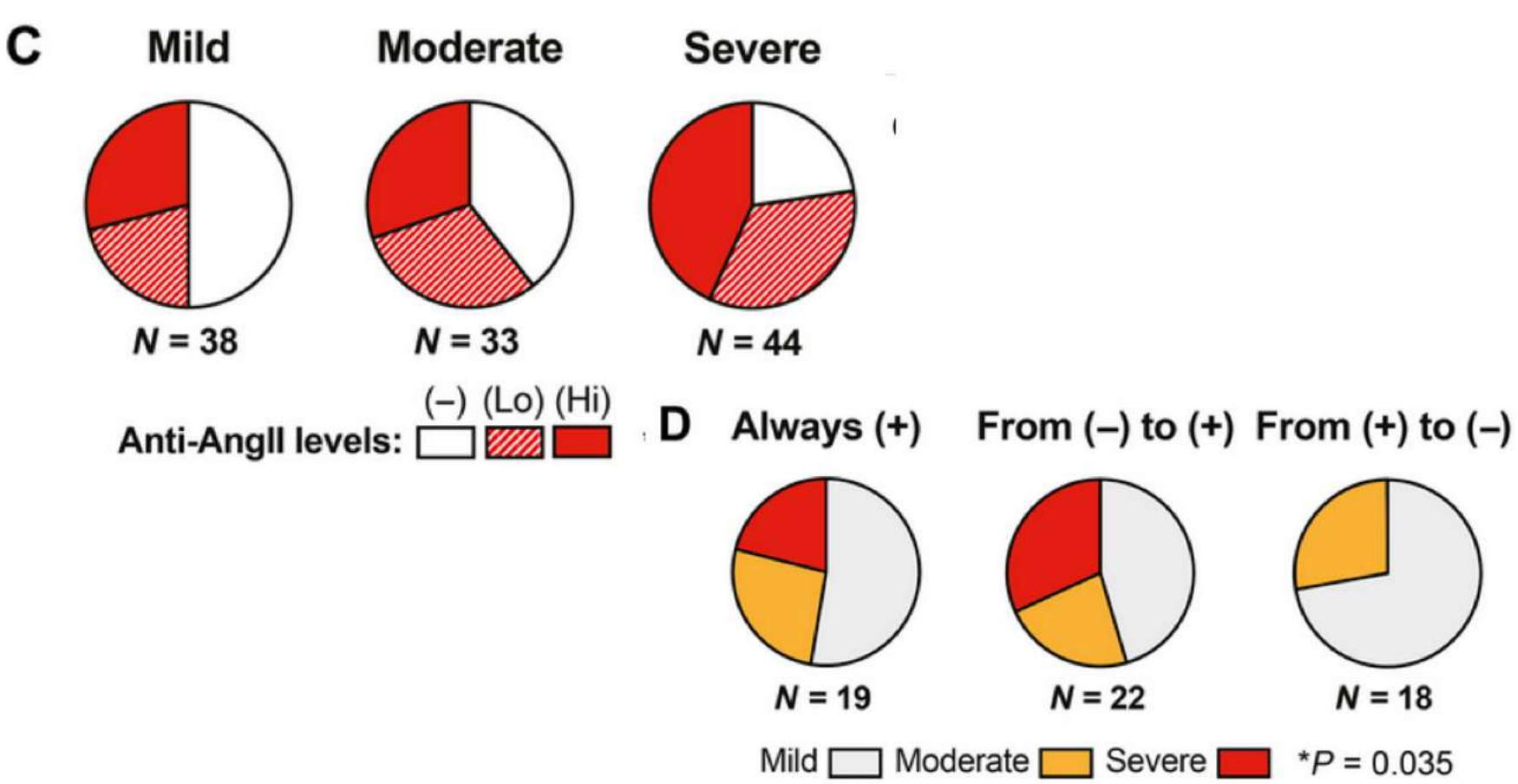


**Fig. 5. Anti-AngII autoantibodies correlates with reduced pulse oxymetric saturation $SpO_2/FiO_2$ (SF ratio) in hospitalized patients with COVID *N* = 115).**

( Gray threshold indicates positivity of anti-AngII. (**A**) SF ratio of patients with COVID who are negative (−) or positive (+) for anti-AngII autoantibodies (Mann-Whitney test). SF ratio values are used to define disease severity as being mild, moderate, or severe. (**B**) Levels of anti-AngII antibodies in patients suffering from mild, moderate, or severe form of COVID, as defined based on SF ratio values (Kruskal-Wallis test with Dunn's posttest). (**C**) Proportion of patients with negative (−), low (Lo), or high (Hi) levels of anti-AngII antibodies according to their disease severity ($\chi^2$ test). (**D**) Of the 75 patients with COVID who were analyzed multiple times after symptoms, proportion of patients who had severe, moderate, or mild disease among patients who were always anti-AngII(+) during their hospitalization [always (+), left], patients who were anti-AngII (−) who turned (+) during their hospitalization [from (−) to (+), middle], and patients who were anti-AngII (+) and who became (−) during their hospitalization [from (+) to (−), right].

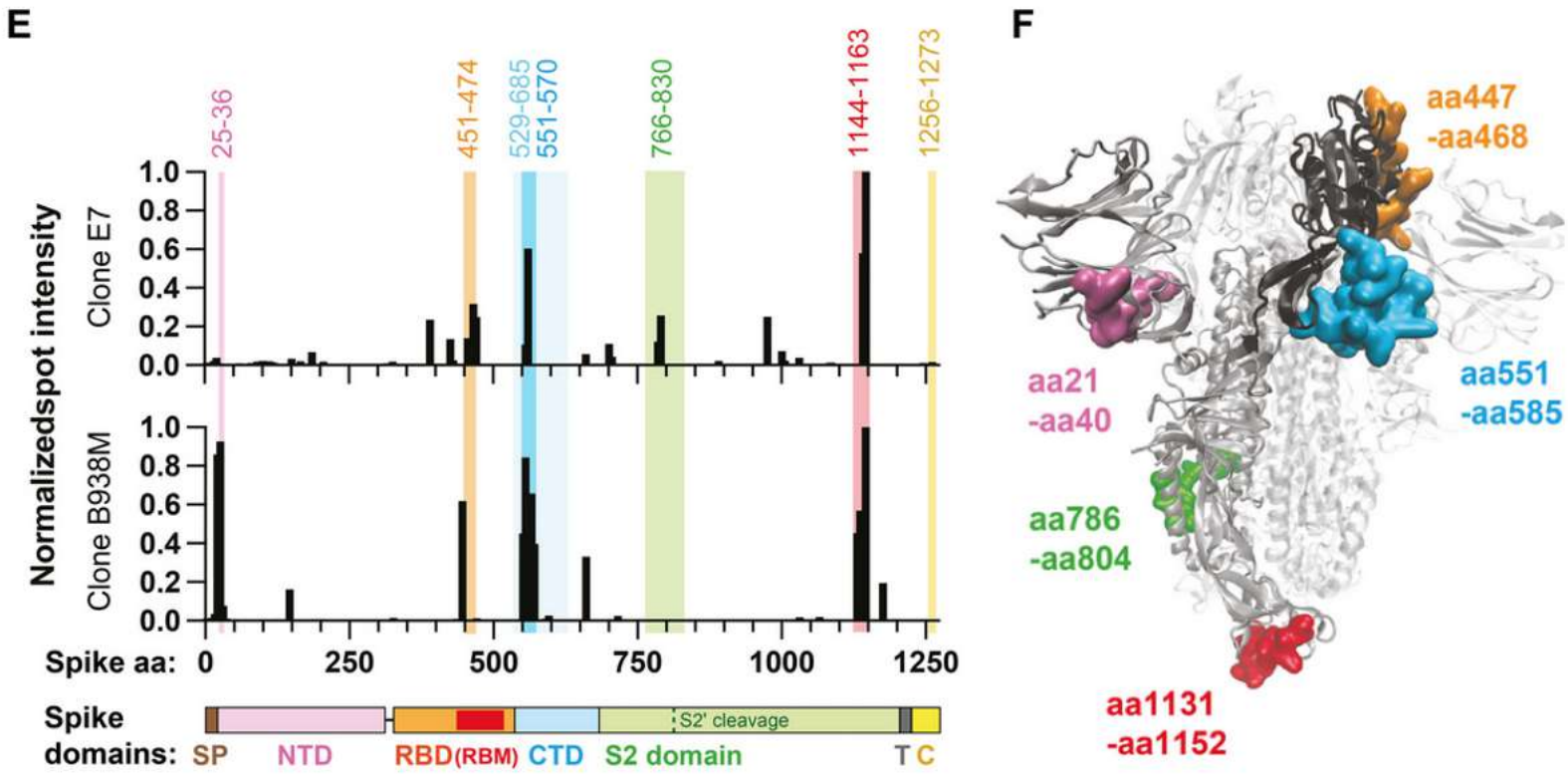


**Fig. 6. Cross-binding of anti-AngII antibodies to the SARS-CoV-2 Spike and RBD antigens.**

(**A**) Binding of two commercial monoclonal anti-AngII (clone E7 and clone B938M) to recombinant Spike and RBD at various concentrations by ELISA. BSA was used as a control for nonspecific binding. (**B**) Inhibition of AngII binding to its cognate receptor AT1 in the presence of the anti-AngII (clone E7 and B938M) on CHO-AT1 cells, measured by flow cytometry (analysis of variance test with Tukey's posttest). mAb, monoclonal antibody. (**C**) Binding of a library of monoclonal anti-RBD antibodies against AngII by ELISA (9 of 36 tested showed signals of low binding). (**D**) Binding of three selected monoclonal anti-RBD (S24-902, S564-265, and S24-1002) to AngII at various concentrations as compared to a non–AngII-binding anti-RBD (S564-14). (**E**) Binding of monoclonal anti-AngII (clone E7 or B938M) to Spike linear epitopes using a peptide array. Highlighted colored regions represent the most immunogenic and recurrent B cell epitopes of Spike found in patients with COVID [Shrock *et al.* (*14*) and Li *et al.* (*15*)], and the associated numbers indicate the amino acid positions that delineate these regions. The *x* axis represents the full length of Spike (SP, signal peptide; NTD, N-terminal domain; RBD, receptor-binding domain; RBM, receptor-binding motif; CTD, C-terminal domain; NTD, RBD, and CTD together constitute the S1 domain of Spike; T, transmembrane domain; C, cytoplasmic tail). (**F**) Visualization of the main domains targeted by the monoclonal anti-AngII antibodies on the three-dimensional structure of Spike [Protein Data Bank: 6VXX; (*24*)]. Domains are highlighted in colors on one monomer of the trimeric Spike structure (RBD is in black; aa#, amino acid position of Spike).