

The Value of Convalescent Plasma Therapy as a Strategy to Decrease Hospitalization in COVID-19 Patients: A Randomized Clinical Trial

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ABSTRACT

Background. Convalescent plasma therapy (CPT) has been utilized as an emergency and last-resort treatment for viral infections, particularly in the absence of vaccine. During the COVID-19 pandemic, CPT was implemented worldwide based on its potential to provide passive immunity through SARS-CoV-2 antibodies. While numerous studies explored the effectiveness of CPT to cure COVID-19 patients, there has no research specifically focused on superiority of CPT impact on the length of hospitalization.

Objective. This study aimed to evaluate the effect of CPT on the length of hospital stay among patients with moderate COVID-19.

Methods. This is a single blind randomized controlled trial (RCT) study involved 30 moderate-grade COVID-19 patients age 18-75 years with positive PCR result treated at Unggul Karsa Medika Hospital Bandung from February 2 to May 31, 2022. Moderate-grade COVID-19 defined by clinical pneumonia symptoms based on World Health Organization (WHO) criteria. Eligible patients were randomly assigned (1:1 ratio) and outcome assessors were blinded, while care providers and patients were not due to the intervention nature. The intervention arm (n=15) received 200 ml of high-titer CPT within 24 hours of admission with standard care and the control arm (n=15) received standard care only. The primary outcome measured was the length of stay (LOS) in both the Emergency Room (ER) and COVID-19 High Care Unit (HCU). Data were analyzed using independent T-tests.

Results. Thirty (30) eligible patients (mean age 40 years; 53% female) were analyzed for the primary outcome and all completed follow-ups. The CPT group had significantly shorter LOS than controls (mean difference for ER:-32.7 hours [95% CI:-45.0,-20.4]; HCU:-33.3 hours [95% CI:-45.8,-20.8]; $p < 0.001$ for both). This result attributed to the neutralizing antibodies present in convalescent plasma, which could inhibit viral replication and accelerate recovery. No adverse events were observed in either group.

Conclusion. The administration of CPT may reduce the LOS in moderate COVID-19 patients. However, the small sample size can limit the generalizability of this result and larger sample studies are needed to strengthen this finding. Early CPT implementation may improve patient management and optimize healthcare resource utilization during the pandemic.

Keywords: convalescent plasma therapy, COVID-19, length of stay, antibodies, hospitalization

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INTRODUCTION

Convalescent plasma therapy (CPT) has long been used as emergency and last-resort treatments for various viral infections, both old and emerging, particularly in the absence of available vaccines. During the COVID-19 pandemic, CPT gained global attention worldwide due to its potential to provide passive immunity through SARS-CoV-2 antibodies. This therapy involves transfusing plasma from individuals who have recovered from COVID-19, whose blood contains antibodies against the virus, into patients who are still battling the infection. These naturally developed antibodies may help the recipient's immune system combat the virus more effectively.¹⁻⁵

As of June 2022, the COVID-19 pandemic had infected nearly 532 million people worldwide resulting in over 6.3 million deaths. In Indonesia, almost six million people were infected, with more than 156,000 fatalities. This disease caused by the SARS-CoV-2 virus, primarily targets the respiratory system and can affect individuals of all ages including infants, children, adults, the elderly, pregnant women, and breastfeeding mothers. Clinical symptoms can worsen rapidly, leading to respiratory failure and death. Symptoms may appear between 2 to 14 days after exposure to the virus and tend to be more severe and higher mortality in the elderly, pregnant women, individuals with comorbidities, smokers, or those with weakened immune systems.⁶⁻⁹

Several studies have examined the efficacy of CPT in COVID-19 patients, showing generally promising but heterogeneous results. Evidence demonstrates that early administration of high-titer CPT can reduce progression to severe disease, lessen mortality risk, and shorten hospital length of stay (LOS). Nonetheless, CPT is associated with potential risks. Reported adverse events include allergic transfusion reactions, febrile non-hemolytic responses, transfusion-related acute lung injury (TRALI), and rarely severe immunologic complications. Even though, the therapeutic advantages, particularly the passive transfer of neutralizing antibodies that enhance viral clearance and modulate immune function, substantially outweigh the potential risks. Consequently, convalescent plasma has represented an important supportive treatment modality, especially for patients with severe disease or compromised immune responses.¹⁰⁻¹²

While many studies have explored the effectiveness of CPT to cure COVID-19 patients, there has no research that specifically examined CPT impact on the length of hospitalization in Indonesia. Beyond its role as a life-saving therapy, CPT may also shorten recovery time, reduce hospital stays, ease the burden on healthcare workers and lower medical costs. Early administration of CPT could enhance patient management and optimize resource utilization during the pandemic. Furthermore, this study result showed CPT can be a strategic tool to increase efficiency and become a reference basis if similar conditions occur in the future.¹³

OBJECTIVES

The primary objective of this study was to evaluate the effectiveness of convalescent plasma therapy (CPT) in reducing the length of hospital stay in patients diagnosed with moderate COVID-19. Specifically, the study assessed the duration of hospital stay in both the ER and the COVID-19 HCU following CPT administration, thereby potentially improving patient outcomes, and alleviating the burden on hospital resources.

This study also aims to provide preliminary evidence that could serve as a pilot model for implementing CPT or similar passive immunotherapy strategies in future outbreaks of novel viral infections, particularly when effective vaccines or treatments are not yet available.

MATERIALS AND METHODS

Study Design

This study was a single-center, single blind, parallel-group RCT involving 30 patients diagnosed with moderate-grade COVID-19 who were admitted and hospitalized at Unggul Karsa Medika Hospital Bandung, Indonesia, conducted from February 2 to May 31, 2022. This study was designed as a randomized controlled trial aiming to evaluate whether CPT is superior to standard therapy in reducing the length of hospital stay among moderate COVID-19 patients. The trial hypothesis was that CPT would significantly shorten hospitalization duration compared to standard care alone, reflecting improved clinical outcomes. Unggul Karsa Medika Hospital is a private and secondary level hospital with full accreditation score, certificate number 0002/U/VIII/2022, approved by Lembaga Akreditasi Rumah Sakit (LARS) as an accreditation agency appointed by the Indonesian government. This study approved by Ethical Committee of Unggul Karsa Medika Hospital with approval number 003/KEP-LIT/II/2022.

Population and Sample

The sample size of 30 was calculated to detect a mean difference of 24 hours in hospital length of stay (LOS) between the convalescent plasma therapy (CPT) and control groups. This target difference was based on prior observational data and clinical judgment suggesting a meaningful clinical impact on hospitalization duration. We assumed a standard deviation of 20 hours for LOS in each group, supported by similar published studies. Using a two-sided, two-sample t-test with a significance level (alpha) of 0.05 and power (1-beta) of 80%, the calculated sample size was 15 participants per group, total 30 patients. No adjustments were made to account for potential missing data or non-adherence due to expected high compliance and complete follow-up in the hospital setting. The sample size calculation was performed using IBM SPSS Statistics software version 29 (IBM Corp., Armonk, NY, USA). No interim analyses were planned or

conducted during the trial. There were no predefined criteria for early stopping or trial modification based on interim results. These decisions were intentionally omitted due to the pilot nature and limited sample size of the study.

Inclusion criteria included adult patients aged 18 to 75 years with confirmed moderate COVID-19, a positive PCR result, no prior CPT and informed consent. Moderate-grade COVID-19 defined by the presence of clinical pneumonia symptoms including fever, cough, shortness of breath, and tachypnoea, without signs of severe disease such as oxygen saturation <93%, respiratory rate >30 breaths/min or lung infiltrates affecting >50%, based on World Health Organization (WHO) criteria. Exclusion criteria included pregnancy, critical illness on admission, known allergy to plasma products and refusal of consent. Participants were recruited consecutively through direct hospital admission to Unggul Karsa Medika Hospital. Eligible patients were identified by screening the hospital inpatient admissions list daily. Recruitment was conducted via direct referral from attending physicians, without use of public advertisements or self-selection. This approach ensured representative enrolment of moderate COVID-19 cases presenting for clinical care.

Each eligible participants were selected using a simple random sampling with an allocation ratio 1:1 ensuring each patient had an equal chance being included in the study. The random allocation sequence was generated by a computerized random number generator and securely maintained by an independent statistician who was not involved in participant recruitment or clinical care. The sequence was concealed from all study personnel involved in patient enrolment and intervention assignment. Participants were enrolled consecutively by the healthcare staff assigned to the COVID-19 ward, who assessed eligibility and obtained informed consent. After enrolment, the healthcare staff contacted the statistician to receive group assignment based on the concealed randomization sequence. The healthcare staff responsible for enrolment and assignment of participants did not have prior access to the random allocation sequence, ensuring allocation concealment and minimizing selection bias. Outcome assessors and data analysts were blinded to the treatment allocation to minimize detection and analysis bias. Specifically, clinical staff responsible for evaluating patient outcomes, as well as statisticians conducting the data analysis, were kept unaware of which participants received convalescent plasma therapy (CPT) or standard care. Due to the nature of the intervention, trial participants and care providers administering treatments were not blinded. The CPT was administered as an intravenous transfusion which differs visibly from standard care; therefore, full blinding of patients and clinical staff was not feasible.

Study Procedure

After enrolment, patients were assigned into two groups, one group received CPT in addition to standard care, while the control group received standard therapy alone without

CPT. Administration of CPT was initiated within the first 24 hours of hospital admission. Convalescent plasma therapy was administered as a 200 ml transfusion in three hours and originated from donor with confirmed antibody titer above 1:320 based on Indonesian Red Cross (PMI) regulation. Each patient received one bag of convalescent plasma. No dose adjustments or tailoring of the plasma volume were performed for individual participants. The standard therapy (control intervention) comprised hospital routine supportive care, including supplemental oxygen as needed, antipyretics, hydration, and symptom management according to institutional COVID-19 treatment protocol. Use of corticosteroids, antivirals, and antibiotics followed hospital guidelines and were permitted in both groups if clinically indicated. No prohibitions were imposed on concomitant medications. Modifications to the trial intervention were not planned; however, plasma transfusion could be discontinued prematurely upon participant request, occurrence of adverse events, or clinical judgment indicating potential harm. All participants in the intervention group continued to receive standard therapy alongside CPT. This description ensures transparency regarding the interventions, concomitant care, and possible modifications during the trial. Clinical parameters were closely monitored, with particular focus on the LOS in both the ER and the COVID-19 HCU, until patient discharged from the hospital. There were three patients (10%) who were not included in the study, two patients refused to be hospitalized, and one patient refused CPT. No patient experienced adverse effect and worsening conditions in this study. However, an ICU was provided for those who did.

The primary outcome measure was the length of hospital stay (LOS), defined as the total number of hours from admission to discharge separately for the Emergency Room (ER) and the High Care Unit (HCU). The analysis metric was the mean LOS per participant. For each trial group, the primary outcome was aggregated as the mean LOS \pm standard deviation. Secondary outcomes included markers of clinical improvement, such as resolution of fever, oxygen saturation levels, and symptom scores, as well as the incidence and nature of adverse events. These were measured using standardized clinical assessment tools and hospital records. The secondary outcomes were summarized by frequency, mean, or median values as appropriate for each variable. All outcome assessments were conducted by trained clinical staff blinded to treatment allocation to minimize detection bias. No changes or modifications to the primary or secondary trial outcomes occurred after trial commencement.

Participant recruitment commenced on February 2, 2022, and was completed on May 31, 2022. The final follow-up assessment was conducted upon patient discharge from the hospital, occurring by June 15, 2022. The duration of follow-up for each participant spanned from hospital admission to discharge, typically ranging from several days to a few weeks depending on clinical status. The trial was concluded

as planned with completion of recruitment and follow-up of all enrolled participants. There was no early stopping or premature termination. The decision to end the trial was made by the principal investigator based on reaching the target sample size, in accordance with the approved protocol. The study received no external funding, and thus, no funder influenced any trial decision including termination.

Data Analysis

Data were analyzed on an intention-to-treat basis. Continuous variables, including the primary outcome of hospital length of stay (LOS), were summarized using means and standard deviations (SD). The main statistical comparison between intervention and control groups for continuous outcomes was performed using independent two-sample t-tests. Effect measures were expressed as mean differences with corresponding 95% confidence intervals (CIs). Statistical significance was evaluated at a two-sided alpha level of 0.05. No deviations from the prespecified statistical analysis plan occurred. All analyses described were planned a priori, and no post-hoc or exploratory analyses were performed. No additional analyses such as subgroup analyses or adjusted analyses were performed in this trial. All analyses conducted were prespecified as part of the original protocol and statistical analysis plan. Given the relatively small sample size and pilot nature of the study, no exploratory or post-hoc analyses were conducted. Statistical analyses were performed using IBM SPSS Statistics version 29 (IBM Corp., Armonk, NY, USA).

No important changes were made to the original trial protocol after commencement. This includes no modifications to the randomization ratio, eligibility criteria, interventions, outcome measures, target sample size, number of trial arms, duration of follow-up, or statistical analysis methods. All outcomes and analyses were pre-specified in the trial protocol. The conduct of the trial was consistent with the original protocol without dropping sites or other significant alterations. The stages of this study described in Figure 1.

RESULTS

A total of 30 patients participated in this study at Unggul Karsa Medika Hospital Bandung. The study compared LOS between patients who received CPT and standard therapy without CPT. All subjects were moderate-grade COVID-19 patients with positive PCR result who received treatment in the ER and the COVID-19 HCU. Participants were randomly assigned to receive CPT (n=15) or standard therapy without CPT (n=15).

All randomized participants completed the study protocol and were included in the intention-to-treat analysis. At the time of primary outcome assessment (hospital length of stay), data were available for all participants (100% data completeness). There were no missing data for the primary or secondary outcomes. No participants dropped out or

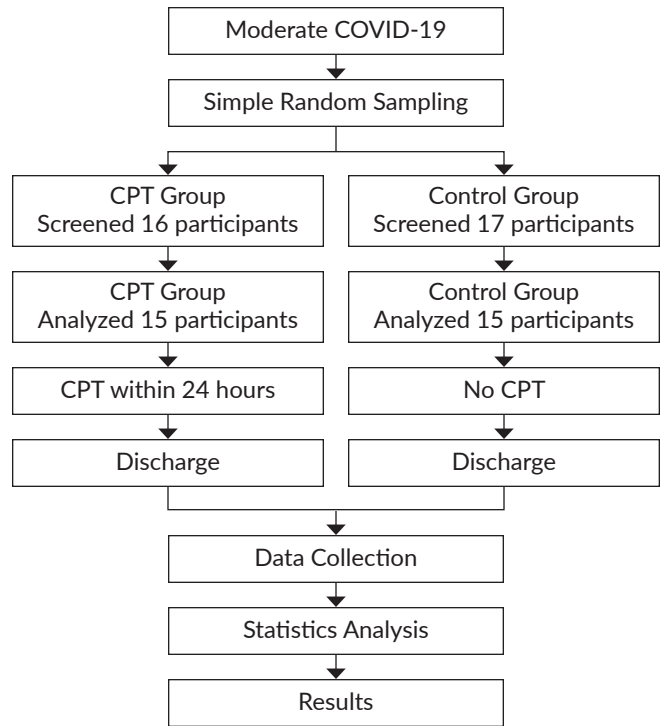


Figure 1. Study flow diagram.

were lost to follow-up, and there were no exclusions post-randomization.

No deaths occurred in either the convalescent plasma therapy (CPT) group or the standard care group during the study period. No serious adverse events, such as transfusion-related acute lung injury (TRALI) or anaphylaxis, were recorded. There were no withdrawals or discontinuations of the trial intervention due to adverse effects or harms. Overall, the interventions were well tolerated, and no safety concerns arose during the trial.

Demographic characteristics are summarized in Table 1. There were more female (80%) than male (20%) patients in the CPT group, on the contrary with the control group where there were more males (46.7%) than female (53.3%) patients. The average age was 40.03 years with range from 19 to 72 years. The average age for the CPT group was 39.2 years, with five patients as the largest number in the age group between 18 and 25 years old and followed by four patients in the age group 26 to 35 years old. The average age for the group and 40.9 years for the control group, with ten patients in the age group 26 to 35 years old and followed by five patients in the age group more than 65 years old. More than half of patients, eight patients in CPT group (53.33%) and ten patients in control group (66.67%), have one or more comorbidities. Patients in the control group had more comorbidities than those in the CPT group.

There was a statistically significant difference in hospital stay duration between the CPT and control groups both in the ER and HCU (Table 2). Patients in CPT group have

Table 1. Patient Characteristics

Variable	CPT Group (n=15)	Control Group (n=15)	Total (n=30)
Sex			
Male	3 (20%)	8 (53.3%)	11 (43.3%)
Female	12 (80%)	7 (46.7%)	19 (56.7%)
Age (years)			
18-25	5 (33.3%)	1 (6.7%)	4 (13.3%)
26-35	4 (26.7%)	6 (40%)	10 (33.3%)
36-45	1 (6.7%)	1 (6.7%)	2 (6.7%)
46-55	1 (6.7%)	2 (13.3%)	3 (10%)
56-65	2 (13.3%)	2 (13.3%)	4 (13.3%)
>65	2 (13.3%)	3 (20%)	5 (16.7%)
Comorbidities			
0	7 (46.67%)	5 (33.3%)	12 (40%)
1-2	7 (46.67%)	7 (46.67%)	14 (46.67%)
≥3	1 (6.66%)	3 (20%)	4 (13.33%)
Moderate-grade COVID-19	15 (100%)	15 (100%)	30 (100%)

Table 2. Length of Stay (LOS)

Variable	CPT Group (Mean ± SD)	Control Group (Mean ± SD)	p-value	Mean Difference (95% CI)
ER LOS (hours)	65 ± 10.36	97.70 ± 23.02	<0.001	-32.7 (-45.0 to -20.4)
HCU LOS (hours)	61 ± 9.88	94.33 ± 23.75	<0.001	-33.3 (-45.8 to -20.8)

shorter LOS than control group ($p < 0.001$), with mean difference 32.7 hours for ER LOS and 33.3 hours for HCU LOS. Furthermore, a minor within-group difference was noted between ER and HCU LOS, with mean differences of approximately 4 hours in the CPT group and 3.5 hours in the Control group. These variations are inherent to hospital workflows and are unlikely to represent clinically meaningful differences, particularly given the consistent and significant overall reduction in LOS observed in the CPT group compared with the control group.

DISCUSSION

This study examined the effect of convalescent plasma therapy (CPT) on the length of hospital stay in patients with moderate COVID-19 by comparing outcomes between those who received CPT and those treated with standard therapy alone. All participants were moderate-grade COVID-19 patients admitted to the ER and the COVID-19 HCU. The average age across all participants was 40.03 years, with minimal age variation between the two groups, 39.2 years in the CPT group and 40.9 years in the control group. Notably, the control group presented a higher prevalence of comorbidities, which could influence clinical outcomes and prolong hospitalization.

CPT was administered to patients classified as having moderate COVID-19, defined by the presence of clinical pneumonia symptoms such as fever, cough, shortness of breath, and tachypnoea, without signs of severe disease and had PCR positive results. While CPT is also indicated for

severe or critical patients characterized by respiratory distress, oxygen saturation $< 93\%$, respiratory rate > 30 breaths/min or lung infiltrates affecting $> 50\%$, based on WHO criteria, its application in moderate cases may offer a strategic advantage by intervening before disease progression.¹⁴

The CPT group had a significantly shorter hospital stay, by approximately 1.5 days compared to the control group, with mean differences -32.7 (-45.0 to -20.4) for ER LOS and -33.3 (-45.8 to -20.8) for HCU LOS. This supports previous studies suggesting that CPT can expedite recovery. Clinical efficacy, immediate availability and potential cost effectiveness could be considered as main advantages of convalescent plasma therapy. This clinical study provides strong evidence to support the efficacy of convalescent plasma therapy in COVID-19 patients and recommends this treatment for management of these patients.¹⁵⁻²⁰

One multi-centre clinical study reported that CPT reduced hospital stays by up to three days ($p < 0.01$). This study consists of 189 COVID-19 positive patients including 115 patients in plasma therapy group and 74 patients in control group, registered in the hospitals with confirmed COVID-19 infection, found 98 (98.2 %) patients who received convalescent plasma were discharged from hospital which is substantially higher compared to 56 (78.7%) patients in control group. Length of hospitalization days was significantly lower (9.54 days) in convalescent plasma group compared with that of control group (12.88 days). Only 8 patients (7%) in convalescent plasma group required intubation while that was 20% in control group. However, it is important to recognize that several patient-specific factors including

intubation, corticosteroid use, presence of comorbidities, and older age (particularly >65 years), have been associated with prolonged hospitalization and may attenuate the benefits of CPT.¹⁵

Convalescent plasma appears to function through multiple mechanisms, including neutralizing circulating viruses, reducing systemic inflammation, improving oxygenation, and promoting lung tissue healing. Additionally, CPT may augment innate immune functions such as cytotoxicity and phagocytosis, particularly when used in conjunction with antiviral agents. Its role is especially relevant in immunocompromised patients, who may benefit from CPT as an alternative treatment option due to their impaired ability to mount an adequate immune response.¹⁸⁻²⁴

This result is comparable with another study which demonstrated that early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduced the progression of COVID-19, supporting its use as an effective and low-cost intervention strategy when given early in the course of illness. A review study of 30 available RCTs demonstrated signals of efficacy, including reductions in mortality, were more likely if the CCP neutralizing titer was >160 and the time to randomization was less than 9 days. One study found a potential benefits of convalescent plasma, when used early, to prevent progression to severe disease and convalescent plasma was significantly associated with better ICU-related outcomes in trials conducted in Europe. Other recent studies showed that earlier administration of CPT in patient within five days from symptom onset associated with higher number of discharges.²⁵⁻²⁹

From a broader healthcare perspective, the results of this study suggest that CPT can play a vital role not only as a life-saving therapy but also in reducing the length of hospitalization, thus alleviating the burden on medical staff and healthcare systems. Shorter hospital stays can translate into faster patient turnover, reduced hospital congestion, decreased burnout among healthcare workers, and lower treatment costs. There are also some other important features specifically related in Indonesia support CPT. First, every COVID-19 patient with positive PCR tests and a member of Indonesian Social Health Insurance Administration (Badan Penyelenggara Jaminan Sosial Kesehatan Indonesia/ BPJS) will receive free three bags of plasma. Second, one bag of convalescent plasma in Indonesia is only around 2-3 million rupiah, much cheaper and more affordable than the use of antiviral drugs, which have significantly increased in price during the COVID-19 pandemic. These benefits are particularly significant in resource-limited settings or during healthcare crises, such as pandemics.^{22,25,26}

No adverse effects were reported in this study. However, transfusion-related allergic reactions are common adverse effects associated with blood and blood component transfusions, such as urticaria, itching, rash, or fever in mild case and difficult to breathe, bronchospasm or even anaphylaxis

in severe cases. This condition can prolong hospitalization and alter the positive effects of CPT. Careful screening and close monitoring, especially during CPT, can minimize the adverse effects, provide immediate treatment, and maintain LOS efficiency.

The findings contribute valuable insights into the practical benefits of CPT in moderate COVID-19 cases. They also underscore the importance of early administration and patient selection in optimizing outcomes. The mark of early CPT yields better result is the basis and in line with the result of this study where CPT was given 24 hours after patient admission. Finally, this study may serve as a reference for the use of CPT in future outbreaks involving novel respiratory viruses.²⁴⁻²⁹

Limitations

The findings provide preliminary evidence on the potential benefits of CPT in reducing hospital length of stay among moderate COVID-19 patients. However, the generalizability of these results may be limited by several factors. The study population was relatively small and recruited from a single private hospital in Bandung, Indonesia, which may differ in patient demographics, healthcare resource availability, and standard care practices compared to other settings. Control patients had more comorbidities potentially biasing results towards longer LOS. Unlike larger scale RCTs and recent guidelines emphasizing CPT in severe illness, this study highlights potential benefit in earlier moderate cases. The reported average LOS reduction of 1.5 days could translate into substantial clinical and economic benefits, though cost-effectiveness and adverse event analyses were not performed, warranting further research. Further larger, multi-center trials involving heterogeneous populations are needed to confirm these results and to assess the broader applicability and scalability of CPT as a treatment strategy for earlier moderate COVID-19 across different populations. This study was conducted before the establishment of a national research registration system and the institutional ethical approval obtained was considered sufficient. The trial registration to International Registry could enhanced this study value for future trial.

CONCLUSION

Early administration of convalescent plasma therapy in moderate COVID-19 patients may reduce hospital length of stay compared to standard treatment alone, as shown by this study result. The presence of SARS-CoV-2 antibodies in the convalescent plasma likely contributes to this effect by inhibiting viral replication and promoting faster clinical recovery in earlier stage. These findings support CPT as a potential strategy to optimize patient outcomes and resource utilization including duration of stay and hospital cost during the pandemic. However, larger, well-designed trials are necessary to confirm efficacy, safety, and cost-effectiveness.

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Statement of Authorship

All authors certified fulfilment of ICMJE criteria.

Author Disclosure

All authors declared no conflicts of interest.

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