One-year follow-up of the CAPSID randomized trial for high-dose convalescent plasma in severe COVID-19 patients

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One-year follow-up of the CAPSID randomized trial for high-dose convalescent plasma in severe COVID-19 patients

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ABSTRACT

BACKGROUND. Results of many randomized trials on COVID-19 convalescent plasma (CCP) have been reported but information on long-term outcome after CCP treatment is limited. The objectives of this extended observation of the randomized CAPSID Trial are to assess long-term outcome and disease burden in patients initially treated with or without CCP.

METHODS. Of 105 randomized patients, 50 participated in the extended observation. Quality of life (QoL) was assessed by questionnaires and a structured interview. CCP-donors (n=113) with asymptomatic to moderate COVID-19 were included as a reference group.

RESULTS. The median follow-up of patients was 396 days, the estimated 1-year survival was 78.7% in the CCP and 60.2% in the control group (p=0.08). The subgroup treated with a higher cumulative amount of neutralizing antibodies showed a better 1-year survival compared to the control group (91.5% versus 60.2%; p=0.01). Medical events and QoL assessments showed a consistent trend for better results in the CCP group without reaching statistical significance. There was no difference in the increase of neutralizing antibodies after vaccination between CCP and the control group.

CONCLUSION. The trial demonstrated a trend towards better outcome in the CCP group without reaching statistical significance. A pre-defined subgroup analysis showed a significant better outcome (long-term survival; time to discharge from ICU and time to hospital discharge) among those who received a higher amount of neutralizing antibodies compared to the control group. A substantial long-term disease burden remains after severe COVID-19.

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INTRODUCTION

The use of COVID-19 convalescent plasma (CCP) from patients recovered from a SARS-CoV-2 infection was evaluated in many randomized trials during the pandemic (1-21). The trials were heterogeneous in design and differed in terms of patient populations. Some included patients early in the disease course with mild to moderate disease in an outpatient setting (10,17-19) and others hospitalized patients with more severe disease (1-9,11-16). Some of the trials considered different kind of risk factors like age or concomitant disease (10). Some non-randomized trials suggested efficacy in immunocompromise patients (22-25).

Of note, the studies differed substantially in quality and quantity of CCP in terms of neutralizing antibody titers and CCP volume and timing of administration (1-19). Patients with severe disease had usually a longer interval since diagnosis. In most of the trials, the primary endpoint was not met and the results were inconclusive. When looking into detail there is a signal of efficacy of CCP with high titers of neutralizing antibodies especially when used early in the course of the disease (10,18,19). Most trials report outcome data up to 30 days after randomization (2-19). So far, none of them has reported long-term results. Because COVID-19 can lead to long-lasting symptoms sometimes with significant impairment, termed “long COVID-19” (26-30), it is of great interest to determine whether CCP has any impact on the disease burden in the long-term. Immunization by vaccines or infection are effective in the prevention of severe disease. However, so far there is limited information on the vaccination response after the use of CCP.

Here we report the long-term outcome of the CAPSID randomized clinical trial, which included hospitalized severe COVID-19 patients (1). Hospitalized patients were stratified according their need for ECMO, mechanical ventilation or ICU treatment and then randomized to receive either standard of care or standard of care plus 3 units of CCP on day 1, 3 and 5. The trial showed a trend towards a better outcome in the CCP group but did not reach statistical significance and therefore missed the primary endpoint which was defined as survival and no longer severe COVID-19 on day +21 after enrollment. In a pre-specified subgroup analysis, CCP showed significant better overall survival and improvement in other important clinical outcomes among patients who received a larger amount of neutralizing antibodies (1)

The per protocol follow-up time of this first part of the trial was 60 days (median follow-up 60 days) (1). Here we report a long-term follow-up of the patients (median follow-up 396 days) and also included the convalescent plasma donors as a reference group. All plasma donors had experienced only mild to moderate symptoms of COVID-19 prior to CCP donation. To our knowledge this is the first long-term follow-up of a randomized clinical trial of CCP treated patients.
RESULTS

Study population

One hundred and sixty-three participants were included in the long-term follow-up. Of the 77 survivors (day 60) treated within the CAPSID trial 50 patients (Control group: n=20, high titer CCP: n=16 low titer CCP n=14) (Fig. 1) and 113 donors participated in the long-term follow-up evaluation. The median follow-up time for patients was 396 (379–417) days after randomization and 519 (480–553) days after the first plasmapheresis for donors. Among the included donor population the median time from symptom onset to first plasmapheresis was 101 days (interquartile range (IQR) 73-124). Among the patient cohort of the extended follow-up the median time from onset of symptoms to randomization was 8 days (5-11). The donors were mostly infected during the first wave in Germany while the patients predominantly in the second wave.

Baseline characteristics are summarized in Table 1. The donor population was significantly (p<0.0001) younger (42.0 (31.0-52.0) years) than the patient population (58.5 (54.0-65.0) years). The patient cohort included more males (74%) than the donor cohort (52%). Donors had a significantly lower body mass index (25.9 (23.3-30.0) kg/m2) than patients (29.8 (26.6-33.0) kg/m2) (p=0.0003). In the donor cohort mild disease (88.5%) predominated. Of the patients 68% were graded ≥5 on the 8-point WHO severity scale and 90% reported comorbidities (Table 1).

Primary and secondary outcomes

No deaths have been reported in the donor population. Two patients in the control group died after day 60 (Fig. 2A). The 1-year overall survival (OS) was 78.1% (95% confidence interval (CI) 64.7-87.6%) in the CCP group and 60.2% (95% CI 44.4-72.9%) in the control group (p=0.08). Patients which were treated with a higher cumulative amount of neutralizing antibodies showed a significant better long-term OS when compared to the control group (1-year overall survival 91.5% (95%-CI: 70.0-97.8%) vs. 60.2% (95%-CI: 44.4-72.9%)(p=0.01) or to the subgroup that was treated with a low cumulative amount of neutralizing units (1-year OS 67.4% (95%-CI 46.6%-81.5%); p=0.03) (Fig. 2 B). As we have previously shown the amount of neutralizing antibodies in CCP-donors increases with the amount of reported symptoms (31). In a pandemic situation with a newly emerging pathogen validated tests for neutralizing antibodies are usually not immediately available in the very beginning of the pandemic. Therefore, in this period other criteria than antibody content might be important for donor selection. We therefore analyzed the OS stratified by the number of symptoms reported by donors. In this evaluation, there is a trend towards a better outcome in patients treated with CCP from donors with more than 3 symptoms compared to the control group (p=0.061) (Fig. 2C). However, the difference is not significant and much smaller than in the
comparison based on the cumulative amount of transfused neutralizing units (Fig. 2B and 2C). The better outcome of the subgroup which has received a higher cumulative amount of neutralizing units was confirmed in the final data set including long-term observation. It shows a significant shorter time to first negative SARS-CoV-2-PCR (p=0.02), a shorter time to discharge from ICU (p=0.02) and discharge from hospital (p=0.02) (log rank test, Fig. 3 A to D). The primary outcome of the study, i.e. survival and no longer fulfilling criteria of severe COVID-19 on day 21, remained non-significant. In the final data set, among those who received a high or low cumulative amount of neutralizing units, the primary outcome occurred in 56.0% and in 32.1%, and in 30.8% in the control group (p=0.046 high titer vs. control).

Medical events during long-term follow-up

Patients reported GI symptoms (including abdominal pain, diarrhea, nausea, weight loss), pulmonary symptoms, dyspnea pain symptoms, confusion, dizziness, hypersomnia, insomnia, conjunctivitis or alopecia (Table 2). The control group patients reported numerically less often gastrointestinal, or pain symptoms than the CCP group (p=n.s.) Pulmonary symptoms were reported in 47% of patients in the CCP group and 70% of patients in the control group (p=0.15) and during extended follow-up supplemental oxygen was needed in 10% of patients in the CCP group but in 30% of patients in the control group (p=0.13). During the extended follow-up period, 18% of patients were hospitalized and 18% of patients needed supplemental oxygen. Twenty percent of patients in the CCP group and 15% of the control group were hospitalized (p=0.724). The duration of hospitalization in the CCP group was 5 (3-6) days compared to 15 (6-77) days in the control group (p=0.09). The proportion of hospitalization did not significantly differ between patients who have received a high cumulative amount of neutralizing units compared to those treated with a low cumulative amount of neutralizing units (6.2% vs. 35.7%, p=0.07). The use of radiologic imaging of the chest was comparable between all groups.

Functional limitations assessed by the post COVID-Scale (i.e. grade 1 to 4) were reported by 56% of patients (Fig. 4 A). Grade 2-4 functional limitations were reported by 48% of patients. The number of patients reported to be free of limitations was not significantly different between CCP group (53%) and control group (30%) (p=0.136) (Fig. 4 A).

Any medical event during follow-up was reported in 73% of donors and 84% of patients. Events rated as grade 3 or higher occurred in 8% of donors and in 22% of patients (p=0.018). In donors, the most frequent symptoms were neurologic symptoms (57.5%), pulmonal symptoms (37.2%) and pain symptoms (15.9%) (Supplementary Table 1). Significantly more patients (18%) than donors (3%) needed oxygen (p=0.0014). Hospitalization for any cause occurred in 7% of donors and in 18% of patients during the extended follow-up period (p=0.051).
The proportion of donors with functional limitations assessed by the post-COVID-Scale was lower than
the proportion in patients (22% vs. 56%, p<0.001), and correspondingly, the subgroup with grade 2-4
limitations was also lower in donors (10.6% vs. 48%, p<0.001)(Fig. 4 A).

Quality of life

A substantial proportion of patients (24%) reported a decrease in their socioeconomic status during
follow-up with only slight numerical difference between CCP group and control group patients (26.7% vs.
20.0%, p=0.74) (Fig. 4B).

Figure 5 shows a summary of total scores of the reported quality of life questionnaires. In the EQ 5D 5L
questionnaire the patients of the CCP group reported numerically better outcomes than the control group
in all five dimensions, i.e. mobility, self care, usual activities, pain/discomfort and anxiety (Supplemental
Table 2). The dimensions self-care, usual activities, pain/discomfort, anxiety and your health today were
not statistically different between CCP and control group, while a significantly higher proportion of
patients of the CCP than the control group reported that they have no problems in walking about (63%
vs. 40%, p=0.0395)(Supplemental Table 3). There was no relevant difference of the EQ-5D-5L items
between the patients of the low and high titer CCP group (Figure 5A; Supplemental Table 4). The results
of the FACIT-dyspnea and FACIT-fatigue questionnaires show similar patterns: Scores were numerically
better in the CCP group than the control group without reaching statistical significance (Fig 5 B;
Supplemental Table 6 and 9). The difference between subgroups by cumulative amount of neutralizing
antibodies was small with a consistent trend for better scores in most of the items in the subgroup that
has received a higher cumulative amount of neutralizing units (Figure 5B, Supplemental Table 7 and 10).

FACIT-Fatigue score and the individual items did not differ significantly in the comparisons by
randomization group (Supplemental Table 12) and by cumulative amount of transfused units
(Supplemental Table 14).

Significantly more patients (24%) than donors (2.7%) reported a decrease in their socioeconomic status
during follow-up (p<0.0001)(Fig.4B). In the EQ-5D-5L questionnaire donors reported significant better
outcomes in all five dimensions than patients (Supplemental Table 2). The visual scale score of the item
“your health today” was significantly higher in donors than in patients (p<0.0001)(Figure 5A;
Supplemental Table 2).

In all the quality of life questionnaires used in this study the donors showed significant better results
(Fig.5A – C).
The score of the FACIT-Fatigue scale was significantly higher in donors than patients, indicating less fatigue in the donor group \( (p=0.0038) \) (Fig. 5C, Supplemental Table 11). The majority of items, in particular “I have energy”, “I am able to do my usual activities”, “I am too tired to eat”, “I need help doing my usual activities” and “I have to limit my social activity because I am tired” indicate significantly greater impairment in the patient population (Supplemental Table 11).

Because of the differences between the donor and patient population the outcomes might be influenced by other factors than severity of COVID-19. We therefore identified 26 pairs of donors and patients by propensity score matching for the variables age, sex and BMI (Supplemental Table 15). In this matched cohort the differences between donors and patients were significant for the change of socioeconomic status and the Post-COVID-Scale (Supplemental Figure 3A and 3B), the EQ-ED-SDL visual scale and EQ-ED-SDL cross walk score (Supplemental Fig.4A), and the FACIT Dyspnea 2 score (Supplemental Figure 4B). FACIT Fatigue and FACIT Dyspnea 1 score did not significantly differ between patients and donors in the propensity score matched groups (Supplemental Fig.5B and 5C).

Neutralizing antibodies

None of the participants was vaccinated prior to the infection. Most of the patients (86%) and donors (93%) were vaccinated at least once after their infection (Table 1). The median time from infection to first vaccination in patients and donors was 212 (189-237) days and 418 (390-443) days \( (p<0.0001) \). The median interval from the last vaccination to blood sampling for the follow-up antibody test in patients and donors were 77 (15-158) days and 131 (31-175) days \( (p=0.1729) \) Figure 6 shows the results of the neutralizing titer causing 50% inhibition in plaque-reduction neutralization test (PRNT50) at baseline or first apheresis and after the long-term follow-up. Among vaccinated participants with available baseline and follow-up data, patient PRNT50 titers increased from 1:80 (1:20-1:480) to 1:5120 (1:3840-1:5120). A significant increase of PRNT50 titers from 1:80 (1:20-1:320) to 1:5120 (1:1600-1:5120) was also observed in the patients randomized to CCP \( (p<0.0001) \) (Figure 6C).

Anti-SARS-CoV-2 IgG and IgA antibodies measured by ELISA increased significantly after vaccination of patients. The use of CCP seems to have no effect on the increase of IgG or IgA by vaccination (Supplemental Figure 2C).

Baseline PRNT50-titers in patients (1:120 (1:40 – 1:320)) were significantly higher than in donors (1:80 (1:20-1:160)) \( (p=0.045) \) (Figure 6A). Donor PRNT50 titers increased from 1:80 (1:20-1:160) to 1:2500
(1:1280 to 1:5120) (Figure 6A). Vaccinated patients had significantly higher PRNT50 values at follow-up than vaccinated donors (p=0.0005) (Figure 6B).

The baseline anti-SARS-CoV-2 IgG ratio (measured by ELISA) of donors (3.8 (2.9-5.8)) was comparable to that of patients (3.4 (2.2-6.6)) (p=0.5), while the baseline IgA ratio was significantly higher in patients (7.0 (2.2-9.0)) compared to donors (2.3 (1.3-3.9)) (p<0.0001) (Supplemental Figure 2A). At last follow-up vaccinated patients and donors had significantly higher IgG and IgA ratios compared to their respective baseline ratios and IgG and also IgA ratios did not significantly differ between donors and patients at last follow-up (Supplemental Figure 2B).

Marketers of activation of coagulation and markers of inflammation

D-dimers as markers of coagulation and C-reactive peptide (CRP), fibrinogen IL-6 and ferritin as markers of inflammation and pro-NT-BNP remain significantly elevated even more than one year after the acute infection in the clinical trial patients with no significant difference between the control and CCP-group (Supplemental Table 14).

DISCUSSION

To the best of our knowledge, this is the first randomized clinical trial that reports long-term data on the use of CCP with a median follow-up of more than 1 year. While many trials of CCP for COVID-19 at different stages of COVID-19 have been published, they report on short observation periods, often just up to about 1 months or less after randomization (2-19). It is evident that during the pandemic, it was important to make the initial results of the trials publicly available as soon as possible. However, the long-term results must also be taken into account - especially as it became clear that long-term complications involving different organ systems after COVID-19 are very common, significantly affect patients' quality of life and also influence overall survival (26-30).

The risk of Long COVID-19 increases with age, pre-existing conditions and severity of COVID-19 (32-35). Patients who had to be treated in hospital or patients who required intensive care have a higher risk of Long COVID-19 than patients with a mild to moderate course who could be treated on an outpatient basis (32,33). Thus, the risk for the manifestation of a long COVID-19 is also increased in the patients in the CAPSID study: The median age in the study was 60 years, all cases had severe COVID-19 and a high proportion of patients (89%) had a previous disease associated with an unfavorable course of COVID-19. Thus, the study population of the CAPSID study represents a group of patients who are particularly at risk for Long COVID-19 and who require follow-up for medical reasons.
The lack of knowledge applies also to CCP donors: Less is known about the long-term course of former CCP donors. Therefore we included CCP donors in this analysis to learn more about their long-term disease burden. They also comprised an additional reference group since they had experienced an asymptomatic to moderate COVID-19 disease as opposed to the CAPSID trial patients who had severe COVIC-19. Results of the CAPSID trial based on the initial 2-month observation period and the CCP donor characteristics have been previously published (1,31). There are several factors which might influence long-term outcome: At the time of the previous analysis not all patients had reached the respective endpoints (clinical improvement, time to discharge from ICU and hospital). Given the burden of long-COVID-19 and persisting organ dysfunction the outcome might change due to long-term sequela. The enrollment to the CAPSID trial was completed a few days prior to availability of SARS-CoV-2 vaccines in Germany. Also new variants evolved thereafter. It was not clear how vaccination and potential re-infections will impact the long-term course. Therefore, we considered an extended follow-up necessary. Here we now provide an update based on a median follow-up of 392 days.

The follow-up demonstrated a long-term OS which was numerically higher in the CCP group compared to the control group – but the difference was not statistically significant. A pre-defined subgroups analysis of the initial 2-months observation periods showed a significant benefit of CCP among patients who received a higher amount of neutralizing antibodies (1). The significant effect of transfusion of a larger amount of neutralizing units tended to be even more pronounced in the long-term observation across several endpoints. In the previous report the day-60 probability of survival was 91.6% in the subgroup that received a higher cumulative amount of neutralizing antibodies and 68.1% in the control group (p=0.02) (1). Due to additional deaths during extended follow-up, 1-year survival is now 91.5% vs. 60.2% (p=0.01) in the high-titer plasma versus the control group. This confirmed the previous report on the importance of the antibody dose (1) – in line with other studies which have demonstrated a dose effect (10,36-38) One study demonstrated that treatment with highly neutralizing plasma was significantly associated with faster virus clearance, but even after adjustment for their pretransfusion endogenous neutralization status, recipients benefitted (38). This observation is in line with the dose effect in the CAPSID trial on several outcomes – including the shorter time to first negative SARS-CoV-2 PCR from a nasopharyngeal swab in the group who received a high cumulative amount of neutralizing antibodies compared to the control group (Fig. 3A).

A correlation of this hyperinflammation and cytokine release syndrome with the severity and outcome of COVID-19 has been reported (39-42). Increased levels of several cytokines have been associated with severity (42-49). An anti-inflammatory role of CCP independent of its neutralizing antibody content has been demonstrated (50). Neutralizing antibodies as well as reductions in circulating in interleukin-6 and interferon gamma induced protein 10, contributed to marked rapid reductions in hypoxia in response to CCP (50).
At the very beginning of the pandemic reliable quantification of anti-SARS-CoV-2 antibodies was a challenge. Others and we have shown signals of benefit of CCP with high antibody titers and on the other hand it has been shown that the severity of COVID-19 and the number of symptoms correlates well with the PRNT-titers in CCP donors. We therefore studied whether the severity of COVID-19, as assessed by the number of symptoms, in the CCP donors correlated with the clinical efficacy of CCP units from those donors. We could show a trend for better outcomes after treatment with CCP from donors with a higher number of symptoms. Based on the lessons learned during the COVID-19 pandemic the selection of high-titer CCP should be based on appropriate antibody assays – if available. However, in the very beginning of a pandemic with a newly evolving pathogen and absence of validated tests for the quantification of the antibodies in CCP, number of symptoms might provide a surrogate for donor selection in the bridging period until the availability of a validated test. From our data, at least we could not see any harm regarding efficacy or adverse events using such an approach.

It has been demonstrated that the combination of SARS-CoV-2 infection with a SARS-CoV-2 vaccination (in either order) causes both an enhancement of all aspects of the humoral immune response and a broad immune reaction even against new variants (51-55). The underlying mechanisms involve ongoing antibody somatic mutation, memory B cell turnover, and development of antibodies that are resistant to SARS-CoV-2 RBD mutations, including those found in variants of concern (51). Repeated antigen exposure can confer potency, breadth, and resilience to viral escape mutations (56). Therefore, for future CCP programs, priority should be given to superimmunized donors with very high antibody concentration due to previous SARS-CoV-2 infection and vaccination (54,55,57).

We used several instruments to assess QoL of donors and patients during the extended observation period (EQ-5D-5L; FACIT-Fatigue; FACIT Dyspnea). Notably, the long-term disease burden in the group of donors are not at all negligible as a substantial subgroup of donors reported slight functional limitations (8.8% to 32.5%) in at least one of the dimensions of the EQ-5D-5L questionnaire and in all QoL scores there are few donors with results below the median scores of the patients. Fifty seven percent of donors reported neurologic symptoms which is comparable to the proportion of the patients reporting neurological symptoms (64%). Conversely, the disease burden in the group of patients is very substantial.

None of the patients improving their socioeconomic status, but a significantly higher proportion of patients than donors reported a decreased socioeconomic status deterioration. A majority of patients reports functional limitations assessed by the post-COVID-19 scale and patients report consistently more frequently about gastrointestinal, neurological, and pulmonary symptoms with a higher grade of severity. The CCP group and especially the subgroup that received a higher cumulative amount of neutralizing antibodies showed consistently numerically better results but the differences did not reach statistical significance for the individual item with the exception of the lower hospitalization rate in the high dose
subgroup. Nevertheless, the trend for better for less constraints in the CCP group was very consistent across three different QoL instruments which cover different dimensions (Supplemental Tables 3, 6, 7 and 8). Also, the proportion of patients without pulmonary symptoms was lower in the CCP group compared to the control group (53% vs. 30%), together with a lower proportion of patients with need for any type of ventilation support during follow-up after the initial observation period in the CCP group compared to the control group (20% vs. 60%). This might suggest less pulmonary impairment in the CCP group during the extended follow-up period.

The frequency of Long COVID-19 varies greatly in the literature and ranges up to a proportion of over 80% of patients who report at least one Long COVID-19 symptom (26,58,59). Common symptoms of Long COVID-19 are fatigue (98%), myalgias (87%), headache (83%) and dyspnea (88%) (COVERSCAN study data, based on patients with persistent symptoms) (58). Organs whose function may be impaired in Long COVID-19 include lungs, heart, liver, kidneys and nervous system (29,33,58,60). The COVERSCAN study reported that 70% of patients with Long COVID-19 symptoms still had impairment in at least one organ system at least 4 months after acute COVID-19 disease (58). In a large cohort study from Wuhan, patients reported mainly fatigue and muscle weakness (63%), sleep disturbance (26%), and anxiety and depression (23%) after a median time of 176 days (34). Pulmonary diffusion disorders were detectable during follow-up of 56% of patients with WHO grade 5 or 6 COVID-19 (34). A high proportion of patients also reported memory loss, concentration and sleep disturbances, and persistent loss of smell or taste (61-63). Other studies also report similar frequencies and variety of symptomatology as well as organ involvement in Long COVID-19 (27-29,33,35,59-67). A subgroup of patients has structural organ damage (lung, heart, neural systems whereas the rest has functional complaints without organ damage (“functional long COVID-19”)) (68). Overall, the pattern of symptoms, their frequency and severity in the long-term observation is consistent with reports on COVID-19 in the literature, but for the first time provides data on donors and patients in a randomized CCP trial.

The vast majority of both donors and patients got vaccinated and responded well to vaccination, while patients showed a significantly more pronounced increase in their antibody titers. At baseline, the amount of anti-SARS-CoV-2 IgG-antibodies were comparable between the donors and the patients, but patients showed a substantial higher level of anti-SARS-CoV-2 IgA. This might reflect the different severity of COVID-19 in the patient and CCP donor population and the different timing of sampling. At baseline CCP donors had recovered, while patients were in the acute phase of the infection. The higher antibody titers in patients compared to donors might be associated with the different severity of COVID-19. However, we cannot rule out that the difference is due to other confounding variables that might influence antibody levels, e.g. age, BMI, or a different timing of immunization events. Patients are significantly older and their interval since last vaccination and antibody measurement was longer than in donors (Table 1). There has
been the concern that CCP treatment might impair response to vaccination later on (69). Our limited data set does not support this notion. This aspect needs further investigation as we continue to use and design antibody-based therapies for COVID-19 and other infectious diseases.

The main shortcoming of our study is the limited sample size that included only 50 patients into the long-term follow-up. The CAPSID trial treated patients with severe COVID-19. More than 50% of patients included in this long-term observation period had a baseline WHO score of 5 or higher and the duration from symptom start to randomization was 8 (5.0 – 11.0) days. Meanwhile there are trials and registry studies that suggest a higher efficacy of CCP when it is given early in the course of COVID-19 to patients with mild symptoms (10,18,36,70,71). Therefore, the long-term effect of CCP might be too subtle in this small cohort which represents a subgroup of patients with poor prognosis due to advanced disease and late CCP treatment. The small sample size limits also a more detailed analysis of quality of life and antibody-responses in the subgroups treated with low or high amounts of neutralizing antibodies. Nevertheless, these data can provide a reference for the long-term burden of disease in patients treated in a CCP trial – in particular since several validated and internationally widely used QoL instruments have been used and a reference cohort of patients with mild to moderate disease (donors) was included.

In conclusion, the consistent trend for a benefit across several endpoints (overall survival, time to first negative SARS-CoV-2 PCR, discharge from ICU, discharge from hospital) among patients who received a larger cumulative amount of neutralizing antibodies is confirmed in the extended observation period. There is also a consistent trend for an improved QoL for patients treated with CCP across several dimensions by three different QoL instruments. Given the substantial long-term disease burden in some patients the therapeutic long-term effects of CCP is of great interest and long-term observations shall be reported from CCP clinical trials conducted so far, and should in particular be further investigated in upcoming larger clinical trials that take into account the lessons learned so far regarding the selection of CCP units, dose and timing of administration and the vulnerable patient population.

MATERIAL AND METHODS

Design

This is a long-term follow-up of the CPASID trial, a multicenter, open-label randomized clinical trial to evaluate the efficacy and safety of CCP added to standard therapy (CCP group) vs. standard therapy alone (control group) in hospitalized patients with COVID-19 (Figure 1). Patients in the CCP group received three units of plasma with a median total volume of 846 ml. The CAPSID trial recruited 106 patients from 13 hospitals in Germany in the period from August 30, 2020 to December 24, 2020. The initial protocol included a follow-up for 60 days that was completed on February 23, 2021: Results of the first analysis of
patients based on an interim data cutoff on April 28, 2021 and the analysis of donor and CCP characteristics have been published previously (1,31). In a protocol amendment a follow-up period up to 15 months was included for patients and CCP donors. The CCP donors were included as reference group with asymptomatic to moderate disease for comparison of the burden of disease in the clinical trial patients. The objectives of the extended follow-up were to analyze long-term survival, the frequency and severity of long COVID-19 in CCP donors and patients, to study the impact of CCP treatment and the CCP dose (in terms of cumulative amount of neutralizing antibodies) on long COVID-19 and long-term immunity.

**Patients and Donors**

A total of 50 patients and 113 donors in 12 hospitals and 7 donor centers in Germany participated in the long-term follow-up between 05 November 2021 to 19 February 2022.

Inclusion criteria for the long-term follow were as follows: (1) patients which were enrolled to the CAPSID-Trial or recruited CCP donors for the CAPSID trial. (2) signed informed consent for the participation in the follow-up. Inclusion criteria for patients and donors were published recently (1,31).

One outpatient visit between day 240 and 540 after randomization or first plasma donation was planned. The following assessments and data collections were performed: medical history including symptoms, complications, hospital treatments, medication and chest imaging since the previous end of study, heart rate and blood pressure, Quality of life-questionnaires (EDQ5, FACIT fatigue and FACIT Dyspnea), and blood tests for inflammation markers, coagulation markers, anti-SARS-CoV-2 immunity and organ function. A structured interview was performed using a pre-specified questionnaire and the long COVID-Scale (72).

Patients who could not visit the study center could also participate by telephone. In these cases, no laboratory values were collected and no functional tests were performed.

**SARS-CoV-2-Antibody Assays**

A plaque reduction neutralization test (PRNT) and an ELISA for the detection of IgG and IgA to the S protein of SARS-CoV-2 were performed as previously described (1,73-75).

**Outcome measures**

The outcome measures of the long-term follow-up were as follows: (1) long-term survival up to 18 months after randomization (patients in CCP group compared to control group) or first plasma donation (CCP donors). (2) Frequency, severity and duration of long COVID-19 up to 18 months after randomization (patients in CCP group compared to control group) or first plasma donation (CCP donors) (3) Resolution of pneumonia and functional recovery in patients (CCP group compared to control group and donors) (4)
Fatigue, Quality of life and utilization of health care resources. (5) Anti-SARS-CoV-2 immunity and inflammation, the effect of SARS-CoV-2 vaccination. For all endpoints (1-5) subgroup analysis by the cumulative amount of transfused neutralizing units in the CCP was planned.

The 5Q-5D-5L questionnaire assesses 5 dimensions: mobility, self care, usual activities, pain/discomfort, anxiety in 5 categories and one’s health today by a visual analogue scale giving an EQ-5D-5L index score (76). FACIT fatigue and FACIT Dyspnea were also used. The FACIT fatigue questionnaire, which consists of 13 questions, was originally developed to understand the impact of anemia and fatigue on the daily activities of cancer patients, but it has also been used for many other chronic diseases (77). For each question, there are 5 response options depending on the severity from "not at all" to "frequently." The total score is on a numerical scale from 0 to 52, whereby the higher the score, the lesser the fatigue.

The FACIT-Dyspnea questionnaire consist of 10 questions and 10 ratings (78). It has originally been developed to measure dyspnea severity and related functional limitations in patients with chronic obstructive pulmonary disease, but it has also been used for many other diseases (78,79). Details of QoL questionnaires with questions are listed in the supplement (Supplementary tables I-XII). The Post-COVID-Scale grades the functional limitations from no functional limitations, grade 0 to severe functional limitations, grade 4 by 4 questions: 1. Can you live alone without any assistance from another person? (e.g. independently being able to eat, walk, use the toilet and manage routine daily hygiene) 2. Are there any duties/activities at home or at work which you are no longer able to perform yourself? 3. Do you suffer from symptoms, pain, depression or anxiety? 4. Do you need to avoid or reduce duties/activities or spread these over time? (72) The complete algorithm is shown in the supplement (supplementary figure 1).

Outcome measures for the primary and secondary outcome have been previously reported (1). Patients who died during the observation period without reaching the secondary outcome were censored as if they had reached the end of observation to account for the competing risk setting. The primary and secondary outcomes were also analyzed in a subgroup analysis by transfused neutralizing units. Since the total amount of neutralizing antibodies depends on both the volume and the antibody titer of CCP we used “neutralizing units” to take into account both variables. One neutralizing unit was arbitrarily defined as one ml of CCP with a PRNT50 titer of 1:20. The neutralizing units of a CCP transfusion unit were then calculated by dividing the titer by 20 and multiplying by volume (ml) (1). CCP group was divided by the cumulative amount of neutralizing units per patient (all 3 CCP transfusions) in a low neutralizing unit group (≤ median) and a high neutralizing unit group (> median).

Symptoms were documented and reported according to CTCAE Version 4.0.
**Statistical Analysis**

All patients with long-term follow-up information and all participating donors were considered for analysis of overall survival. Unless otherwise stated, the quantitative results indicate the median of the respective group and the numerical values in brackets indicate the interquartile range (IQR).

Nominal and ordinal variables were analyzed using absolute frequencies and percentages. Missing values were considered as a separate category. Continuous variables like QoL or laboratory values including PRNT50 are described by reporting the median and interquartile range (IQR) for the total number of patients and donors who provided values.

Secondary outcomes were analyzed using a Kaplan-Meier estimation procedure. Patients who died during observation without reaching the secondary outcome were censored as if they had reached the end of observation to account for competing risk. In pre-specified subgroup analyses, outcomes were assessed in patients with low or high levels of neutralizing units (cumulative neutralizing units of all CCP products transfused equal to or below the median or above the median) and in subgroups created by the amount of donor symptoms with the corresponding CCP units.

An unpaired two-tailed Mann-Whitney test or a two-tailed paired Wilcoxon matched pair test was used to analyze the continuous variables. A p-value < 0.05 was considered to be statistically significant.

Statistical analyses were performed according to the statistical analysis plan using SAS® (version 9.4M6 or newer, [www.sas.com](http://www.sas.com)) or GraphPad Prims software version 9.0.3. The analysis for this manuscript is based on a final data-cut off on March 16, 2022.

**Study approval**

The trial was approved by the Federal Authority Paul-Ehrlich-Institute and by the Ethical Committee of the University of Ulm and the ethical committees of the participating hospitals. The trial is registered: EudraCT number 2020-001310-38 and NCT04433910. Written informed consent was obtained from all study participants or their legal representatives.
Contributions:

HS and SK: Wrote study protocol, coordinated the study, analyzed and interpreted data, wrote the manuscript. HS, SK and ES applied for funding.

HS and ES: Lead Investigators

BG, DZ, TW, KZ, PS, PR, GP, TT, JK, MD, JK, MB, GSS, PML, LE, HW, MW, JMK: clinical advice, patient enrollment, patient care, data collection including extended observation period.


VMC, BJ: analysis of SARS-CoV-2 antibodies; MS: SARS-CoV-2 PCR

TA, MR: project management, sample management.

BM, PSch: statistical advice

All authors have approved the manuscript

Acknowledgement

We thank all patients and donors who participated in this trial. We thank the clinical research teams, physicians, study nurses and data managers in all clinical trial centers and the team of the CRO Alcedis. Conducting a clinical trial during a pandemic is a challenge. The commitment to take on substantial extra work when health care resources are already fully occupied by daily care for the severely sick patients deserves special recognition!

The clinical trial CAPSID is supported by the Bundesministerium für Gesundheit ("German Federal Ministry of Health").

Gefördert durch:

Bundesministerium für Gesundheit

aufgrund eines Beschlusses des Deutschen Bundestages
Ethics declarations

Conflicts of interest

The clinical trial CAPSID was supported by the German Federal Ministry of Health ("Bundesministerium für Gesundheit"). Dr. Victor M Corman is named together with Euroimmun on a patent application filed recently regarding the diagnostic of SARS-CoV-2 by antibody testing. The other authors have declared that no conflict of interest exists.

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### Table 1: Baseline Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th>Demographic and clinical characteristics</th>
<th>CCP-Donor (n=113)</th>
<th>Patients (CCP + Control) (n=50)</th>
<th>p-value</th>
<th>CCP group (n=30)</th>
<th>Control Group (n=20)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Median age, years (IQR)</td>
<td>42.0 (31.0-52.0)</td>
<td>58.5 (54.0-65.0)</td>
<td>&lt;0.01</td>
<td>56.5 (51.0-63.00)</td>
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<td></td>
<td></td>
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<td></td>
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<td>59 (52.2)</td>
<td>37 (74.0)</td>
<td>&lt;0.01</td>
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<td>15 (75.0)</td>
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<td>8 (26.7)</td>
<td>5 (25.0)</td>
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<tr>
<td>Body Mass Index, kg/m² (IQR)</td>
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<td>29.8 (26.6-33.0)</td>
<td>&lt;0.01</td>
<td>29.4 (26.6-33.0)</td>
<td>30.5 (26.7-32.6)</td>
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<td></td>
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<tr>
<td>Solid Tumor</td>
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<td>19 (63.3)n</td>
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<td>Point Scale at Study entry, n (%)</td>
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<td>3</td>
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<td>2 (10.0)</td>
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<tr>
<td>4</td>
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<td>5 (16.7)</td>
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<td>5 (25.0)</td>
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<td>5</td>
<td>22 (44)</td>
<td>15 (50.0)</td>
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<td>7 (35.0)</td>
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<td>7</td>
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<td>6 (30.0)</td>
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<td>CCP-Donor (n=113)</td>
<td>Patients (CCP + Control) (n=50)</td>
<td>p-value</td>
<td>CCP group (n=30)</td>
<td>Control Group (n=20)</td>
<td>p-value</td>
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<tr>
<td>Severity of disease, n (%)</td>
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<td>2 (1.9)</td>
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<tr>
<td>Mild</td>
<td>92 (88.5)</td>
<td></td>
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<td></td>
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<td>Median time from symptom onset of the SARS-CoV-2 infection to first plasmapheresis or randomization, days (IQR)</td>
<td>101.0 (73.0-124.0)</td>
<td>8.0 (5.0-11.0)</td>
<td>-</td>
<td>8.0 (3.0-10.0)</td>
<td>7.0 (5.0-11.0)</td>
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<td>Vaccination during follow-up n (%)</td>
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<td>Not vaccinated</td>
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<tr>
<td>1</td>
<td>5 (4.4)</td>
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<td>2</td>
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### Table 2: Symptoms during follow-up

<table>
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<tr>
<th>Symptom</th>
<th>Patients (CCP + Control) (n=50)</th>
<th>CCP group High titer + Low titer (n=30)</th>
<th>Control Group (n=20)</th>
<th>p-value*</th>
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<tbody>
<tr>
<td>GI-Symptoms, n (%)</td>
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<tr>
<td>Without Event</td>
<td>30 (60.0)</td>
<td>17 (56.7)</td>
<td>13 (65.0)</td>
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<td>Grade 1-3</td>
<td>23 (46)</td>
<td>16 (53.3)</td>
<td>7 (35.0)</td>
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<tr>
<td>Abdominal pain, n (%)</td>
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<td>Without Event</td>
<td>44 (88.0)</td>
<td>25 (83.3)</td>
<td>19 (95.0)</td>
<td>0.38</td>
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<td>6 (12.0)</td>
<td>5 (16.6)</td>
<td>1 (5.0)</td>
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<tr>
<td>Diarrhea, n (%)</td>
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<tr>
<td>Without Event</td>
<td>43 (86.00)</td>
<td>24 (80.0)</td>
<td>19 (95.0)</td>
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<td>Grade 1</td>
<td>7 (14.00)</td>
<td>6 (20.0)</td>
<td>1 (5.0)</td>
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<tr>
<td>Nausea, n (%)</td>
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<td>24 (80.0)</td>
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<td>Neurologic-Symptoms, n (%)</td>
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<tr>
<td>Grade 1</td>
<td>41 (82.0)</td>
<td>26 (86.6)</td>
<td>15 (75.0)</td>
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<tr>
<td>Confusion, n (%)</td>
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<td>Without Event</td>
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<td>4 (13.3)</td>
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<td>Dizziness, n (%)</td>
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<td>18 (90.0)</td>
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<td>6 (20.0)</td>
<td>6 (30.0)</td>
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<tr>
<td>Symptom</td>
<td>Patients (CCP + Control) (n=50)</td>
<td>CCP group (High titer + Low titer) (n=30)</td>
<td>Control Group (n=20)</td>
<td>p-value*</td>
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<td>---------------------</td>
<td>---------------------------------</td>
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<td>Insomnia, n (%)</td>
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<td>3 (6.0)</td>
<td>2 (6.6)</td>
<td>1 (5.0)</td>
<td></td>
</tr>
<tr>
<td>Pain-Symptoms, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.77</td>
</tr>
<tr>
<td>Without Event</td>
<td>30 (60.0)</td>
<td>17 (56.7)</td>
<td>13 (65.0)</td>
<td></td>
</tr>
<tr>
<td>Grade 1-3</td>
<td>24 (48.0)</td>
<td>16 (53.4)</td>
<td>8 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Pulmonal Symptoms, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>Without Event</td>
<td>22 (44.0)</td>
<td>16 (53.3)</td>
<td>6 (30.0)</td>
<td></td>
</tr>
<tr>
<td>Grade 1-3</td>
<td>35 (70.0)</td>
<td>19 (63.3)</td>
<td>16 (80.0)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>Without Event</td>
<td>23 (46.0)</td>
<td>16 (53.3)</td>
<td>7 (35.0)</td>
<td></td>
</tr>
<tr>
<td>Grade 1-3</td>
<td>27 (54.0)</td>
<td>14 (46.7)</td>
<td>13 (65.0)</td>
<td></td>
</tr>
<tr>
<td>Alopecia, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.49</td>
</tr>
<tr>
<td>Without Event</td>
<td>39 (78.0)</td>
<td>22 (73.3)</td>
<td>17 (85.0)</td>
<td></td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>11 (22.0)</td>
<td>8 (26.7)</td>
<td>3 (15.0)</td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>Without Event</td>
<td>44 (88.0)</td>
<td>28 (93.3)</td>
<td>16 (80.0)</td>
<td></td>
</tr>
<tr>
<td>Grade 1-3</td>
<td>6 (12.0)</td>
<td>2 (6.7)</td>
<td>4 (20.0)</td>
<td></td>
</tr>
</tbody>
</table>
1. **Pain-Symptoms:** Abdominal Pain + Arthralgia + Myalgia + Pain + Pain in extremity + Back pain + Bone pain + Myalgia

2. **Neurologic:** Confusion + Dizziness + Hypersomnia + Insomnia + Concentration impairment + Dysesthesia + Dysgeusia + Fatigue + Headache + Nervous system disorders - Other, specify + Restlessness + Vision decreased + Memory impairment + Amnesia + Generalized muscle weakness

3. **GI-Symptoms:** Weight loss + Vomiting + Nausea + Diarrhea + Constipation + Anorexia

4. **Pulmonary Symptoms:** Productive cough + Non-cardiac chest pain + Dyspnea +

5. **Symptoms without significant differences:** allergic rhinitis, amnesia, anorexia, anosmia, arthralgia, atrial fibrillation, back pain, bone pain, bronchial infection, chest pain – cardiac, concentration impairment, constipation, cough, depression, dry eye, dysesthesia, dysgeusia, eczema, eye infection, fatigue, fever, fracture, generalized muscle weakness, headache, hypertension, impairment, meningismus, muscle cramp, myalgia, myocardial infarction, Non-cardiac chest pain, palpitations, productive cough, rash maculo-papular, rhinitis infective, sinus tachycardia, sleep apnea, surgical and medical procedures, tinnitus, upper respiratory infection, vaginal infection, Ventricular arrhythmia, vision decreased, vomiting

* The p-values refer to the breakdown of medical events into different grades (for full information see Supplemental Table 2).
Table 3: Health care resources during follow-up

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients (CCP + Control) (n=50)</th>
<th>CCP group High titer + Low titer (n=30)</th>
<th>Control Group (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication, n (%)</td>
<td>19 (38.0)</td>
<td>10 (33.3)</td>
<td>9 (45.0)</td>
<td>0.71</td>
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<tr>
<td>Supplemental Oxygen/Ventilation, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplemental oxygen?</td>
<td>9 (18.0)</td>
<td>3 (10.0)</td>
<td>6 (30.0)</td>
<td>0.13</td>
</tr>
<tr>
<td>Invasive ventilation</td>
<td>2 (4.0)</td>
<td>1 (3.3)</td>
<td>1 (5.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Non-invasive ventilation</td>
<td>7 (14.0)</td>
<td>2 (6.7)</td>
<td>5 (25.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Number of Hospitalisations, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>0</td>
<td>41 (82.0)</td>
<td>24 (80.0)</td>
<td>17 (85.0)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8 (16.0)</td>
<td>5 (16.7)</td>
<td>3 (15.0)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1 (2.0)</td>
<td>1 (3.3)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Duration of Hospitalisations, days (IQR)</td>
<td>6 (4-14)</td>
<td>5 (3-6)</td>
<td>15 (6-27)</td>
<td>0.09</td>
</tr>
<tr>
<td>Number of Hospitalisations, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>15 (93.8)</td>
<td>9 (64.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0 (0.0)</td>
<td>5 (35.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1 (6.3)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of Hospitalisations, days (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 (13-13)</td>
<td>4 (3 – 6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiology, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-Ray</td>
<td>6 (12.0)</td>
<td>3 (10.0)</td>
<td>3 (15.0)</td>
<td>0.67</td>
</tr>
<tr>
<td>CT</td>
<td>9 (18.0)</td>
<td>4 (13.3)</td>
<td>5 (25.0)</td>
<td>0.45</td>
</tr>
</tbody>
</table>
FIGURES

Figure 1: Patient and Donor Enrollment to the CAPSID Trial and the extended follow-up

105 patients randomized

- 53 patients included in the ITT analysis
  - 53 patients with evaluable primary endpoint
    - n=25 high neutralizing units CCP
    - n=28 low neutralizing units CCP
  - 11 patients died

- 52 patients included in the ITT analysis
  - 52 patients with evaluable primary endpoint
  - n=22 high neutralizing units CCP
  - n=19 low neutralizing units CCP
  - 0 patients died

- 50 patients included in the long-term follow-up
  - n=16 high neutralizing units CCP
  - n=14 low neutralizing units CCP
  - 2 patients died

53 Donors assessed for eligibility

150 donated CCP

52 randomized to control group (standard treatment)

45 donated for transfused CCP units

100 patients assessed for eligibility

103 patients assessed for eligibility

n=163 included in follow up

113 donors included in the long-term follow up

20 patients included in the long-term follow up
Figure 2

Kaplan-Meier cumulative estimates of probability of overall survival are shown.

(A) Overall survival of donors (dotted magenta line), control (solid green line) and CCP group (dotted red line). Censored patients are indicated by +. \( p=0.083 \) (log-rank test) CCP vs. control group.

(B) Overall survival compared in the CCP subgroup that received a low cumulative amount of neutralizing antibodies (solid red line), the CCP subgroup that received a high cumulative amount of neutralizing antibodies (solid blue line), and the control group (solid green line). Censored patients are indicated by +. High amount versus control: \( p=0.011 \) and high amount versus low amount: \( p=0.032 \) (log-rank test).

(C) Overall survival by amount of donors symptoms control group (solid green line) patients transfused with CCP donors with \( \leq 3 \) symptoms (dotted red line) or transfused from CCP donors \( >3 \) symptoms (dotted blue line). Censored patients are indicated by +. CCP donors with \( >3 \) symptoms versus control: \( p=0.061 \) (log-rank test).
Figure 3: Long-Term Occurrence of Secondary Outcomes by Amount of Transfused Neutralizing Units

(A) The key secondary outcome time to clinical improvement compared in the CCP subgroup which received a low cumulative amount of neutralizing units (red), the CCP subgroup that received a high cumulative amount of neutralizing units (blue) and the control group (green line). Censored patients are indicated by +. p=0.088 (log-rank test; high amount vs. control group).

(B) Time to first negative PCR compared in the CCP subgroup which received a low cumulative amount of neutralizing units (red), the CCP subgroup that received a high cumulative amount of neutralizing units (blue) and the control group (green line). Censored patients are indicated by +. p=0.019 (log-rank test, high amount vs. control group).

(C) Probability of discharge from ICU compared in the CCP subgroup which received a low cumulative amount of neutralizing units (red), the CCP subgroup that received a high cumulative amount of neutralizing units (blue) and the control group (green line). Censored patients are indicated by +. p=0.025 (log-rank test, high amount group vs. control group).

(D) Probability of discharge from hospital compared in the CCP subgroup which received a low cumulative amount of neutralizing units (red), the CCP subgroup that received a high cumulative amount of neutralizing units (blue) and the control group (green line). Censored patients are indicated by +. p=0.017 (log-rank test, high amount vs. control group).
Figure 4: Post-COVID-19-Scale and Socioeconomic Status

(A) Relative proportion of donors (upper row), CAPSID trial patients (second row) (p<0.0001), and patients stratified by randomization group (CCP group and control groups) (middle rows) (p=0.089) and patients which received a high or low amount of neutralizing units (lower rows) (p=0.1304) according to the Post-COVID-19 scale from grade 0 to grade 4.

(B) Relative proportion of donors (upper row), CAPSID trial patients (second row), and patients stratified by randomization group (CCP group and control groups) (middle rows) and patients which received a high or low amount of neutralizing units (lower rows) (p=0.4171) according to their change of socioeconomic status (increased, unchanged, decreased).
Figure 5: Quality of Life Score

Data given as Median and interquartile ranges.

(A) EQ-ED-SDL visual scale: Donors (n=107) versus patients (n=46 (p<0.0001), control group (n=19) versus CCP group (n=27) (p=0.355) and control group versus CCP that received a high cumulative amount of neutralizing units (n=16) (p=0.730). No test performed for the group that received low cumulative amount of neutralizing units (n=11). Cross walk score: donors (n=105) versus patients (n=47) (p<0.0001) control group (n=19) versus CCP group (n=28) (p=0.280) and control group versus CCP subgroup that received a high cumulative amount of neutralizing units (n=16) (p=0.702). No test performed for the group that received low cumulative amount of neutralizing units (n=12).

(B) FACIT Dyspnea Score 1: Donors (n=107) versus patients (n=48) (p<0.0001), control group (n=19) versus CCP group (n=29) (p=0.196) and control group versus CCP subgroup that received a high cumulative amount of neutralizing units (n=16) (p=0.518). No test performed for the group that received low cumulative amount of neutralizing units (n=13). FACIT Dyspnea Score 2: Donors (n=107) versus patients (n=46) (p<0.0001, ) control group (n=18) versus CCP group (n=28) (p=0.15) and control group versus CCP subgroup that received a high cumulative amount of neutralizing units (n=15) (p=0.446). No test performed for the group that received low cumulative amount of neutralizing units (n=13).

(C) FACIT Fatigue Score: Donors (n=105) versus patients (n=47) (p=0.004), control group (n=19) versus CCP group (n=28) (p=0.306) and control group vs. CCP subgroup that received a high cumulative amount of neutralizing units (n=15) (p=0.492). No test performed for the group that received low cumulative amount of neutralizing units (n=13).
Figure 6: Neutralizing anti-SARS-CoV-2 antibodies (PRNT50) at baseline and last follow-up.

(A) Neutralizing antibodies of all study participants as available. Follow-up data of patients (n=25) and donors (n=95). Baseline values donors (n=97) versus patients (n=48): p=0.045.

(B) Neutralizing antibodies of vaccinated study participants during follow-up with available baseline and follow-up data. Patients (n=21) baseline versus follow-up values: p<0.0001. Donors (n=76) baseline versus follow-up values: p<0.0001. Follow-up values patients versus donors: p=0.0005.

(C) Vaccinated patients with available baseline and follow-up data by randomization group (CCP (n=16) and control group (n=5)). Baseline versus follow-up in CCP patients p<0.0001.

No test was performed for control because of the low patient number.

Horizontal lines indicate the median and interquartile ranges. A Mann-Whitney-Test was used for calculation of p-values for unpaired analysis and a Wilcoxon Matched-paired for comparison of matched pairs.


