

1 **Serum from COVID-19 patients early in the pandemic shows limited evidence of cross-neutralization**  
2 **against variants of concern**

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20

21 **Abstract**

22 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) results in a variety of clinical symptoms  
23 ranging from no or mild to severe disease. Currently, there are multiple postulated mechanisms that  
24 may push a moderate to severe disease into a critical state. Human serum contains abundant evidence  
25 of the immune status following infection. Cytokines, chemokines, and antibodies can be assayed to  
26 determine the extent to which a patient responded to a pathogen. We examined serum and plasma  
27 from a cohort of patients infected with SARS-CoV-2 early in the pandemic and compared them to  
28 negative-control sera. Cytokine and chemokine concentrations varied depending on the severity of  
29 infection, and antibody responses were significantly increased in severe cases compared to mild to  
30 moderate infections. Neutralization data revealed that patients with high titers against an early 2020  
31 isolate had detectable but limited neutralizing antibodies against newly circulating SARS-CoV-2 variants  
32 of concern. This study highlights the potential of re-infection for recovered COVID-19 patients.

33

34 **Keywords**

35 SARS-CoV-2; antibodies; cytokines; chemokines; variants of concern; VOC; alpha variant; beta variant;  
36 delta variant

## 37 **Introduction**

38 In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in  
39 the city of Wuhan, Hubei province, China, causing variably severe respiratory tract pathology termed  
40 coronavirus disease 2019 (COVID-19). COVID-19 is often a mild disease associated with low-grade fever  
41 and loss of taste and smell. However, critical cases of COVID-19 do occur, and are characterized by  
42 severe pneumonia and acute respiratory distress syndrome (1) leading to organ failure and death (2). As  
43 of October 20<sup>th</sup> 2021, over 241 million cases have been reported worldwide, and over 4.9 million people  
44 have died of COVID-19 (<https://coronavirus.jhu.edu/map.html>).

45 The spectrum of disease caused by SARS-CoV-2 ranges from no or mild to critical. Mild to  
46 moderate cases are characterized by mild symptoms ranging to mild pneumonia and account for up to  
47 81% of infections. Severe cases account for 14% of cases, which involve dyspnea, hypoxia, or greater  
48 than 50% lung involvement as determined by imaging. Five percent of patients are deemed critical  
49 based on conditions of respiratory failure, shock, or multiorgan system dysfunction (3, 4). In many  
50 severely affected patients, SARS-CoV-2 infection triggers an overactive immune response known as a  
51 “cytokine storm.” Immune cells produce high levels of inflammatory cytokines leading to systemic shock  
52 and death (5). As such, cytokines have been studied extensively in the context of SARS-CoV-2 infection  
53 and have been found to be central to the pathophysiology of COVID-19 (6, 7).

54 A thorough understanding of appropriate immune responses is vital to the development of  
55 effective medical intervention strategies and vaccines. Besides cytokine and chemokine production  
56 following infection, antibodies generated by COVID-19 patients have been studied and reported in  
57 detail. Infection with SARS-CoV-2 has been found to induce non-class-switched, class-switched, and  
58 neutralizing antibodies in immunocompetent patients (8-12). The long term stability of the antigen-  
59 specific and neutralizing antibody response has been found to be up to 13 months in patients (13-16).  
60 Pre-existing antibody populations may also contribute to disease severity such as autoantibodies to type  
61 I interferons (17). As SARS-CoV-2 mutates, changes to the sensitivity of pre-existing neutralizing  
62 antibody populations may be effected (18). As such, the beta and delta variants both have displayed  
63 decreased sensitivity to pre-existing neutralizing antibodies (15, 19-21).

64 In this study, we evaluated 131 serum and plasma samples from 55 COVID-19 patients alongside  
65 serum and plasma from 20 uninfected patients for the presence of 38 cytokines and chemokines, anti-  
66 SARS-CoV-2 spike protein-specific IgG, and neutralizing antibodies. Our results indicate that infection  
67 with SARS-CoV-2 results in changes in a number of cytokines and chemokines that correlate to disease

68 severity. We also found that COVID-19 patients exhibit increased titers of antigen-specific IgG and  
69 neutralizing antibody titers compared to uninfected individuals. Furthermore, we determined that the  
70 neutralizing activity of our sample cohort extended to three new SARS-CoV-2 variants of concern (VOC),  
71 Alpha ( $\alpha$ ; B.1.1.7), Beta ( $\beta$ ; B.1.351), and Delta ( $\delta$ ; B.1.617.2) which emerged months after the start of  
72 the pandemic. This study corroborates previous data examining serum concentrations of cytokines,  
73 chemokines, and antigen-specific antibodies in COVID-19 patients. Most importantly, it highlights the  
74 cross-reactive neutralization capabilities of unvaccinated COVID-19 survivors against emerging SARS-  
75 CoV-2 variants and the potential for re-infection.

76

## 77 **Materials and Methods**

### 78 *Cells and Viruses*

79 Vero E6 cells (mycoplasma negative) were grown at 37°C in 5% CO<sub>2</sub> in Dulbecco's modified Eagle's  
80 medium (DMEM) (Sigma-Aldrich, St. Louis, MO) containing 10% fetal bovine serum (FBS) (Wisent Inc.), 2  
81 mM L-glutamine (Thermo Fisher Scientific, Waltham, MA), 50 U/mL penicillin (Thermo Fisher Scientific),  
82 and 50 µg/mL streptomycin (Thermo Fisher Scientific). SARS-CoV-2 isolate nCoV-WA1-2020  
83 (MN985325.1) (22), SARS-CoV-2 isolate B.1.351 (hCoV-19/South African/KRISP-K005325/2020), SARS-  
84 CoV-2 isolate B.1.1.7 (hCoV\_19/England/204820464/2020), and SARS-CoV-2 isolate B.1.617.2 (hCoV-  
85 19/USA/KY-CDC-2-4242084/2021) were used for the neutralizing antibody assays. The following reagent  
86 was obtained through BEI Resources, NIAID, NIH: Severe Acute Respiratory Syndrome-Related  
87 Coronavirus 2, Isolate hCoV-19/England/204820464/20200, NR-54000, contributed by Bassam Hallis.  
88 SARS-CoV-2 B.1.351 was obtained with contributions from Dr. Tulio de Oliveira and Dr. Alex Sigal  
89 (Nelson R Mandela School of Medicine, UKZN). SARS-CoV-2 B.1.617.2 was obtained with contributions  
90 from B. Zhou, N. Thornburg and S. Tong (Centers for Disease Control and Prevention, USA). All viruses  
91 were grown and titered on Vero E6 cells, and sequence confirmed.

92

### 93 *Serum and plasma samples*

94 A total of 131 serum and plasma samples collected from 75 unique individuals were analyzed in this  
95 study. All samples were either remnant sera or plasma (from EDTA-anticoagulated whole blood),  
96 originally collected for standard-of-care diagnostic testing from inpatients being treated for COVID-19 (n  
97 = 55 [73%]) or were from SARS-CoV-2-uninfected volunteers (n = 20 [27%]; referred to as "normal"  
98 samples). Of the patients, the average age was 58 years (range 13-93 years), 25 (45%) were female and

99 27 (49%) had more than one specimen assessed. Based on review of clinical charts and according to CDC  
100 criteria ([www.cdc.gov/coronavirus/2019-ncov](http://www.cdc.gov/coronavirus/2019-ncov)), patients were grouped into three illness severity  
101 categories: Mild to moderate (mild symptoms to mild pneumonia), severe (dyspnea, hypoxia or more  
102 than 50% lung involvement on imaging), and critical (respiratory failure, shock or multiorgan system  
103 dysfunction). Of the normal samples, volunteers who provided a one-time sample were an average age  
104 of 44 years (range 26-89 years) and 15 (75%) were female. All samples, including patients and  
105 volunteers, were deidentified and assigned study-specific identifiers to protect patient confidentiality.  
106 Samples were then aliquoted and frozen at -80°C until shipment to the Rocky Mountain Laboratories for  
107 analysis. Samples were  $\gamma$ -irradiated (4 MRad) to inactivate potential infectious pathogens upon receipt  
108 and prior to analysis. This work was approved by the Indiana University Institutional Review Board (IRB#  
109 2004155084).

110

#### 111 *Cytokine analysis*

112 Samples were diluted 1:2 in serum matrix for analysis with Milliplex Human Cytokine/Chemokine  
113 Magnetic Bead Panel as per manufacturer's instructions (EMD Millipore Corporation). Concentrations  
114 for analytes (EGF, FGF-2, Eotaxin, TGF- $\alpha$ , G-CSF, Flt-3L, GM-CSF, Fractalkine, IFN $\alpha$ 2, IFN $\gamma$ , GRO, IL-10,  
115 MCP-3, IL-12p40, MDC, IL-12p70, IL-13, IL-15, sCD40L, IL-17A, IL-1RA, IL-1 $\alpha$ , IL-9, IL-1 $\beta$ , IL-2, IL-3, IL-4, IL-  
116 5, IL-6, IL-7, IL-8, IP-10, MCP-1, MIP-1 $\alpha$ , MIP-1 $\beta$ , TNF $\alpha$ , TNF $\beta$ , and VEGF) were determined for all samples  
117 using the Bio-Plex 200 system (BioRad Laboratories, Inc.).

118

#### 119 *Antibody level determination*

120 Antibody titers were determined using enzyme-linked immunosorbent assay (ELISA). Flat-bottom  
121 immuno 96-well plates (Nunc Maxisorp, Thermo Fisher Scientific) were coated overnight with 1  $\mu$ g/ml  
122 SARS-CoV-2 (2019-nCoV) Spike Receptor Binding Domain (polyhistidine-tagged) recombinant protein  
123 (Sino Biological) diluted in PBS. Plates were washed and blocked the following day with 3% milk. After  
124 washing, serum and plasma samples were diluted 1:100, and then serially diluted 1:4 in 1% milk and  
125 incubated for one hour at room temperature. Plates were washed before addition of peroxidase-labeled  
126 anti-human IgG (KPL). Following a one-hour incubation at room temperature, plates were washed and  
127 ABTS 2-component Microwell Peroxidase Substrate (SeraCare) was added. Plates were incubated for 30  
128 minutes in the dark before being read at 405 nm on a GloMax Explorer (Promega).

129

#### 130 *Neutralizing antibody assay*

131 Neutralization antibody assays were performed as detailed in van Doremalen et al. (1). Briefly, serum  
132 and plasma samples were heat-inactivated for 30 minutes at 56°C. They were diluted 1:10 and then 1:2  
133 for subsequent dilutions. SARS-CoV-2 virus stocks were diluted to 2,000 TCID50/ml and 70 µl was then  
134 added to each well of diluted sample. Following a one-hour incubation at 37°C, the serum-virus mixture  
135 was transferred to 96-well plates containing high-passage Vero E6 cells. After six days, cytopathic effect  
136 (CPE) was read. The virus neutralization titer was determined to be the lowest concentration of serum  
137 antibody where CPE was not observed.

138

#### 139 *Statistical analysis*

140 Statistical analysis was performed using Prism 8. Statistically significant differences between groups for  
141 cytokines were determined using one-way ANOVA; IgG and neutralizing titers were evaluated applying  
142 Mann-Whitney test. Significance is indicated as follows:  $p < 0.0001$  (\*\*\*\*),  $p < 0.001$  (\*\*\*),  $p < 0.01$  (\*\*) and  
143  $p < 0.05$  (\*).

144

## 145 **Results**

### 146 *COVID-19 patients exhibit different levels of cytokines and chemokines, which correlate with disease* 147 *severity*

148 We received 111 patient serum and plasma samples that were categorized according to CDC guidelines  
149 into mild to moderate and critical cases. In addition, we obtained 20 serum and plasma samples from  
150 healthy adult volunteers designated “normal” controls in our studies. We first sought to determine the  
151 circulating immune status by assessing the presence of 38 different cytokines and chemokines in the  
152 serum and plasma of patients infected with SARS-CoV-2, alongside uninfected volunteers. We found  
153 that infection with SARS-CoV-2 resulted in significant changes in multiple cytokines and chemokines  
154 compared to negative control serum and plasma (Figure 1). This phenomenon was evident in both mild  
155 to moderate and critical infections. For instance, serum and plasma from patients with a mild to  
156 moderate infection contained significantly greater levels of MCP-3, IL-1 $\alpha$ , TNF $\beta$ , IL-4, IL-5, IL-6, IL-8, IL-9,  
157 and IL-13 compared to serum and plasma from patients that were critically ill (Figure 1A). Mild to  
158 moderate infections also showed significant increases in these cytokines, along with IL-15, compared to  
159 healthy adults (Figure 1B). Critical infections resulted in significantly increased levels of sCD40L, IP-10,  
160 and IL-15 compared to normal controls (Figure 1 B). All of the other cytokines and chemokines tested  
161 showed no significant differences between control and infected patients (Supplementary Figure 1) .

162

163 *Cytokine levels remain steady when measured over time*

164 Nine of the COVID-19-infected patients were sampled more than once. We determined longitudinally  
165 whether cytokine and chemokine concentrations varied over time. Overall, there were no significant  
166 changes in any of the evaluated cytokines or chemokines during the periods of time that were sampled  
167 (Supplementary Figure 2).

168

169 *Failure to recover from critical COVID-19 is correlated with increased levels of IL-6 and IP-10 coupled with*  
170 *insufficient levels of sCD40L*

171 Amongst critical patients, we found that the serum and plasma of those who succumbed to the infection  
172 contained significantly more IL-6 and IP-10 than control patients. Additionally, patients who survived  
173 infection had significantly increased sCD40L compared to normal controls (Figure 2). Although serum  
174 and plasma from fatal disease patients contained more sCD40L than serum and plasma of normal  
175 controls, it was not significantly increased relative to serum and plasma from patients who recovered  
176 from infection, indicating that this soluble mediator may be important for surviving COVID-19.

177

178 *Critically infected patients develop strong anti-SARS-CoV-2 IgG and neutralizing antibody responses*

179 Next, we assessed whether serum and plasma of COVID-19 patients contained IgG specific for the  
180 receptor-binding domain (RBD) of the SARS-CoV-2 spike protein. We found that half of the patients who  
181 had a mild to moderate infection produced RBD-specific IgG, and the data was statistically significant  
182 compared to healthy controls (Figure 3A). In contrast, critically-infected patients developed high titers of  
183 RBD-specific IgG, which was significantly greater than both healthy controls and those with mild to  
184 moderate COVID-19. The presence of RBD-specific IgG did not predict disease outcome, as there was no  
185 significant difference in titers between patients that recovered from infection and those that did not  
186 (Figure 3B).

187 Three of the healthy control serum and plasma samples contained SARS-CoV-2-specific IgG  
188 without COVID-19 medical history. We postulated that the presence of IgG may not translate to the  
189 ability to neutralize SARS-CoV-2. Therefore, we assessed the serum and plasma for neutralizing  
190 antibodies against SARS-CoV-2. The majority of control serum and plasma did not contain detectable  
191 levels of neutralizing antibodies, with the exception of one patient who exhibited a detectable, albeit  
192 very low, titer (Figure 4A). However, mild to moderate infection led to the production of significantly  
193 higher levels of neutralizing antibody titers compared to controls. Patients that were critically infected

194 exhibited high titers of neutralizing antibodies, approximately two logs greater than healthy controls and  
195 one-and-a-half logs higher than patients with mild to moderate disease.

196 Some COVID-19 patients that participated in this study were sampled repeatedly over the  
197 course of infection and recovery. Therefore, we determined whether their neutralizing antibody titers  
198 remained stable over time. We found that these patients continued to produce neutralizing antibodies  
199 against SARS-CoV-2 over the course of the disease (Supplementary Figure 3). Antibody titers remained  
200 nearly the same, exhibiting less than a log change, from the first to the final day of sampling (up to nine  
201 days post-admission). Unfortunately, no further time points were sampled from the patients.

202

### 203 *COVID-19 serum and plasma contains neutralizing antibodies against VOC*

204 Finally, we sought to determine whether human COVID-19 serum and plasma contains antibodies  
205 capable of neutralizing three VOC that emerged later in the pandemic – Alpha, Beta, and Delta variants.  
206 Therefore, we tested serum and plasma samples that contained high titers of neutralizing antibodies  
207 against the original virus, but this time we assessed neutralizing antibodies against the 3 VOC. We found  
208 that the serum and plasma contained antibodies capable of neutralizing these SARS-CoV-2 variants, but  
209 the antibody titers were significantly lower than the titers against the original virus (Figure 4B).  
210 Interestingly, the titers against the Alpha variant were significantly higher than those for the Beta and  
211 Delta variants indicating limited protection from re-infection with the currently circulating Delta variant  
212 (Figure 4B).

213

## 214 **Discussion**

215 Since the beginning of the COVID-19 pandemic, clinicians and scientists have sought to investigate the  
216 components of patient serum for evidence of either sufficient or aberrant immune responses.  
217 Components of serum have been shown to be effective in the treatment of those suffering from COVID-  
218 19, as convalescent plasma infusion can lead to a decrease in the severity of disease (23, 24).  
219 Understanding the difference between an immune response that leads to recovery from infection and  
220 one that leads to a negative outcome (aberrant) is essential in the design of treatments and vaccines,  
221 which are necessary to bring an end to this devastating pandemic.

222 One avenue taken by investigators has been to explore the presence or absence of various  
223 cytokines and chemokines in patient serum. Severe disease has been associated with an aberrant  
224 immune response termed “cytokine storm,” which is characterized by an overactivation of the immune



225 system leading to exaggerated levels of cytokines released into the circulation. Multiorgan dysfunction  
226 and failure associated with septic shock can be fatal (5, 25). In contrast, those with mild disease exhibit  
227 functional immune responses characterized by appropriate levels and types of cytokines, leading to  
228 disease resolution (7). One cytokine that has been highlighted amongst research studies is IL-6. For  
229 instance, Herold et al. found that IL-6 was a key predictor of respiratory failure in hospitalized COVID-19  
230 patients (26). Other studies have yielded similar results, indicating a role for IL-6 in the severity and  
231 outcome of the disease (27-29). Our study supports previous studies showing that high levels of IL-6 lead  
232 to poor outcomes for COVID-19 patients.

233 Interestingly, our data show that moderate levels of key cytokines and chemokines are evident  
234 in mild to moderate cases of COVID-19. It is the “Goldilocks” phenomenon: too much or too little of  
235 some cytokines is not good; rather, the levels must be “just right”. In support of this concept, Yang et al.  
236 observed that serum IL-1 $\beta$ , IL-1Ra, IL-6, IL-7, IL-10, IP-10, and TNF- $\alpha$  are all important in classifying  
237 COVID-19 cases into mild, moderate, and severe (30). This study also found that IP-10 was significantly  
238 higher in severe cases of COVID-19 compared to mild cases. Another study found that IP-10 levels were  
239 highest in patients that required ICU admission (31). Our study supports the previous work finding very  
240 high levels of IP-10 in the serum of patients who succumbed to SARS-CoV-2 disease.  
241 Serum antibodies are known to be important for both protection and treatment of COVID-19. Effective  
242 humoral immune responses to vaccination or infection lead to the production of neutralizing antibodies  
243 that contribute to clearance of the virus. Our data demonstrate that infection with SARS-CoV-2 results in  
244 increased levels of antigen-specific IgG, and that severe infection leads to higher levels compared to  
245 mild to moderate infection, corroborating other studies. For instance, Chen et al. determined that  
246 symptom severity correlated directly with the magnitude and durability of class-switched serum  
247 antibodies, as well as other studies (13, 32, 33). However, little is known if the magnitude of antibody  
248 level correlates with re-infection potential particularly with VOC.

249 Although presence of IgG is evidence of an effective immune response, it is important to  
250 decipher whether these antibodies are capable of neutralizing virus. It has been found that not all  
251 recovered COVID-19 patients develop sufficient neutralizing antibody titers (12). Our study showed that  
252 while SARS-CoV-2 cross-reactive IgG antibodies were present in control patients, these antibodies were  
253 not capable of neutralizing SARS-CoV-2. A recent study suggests that exposure to a seasonal coronavirus  
254 can induce the production of antibodies against SARS-CoV-2, but these antibodies are not protective  
255 against the virus (34). Therefore, detection of IgG alone cannot always predict protection from  
256 reinfection. This is an important distinction that clinicians need to make when examining data from

257 recovered patients. Optimally, a test to determine the presence of specific neutralizing antibodies  
258 would be more informative than our current ELISA, which only detects antibodies that are specific for  
259 SARS-CoV-2.

260 A key feature of SARS-CoV-2 is its high mutation rate (35, 36). Selective pressures acting on the  
261 virus have led to mutations that allow the virus to spread more efficiently and to evade host immune  
262 responses (37). Fortunately, we and others have found that there appears to be some albeit limited  
263 cross-protection against the circulating VOC (38, 39). In our hands, patients who survived infection with  
264 the original SARS-CoV-2 generate antibody responses capable of neutralizing three different VOC, and  
265 these antibodies are more effective against the Alpha variant compared to the Beta and Delta variants.  
266 It is important to note that the cross-reactive neutralizing potential from the original SARS-CoV-2 was  
267 significantly less for all three of the VOC tested. However, recent studies provide hope that even low  
268 levels of neutralizing antibodies will lead to better outcomes after re-infection with VOC for patients  
269 who have been vaccinated or survived natural infection with SARS-CoV-2 early in the pandemic (38, 40,  
270 41). It has been demonstrated that individuals whom have been previously infected more rapidly  
271 develop neutralizing antibodies post-vaccination with an mRNA vaccine. The neutralizing antibody titer  
272 is blunted across multiple VOC with the Beta and Gamma variants have the most dramatic decrease  
273 followed by the Delta variant (42). The decrease in neutralization efficiency can be attributed to the  
274 mutations the spike protein has acquired, specifically the dominant epitopes that are targeted by  
275 neutralizing antibodies to each variant. It has recently been shown that patients infected with an earlier  
276 isolate, similar to the ancestral WA1 isolate we used in this study, develop neutralizing antibodies  
277 against class 2 epitopes, while patients infected with the Beta variant develop neutralizing antibodies  
278 against class 3 epitopes (43). It would be interesting to know if protection against newly emerging VOC is  
279 enhanced by the neutralizing antibody response in one group or the other.

280 Our study provides additional support for the growing body of literature examining human  
281 COVID-19 serum samples. Our data supports established work that increased levels of IL-6 and IP-10  
282 contribute to enhanced disease phenotype. In addition, our study highlights the importance of both the  
283 antigen-specific antibody response and its functionality to neutralize emerging VOC. The more fully we  
284 understand effective immune responses to this pathogen, the greater our ability to successfully treat  
285 those who are infected, and vaccinate those we hope to protect against infection.

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287

288 **Competing interest**

289 The authors declare no conflicts of interest.

290

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293

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296 Branch (all NIAID) for their efforts to obtain and characterize the SARS-CoV-2 isolates.

297

298 **Author contributions**

299 A.M. and R.F.R. conceived the idea. A.M. secured funding. A.J.G., R.F.R., and A.M. designed the

300 experiments. P.M.R., J.-P.L., M.K.Z., and R.F.R. collected and provided the serum samples and

301 coresponding clinical chart data. A.J.G., and K.L.O conducted the experiments and acquired the data.

302 A.J.G., K.L.O, K.S., R.F.R. and A.M. analyzed and interpreted the data. A.J.G., K.L.O., and A.M. prepared

303 the manuscript. All authors approved the submitted manuscript.

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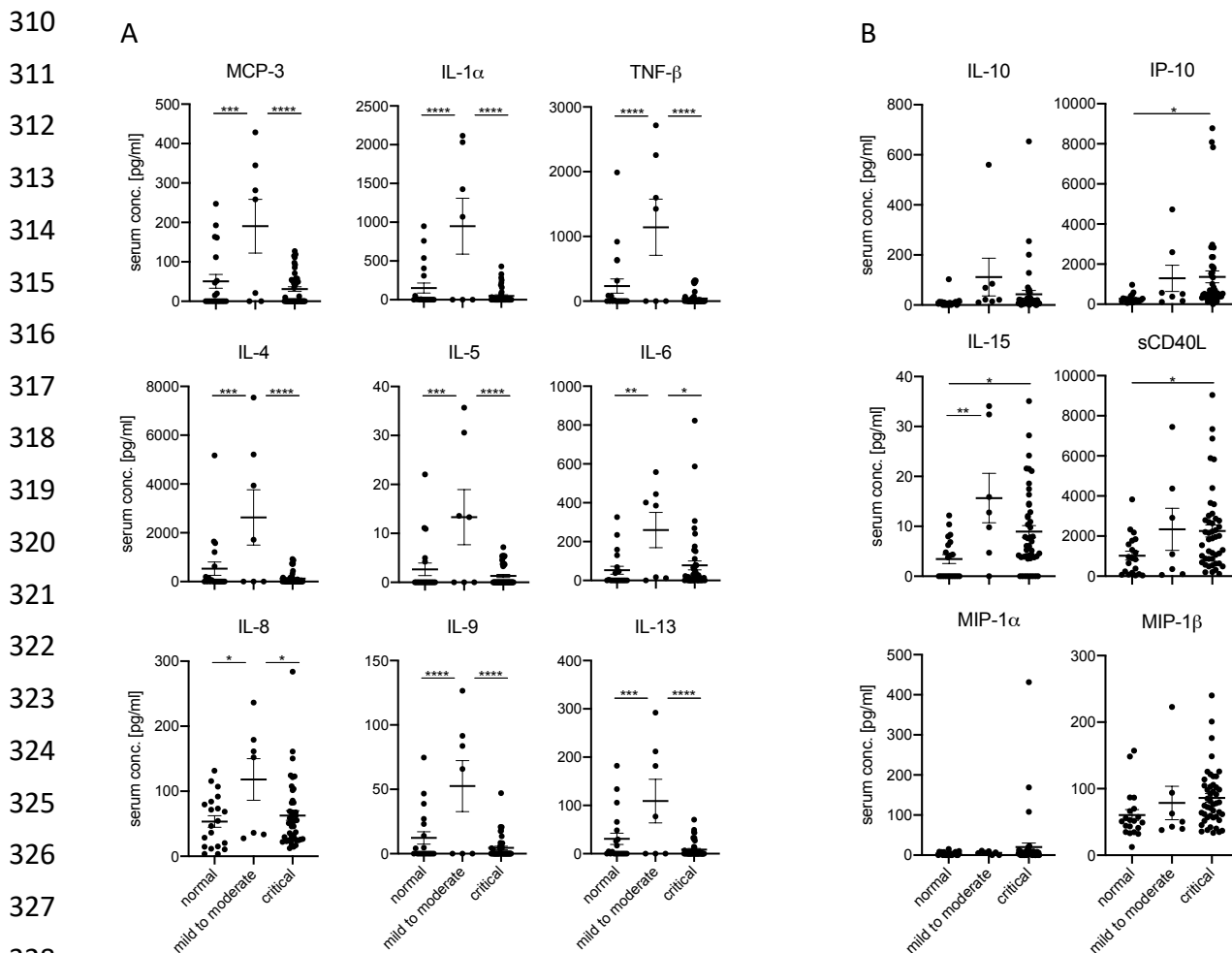
305 **Data availability**

306 All data is available in the manuscript.

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309 **Figures:**

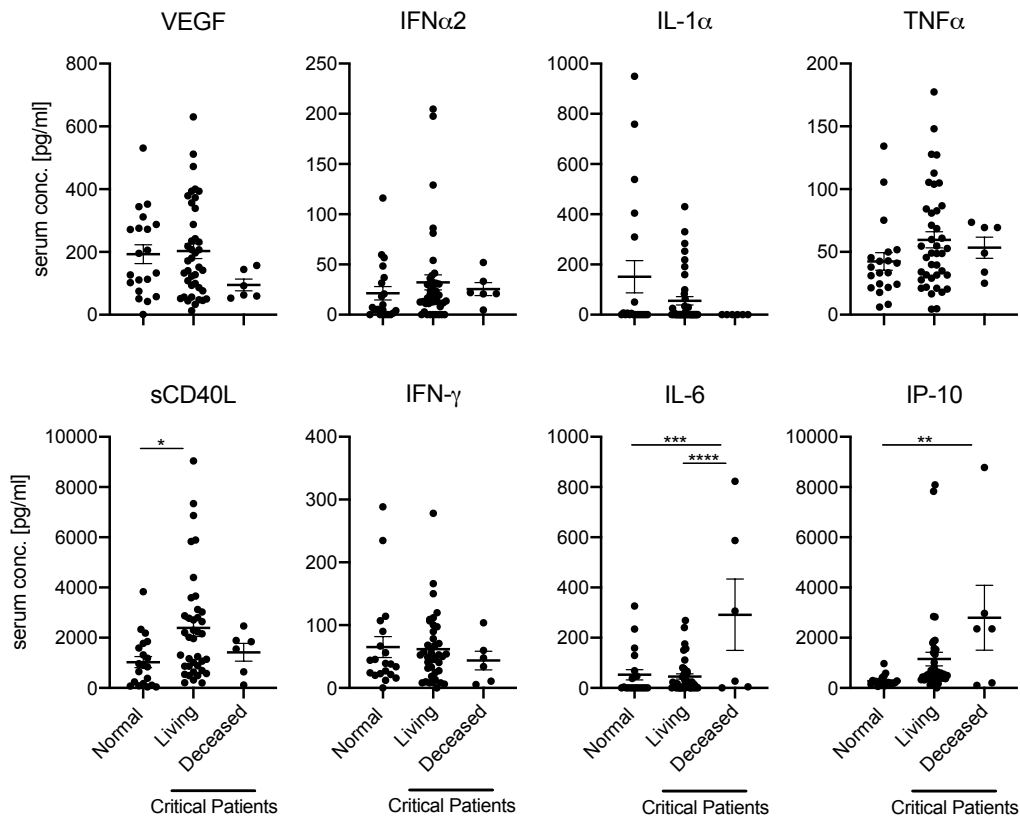


330 **Figure 1. COVID-19 patients exhibit varying levels of cytokines and chemokines that correlate with**  
331 **disease severity.** Cytokine and chemokine levels for day-of-admission COVID-19 serum samples  
332 alongside 20 normal samples. Error bars represent standard error. Statistically significant differences as  
333 determined by one-way ANOVA are indicated as  $p < 0.0001$  (\*\*\*\*),  $p < 0.001$  (\*\*\*),  $p < 0.01$  (\*\*), and  
334  $p < 0.05$  (\*).

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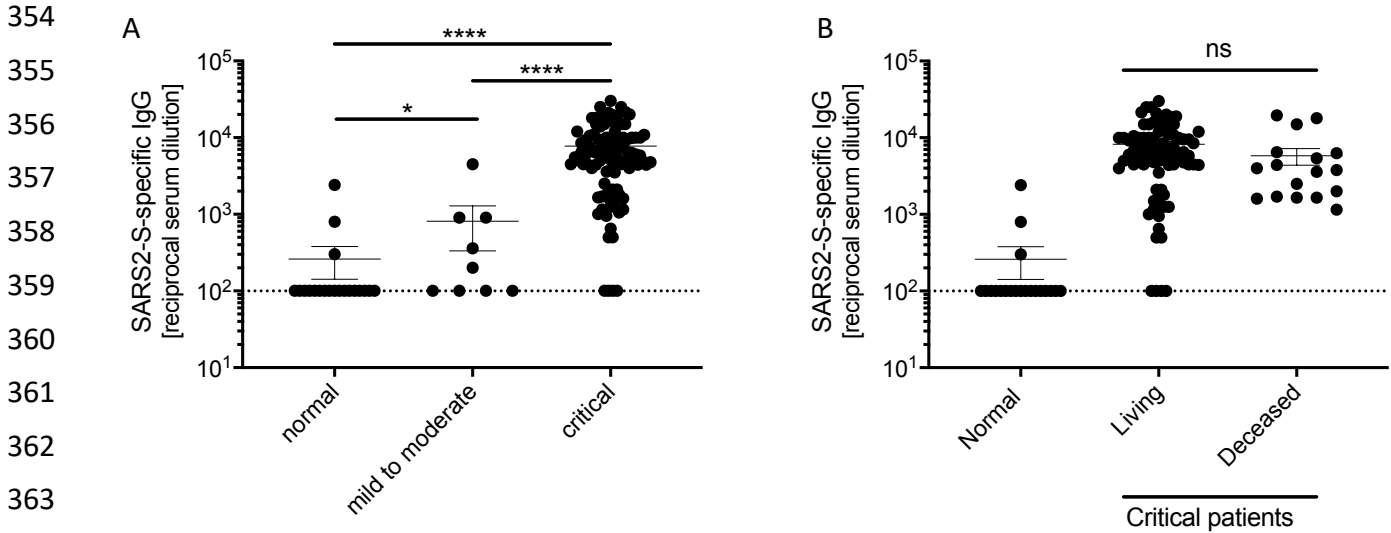
345

346 **Figure 2. Serum IL-6, IP-10, and sCD40L predict disease outcome in COVID-19 patients.** Cytokine and  
347 chemokine levels for day-of-admission critically infected COVID-19 patients who either recovered from  
348 infection (living) or failed to recover (deceased), alongside 20 uninfected (normal) patients. Error bars  
349 represent standard error. Statistically significant differences as determined by one-way ANOVA are  
350 indicated as  $p < 0.0001$  (\*\*\*\*),  $p < 0.001$  (\*\*\*),  $p < 0.01$  (\*\*), and  $p < 0.05$  (\*).

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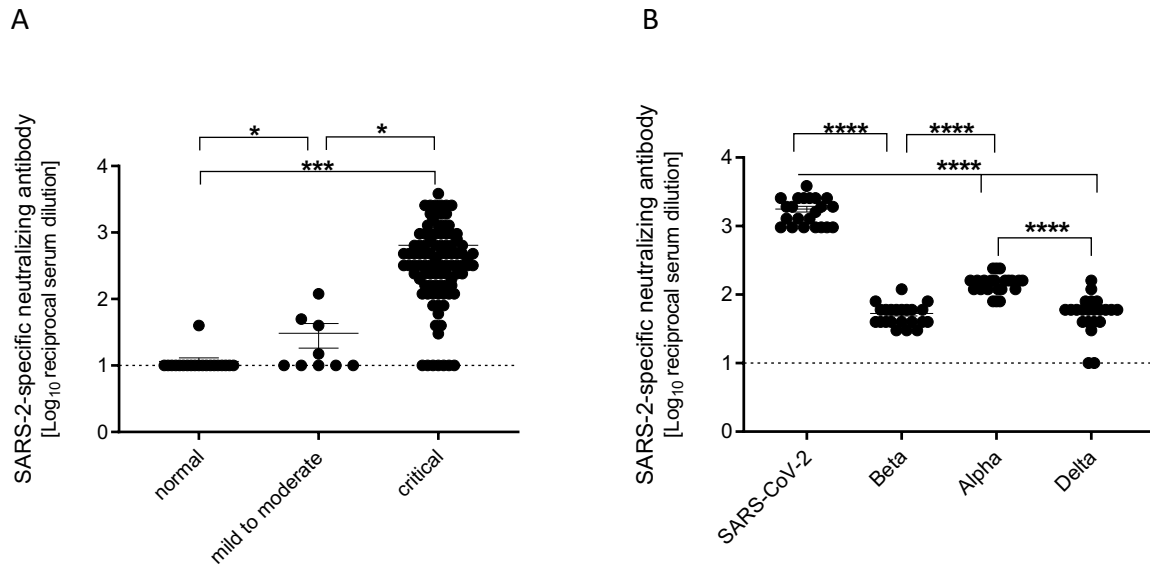


365 **Figure 3. Critical COVID-19 induces high titers of anti-SARS-CoV-2 IgG. (A)** IgG titers specific to SARS-  
366 CoV-2 spike receptor-binding domain for COVID-19 and normal serum samples. **(B)** IgG titers of critically  
367 infected COVID-19 patients who either recovered from infection (living) or failed to recover (deceased),  
368 alongside 20 uninfected (normal) patients. Error bars represent standard error. Statistically significant  
369 differences as determined by Mann-Whitney test are indicated as  $p < 0.0001$  (\*\*\*\*),  $p < 0.001$  (\*\*\*), and  
370  $p < 0.05$  (\*).

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389

390 **Figure 4. Critical COVID-19 induces high titers of anti-SARS-CoV-2 neutralizing antibodies.** (A) SARS-  
391 CoV-2-specific neutralizing antibody titers for COVID-19 and normal serum samples. (B) Neutralizing  
392 antibody titers for COVID-19 serum samples comparing SARS-CoV-2 variants USA-WA1, Beta, Alpha, and  
393 Delta. Error bars represent standard error. Statistically significant differences as determined by Mann-  
394 Whitney test are indicated as  $p < 0.0001$  (\*\*\*\*),  $p < 0.001$  (\*\*\*), and  $p < 0.05$  (\*).

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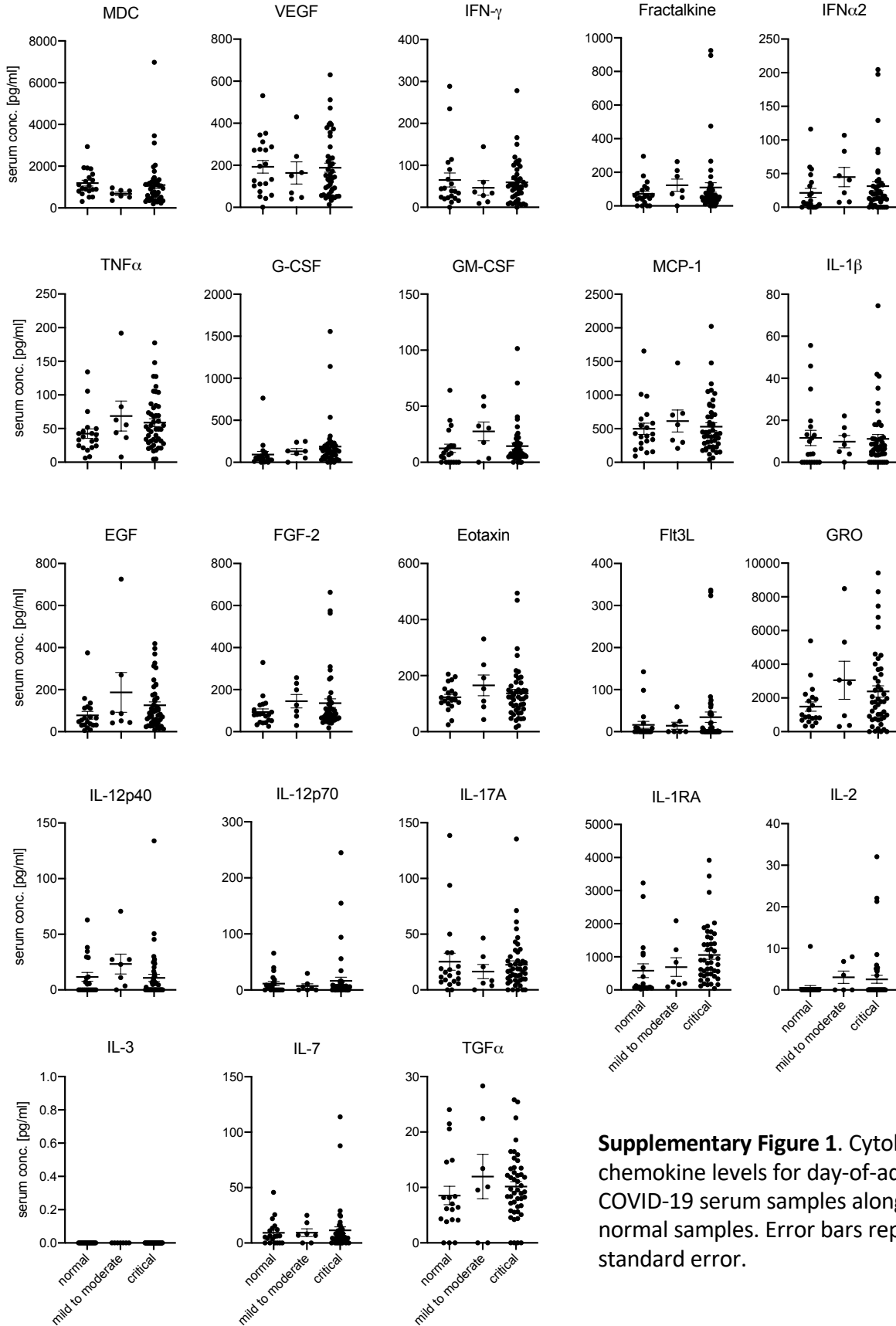
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Supplementary Figure 1

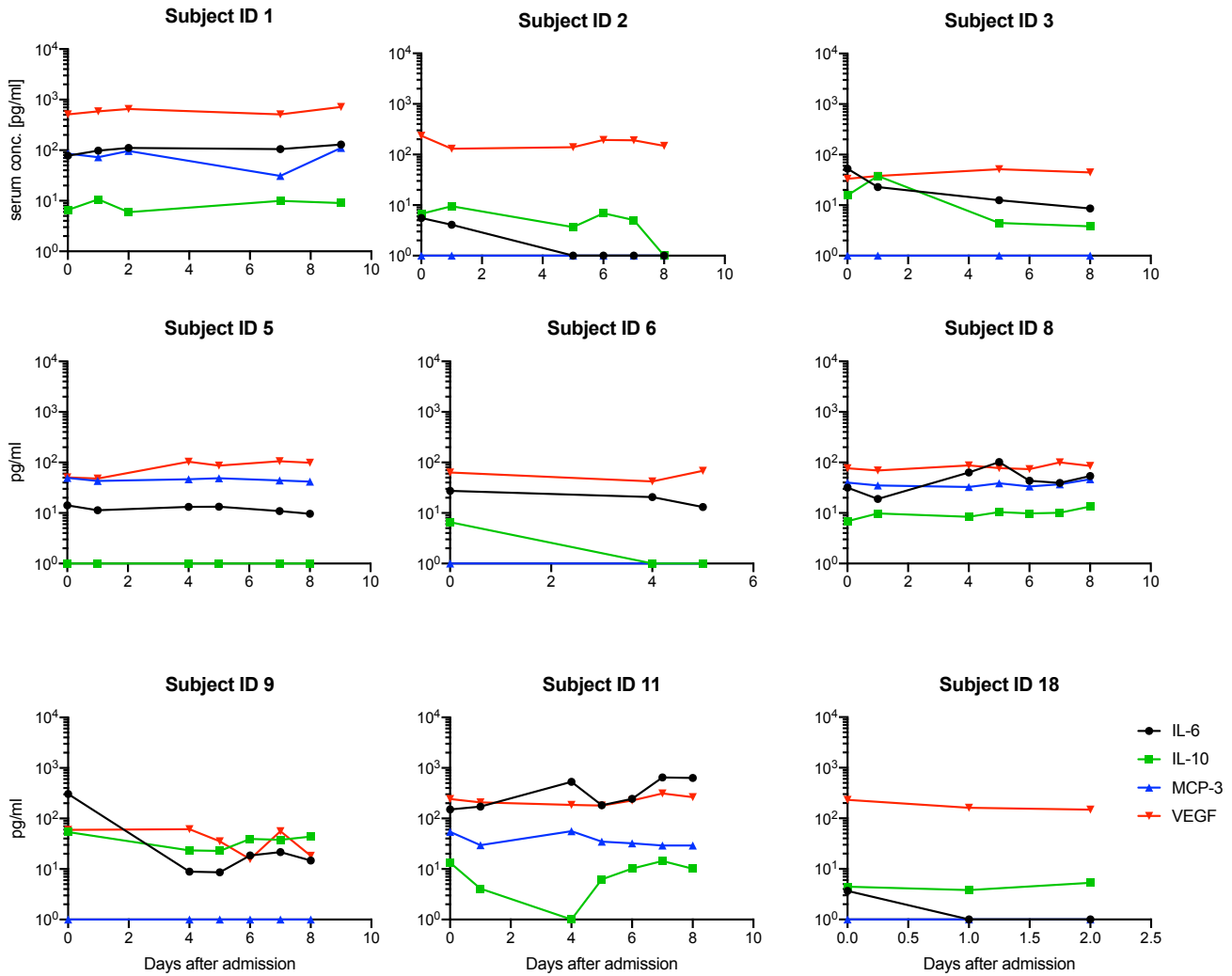
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**Supplementary Figure 1.** Cytokine and chemokine levels for day-of-admission COVID-19 serum samples alongside 20 normal samples. Error bars represent standard error.

Supplementary Figure 2

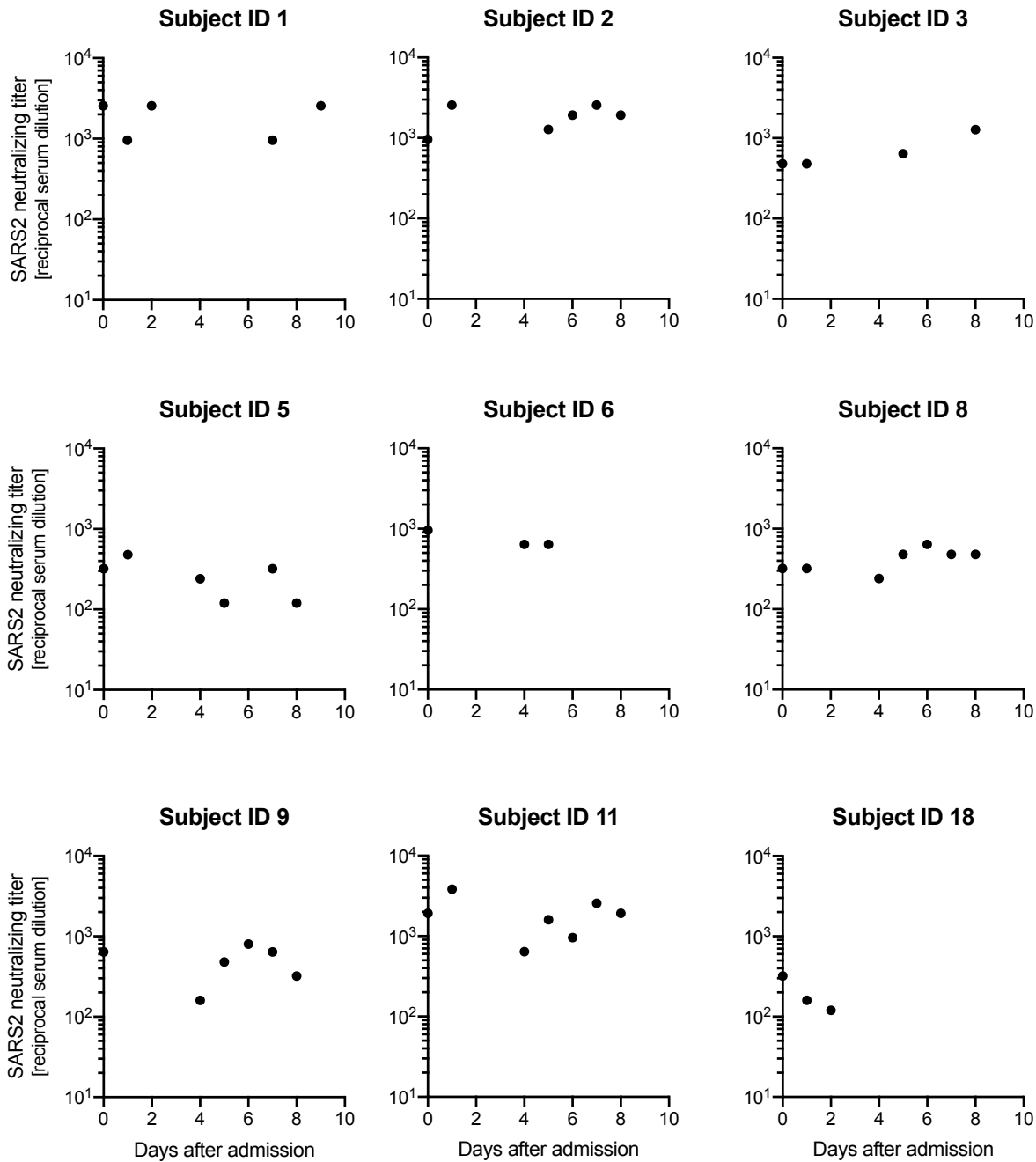
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Supplementary Figure 2. Cytokine and chemokine levels of selected patients over time.

Supplementary Figure 3

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**Supplementary Figure 3.** Anti-SARS-CoV-2 neutralizing antibodies remain steady over time in selected patients.