

Short Communication

Successful treatment of COVID-19 infection with convalescent plasma in B-cell-depleted patients may promote cellular immunity

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Treatment with convalescent plasma has been shown to be safe in coronavirus disease in 2019 (COVID-19) infection, although efficacy reported in immunocompetent patients varies. Nevertheless, neutralizing antibodies are a key requisite in the fight against viral infections. Patients depleted of antibody-producing B cells, such as those treated with rituximab (anti-CD20) for hematological malignancies, lack a fundamental part of their adaptive immunity. Treatment with convalescent plasma appears to be of general benefit in this particularly vulnerable cohort. We analyzed clinical course and inflammation markers of three B-cell-depleted patients suffering from COVID-19 who were treated with convalescent plasma. In addition, we measured serum antibody levels as well as peripheral blood CD38/HLA-DR-positive T-cells *ex vivo* and CD137-positive T-cells after *in vitro* stimulation with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-derived peptides in these patients. We observed that therapy with convalescent plasma was effective in all three patients and analysis of CD137-positive T-cells after stimulation with SARS-CoV-2 peptides showed an increase in peptide-specific T-cells after application of

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convalescent plasma. In conclusion, we here demonstrate efficacy of convalescent plasma therapy in three B-cell-depleted patients and present data that suggest that while application of convalescent plasma elevates systemic antibody levels only transiently, it may also boost specific T-cell responses.

Keywords: B-cell deficiency · convalescent plasma · COVID-19 · SARS-CoV-2 · T-cell immunity



Additional supporting information may be found online in the Supporting Information section at the end of the article.

Introduction

Coronavirus disease in 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to a pandemic with currently more than 175 million infected people worldwide and nearly 4 million deaths (status: June 2021; <https://coronavirus.jhu.edu/map.html>). In particular, older people and patients with immune defects are likely of high risk to develop a severe course of disease. So far, no specific antiviral medications are available. The use of antibody-containing plasma from recently recovered patients is a potential therapeutic option, which was first tested experimentally in diphtheria-infected animals in 1880 [1] and was later given clinically, for example, in the Spanish influenza pandemic in 1918, for MERS-CoV and H1N1 influenza and recently in the Ebola outbreak in West Africa [2, 3]. Convalescent plasma therapy (CPT) for B-cell-competent patients suffering from COVID-19 has achieved varying levels of success and seems to be most effective when using plasma with very high antibody titers in mild to moderate disease [4–6]. Reports of efficacy in B-cell-deficient patients have been more universally encouraging [7–9]. It remains unclear, however, whether the effect of CPT relies solely on the short-lived virus-neutralizing effect of antibodies or may have a more enduring effect on the immune response. Although Hueso et al. [7] reported functional T-cell responses prior to CPT of B-cell-depleted COVID-19 patients, they did not monitor changes in the magnitude of the T-cell response during and after treatment.

We here report three cases of B-cell-depleted patients with COVID-19 who successfully received CPT and monitor the effect on antigen-specific T cells.

Results and discussion

Clinical course of B-cell-depleted patients treated with convalescent plasma

We treated and analyzed three patients with SARS-CoV-2 immune plasma. All patients were completely B-cell-depleted due to prior treatment with rituximab for hematological malignancies and were in complete remission (Table 1). Patient 1 is an 18-year-old male diagnosed with progenitor B-cell acute lymphoblastic leukemia in June 2019 and treated with poly-chemotherapy plus

rituximab. The last administration of rituximab had been on January 31, 2020. On March 19, 2020, he was admitted in complete leuco- and lymphopenia with fever and respiratory symptoms about 1 week after administration of consolidation therapy with cyclophosphamide/cytarabine. SARS-CoV-2 infection was confirmed by RT-PCR. Due to the increased risk of the lymphopenic patient, a therapy with hydroxychloroquine was started. Two weeks later, the patient presented in reduced condition, still lymphopenic and inflammatory markers (C-reactive protein [CRP], ferritin) increased further. On April 16 and 17, a total of three units (900 mL) of convalescent plasma were administered. This was repeated on May 5 and 6. Thereafter, viral loads dropped and have remained negative since (Fig. 1A). Patient 2 is a 70-year-old male with relapsed mantle cell lymphoma after allogeneic stem cell transplantation in 2015. The relapse was treated with ibrutinib before therapy was switched to rituximab and bendamustin and complete remission could be achieved. For consolidation therapy, the patient was treated with donor lymphocyte infusion and rituximab maintenance therapy until November 2019. On April 6, 2020, the patient was admitted to a local hospital with increasing dyspnoea and confirmed SARS-CoV-2 and influenza A infection (nasopharyngeal swab from April 1, 2020). First onset of symptoms was already on March 27 with headache, throat pain, cough, and fever. Influenza therapy with oseltamivir was initiated. On April 21, he was admitted to our intensive care unit. The patient was treated with broad-spectrum antibiotics, hydroxychloroquine and intravenous immunoglobulin (IVIg), due to secondary antibody deficiency. We administered three units of convalescent plasma on April 23 and 24, which was repeated on May 15 and 16. The patient tested negative for SARS-CoV-2 on May 22 and has remained negative since. Patient 3 is a 49-year-old male who was first diagnosed with pancytopenia and splenomegaly in May 2020. Bone marrow puncture revealed infiltration with indolent B-cell lymphoma. A computed tomography (CT) scan showed no further manifestation. Immunotherapy with rituximab/bendamustin was initiated and the patient achieved complete remission after three cycles. On September 17 and 18, 2020, the patient received the fourth cycle of rituximab/bendamustin. Ten days later, the patient presented at our emergency room with 1-day history of fever and cough and tested SARS-CoV-2 positive. Due to neutropenia after chemotherapy, treatment with G-CSF and antibiotics were initiated. A chest CT scan showed bilateral infiltrates. As the patient had no need for

Table 1. Characteristics of B-cell-deficient patients with COVID-19 infection

Patient ID	Age	Sex	Underlying disease	Remission status	Last dose of rituximab	First positive SARS-CoV-2 PCR	Circulating B cells at time of infection (% of PBMC)	COVID-19 severity score	Outcome
1	18	M	Progenitor B-ALL	Complete	January 2020	March 19, 2020	0	5	Virus cleared
2	70	M	Mantle cell lymphoma	Complete	November 2019	April 01, 2020	0	2	Virus cleared
3	49	M	Indolent B-cell lymphoma	Complete	September 2020	September 27, 2020	0	5	Virus cleared

ALL, acute lymphoblastic leukemia.

oxygen substitution, no further treatment such as dexamethasone or remdesivir was administered. On October 2 and 3 and 6 and 7, a total of six units of convalescent plasma were administered. On October 10, fever subsided and CRP levels declined.

After administration of three units of immune plasma, patients 1 and 2 reached anti-SARS-CoV-2 antibody titers above the level of positivity (>10 AU/mL). Patient 3, whose first CPT had a lower specific antibody titer of 51 AU/mL compared to 61 and 81 AU/mL for patients 1 and 2, respectively, required a second application to reach this threshold. Importantly, in all patients seropositivity waned within 10–15 days (Fig. 1A). Despite the transient presence of the specific antibodies, all patients cleared the virus successfully. In all cases, application of the immune plasma was well tolerated and did not cause any adverse events. Shortly after administration, all patients improved in terms of clinical status and CRP values (Fig. 1B).

Specific T-cell activation and expansion after application of convalescent plasma

In patient 3 in particular, the reduction in viral load continued gradually for weeks after serum antibody levels had dropped to below the 10 AU/mL threshold. This raised the question whether antigen-specific T-cell responses, known to contribute to recovery from SARS-CoV-2 infection in B-cell-competent individuals, were affected by CPT. We, therefore, studied the presence of activated CD38⁺HLA-DR⁺ T cells ex vivo in available peripheral blood samples, retrospectively. Moreover, we looked at the expression of the activation marker CD137 on CD4⁺ and CD8⁺ T cells after overnight restimulation in vitro with peptides that together span the lengths of SARS-CoV-2 S and N proteins. We previously found CD137 to be a good marker for T cells that recognize SARS-CoV-2 epitopes with high affinity [10]. In patient 1, CD38⁺HLA-DR⁺ CD4⁺ and CD8⁺ T cells showed a remarkable increase after the first plasma administration but remained stable after the second dose (Fig. 2A). A similar increase was seen in patient 3 after both the first and second CPT. The second dose of plasma, with a higher SARS-CoV-2-specific antibody titer, had a greater effect than the first dose. In concordance with the ex vivo result, the number of CD137⁺ CD4⁺ and CD8⁺ T cells after in vitro restimulation peaked shortly after the first plasma dose in patient 1. For patient 2, unfortunately there were no samples available for FACS analysis from before the first plasma dose, so we could not confirm that this patient too showed a similar response. However, we could detect a marked increase in absolute lymphocytes numbers after the first plasma dose, as also seen in patient 1 (Fig. 2A).

As longevity of SARS-CoV-2 specific antibody responses is under debate even in B-cell-competent individuals [11, 12], we were interested in the persistence of SARS-CoV-2-specific CD4⁺ and CD8⁺ T cells in our B-cell-depleted patients after infection. Restimulation of PBMCs from patients 1 and 2 with SARS-CoV-2 S and N proteins 6 months after infection demonstrated the retained presence of antigen-specific T cells, as evidenced by the upregulation of the activation marker CD137 on CD4⁺ (Fig. 2B)

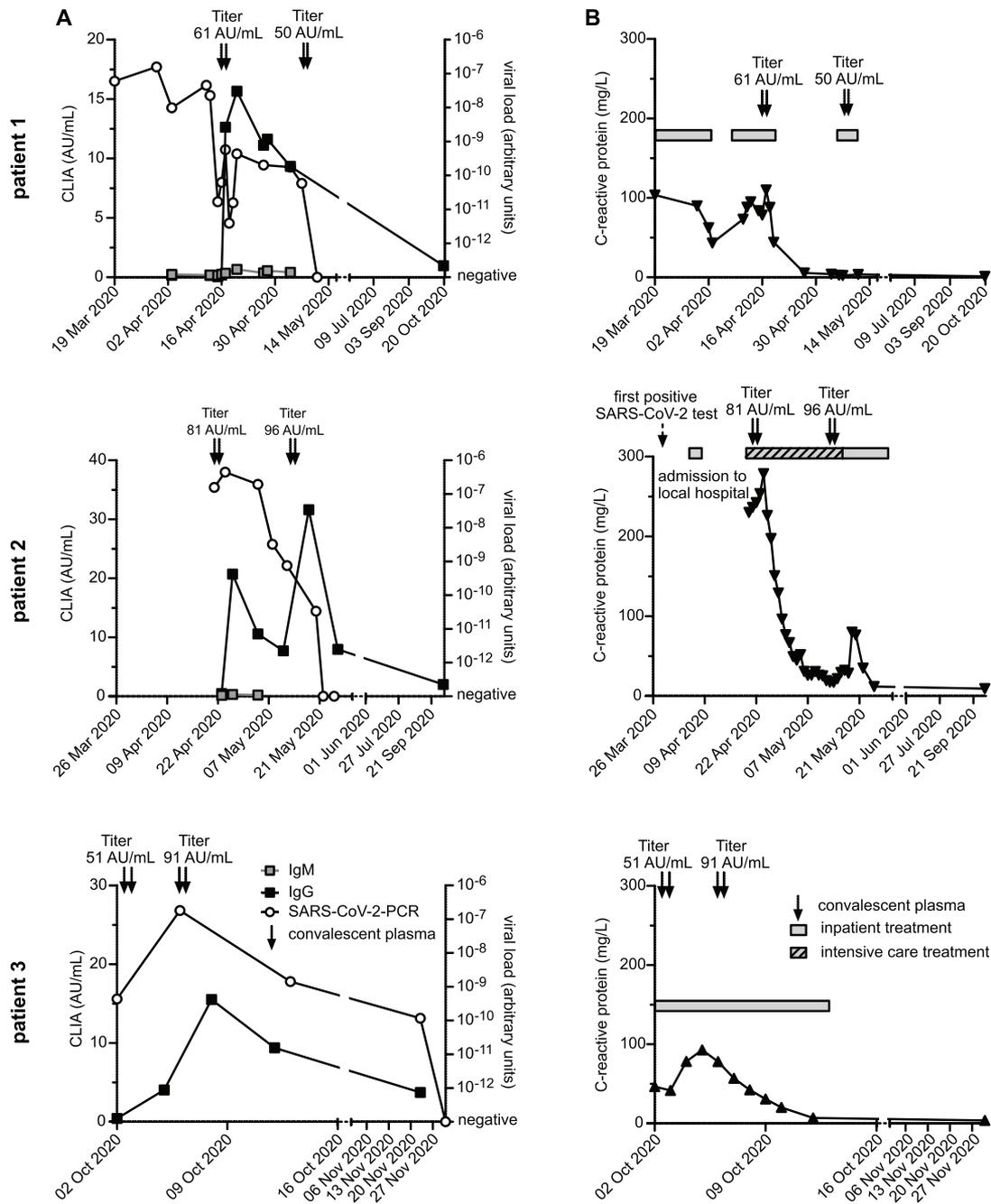


Figure 1. Clinical parameters of B-cell-depleted patients suffering from COVID-19. (A) IgG/IgM serum levels during the course of disease (left y-axis) and SARS-CoV-2 viral load (right y-axis) for each of the three patients and measured by CLIA and qPCR, respectively. (B) C-reactive protein (CRP) levels during course of disease and time periods of inpatient treatment and measured by ELISA. Administration of three units of immune plasma via intravenous infusion over 2 days is indicated by the black arrows and SARS-CoV-2-specific antibody titers in the plasma products are indicated. Each data point corresponds to single measurements in the individual patient.

and CD8⁺ (Fig. 2C) T cells. We could not acquire a 6 months postinfection sample from patient 3. The incidence of antigen-specific T cells in B-cell-depleted donors was not lower than in the B-cell-competent plasma donors [6,7].

There are several reports on patients with B-cell-deficiencies suffering from COVID-19, with diverse outcomes. While most reports are either on patients with agammaglobulinemia or with

rituximab treatment for autoimmune diseases [13–17], there are fewer reports on COVID-19 in patients with rituximab treatment for hematological malignancies [18]. Patients with agammaglobulinemia generally seem to have a rather mild course of disease or can at least spontaneously recover from infection, indicating that the presence of B cells is not strictly required to overcome disease and supporting the notion of compensatory effects

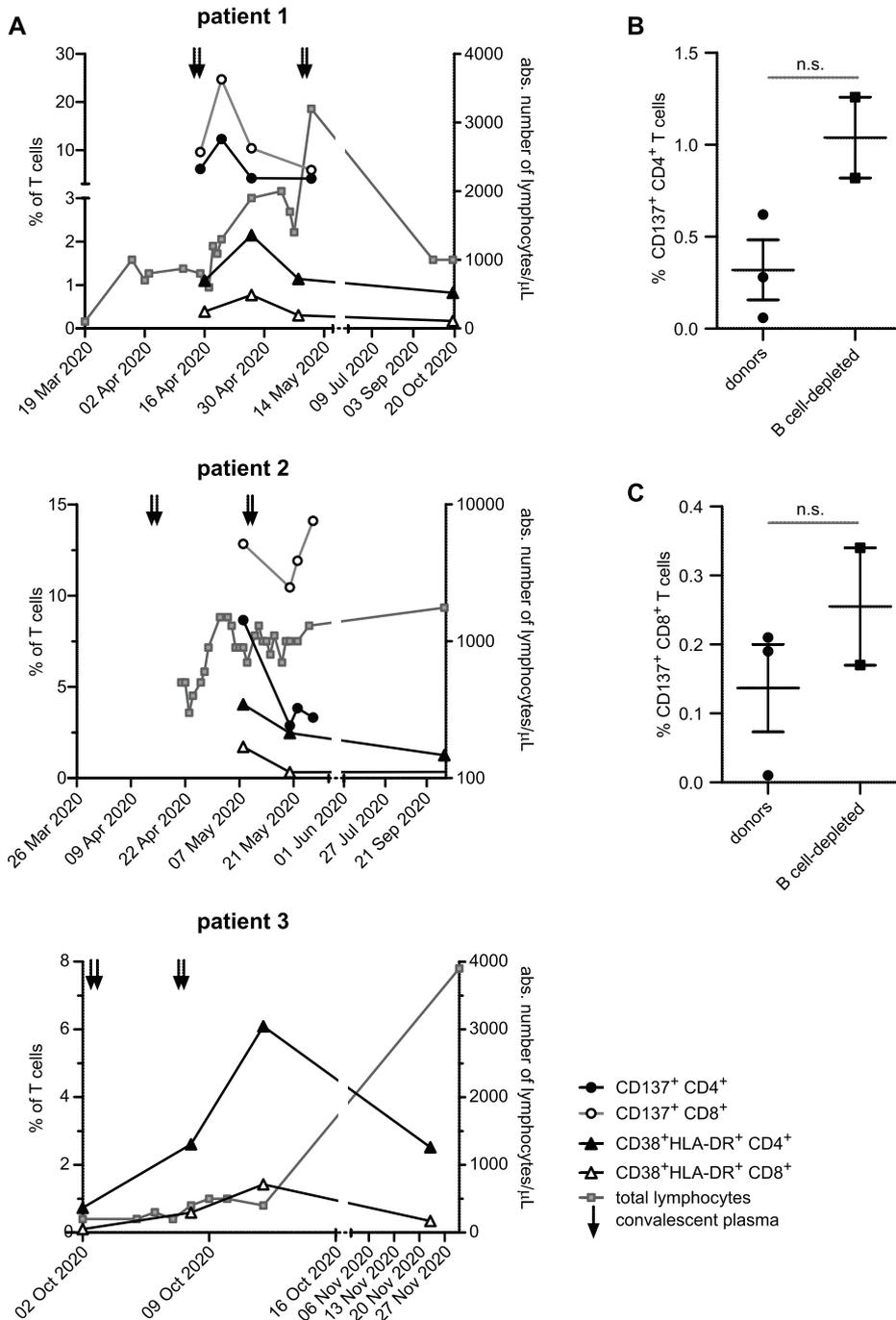


Figure 2. T-cell responses after convalescent plasma therapy. (A) Percentage (left y-axis) of CD38⁺HLA-DR⁺, activated CD4⁺ and CD8⁺ T cells in peripheral blood ex vivo (circles), as well as percentage of CD137⁺ CD4⁺ and CD8⁺ T cells after overnight in vitro stimulation with overlapping peptides that together span the full length of SARS-CoV-2 S and N proteins (triangles) and measured by flow cytometry. Additionally, the absolute number of lymphocytes in peripheral blood is depicted (right y-axis). Each data point corresponds to single measurements in the individual patient. Intravenous administration of three units of immune plasma over 2 days is indicated by the black arrows. (B and C) CD137 expression on CD4⁺ and CD8⁺ T cells after overnight in vitro stimulation with overlapping peptides that together span the full length of SARS-CoV-2 S and N proteins and measured by flow cytometry. Three B-cell-competent convalescent plasma donors and B-cell-depleted COVID-19 patients and B-cell-depleted COVID-19 patients 1 and 2, 6 months after the first detection of SARS-CoV-2 infection. Individual values as well as mean ± SEM are shown. n.s. = not significant, Mann-Whitney test.

of other immune mechanisms. In contrast, patients with hematological malignancies, where rituximab therapy is routinely combined with chemotherapy, have been reported to suffer from persisting SARS-CoV-2 infection with fatal outcome [19]. The worse outcome could be speculated to be due to the role of T cells in the antiviral response as in these patients T-cell counts and function are often disturbed. Our limited data hint at a potential increase in the number of activated, antigen-specific T cells after CPT. This would be in line with reports from other infec-

tious diseases like influenza and Ebola that administration of specific antibodies induces formation of antigen-antibody complexes, which enhance cellular immune responses [2, 3, 19]. This mechanism has been described to involve an increased uptake by APCs through the Fc receptor, a FcR-dependent enhancement of MHC class I-restricted cross-presentation, a shift in presentation of class II-restricted determinant, and changes in cytokine expression by APCs and T cells [19]. More extensive data would be required to confirm a similar mechanism at play after CPT in B-cell-depleted

COVID-19 patients. Additionally, it remains currently unclear if the increase in antigen-specific T cells following CPT is unique to B-cell-depleted individuals. Nonetheless, if our results can be confirmed in larger studies, this could have major implications for long-term protection against reinfection in these patients.

Concluding remarks

In conclusion, our data demonstrate efficacy of treatment with convalescent plasma in three B-cell-depleted patients with COVID-19. Although transferred antibody levels were only short-lived, our data suggest promotion of specific cellular immunity by application of convalescent plasma.

Materials and methods

All patients and donors provided written informed consent according to the Declaration of Helsinki.

Detection of viral load

SARS-CoV-2 viral loads were determined by RT-PCR on nasopharyngeal swabs or, when patients were on mechanical ventilation, tracheal secretion. COVID-19 disease severity scores were based on the NIH ordinal scale [20].

Flowcytometric analysis

Peripheral blood mononuclear cells (PBMCs) were isolated at several time points for each donor, cryopreserved, and stored in liquid nitrogen. All samples from one donor were analyzed at the same time for consistency. Unstimulated PBMCs of the patients were stained with antibodies to CD3 (clone HIT3 α), CD4 (SK3), CD8 (RPA-T8), CD38 (HB7), and HLA-DR (L243) plus 7AAD (all from BD Bioscience) to detect activated T cells, *ex vivo*. To determine SARS-CoV-2 specific T-cell responses, PBMCs of the patients or donors were incubated with 1 μ g/mL of overlapping peptides covering the whole nucleocapsid (N) and spike (S) proteins of SARS-CoV-2 (JPT). After overnight incubation, antigen-specific CD137⁺ T cells were detected using antibodies against CD3 (HIT3 α), CD4 (RPA-T4), CD8 (SK1), and CD137 (4B4-1) as well as 7AAD (BD Bioscience) or Zombie Green viability dye (Biolegend). Upregulation of CD137 expression after antigen stimulation versus a DMSO-only control was confirmed for two samples for each donor. Background CD137 expression remained very low and stable between donors and samples (not shown). Data are displayed as total CD137 expression. Samples were run on a BD Canto II flow cytometer and analyzed with Kaluza Analysis 2.1 (Beckman Coulter) or FlowJo 10.5.3 (BD Life Sciences) software. Gating strategy and representative CD137 expression versus controls are depicted in Supporting Information Figure S1.

Manufacturing of convalescent plasma

COVID-19 convalescent plasma was produced according to EU guidelines after approval by local authorities (“Regierung von Oberfranken”; Nr: ROF-SG55-2-2678 3-6-26-29) and informed, written consent from donors. Donors were tested positive for anti-S IgG SARS-CoV-2 antibodies by two independent assays, an anti-S IgG ELISA (Euroimmune) and anti-S1/S2 IgG CLIA (DiaSorin). Additionally, S- and N-specific IgG level in the patient sera were measured by a fully automated CLIA (Shenzhen Yhlo Biotech). Finally, the neutralizing capacity of the donors’ plasma were determined in an immunofluorescence focus assay and the NT₅₀ were confirmed to be higher than 160.

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Ethics approval: All patients and donors provided written informed consent according to the Declaration of Helsinki. Ethics approval for plasma manufacturing was given by the “Regierung von Oberfranken”; Nr: ROF-SG55-2-2678 3-6-26-29 and for collection of blood specimen by the local ethics committee; Nr: 174_20B.

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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- Abbreviations:** COVID-19: coronavirus disease in 2019 · CPT: convalescent plasma therapy · CRP: C-reactive protein · SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
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