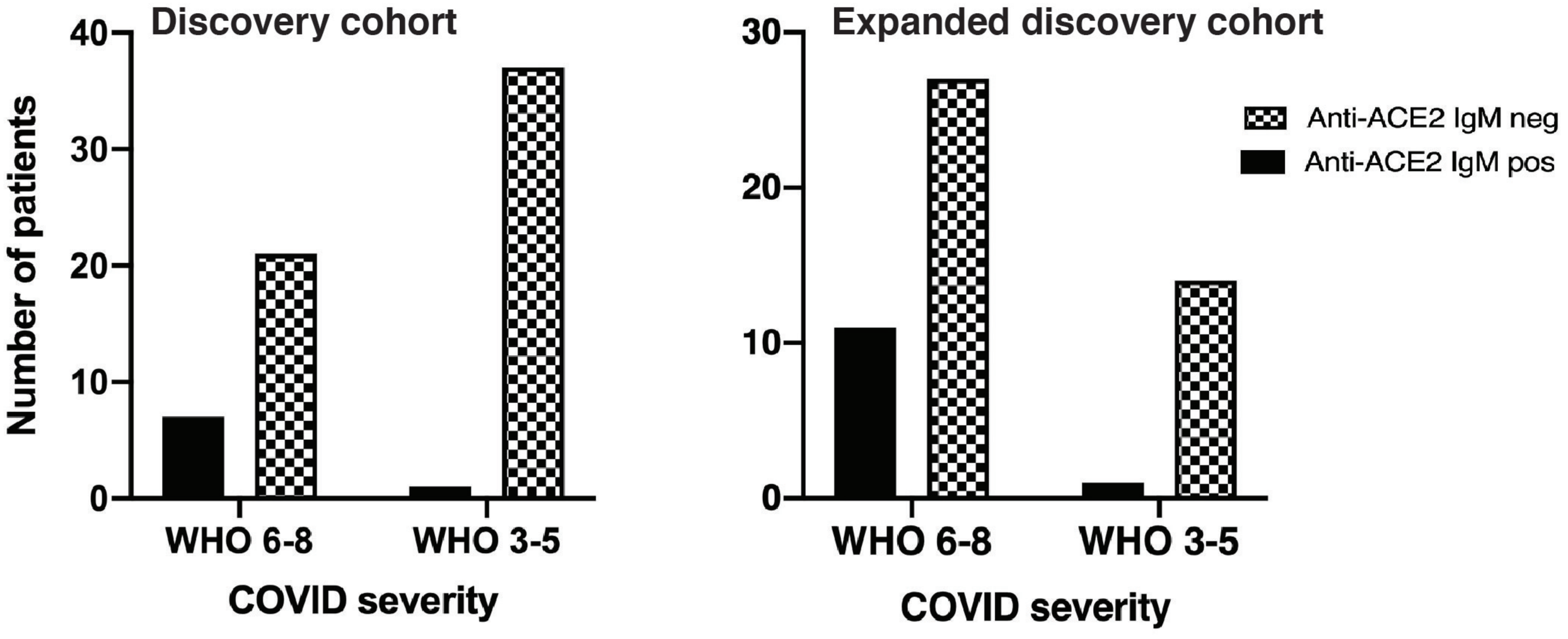
Supplemental Table 1. Demographics of the study population

			N
Total			118
Demographics			
Age (years)	60 (50-71)		
Male gender		56%	66
White race/ethnicity		26%	31
Black race/ethnicity		41%	48
Hispanic race/ethnicity		23%	27
Asian race/ethnicity		3%	3
Other		8%	9
BMI (kg/m2)	30.2 (26.0-34.9)		
Comorbidities			
Diabetes mellitus		47%	56
Hypertension		64%	76
Coronary artery disease		24%	28
Congestive heart failure		23%	27
Chronic lung disease		26%	31
Maximum WHO class			
Minimal oxygen		28%	34
HFNC/NIPPV		15%	18
Mechanical ventilation		32%	38
Dead		24%	28

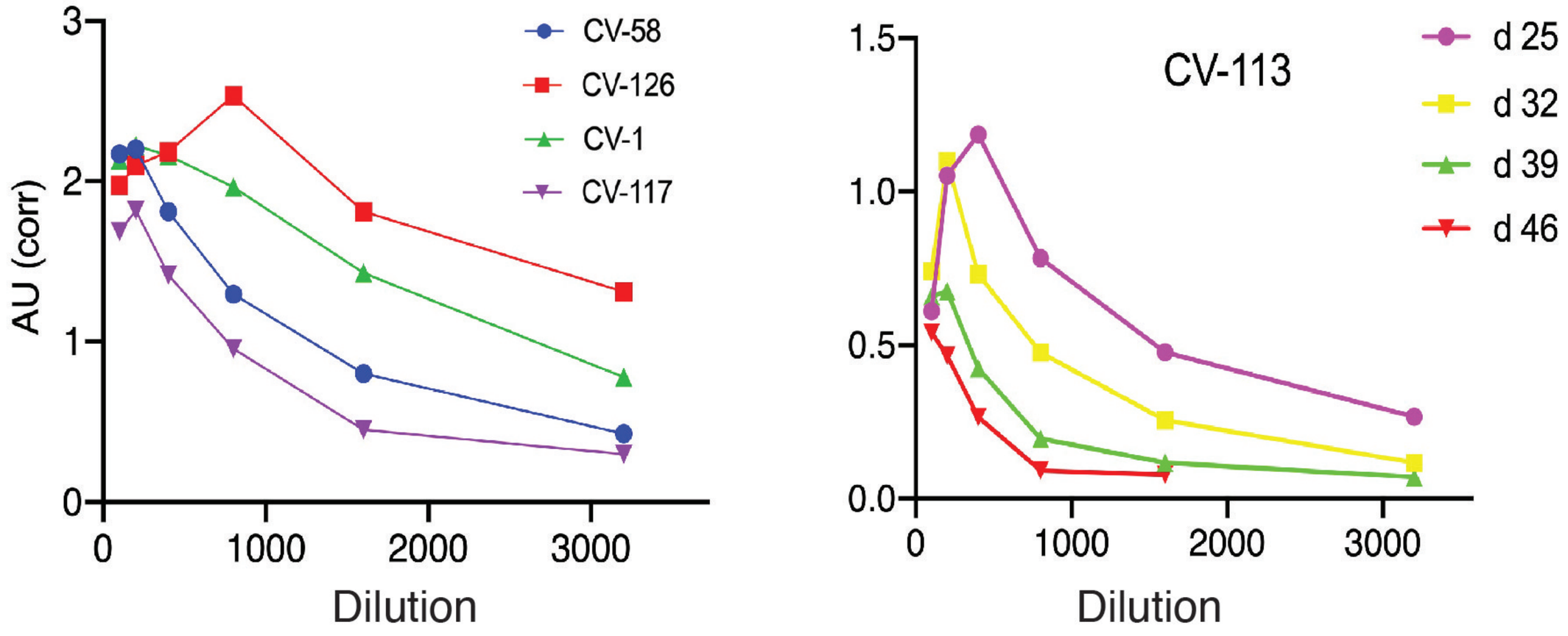
Continuous variables are median +/- interquartile range
Categorical variables are percentages

SUPPL FIG 1

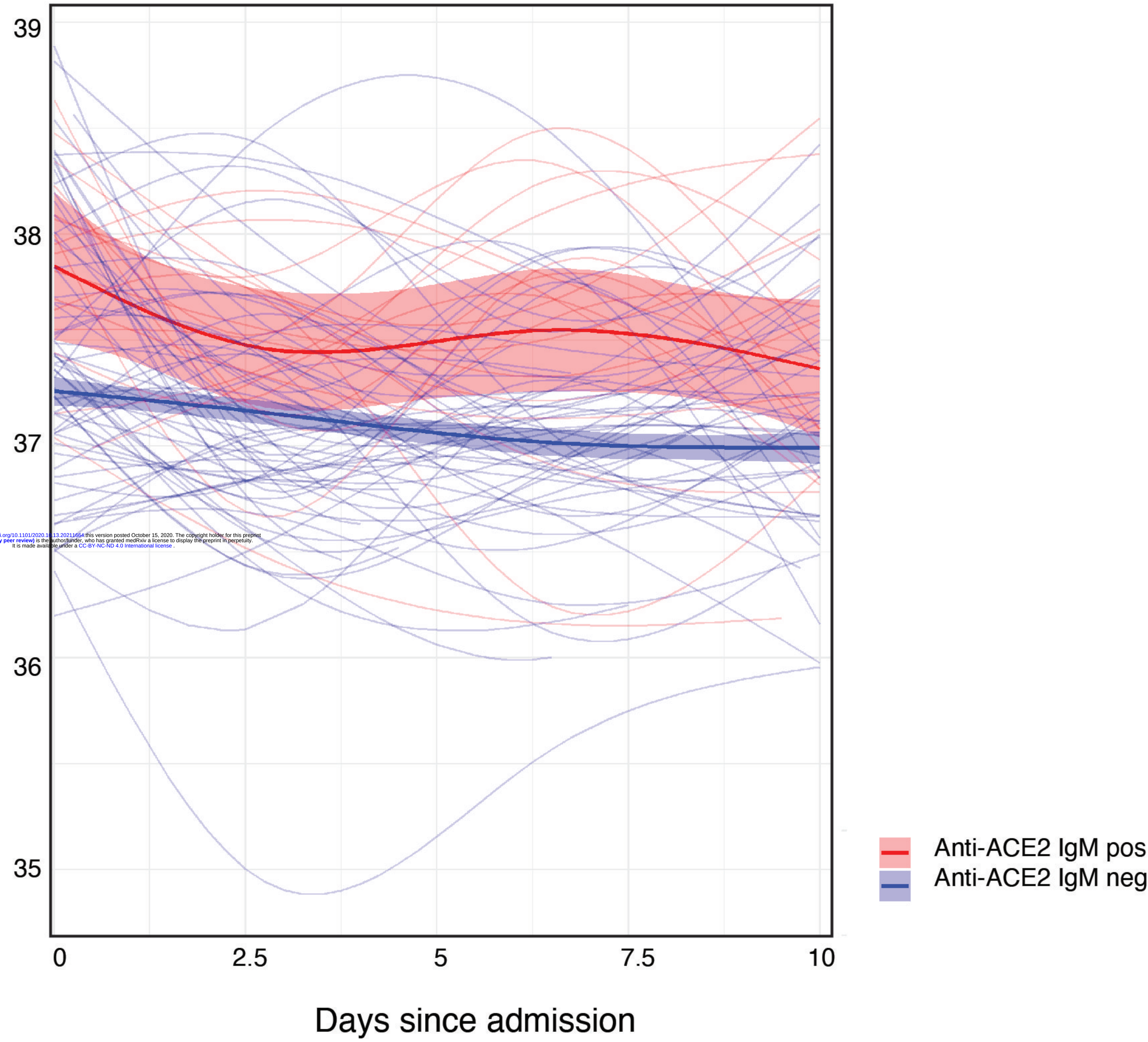
A. Anti-ACE2 IgM antibodies in COVID cohorts



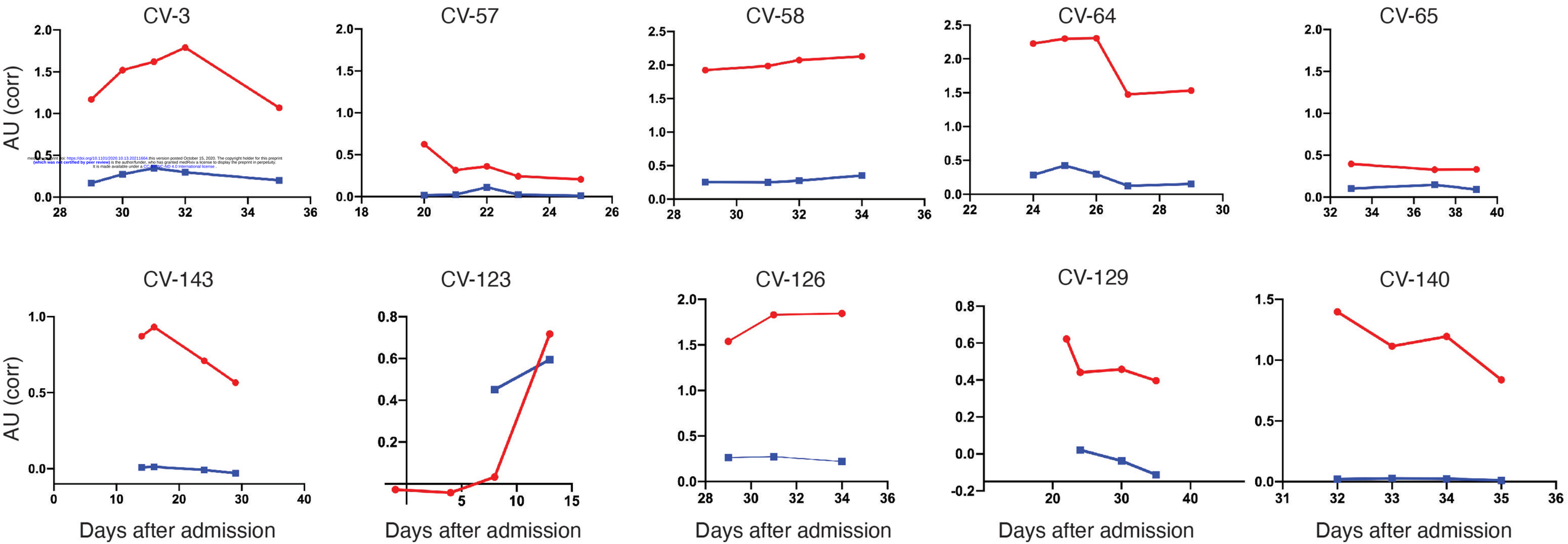
B. AUC plots for anti-ACE2 IgM antibodies



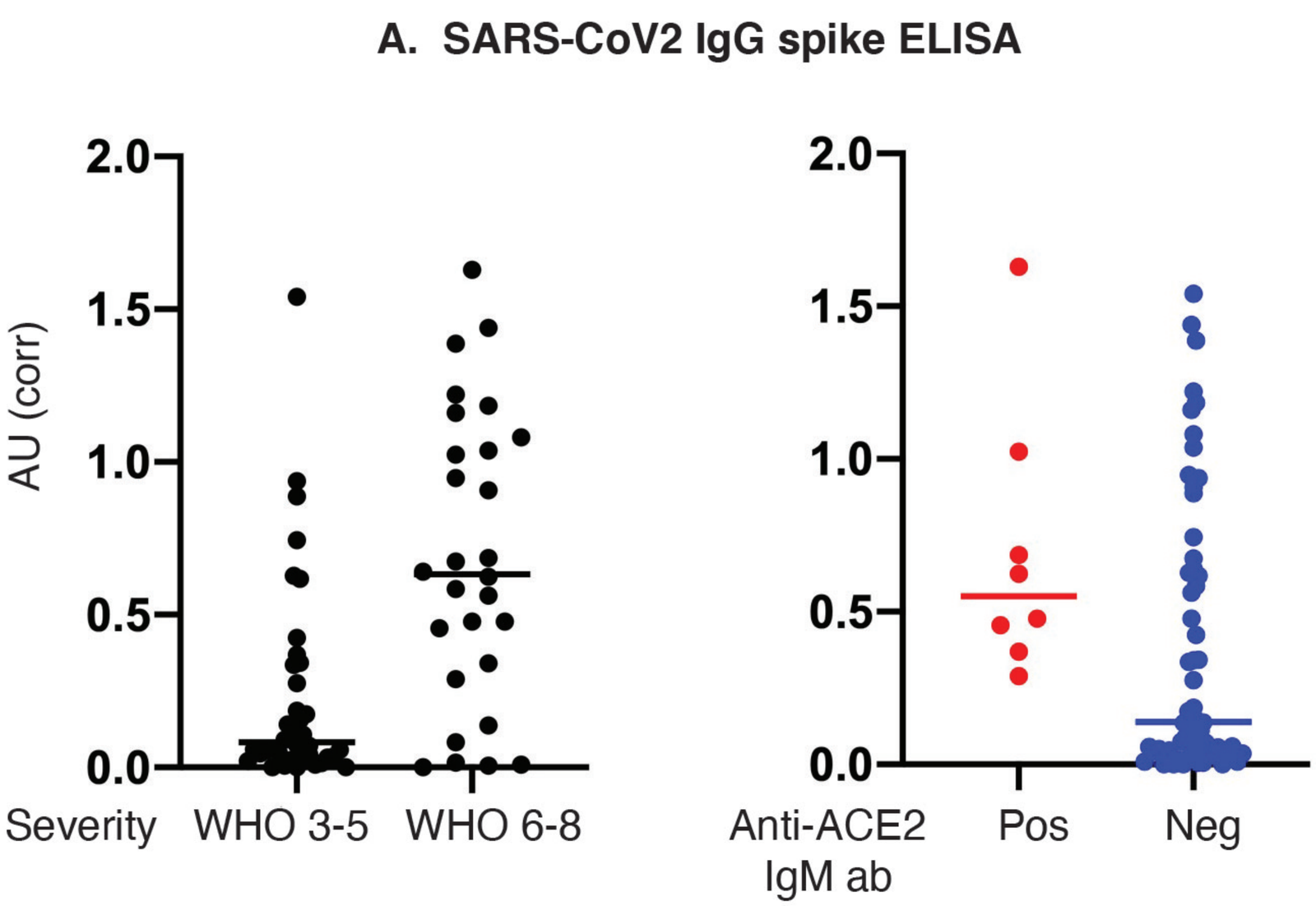
SUPPL FIGURE 2



Suppl Figure 3

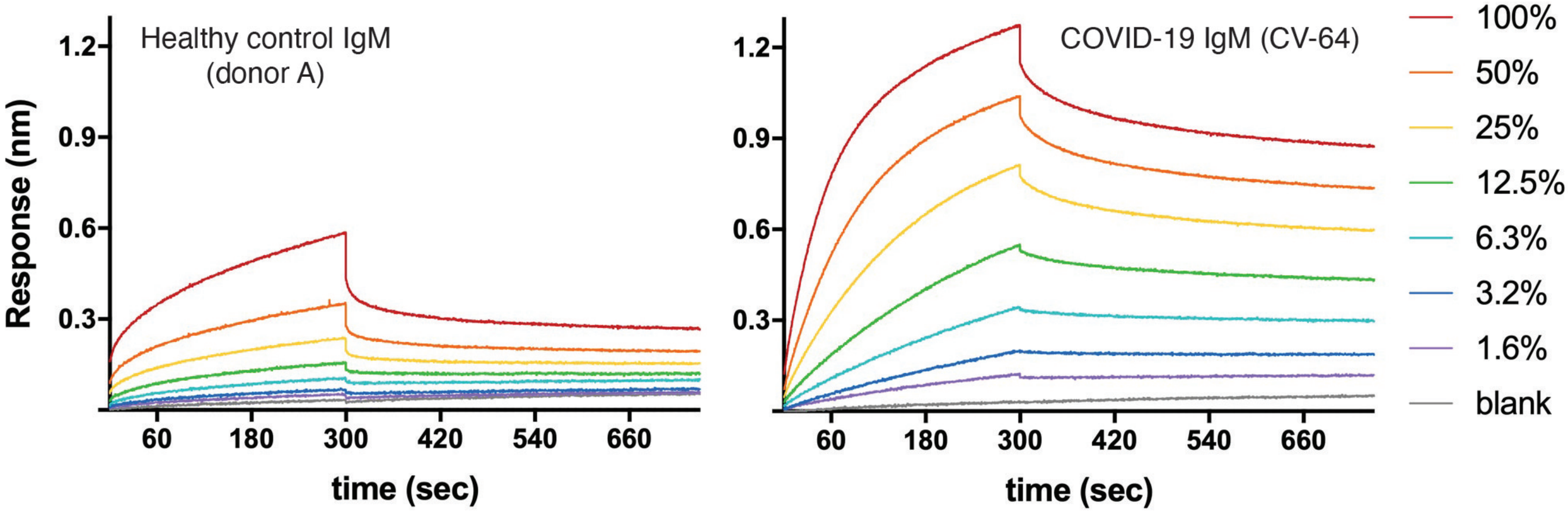


SUPPL FIGURE 4

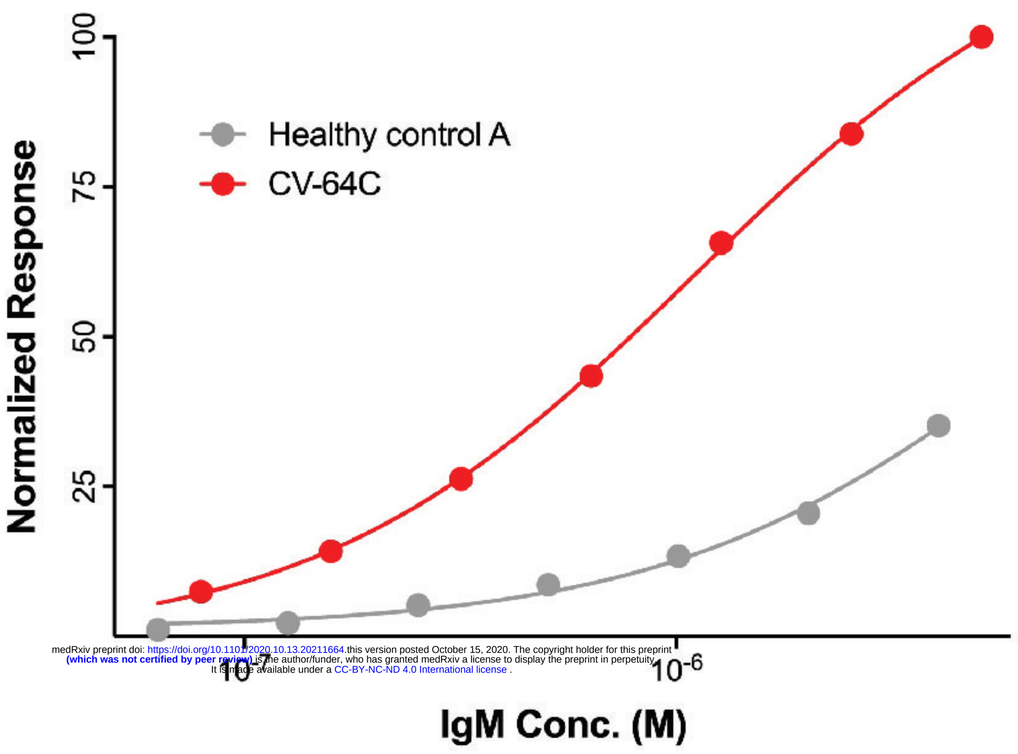


SUPPL FIGURE 5

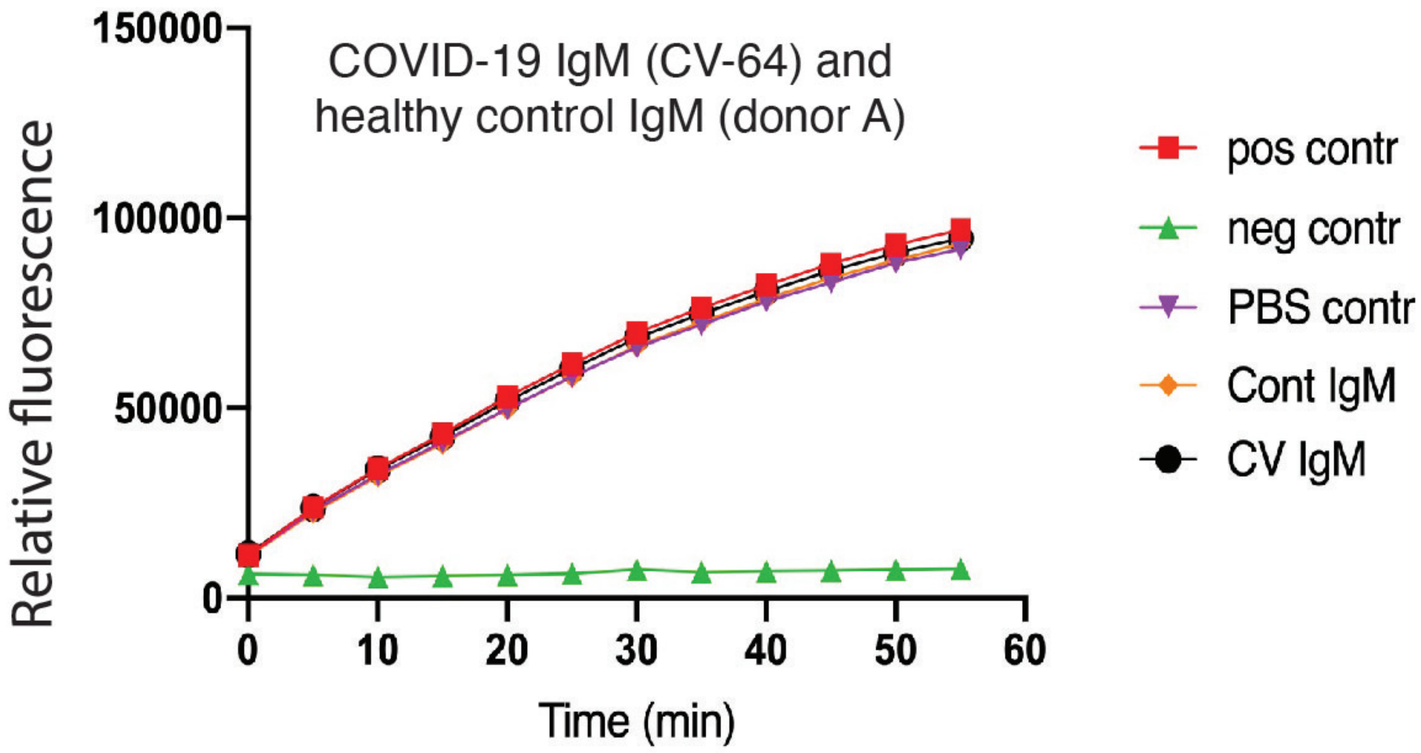
A. Kinetic Traces



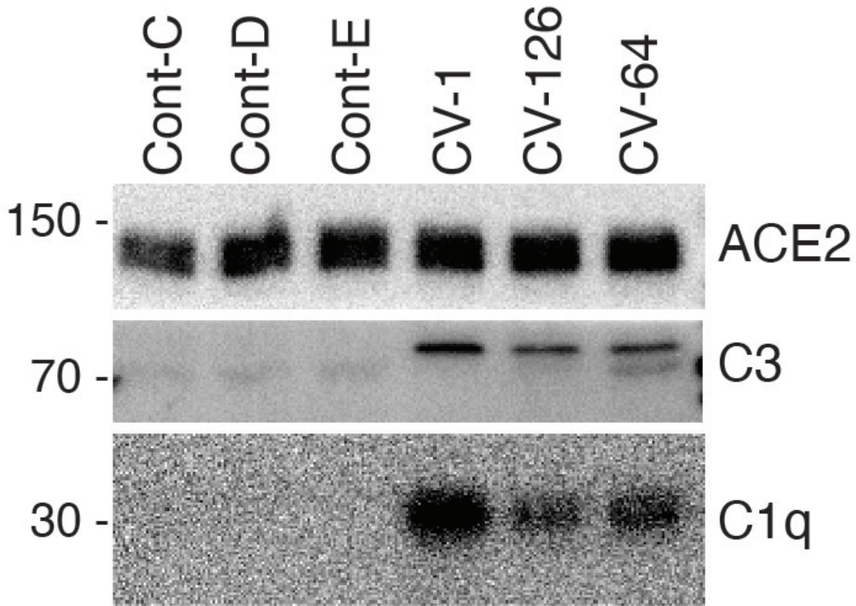
B. Equilibrium Binding



C. ACE2 activity assay



D. Complement Assay



SUPPLEMENTAL FIGURE LEGENDS

Supplemental Fig 1: Anti-ACE2 IgM antibodies in COVID-19 patients. A. Anti-ACE2 IgM ELISAs were performed as described in the Methods section. In the Discovery cohort (left panel), 8/66 patients with COVID-19 were positive for anti-ACE2 IgM antibodies. Of these, 25% of the WHO 6-8 group were positive compared to 2.6% of the WHO 3-5 group (p=0.0084, Fisher's exact test). An additional 52 COVID-19 patients were assayed ("Expanded discovery", right panel); the frequency of anti-ACE2 IgM in these patients was similar to the initial group. Data from the combined cohorts (N = 118) is shown in Fig 1A. B. Anti-ACE2 IgM ELISAs were performed using serial serum dilutions (1:100 to 1:3,200 range). Data obtained from four different patients is shown in the left panel, each assayed using serum from a single bleed. Data from a fifth patient is shown in the right panel, using serum made from blood draws on 4 different days. Area under the curve ("AUC") plots are shown in both panels.

Supplemental Fig. 2: The higher average body temperature measurements in IgM anti-ACE2 patients are not a function of disease severity. IgM anti-ACE2-positive group had statistically significantly higher average temperatures over the first 10 days of hospitalization than the IgM-negative group (Fig. 2D). The analysis here is restricted to the severe IgM-positive patients compared to all severe COVID-19 patients from the CROWN Registry for whom IgM status was unknown. The results are unchanged, implicating the increased temperature as a function of IgM status rather than disease severity (IgM-positive: mean = 37.53, S^2 = 0.64, N = 721 on M = 18 unique patients, IgM-unknown: mean = 37.11, S^2 =0.59, N =14827 on M = 473 unique

patients; chisq = 19.98, p = 0.0005 from linear mixed-effects model Wald test with 4 degrees of freedom.

Supplemental Fig 3: Longitudinal analysis of anti-ACE2 IgM antibodies in patients hospitalized with severe COVID-19. For all those anti-ACE2 IgM-positive patients with multiple banked sera, anti-ACE2 IgM and IgG antibodies were quantitated over time. Red and blue lines on each plot denote anti-ACE2 IgM and IgG antibodies, respectively. The following patients were on steroid treatment: CV-58 (days 20-24 and 29-36); CV-65 (days 26-28) and CV-129 (day 20 to beyond day 60). Additional examples are shown in Fig. 1B.

Supplemental Fig. 4: Antibodies against SARS-CoV-2 S-protein in anti-ACE2-positive COVID-19 patients. A: Anti-SARS-CoV-2 S-protein IgG antibodies were assayed by ELISA (N=66). Patients are shown grouped by disease severity in (left panel), and by anti-ACE2 IgM antibody status in (right panel). The mean ODs of anti-S antibodies were significantly higher in patients with severe compared to mild COVID (P<0.0001, Chi-squared). The median anti-S-antibody level was significantly higher in anti-ACE2 IgM-positive patients compared to anti-ACE2 IgM-negatives (P=0.028, Mann-Whitney test). B: Anti-S and -RBP antibodies assayed by the CoronaChek point of care assay. 8/8 (100%) of anti-ACE2 IgM-positive patients had a positive IgG result, compared to only 31/58 (53.4%) of anti-ACE2 IgM-negative patients (p=0.017, Fisher's exact test). Red and blue denote anti-ACE2 IgM antibody-positive and -negative patients, respectively.

Supplemental Fig 5: Properties of anti-ACE2 IgM antibodies. (A-B): Kinetics. A: Kinetic traces of the binding interactions between immobilized human ACE2 and purified IgM, as determined by biolayer interferometry. Percentages represent twofold dilutions of IgM from patient CV-64 and Control A. B: Equilibrium binding titrations. Normalized responses at the indicated concentrations of purified IgM from the donors shown in (A) are plotted (see Fig.3A&B for data obtained from CV-1 and control B). Kinetic parameters are provided in Fig. 3C. C: Anti-ACE2 IgM antibodies do not inhibit ACE2 activity. ACE2 activity, in the presence or absence of IgM from patient CV-64 or Control A, was measured using a fluorescent substrate in a time course assay. The positive control was ACE2 alone, and the negative control was ACE2 plus ACE2 inhibitor (see Fig 3C for data from CV-1 and control B). D: Complement activation induced by IgM antibodies to ACE2. Dynabeads containing immune complexes of ACE2 and purified IgM from controls (cont) or anti-ACE2 IgM from COVID-19 patients (CV) were incubated with human complement. Deposition of C1q and C3 was visualized by immunoblotting. ACE2 is shown as a loading control.