

# Effectiveness of Convalescent Plasma Therapy in Critically Ill COVID-19 Patients: Early Experience from a Dedicated ICU of Bangladesh

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## Abstract

**Introduction:** The management of severe or critical COVID-19 patients in the ICU includes supportive care as well as repurposed drugs and revival of old strategies like human convalescent plasma therapy (CPT) in the absence of specific therapy against SARS-CoV-2 virus. CPT appears to be an attractive treatment option as passive antibody transfer, but efficacy remains controversial.

**Objectives:** To determine the effectiveness of convalescent plasma therapy in management of critically ill COVID-19 patients admitted at the dedicated intensive care unit of Kurmitola General Hospital, Dhaka.

**Study Method:** All patients admitted in the ICU of Kurmitola General Hospital, Dhaka from 1<sup>st</sup> May to 30<sup>th</sup> September 2020 were included in this retrospective observational cohort study. The protocol was approved by the Ethical and Scientific Committee of the hospital. The clinical and treatment data of all participants were collected; and the association of CPT and mortality benefit was observed between the patients who received plasma therapy during ICU stay and who didn't. The statistical analysis was performed using the Windows based statistical software package SPSS version 25.

**Results:** A total of 228 critically ill COVID-19 patients were admitted to the ICU of Kurmitola General Hospital in the specified time period. Among them, 160 (70%) were male and 68 (30%) females. Mean age was 57.97 (95% CI 56.23-59.70) years. Important co-morbidities were obstructive airway diseases 160 (70.17%), hypertension 117 (51.31%) and diabetes mellitus 103 (45.17%). Only 53 (23.25%) patients received CPT during ICU stay. The median day of receiving CPT from the day of symptom onset was 12 (IQR 10-14) days in the survivor group and 18 (IQR 16-19) days in the non-survivor group ( $p < 0.0001$ ). All-cause ICU mortality was 29 (54.7%) in CPT group vs. 115 (65.7%) in Non-CPT group ( $p = 0.146$ ). The odds ratio of survival in CPT group was 0.757 (95% CI 0.528-1.085).

**Conclusion:** This retrospective cross-sectional study suggested that the efficacy of use of convalescent plasma in critical or severe COVID-19 patients admitted to ICU is conflicting for mortality benefit.

**Key words:** COVID-19, Convalescent plasma therapy, Intensive care unit, Bangladesh

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## Introduction:

The rapidly emerging coronavirus COVID-19 pandemic is the defining global health crisis of our time and the greatest challenge we have faced since World War Two. Since its emergence in Asia in 2019, the virus has spread to every continent and now reached the tragic milestone of more than two million deaths.<sup>1</sup>

COVID-19 has a seemingly variable clinical presentation and progression, presenting with mild infection to severe disease to fatal illness.<sup>2</sup> Reports suggest that among those infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), up to 20 percent develop severe disease requiring hospitalization.<sup>3,4</sup> Approximately 14 to 29% of hospitalized patients with COVID-19

pneumonia require intensive care, primarily for respiratory support in the setting of hypoxic respiratory failure.<sup>5</sup> The other common complications of COVID-19-related ARDS include acute kidney injury (AKI), elevated liver enzymes, and cardiac injury including cardiomyopathy, pericarditis, pericardial effusion, arrhythmia, and sudden cardiac death.<sup>6</sup>

Most infected people with SARS-CoV-2 have mild or moderate symptoms and recover without the need for extensive treatment. However, the management of patients suffering from severe or critical illness is challenging as there is no specific effective antiviral treatment currently available.<sup>7</sup> Besides supportive care, healthcare providers across the globe are using repurposed drugs and older strategies to manage the COVID-19 patients admitted in hospital. Revival of convalescent plasma therapy (CPT) is such an old strategy.<sup>8</sup>

CPT has been used since the 1900s in the prevention and management of various infectious diseases.<sup>7</sup> Its use was associated with reduced mortality during the 1918 influenza, 2003 SARS and 2009 influenza H1N1 pandemics.<sup>9</sup> In this context, our national guideline has issued guidance for the administration of human convalescent plasma in severe or life threatening COVID-19.<sup>10</sup>

CPT is a passive immunization strategy. It involves infusing patients with plasma obtained from people who have recovered from COVID-19. Convalescent plasma (CP) contains neutralizing antibodies, anti-inflammatory cytokines, clotting factors, natural antibodies, defensins, pentraxins and other undefined proteins, which help to neutralize the pathogen by potent anti-viral activity. Besides, CPT may cause immunomodulation via amelioration of severe inflammatory response seen in cases of COVID-19 with “Cytokine storm” driven by IL-1 $\alpha$ , IL-2, IL-6, IL-17, IL-8 and TNF $\alpha$ . Thereby reducing pulmonary damage and fibrosis.<sup>11</sup>

However, there is conflicting evidence about the efficacy of convalescent plasma for treating COVID-19. Many observational studies have found the association between convalescent plasma and reduced mortality, hospital stay and viral load in patients with COVID-19. But, out of only three randomized controlled trials published till now, neither have shown mortality benefit. So, published systematic review remained undecided

on both safety and effectiveness of CPT as a treatment option in patients admitted to hospital with COVID-19.<sup>8,12</sup>

Our ICU population of Kurmitola General Hospital (KGH), Bangladesh comprises of patients with “Severe” and “Critical” COVID-19. The purpose of this study was to find out the outcome of CPT in our patients with COVID-19 by retrospective analysis of patients’ data and to highlight the role of CPT as a therapeutic option in the management of the current global pandemic COVID-19 pandemic in a resource constraint setting like Bangladesh.

### Materials and Methods:

This retrospective observational cohort study was conducted in the COVID dedicated ICU of Kurmitola General Hospital, Dhaka from 1<sup>st</sup> May to 30<sup>th</sup> September 2020. A total of 228 RT-PCR confirmed critically ill COVID-19 patients who had been admitted in this specified time period were enrolled in this study. The protocol was approved by the Ethical and Scientific Committee of KGH. Patients data were collected in a Case Record Form (CRF) by analyzing patients’ registrar, patient assessment and treatment sheet and ICU follow up form. The administration of CPT was decided solely by the treating physician. Patients who received convalescent plasma therapy were compared to patients who didn’t. The primary outcome was all cause ICU mortality. Categorical variables were reported as count and percentage. Normally distributed continuous data were presented as mean and 95% confidence interval whereas non-normally distributed data as median and interquartile range (IQR). To determine any association between two categorical variables Chi-square test or Fisher’s exact test was used. Quantitative data was compared using Mann-Whitney U test. All p-value at or below 0.05 was considered as significant. The statistical analysis was performed using the Windows based statistical software package SPSS version 25.

### Results:

A total of 228 RT-PCR confirmed COVID patients were admitted to the ICU of Kurmitola General Hospital between May, 2020 to September, 2020.

Figure-1 shows distribution of participants according to sex. Among 228 patients, 160 (70%) were male and 68 (30%) females. Male: Female was 2.35:1.

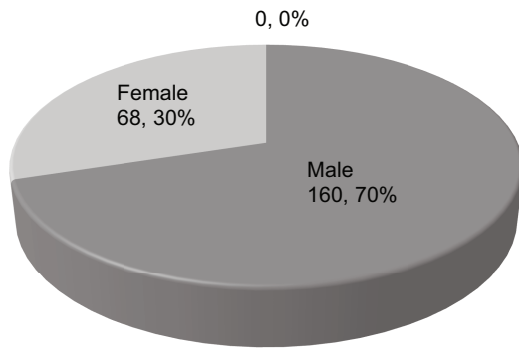


Figure-I Distribution of patients according to sex (N=228)

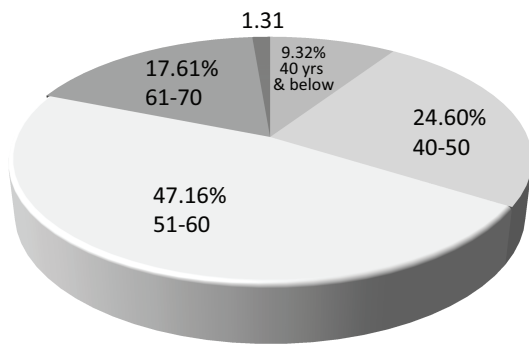
Table-I shows the age distribution of study subjects. Twenty-eight point five one percent patient belonged to 51-60 year age group and 25% patients belonged to 61-70 year age group. Their mean age was 57.97 (95% CI 56.23-59.70) years.

**Table-I** Distribution of patients according to age (N=228)

| Age Group   | Frequency (n) | Percentage (%) |
|-------------|---------------|----------------|
| ≤40 years   | 23            | 10.09%         |
| 41-50 years | 40            | 17.54%         |
| 51-60 years | 65            | 28.51%         |
| 61-70 years | 57            | 25.00%         |
| ≥71 years   | 43            | 18.86%         |
| Total       | 228           | 100%           |

**Mean** (95% CI) 57.97 (56.23-59.70)

Figure-II shows distribution of patients receiving CPT stratified by age group. Though highest 65 (28.51%) patients were within the age group of 61-70 years, it was the age group 51-60 years that received the most plasma therapy 18 (47.17%) followed by age group 41-50 years.



**Figure 2** Distribution of patients receiving CPT stratified by age group

Table-II shows distribution of co-morbidities stratified by CPT. Important co-morbidities were obstructive airway diseases 160 (70.17%), hypertension 117 (51.31%) and diabetes mellitus 103 (45.17%). All patients received Anticoagulant and Corticosteroid. But, out of 228, only 53 (23.25%) patients received one unit (200 ml) of CPT.

**Table-II**: Distribution of co-morbidities stratified by CPT

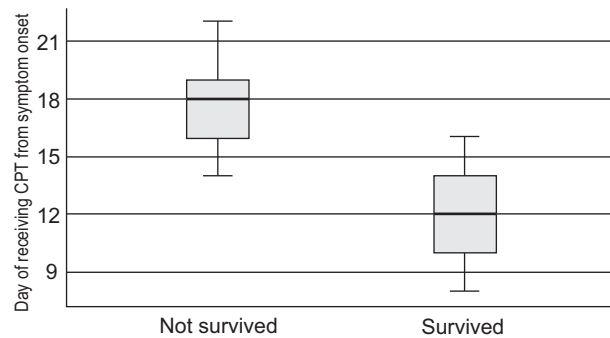
| Co-morbidities             | Convalescent Plasma Therapy |     | Total (% of population) |
|----------------------------|-----------------------------|-----|-------------------------|
|                            | Yes                         | No  |                         |
| Hypertension               | 36                          | 81  | 117 (51.31%)            |
| Ischaemic heart disease    | 17                          | 51  | 68 (29.82%)             |
| Diabetes mellitus          | 30                          | 73  | 103 (45.17%)            |
| Chronic kidney disease     | 9                           | 31  | 40 (17.54%)             |
| Obstructive airway disease | 41                          | 119 | 160 (70.17%)            |
| Stroke                     | 2                           | 53  | 55 (24.12%)             |
| Obesity                    | 8                           | 48  | 56 (24.56%)             |
| Chronic liver disease      | 7                           | 20  | 27 (11.84%)             |
| Malignancy                 | 2                           | 6   | 8 (3.50%)               |
| No co-morbidities          | 13                          | 20  | 33 (14.47%)             |

Table-III shows that all-cause ICU mortality was 29(54.7%) in CPT group vs. 115(65.7%) in Non-CPT group, but didn't reach statistical significance ( $p=0.146$ ). The odds ratio of survival in CPT group was 0.757 (95% CI 0.528-1.085).

**Table-III** All-cause ICU mortality in relation to CP

| CPT                | Mortality   | Survived   | p-value |
|--------------------|-------------|------------|---------|
| (% with CPT group) |             |            |         |
| Yes (n=53)         | 29 (54.7%)  | 24 (45.3%) | 0.146   |
| No (n=175)         | 115 (65.7%) | 60 (34.4%) |         |

The median day of receiving CPT from the day of symptom onset was 12 (IQR 10-14) days in the survivor group and 18 (IQR 16-19) days in the non-survivor group (Figure-III), Mann Whitney U test revealed  $p<0.0001$  which was statistically significant.



**Figure-3** Day of receiving CPT from symptom onset stratified by survivability (n=53)

### Discussion:

Taking into account the limited data available for the treatment of COVID-19, long-established and traditional interventions have re-emerged as viable options in the regulation of this disease. Nevertheless, convalescent plasma therapy (CPT) has recently become the focus of attention as it has earlier evidence supporting this CPT as a treatment option among COVID-19 patients.<sup>13</sup>

In this retrospective analysis of a cohort of 228 patients admitted in ICU of KGH over a period of five months, male were found to be more than female (M:F=2.35:1) which correlates with other studies.<sup>14,15</sup> Older age group is vulnerable for COVID-19 as well as ICU hospitalization,<sup>10</sup> but it was found in our observation that besides older age (>60 years), a significant proportion of our ICU population was below 50 years of age (27%).

Out of 228 patients, only 33 (14.47%) patients had no past co-morbidities. A history of obstructive airway diseases was found in 160 (70.17%) patients besides hypertension 117 (51.31%) and Diabetes mellitus 103 (45.17%). These are known to be the risk factors for COVID-19 disease progression.<sup>16</sup>

Recent studies in Bangladesh<sup>17</sup> and other countries<sup>18,19</sup> revealed convalescent plasma therapy as an evolving defensive treatment option for near-fatal cases of COVID-19. Convalescent plasma therapy (CPT) is also recommended in our national guideline for severe or critical COVID-19 (11-covid guide). However, only 53 (25.23%) patients received CPT in this present observation. Dose was single unit (200 ml) for all patients. The antibody titer was unknown. High antibody titer was found to be effective in some studies.<sup>20,21</sup>

Those patients who survived after CPT actually received it earlier than those who didn't survive. The median day of receiving CPT from the day of symptom onset was 12 (IQR 10-14) days in case of survivor group compared to 18 (IQR 16-19) days for non-survivor group which was statistically significant ( $p < 0.0001$ ). But, when comparison was made against the patients who didn't receive CPT during ICU stay, all-cause mortality was not statistically different between CPT group 29 (54.7%) vs. non-CPT group 115 (65.7%) ( $p = 0.146$ ). The only available published RCT on CPT on COVID-19 till now, the "PLACID" trial concluded that convalescent plasma was not associated with a reduction of severity or all-cause mortality.<sup>8</sup> This study revealed an odd ratio of survival in CPT group 0.757 (95% CI 0.528-1.085) translating to "low to almost no" association between CPT and patient survival. Future research could explore using only plasma with high levels of neutralizing antibodies, to see if this might be more effective.

### Limitations

This observational study was subjected to information bias and confusion bias as all information were collected from record documents. We were unable to collect data on detailed physical examination and standardized laboratory investigations for all cases. Being a retrospective study, attempt to limit the confounders was not possible. The associations of co-morbidities with mortalities in critically ill COVID-19 patients of this study are also needed to be evaluated in further multicenter prospective studies with larger cohort and extended follow-up.

### Conclusion:

This retrospective study represented that the efficacy of convalescent plasma in critical or severe COVID-19 patients admitted to ICU is conflicting. The mortality benefit is yet needed to be established by randomized control trial. The antibody concentration of plasma and day of administration since the onset of symptom as well as disease severity status might play role in determining the mortality benefit in COVID-19. Further prospective studies should be conducted to verify the study findings.

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