



# Efficacy of Convalescent Plasma Therapy (CPT) plus Remdesivir versus Standard Therapy (Remdesivir) In Patients with Severe or Critical COVID-19 Infection in Second and Third Wave of Epidemics in Myanmar: Non-Randomized Interventional Study

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## Abstract

**Background:** Coronavirus disease 2019 (COVID-19), emerged in China at the end of 2019, became a major threat to health around the world as it caused significant morbidity and mortality. Convalescent plasma therapy (CPT) has been one of the treatment options in

Received date: 14 February 2022; Accepted date: 20 February 2022; Published date: 27 February 2022

**Citation:** Phyu Pyar K, Phyo Kyaw A, Lin Maung N, Htet Aung ZN, Min Aung S, Aung Aung, et al. (2022). Efficacy of Convalescent Plasma Therapy (CPT) plus Remdesivir versus Standard Therapy (Remdesivir) In Patients with Severe or Critical COVID-19 Infection in Second and Third Wave of Epidemics in Myanmar: Non-Randomized Interventional Study. SunText Rev Virol 3(1): 128.

DOI: <https://doi.org/10.51737/2766-5003.2022.028>

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patients with SARS-CoV-2 infection since early 2020 as specific anti-viral drugs were underway. Adding CPT to remdesivir may promote recovery in patients with severe COVID-19 infection and it was not clearly known in Myanmar.

**Methods:** A hospital based non-randomized interventional study was conducted in COVID-19 treatment centres in Myanmar- Yangon and Nay Pyi Taw, from October 2020 to August 2021. One dose of 200 mL of convalescent plasma (CP) derived from recently recovered donors, PCR confirmed COVID-19 infection in the past 6 weeks having the total antibody level of at least 32 COI, was transfused to the patients with severe or critical COVID-19 infection as an add on therapy to Standard treatment group (Remdesivir). The primary outcome was survival status; survive or non-survive. The secondary outcome was duration of hospital stay, the requirement for oxygen therapy (increased, same or decreased), changes in chest radiograph (improved, same or worse), and, changes in inflammatory markers. Patient data were stratified by age, sex, body weight, co-morbidities and immune status (immune compromised or normal immune status). Data were collected by using standardized forms and analysis was done.

**Results:** A total of 281 patients with severe/critical COVID-19 infection were enrolled. Base line characteristics in CPT group (n =155) and Standard treatment group (n = 126) were comparable. Nearly 70% of patients in CPT group and 76% of patients in Standard treatment group survived; however, mean duration of hospital stay was shorter in CPT group ( $12.53 \pm 6.83$  days versus  $17.25 \pm 11.17$  days;  $p < 0.001$ ). Nearly 60% of patients in CPT group required less supplementation of oxygen at Day 7 whereas only one third of patients in Standard treatment group made improvement in oxygen supplementation ( $p = 0.01$ ). Both radiological changes and changes in inflammatory markers were not different in both groups.

In view of timing of therapy and survival, 85% percent of survivors in Standard treatment group received treatment early ( $p < 0.001$ ); nevertheless, CPT group did not show similar effect ( $p=0.08$ ). None of the recipients had transfusion reaction serious side effects. Survival analysis revealed the followings: (1) younger age group ( $< 60$  years) survived more in CPT group whereas Standard treatment group did not show effect of age on mortality ( $p = 0.003$  versus  $p = 0.1$ ); (2) nearly 80% of those who did not have co-morbidities in CPT group survived whereas Standard treatment group did not significantly reveal the influence of co-morbid status ( $p = 0.07$  versus  $p = 0.4$ ); (3) early treatment had better outcome in Standard treatment group whereas CPT group did not ( $p = 0.001$  versus  $p = 0.08$ ); (4) eighty percent of immune compromised patients in CPT group survived whereas the immune status did not relate with survival in Standard treatment group ( $p = 0.02$  versus  $p = 0.3$ ).

**Conclusions:** In treating patients with severe or critical COVID-19 infection, the survival rate was not different between CPT group (convalescent plasma therapy plus Remdesivir) and Standard treatment group (Remdesivir). In survivors, CPT group had significant good points; shorter duration of hospital stays and decreased oxygen requirement by Day 7 making cost benefit. CPT saved the younger age group than older age group with severe/critical infection. CPT was better than Standard treatment group in saving lives in immune compromised patients with severe/critical COVID-19 infection.

**Keywords:** Convalescent plasma therapy (CPT); Standard treatment; Remdesivir; severe/ critical COVID-19 infection; Survival; Immune compromised

## Introduction

Coronavirus disease 2019 (COVID-19) has been spreading to the whole world since December 2019; it has caused significant morbidity and mortality. In Myanmar, in the first wave of epidemic, COVID-19 reported cases were identified in March, 2020; and, the second wave began in October 2020 and the number gradually dropped in March 2021. Third wave start in May and reached peak in July/August; the number of cases decreased in November, 2021. Convalescent plasma therapy (CPT) has been one of the treatment options in patients with SARS-CoV-2 infection since early 2020 as specific anti-viral drugs were underway. Convalescent plasma, a form of passive antibody immunotherapy, was used to treat an emerging infectious disease: 1918 influenza, severe acute respiratory syndrome, pandemic 2009 influenza A (H1N1), avian influenza A (H5N1), Ebola, and other viral infections. Several studies showed that convalescent plasma therapy decreased the mortality as a

stopgap treatment while new antivirals and vaccines were being developed [1]. CPT was thought to exert an antiviral effect, suppressing virus replication till the plasma recipient could develop own humoral immune responses. In addition to its neutralizing antibody content, a prominent effect of CPT on attenuation of systemic cytokine levels possibly contributed to its benefits. Various treatments such as anti-viral drugs (Remdesivir), immune modulators (corticosteroids, tocilizumab) and direct anti-viral therapy (CPT convalescent plasma therapy) have been used for treatment of severe COVID-19 infection since early 2020. The clinical presentation may vary from asymptomatic, mild, moderate, severe and critical depending on host immunity, co-morbidity, age and virulence of virus. Treatment may be symptomatic if the patient is young, normal immune status, and having mild form. Those with moderate and severe form must be treated with oxygen therapy to maintain oxygen saturation, remdesivir, dexamethasone as anti-inflammatory action, antibiotics and low molecular weight

heparin for anti-coagulation. There were several trials on CPT; some were positive whereas some were negative. The earliest report from Huban, China was very exciting. CPT was effective and safe; three patients who did not combine with antiviral therapy after CPT also obtained viral clearance and clinical improvement. However, CPT failed to save the life of a terminally ill patient. Moreover, another study also believed in CPT; it improved the survival of COVID-19 patients in ICU [2]. The study done demonstrated the use of CPT; the meta-analysis proved too [3-6]. In a double-blind, placebo-controlled, randomized trial of high-titer convalescent plasma in older, non-hospitalized adults with < 72 hours of mild COVID-19 symptoms demonstrated the benefit in reduced progression of respiratory disease. The strength of the study seemed to be weak as it included relatively few participants (80 participants in each arm). The trial from Brazil also provided the evidence, CPT lowered 28 day mortality; but, it was not statistically significant. Furthermore, the study done in Argentina pointed out that CPT was good if it was given early (< 72 hours) particularly in older adults [7-9]. In addition, early administration of high titer CPT reduced outpatient hospitalizations by more than 50%. Therefore, CPT saved cost and it had wide availability; and, it gave rapid resilience to variant emergence from viral genetic drift in the face of a changing pandemic. CPT saved immune compromised patients, patients with haematological cancer with severe COVID-19 infection [10-13]. In case series report, a therapeutic benefit of CPT in patients with primary antibody deficiency was mentioned as safe; and, early re-treatment might be considered in patients with persistent viral shedding [14]. Regarding the relation between the outcome of CPT and age, all age-groups did not show statistically significant clinical benefit; however, significant immediate mitigation of hypoxia, reduction in hospital stay as well as survival benefit was shown in severe COVID-19 patients with ARDS aged less than 67 years receiving CPT [15]. Nevertheless, giving CPT to older adult patients was good. Therefore, age of the recipients was also controversial point in outcome of CPT; old age was mentioned in several reports as poor prognostic factor [16-18]. Several studies pointed that the outcome of CPT was related with antibody level in donated plasma, volume of transfused plasma, timing of plasma infusion, and residence of donor in relation to that of recipient and body weight of donor. As COVID-19 infection cause high morbidity and mortality, and several studies on the various antiviral drugs are still under trial [19-23]. One of the famous trials on CPT done in early 2020 was PLACID trial India. The researchers from India stopped PLACID trial in end of 2020 as CPT did not improve survival of patients with moderate COVID-19 infection. Multi-center randomized controlled trial done in India which included adults with moderate COVID-19 infection concluded that convalescent plasma was not associated with a reduction in

progression to severe covid-19 or all-cause mortality [24]. In DAWn plasma trial, there was no difference in outcome of patients with severe COVID-19 infection which included 320 patients. RECOVERY trial, randomized study involving more than 11,400 patients, confirmed that no significant difference in 28-day mortality between the convalescent plasma arm and the usual care arm; it was also agreed by CONCOR-1 trial and REMAP-CAP trial. C3PO study, a single-blind randomized trial that evaluated high-titer convalescent plasma for the treatment of non-hospitalized patients, showed no benefit [25]. In one study which included nearly 1,000 cases revealed that CPT did not reduce the risk of intubation or death at 30 day in hospitalized patients with COVID-19 [26]. On the other hand, some scientists recommended that future research on CPT in view of prevention and treatment for patients with COVID-19 while other therapeutics are being developed [27]. In Myanmar, there was no previous study regarding the effect of CPT versus Standard treatment (Remdesivir) on outcome of patients with severe/critical COVID-19 infection. It is necessary to investigate in Myanmar, where the results may differ from that of other countries. Therefore, this study aimed to detect the effect of CPT versus Standard treatment (Remdesivir) on outcome of patients with severe/ critical COVID-19 infection in Myanmar.

## Methods

### Study design and population

It was a hospital based non-randomized interventional study conducted from October 2020 to August 2021 in military COVID treatment centres: Defence Services Liver Hospital, Yangon and No. (2) Defence Services General Hospital (1000-Bedded), Nay Pyi Taw. For convalescent plasma collection, the patients recovered from confirmed COVID-19 infection were recruited and the plasma was taken at 30-60 days after recovery. Donor total antibody level was measured at the time of plasma donation. SARS-CoV-2 total antibody was measured with the use of E411 Fully Automated Immune Analyzer [28]. Adequate total antibody or high total antibody titer was defined if the total antibody level was  $\geq 1:32$  COI and plasma from donors with adequate antibody was collected with plasma separator. The plasma packets were stored in 4°C refrigerator at blood bank. Donor total antibody level was checked again prior to transfusion to recipients. The patients were diagnosed COVID-19 using SARS-CoV-2 quantitative real-time reverse transcription polymerase chain reaction (RT-PCR) on nasopharyngeal swab samples at admission. Confirmed cases with COVID-19 severe/critical disease were included after getting informed consent; it was obtained from each patient or their legal relatives if patients on ventilator.

## Operational definitions

Comorbidity was a presence of one or more additional medical conditions or diseases diagnosed by physicians. Day of symptom onset was the day when the initial symptom began such as runny nose, muscle ache, cough, sore throat, dyspnoea, etc. Based on WHO severity score, the severity of COVID-19 was classified as mild, moderate, severe disease and critical disease. Mild disease was symptomatic patients without evidence of viral pneumonia in CXR or hypoxia. Moderate disease was confirmed patients with clinical signs of pneumonia (fever, cough, dyspnoea, and fast breathing), CXR showed pneumonia and SaO<sub>2</sub> on air is  $\geq 95\%$ . Severe disease was confirmed patient with clinical signs of pneumonia (fever, cough, dyspnoea, and fast breathing) adding one of the following: respiratory rate  $> 30$  breaths per min, severe respiratory distress and SpO<sub>2</sub>  $< 90\%$  on room air. Critical disease was confirmed COVID-19 patient with one or more of the followings: ARDS, sepsis, septic shock and acute thrombosis (pulmonary embolism, acute coronary syndrome, and acute stroke). Total antibody titer was defined as adequate if the total antibody level was  $\geq 1:32$  COI; already set criteria for donor total antibody level for convalescent plasma donation. The hospital outcome at the time of discharge from hospital (survival status) was either survivor or non-survivor. The discharge criteria were determined by attending physician. Timing of plasma therapy was “early” if patient obtained CPT or Standard treatment less than 7 days after symptom onset, and “late” if patient obtained CPT or Standard treatment more than 7 days after symptom onset. Early therapy group was those who received CPT or Standard treatment less than 7 days after symptom onset and late therapy group was those who received CPT or Standard treatment more than 7 days after symptom onset. Comorbid status was presence of one or more comorbid diseases like diabetes mellitus, hypertension, chronic kidney disease (eGFR  $> 30$  ml/min), chronic obstructive airway disease, bronchial asthma, stroke, chronic liver disease. The comorbid associated group was having one or more comorbid disease and comorbid non-associated group did not have comorbid disease. Immune status was defined as normal or immune compromised. Immune compromised status was those not having one of immune compromised state transplant recipients, those on oral steroids for more than two weeks, those on immune suppressants, systematic lupus erythematosus, diabetes mellitus, ESRD (eGFR  $< 30$  ml/min), and, haematological malignancy, The primary outcome was survival status; survive or non-survive. Normal immune status was those not having immune compromised state. Secondary outcome was duration of hospital stays, and the requirement for oxygen therapy (increased, same or decreased). Timing/duration of symptoms onset to admission (days) was time from first symptom to arrival at hospital. Duration of hospital stay was total duration of hospital

stay till discharge either in survival state or non-survival state which may be beyond secondary outcome i.e., 28 days. Severity of lung parenchyma involvement in CXR was calculated by Brixia Score as “0 to 18”. Lungs were divided into six zones on a postero-anterior (PA) or antero-posterior (AP) projection. In the second step, a score (0 to 3) is assigned to each zone based on lung abnormalities as follows: (1) “0” if there was no lung abnormalities; (2) “1” if there was interstitial infiltrates; (3) “2” if there was interstitial and alveolar infiltrates with interstitial predominance; and, (4) “3” if there was interstitial and alveolar infiltrates with alveolar predominance. Finally, the scores of the six lung zones are then added to obtain an overall CXR score ranging from 0 to 18. Based on WHO severity score, the clinical severity of COVID-19 infection was classified into four types: mild, moderate, severe and critical. In mild category, patients have symptoms only, CXR is normal and, SaO<sub>2</sub> on air is normal. In moderate category, CXR shows pneumonias and SaO<sub>2</sub> on air is  $\geq 90\%$ . In severe category, respiratory rate is  $> 30$ /min and, SaO<sub>2</sub> on air is  $< 90\%$ . In critical disease category, the patient has ARDS; he may have sepsis with multi-organ dysfunction or septic shock or acute thrombosis (pulmonary embolism, acute coronary syndrome, acute stroke). Absolute lymphocyte count was low if it was less than  $1.0 \times 10^9$  /L. The level of AST was raised if it was more than 37 IU/L; the level of ALT was raised if it was more than 40 IU/L. The level of ferritin was defined as elevated when it was higher than 400 ng/mL (30 - 400 ng/ml). The level of LDH was defined as elevated when it was higher than 225 U/l (135 - 225 U/l). The level of D dimer was defined as elevated when it was higher than 0.5  $\mu\text{g/ml}$  ( $< 0.5 \mu\text{g/ml}$ ). CRP, an acute-phase reactant reflecting the inflammatory activity, was defined as elevated when it was higher than 0.5 mg/dl ( $< 0.5 \text{ mg/dl}$ ). The most recent ferritin, LDH and D dimer and CRP values before CPT or Standard treatment administration was selected as the value of before therapy and the changes of the value after administration was observed for till discharge/ death (24 hour, 72 hour, 1 week, 2 week, 3 week and 4 week).

## Data collection and procedure

Potential donor candidates who had PCR confirmed COVID-19 infection in the past 6 weeks were recruited first. Then, their SARS-CoV-2 total antibody was measured with the use of E411 Fully Automated Immuno Analyzer. Total antibody titer was defined as adequate if the total antibody level was  $\geq 1:32$  COI; it was the already set selection criteria for convalescent plasma therapy. The plasma from donor having adequate antibody level was taken with the use of plasma separator- apheresis machine; they were collected in special plasma packet. The name of the plasma donor and his antibody level were recorded together with blood group- ABO and Rh. Then, they were kept in blood bank. One packet of plasma had 200 cc volume. Prior to transfusion, the

total antibody level in the plasma packet was checked again and noted. Demographic characteristics- sex, age, height, weight, comorbidity (hypertension, diabetes mellitus), immune status, and timing of CPT or Standard treatment from symptom onset were collected using a standardized case report form. Patients with confirmed positive results for nasopharyngeal swab PCR were initially screened for severity of disease according to WHO severity criteria: mild, moderate, severe and critical; those patients with severe and critical disease were selected for initial enrolment. They all received Standard treatment which included remdesivir, dexamethasone, antibiotics, and low molecular weight heparin and oxygen therapy. Some of them were given CPT if there was available matched ABO/Rh plasma, and, the patients himself/close relatives agreed for CPT. For both CPT group and Standard treatment group, remdesivir injection was contraindicated in the following situation: (1) hypertransaminemia (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] more than five times upper limit of normal), (2) estimated glomerular filtration rate (eGFR) < 30 ml/min, (3) pregnancy, (4) lactation, and (5) allergy to remdesivir. The study was approved by “Hospital Research and Ethics Committee” from No. (1) Defence Services General Hospital (1000-Bedded), Mingaladon, Yangon. After getting the informed consent for CPT, blood for grouping and matching was done. One packet of matched plasma was given under supervision of physician. Side effects were monitored and treated accordingly. Timing of CPT in relation to symptom onset was recorded too. The patients were followed up till discharge or death. Patient data were stratified by age, sex, body weight, co-morbidity, immune compromised state, timing of CPT or Standard treatment. Data were collected by using standardized forms and analysis was done. All the data were recorded in proforma. The data were checked by two medical officers and then, supervision, completeness, and consistency of collected data were performed by the principle investigator. The primary outcome was survival status; survive or non-survive. The secondary outcome was duration of hospital stays, the requirement for oxygen therapy (increased, same or decreased), the requirement for ventilatory support (required or not), and changes in chest radiograph (improved, same or worse) on Day 7 after therapy. The blood levels of inflammatory markers (ferritin, LDH, D-dimer and CRP), complete picture, liver enzymes, serum creatinine and sugar were done before and after CPT (24 hour, 72 hour, 1 week, 2 week, 3 week and 4 week). The most recent ferritin, LDH and D dimer, CRP, complete picture, liver enzymes, serum creatinine and sugar values before CPT or Standard treatment administration was selected as the value of before therapy and the changes of the value after treatment was observed till discharge/death (24 hour, 72 hour, 1 week, 2 week, 3 week and 4 week). The clinical outcome of the patients was evaluated daily till 4 week after

treatment. Both clinical, radiological and laboratory data were collected in standardized preform and confidentiality was maintained. The data were checked by two medical officers and then, supervision, completeness, and consistency of collected data were performed by the principle investigator.

### Sample size calculation

The output of the sample size calculation for an equivalence trial with continuous outcome

Standard deviation ( $\sigma$ ) = 0.80

Mean difference between 2 groups ( $\epsilon$ ) = 0.20

Margin ( $\delta$ ) = 0.50

Ratio between 2 groups ( $k$ ) = 1.10

Alpha ( $\alpha$ ) = 0.05, Z (0.950) = 1.644854

Beta ( $\beta$ ) = 0.20, Z (0.900) = 1.281552

$$n_2 = \frac{(z_{1-\alpha} + z_{1-\beta})^2 \sigma^2 (1 + \frac{1}{k})}{(\delta - |\epsilon|)^2}$$

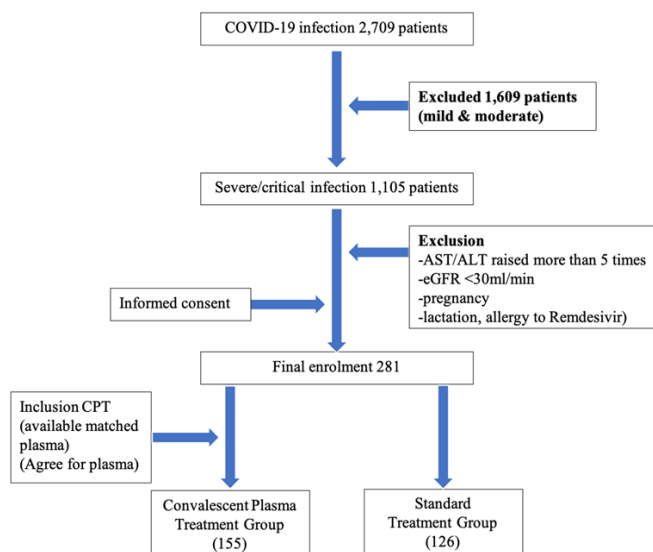
$$\epsilon = \mu_2 - \mu_1$$

$$k = \frac{n_1}{n_2}$$

$$n_1 = kn_2$$

Sample size: n1 = 122, n2 = 122

### Flow Chart



### Statistical analysis

The collected data were entered into Microsoft Excel 2016 and exported to IBM SPSS version 22.0 for Windows for analysis. Descriptive statistics were presented as frequency and percentages for categorical variables and mean (standard deviation, SD), medians and ranges for continuous variables. Categorical variables were expressed as counts and percentages, and compared using the Chi-square as appropriate. Log-rank test was applied to analysis of survival data (viral clearance time among plasma recipients according to patients’ and treatment

variables). Tests were two-sided, and p values < 0.05 were considered statistically significant. Graphs were plotted using Graph Pad Prism version 7.0.

## Results

A total of 281 patients with severe/ critical COVID-19 infection were enrolled. Base line characteristics in CPT group and Standard treatment group was shown in Table (1). The patients in CPT group were older; mean age was  $65.25 \pm 10.33$  years versus

$58.40 \pm 14.85$  years. Moreover, their mean body weight was heavier ( $152.27 \pm 28.12$  lb versus  $143.56 \pm 27.70$  lb); initial SaO<sub>2</sub> on air was lower ( $86.71 \pm 7.90$  % versus  $88.52 \pm 8.70$  %). In addition, the proportion of associated co-morbidities was larger in CPT group (80 % versus 73 %) and immune compromised state (61 % versus 38 %) too. Furthermore, the initial inflammatory markers (CRP and AST) were higher; and, absolute lymphocyte count was lower in CPT group. However, mean CXR severity score by Braxia was not different ( $7.40 \pm 3.72$  versus  $7.42 \pm 4.63$ ) (Table 1-3).

**Table 1:** Baseline Clinical characteristics of two groups CPT group and Standard Treatment group (n=281).

Clinical Characteristics	CPT group (n=155)	Standard Treatment group (n=126)
<b>Age Group</b>		
< 60 years	50 (32.3%)	60 (38.7%)
≥ 60 years	105 (67.7%)	66 (42.6%)
<b>Gender</b>		
Male	104 (67.1%)	66 (52.4%)
Female	51 (32.9%)	60 (47.6%)
<b>Comorbid Status</b>		
No Comorbid	31 (20%)	34 (27.0%)
Presence of Co-Morbid Disease	124 (80%)	92 (73%)
<b>Comorbid Status</b>		
No Comorbid	31 (20%)	34 (27%)
< 3 Comorbid Diseases	95 (61.3%)	62 (49.2%)
≥ 3 Comorbid Diseases	29 (18.7%)	30 (23.8%)
<b>Immune Status</b>		
Normal	94 (60.6%)	88 (69.8%)
Immunocompromised status	61 (39.4%)	38 (30.2%)
<b>Symptom Onset to Treatment</b>		
Early (< 7 days)	87 (56.1%)	87 (69%)
Late (≥ 7 days)	68 (43.9%)	39 (31%)

**Table 2:** Mean values of Clinical characteristics of two groups CPT group and Standard Treatment group (n = 281).

Mean values of Clinical Characteristics	CPT group (n=155)	Standard Treatment group (n=126)	Mean Difference	'p' value
Age (years)	$65.25 \pm 10.33$	$58.4 \pm 14.85$	$6.85 \pm 16.99$	0.16
Weight (Lbs)	$152.27 \pm 28.12$	$143.56 \pm 27.7$	$8.7 \pm 38.5$	0.01
Symptom Onset to Rx(days)	$7.27 \pm 3.52$	$6.73 \pm 2.74$	$0.54 \pm 4.41$	0.17
Initial Sa O <sub>2</sub>	$86.71 \pm 7.99$	$88.52 \pm 8.70$	$1.817 \pm 11.72$	0.84
Initial CXR Score by Braxia Score	$7.4 \pm 3.72$	$7.42 \pm 4.63$	$0.02 \pm 0.56$	0.97

Outcome of two group is demonstrated in (Table 3). Nearly 70% of patients in CPT group and 76% of patients in Standard treatment group survived; however, mean duration of hospital stay was shorter in CPT group ( $12.53 \pm 6.83$  days versus  $17.25 \pm 11.17$ ;  $p < 0.001$ ). Nearly 60% of patients in CPT group required

less supplementation of oxygen at Day 7 whereas only one third of patients in Standard treatment group made improvement in oxygen supplementation ( $p = 0.01$ ). Radiological changes were not different in both groups (Table 4,5).

**Table 3:** Clinical Outcomes of two groups CPT group and Standard Treatment group (n=281).

Outcomes	CPT group (n=155)	Standard Treatment group (n=126)
<b>Survival Outcome</b>		
Alive	106 (68.4%)	96 (76.2%)
Death	49 (31.6%)	30 (23.8%)
<b>Mean Hospital Stay (days)</b>	$12.53 \pm 6.83$	$17.25 \pm 11.17$
<b>O2 Requirement at Day 3 after Rx</b>		
Better	14 (9%)	20 (15.9%)
Same	92 (59.4%)	47 (37.3%)
Worse	48 (31%)	58 (46%)
<b>O2 Requirement at Day 7 after Rx</b>		
Better	93 (60%)	44 (34.9%)
Same	6 (3.9%)	14 (11.1%)
Worse	40 (25.8%)	55 (43.7%)
<b>CXR Improvement at Day 7 after Rx</b>		
Better	68 (43.9%)	55 (43.7%)
Same	37 (23.9%)	47 (37.3%)
Worse	48 (31%)	24 (19%)

**Table 4:** Mean values of Clinical Outcomes of two groups CPT group and Standard Treatment group (n=281).

Mean values of Clinical Outcomes	CPT group (n=155)	Standard Treatment group (n=126)	Mean Difference	'p' value
Hospital Stay (days)	$12.53 \pm 6.83$	$17.25 \pm 11.17$	$4.71 \pm 13.17$	<0.001
Day3 Oxygen Requirement Score	$2.25 \pm 0.66$	$2.29 \pm 0.76$	$0.03 \pm 0.96$	0.7
Day7 Oxygen Requirement Score	$1.49 \pm 1.03$	$1.88 \pm 1.09$	$0.39 \pm 1.68$	0.01
Day 7 CXR score	$6.02 \pm 4.37$	$6.43 \pm 4.21$	$0.41 \pm 1.42$	0.42

**Table 6:** Initial laboratory parameters of two groups CPT group and Standard Treatment group (n=281).

Initial Mean values of Laboratory Parameters	CPT group (n=155)	Standard Treatment group (n=126)	Mean Difference	'p' value
Total WBC	$9.85 \pm 5.35$	$9.39 \pm 4.19$	$0.45 \pm 6.50$	0.65
ALC	$0.76 \pm 0.41$	$1.07 \pm 0.82$	$0.3 \pm 0.89$	0.03
Neutrophil	$9.09 \pm 5.13$	$5.49 \pm 6.12$	$3.50 \pm 7.90$	< 0.001
Platelets	$247.75 \pm 113.57$	$252.11 \pm 107.95$	$4.35 \pm 163.02$	0.77
ESR	$75.26 \pm 31.62$	$64.04 \pm 31.63$	$11.21 \pm 42.69$	0.1
CRP	$122.16 \pm 88.73$	$103.91 \pm 68.71$	$18.25 \pm 82.66$	0.06
Ferritin	$788.73 \pm 467.94$	$795.41 \pm 438.79$	$6.68 \pm 440.12$	0.7
D-dimer	$3216.45 \pm 1817.18$	$2237.67 \pm 2118.28$	$978.78 \pm 814.12$	0.36

**Citation:** Yazicioglu T, Simsek S (2020). The Outcomes of Silicone Tube Intubation in Dacryocystorhinostomy. SunText Rev Med Clin Res 1(2): 114.

LDH	438.11 ± 309.16	471.28 ± 260.66	33.17 ± 224.45	0.44
AST	63.83 ± 61.84	19.41 ± 38.45	44.42 ± 73.09	< 0.001
ALT	53.37 ± 56.47	59.52 ± 78.62	6.15 ± 103.29	0.7
Creatinine	1.05 ± 0.52	1.38 ± 1.98	33 ± 0.03	0.07

**Table 6:** Serial changes of mean inflammatory markers two groups CPT group and Standard Treatment group (n=281).

Serial Changes of Mean Inflammatory Markers	CPT group (n=155)	Standard Treatment group (n=126)	Mean Difference	'p' value
<b>Total WBC</b>				
Day 0	9.85 ± 5.35	9.39 ± 4.19	0.45 ± 6.5	0.65
Day 3	10.64 ± 7.83	7.76 ± 5.97	2.88 ± 9.85	0.001
Day 7	9.14 ± 8.99	9.32 ± 6.32	0.17 ± 10.6	0.85
Day14	14.07 ± 9.96	13.4 ± 5.76	0.66 ± 12.84	0.75
<b>ALC</b>				
Day 0	0.76 ± 0.41	1.01 ± 0.82	0.3 ± 0.89	0.03
Day 3	0.96 ± 0.57	1.06 ± 8.02	1.1 ± 8.01	0.21
Day 7	0.79 ± 0.91	1.07 ± 2.02	2.22 ± 2.99	0.23
Day14	1.14 ± 0.75	1.64 ± 0.84	0.5 ± 1.13	0.9
<b>CRP</b>				
Day 0	122.16 ± 88.73	103.91 ± 68.71	18.24 ± 37.22	0.05
Day 3	98.37 ± 80.31	94.94 ± 58.77	3.43 ± 20.30	0.68
Day 7	80.76 ± 97.73	88.99 ± 47.12	8.23 ± 26.92	0.38
Day14	31.61 ± 56.49	41.88 ± 23.83	10.26 ± 20.86	0.05
<b>Ferritin</b>				
Day 0	788.73 ± 467.94	795.41 ± 438.79	6.68 ± 440.12	0.7
Day 3	751 ± 637.26	719.17 ± 412.32	31.83 ± 97.56	0.62
Day 7	721.62 ± 413.30	693.73 ± 416.94	27.9 ± 125.87	0.5
Day14	658.82 ± 498.31	641.89 ± 203.10	16.93 ± 110.05	0.7
<b>D-dimer</b>				
Day 0	3216.45 ± 1817.18	2237.67 ± 2118.28	978.78 ± 814.12	0.36
Day 3	2377.62 ± 1862.25	2216.01 ± 1918.67	161.61 ± 607.34	0.4
Day 7	1962.52 ± 518.21	1807.68 ± 457.07	154.85 ± 270.96	0.009
Day14	812.61 ± 415.17	903.01 ± 351.16	90.41 ± 181.97	0.05
<b>LDH</b>				
Day 0	438.11 ± 309.16	471.28 ± 260.66	33.17 ± 224.45	0.44
Day 3	418.32 ± 220.08	398.34 ± 268.76	19.98 ± 77.38	0.4
Day 7	353.32 ± 248.36	333.50 ± 123.46	19.82 ± 67.55	0.41
Day14	165.18 ± 182.6	108.23 ± 157.44	56.95 ± 97.51	0.006

**Table 7:** Relationship between clinical characteristics and clinical outcomes of two groups CPT group and Standard Treatment group (n = 281).

Clinical Characteristics	CPT group (n=155)		Standard Treatment group (n=126)	
	Death	Alive	Death	Alive
<b>Age Group</b>				
< 60 years	8 (16%)	42 (84%)	11 (18.3 %)	49 (81.7%)
≥ 60 years	41 (39%)	64 (61%)	19 (28.8%)	47 (71.2%)
'p' value	p = 0.003		p = 0.1	
<b>Gender</b>				
Male	33 (31.7%)	71 (68.3%)	18 (27.3%)	48 (72.7%)
Female	16 (31.4%)	35 (68.6%)	12 (20%)	48 (80%)
'p' value	p = 0.5		p = 0.12	
<b>Comorbid Status</b>				
No Comorbid	6 (19.4 %)	25 (80.6%)	4 (11.8%)	30 (88.2%)
Presence of Co-Morbid Disease	43 (34.7%)	81 (65.3%)	26 (28.3%)	66 (71.7%)
'p' value	p = 0.07		p = 0.4	
<b>Symptom Onset to Rx</b>				
Early (<7 days)	32 (36.8%)	55 (63.2%)	13 (14.9%)	74 (85.1%)
Late (> 7 days)	17 (25%)	51 (75%)	17 (43.6%)	22 (56.4%)
'p' value	p = 0.08		p = 0.001	
<b>Immune Status</b>				
Normal	28 (29.8%)	66 (70.2)	16 (18.2%)	72 (81.8%)
Immunocompromised State	12 (19.67%)	49 (80.32%)	14 (36.8%)	24 (63.2%)
'p' value	p = 0.02		p = 0.3	

Table (5) shows initial laboratory parameters two groups CPT group and Standard treatment group. All the inflammatory markers like ESR, CRP, and ferritin, D-dimer, LDH, ALT and AST were raised. Nevertheless, initial inflammatory markers (CRP, ESR, D dimer and AST) were higher in CPT group; and, absolute lymphocyte count was lower in CPT group. Serial changes of mean inflammatory markers two groups CPT group and standard treatment group is demonstrated in Table (6). There was no significant difference in changes (Table 6,7).

Relationship between clinical characteristics and clinical outcomes revealed three important points. Younger age group (< 60 years) survived more in CPT group (P = 0.003) whereas Standard treatment group did not show effect of age on mortality (p = 0.1). Nearly 80% of those who did not have co-morbidities in CPT group survived (P = 0.07) whereas Standard treatment group did not significantly reveal the influence of co-morbid status (p = 0.4). Eighty percent of immune compromised patients in CPT group survived (p = 0.02) whereas the immune status did not affect survival in Standard treatment group (p = 0.3). In view of timing of therapy, 85% percent of survivors in Standard treatment group received treatment early (p = 0.001); nevertheless, CPT group did not show effect of early treatment on mortality (p =

0.08). None of the recipients had transfusion reaction serious side effects.

### Discussion

Among 281 cases with severe/critical COVID-19 infection, 155 patients received CPT and 126 patients received Standard treatment. Base line clinical characteristics (age, sex, and duration of symptom onset to treatment, initial SaO2 on air, associated co-morbidities and immune status) in CPT group and Standard treatment group were generally comparable; however, those in CPT group were having larger body weight in this study. Nearly 70% of patients in CPT group and 76% of patients in Standard treatment group survived. Therefore, CPT was not superior to Standard treatment; add on plasma therapy to remdesivir did not have benefit on mortality. Thus, this study confirmed previous reports (PLACID trial) (RECOVERY trial) (CONCOR-1 trial) (REMAP-CAP trial). Likewise, in one study which included nearly 1,000 cases revealed that CPT did not reduce the risk of intubation or death at 30 day in hospitalized patients with COVID-19. Moreover, the trial from Brazil also proved that CPT lowered 28 day mortality; but, it was not statistically significant. The factors related with convalescent plasma like the level of

antibody titer and the volume of plasma did alter the outcome of CPT in some findings. In this study, total antibody titer was used and defined as adequate if the total antibody level was  $\geq 1:32$  COI; it was the already set as selection criteria for convalescent plasma therapy. In view of volume of plasma, all the patients received one unit of plasma in this study; and C3PO study, DAWn plasma trial and RECOVERY trial proved that the outcome would not be changed by giving high volume of plasma. Likewise, in C3PO study, a single-blind randomized trial that evaluated high-titer convalescent plasma for the treatment of no hospitalized patients, showed no benefit. It was also confirmed by DAWn plasma trial and RECOVERY trial; transfusion of a high volume of 4 units of convalescent plasma with high neutralising antibody-titres early in hospitalised COVID-19 patients did not result in a significant improvement of the clinical status, nor did the intervention reduce mortality. In CPT group, the mean age was older than Standard treatment group ( $65.25 \pm 10.33$  years versus  $58.40 \pm 14.85$  years). The older age group was reported as one of the poor prognostic factors in several studies; in CPT group older age group ( $> 60$  years) were non-survivors ( $P = 0.003$ ) whereas Standard treatment group did not have the effect of age on mortality ( $p = 0.1$ ). The finding was similar in one report where all age-groups did not show statistically significant clinical benefit; significant immediate mitigation of hypoxia, reduction in hospital stay as well as survival benefit was recorded in severe COVID-19 patients with ARDS aged less than 67 years receiving CPT [29]. Nevertheless, suggested to give CPT to older adult patient. Therefore, age of the recipients was also controversial point in outcome of CPT; old age was mentioned in several reports as poor prognostic factor. In this study in CPT group, the mean weight of the patients was heavier than that of Standard treatment group ( $152.27 \pm 28.12$  lb versus  $143.56 \pm 27.7$  lb;  $p = 0.001$ ); this may be one reason favouring poor outcome of CPT group. As of timing of therapy, the study from Argentina confirmed that CPT was good if it was given early ( $< 72$  hours) particularly in older adults. Generally, the survival rate was better if the treatment was given early; it was more significant in Standard treatment group. In COVID era, the big burden was not only on the government concerned but also on the health care professionals. Therefore, the longer the hospital stay, the slower the turn rate of hospital beds; more costly. In this study, the duration of hospital stay was significantly shorter in CPT group ( $12.53 \pm 6$  days versus  $17.25 \pm 11.17$  days;  $p < 0.001$ ); reducing the workload for health care professional. Thus, CPT provided one of the solutions for preservation of health care workers particularly in the peak of COVID-19 epidemic. Nearly 60% of patients in CPT group required less supplementation of oxygen at Day 7 whereas only one third of patients in Standard treatment group made improvement in oxygen supplementation; saving oxygen too. It confirmed the report by Sullivan; early

administration of high titer CPT reduced outpatient hospitalizations by more than 50%; thus, CPT was economical. In resource poor settings, all the cost- oxygen, remdesivir and CPT were not cheap; moreover, the drugs were in out-of-stock especially at peak of epidemics. We ourselves could collect and arrange CPT; however, we could not produce remdesivir in our country. In the time of shortage of drug, remdesivir, CPT may be our own product. In treating severe COVID-19 infection, immune status plays an essential role. In this study, immune compromised state was noted in 61% of patients in CPT group and 38% in Standard treatment group. Relation between the immune status and survival in two groups was different. In CPT group, immune compromised patients survived significantly than those with normal immune status ( $p = 0.02$ ); the effect of Standard therapy on immune status and survival was not pronounced ( $p = 0.3$ ). Therefore, CPT influenced the outcome in immune compromised patients with severe or critical COVID-19 infection. It provided the previous evidence that CPT saved immune compromised, patients with haematological cancer with severe COVID-19 infection. Likewise, also observed 28 cases of severely immunosuppressed with COVID-19 infection; CPT was found to be helpful. There were several limitations in this study. First, donors for CPT were not easily available especially in third wave of epidemics; thus, most of the recipients for CPT were recovery patients from second wave. It was one reason for having relatively small number of cases. Therefore, it was not possible to perform a large randomized control trial. The cost of Remdesivir was not cheap for developing country; moreover, shortage of drug in peak of third wave. The outcome of both groups would have changed if the patients received them early. If they got the therapy early, they would survived more. In addition, this study would be stronger if it was a randomized control trial with larger number of cases. Furthermore, the sample size was not large though the study covered 1000-bedded and 300-bedded COVID treatment centres. Finally, observation with a sufficient number of COVID-19 patients in a randomized control trial is still needed to document the effectiveness of CPT both view; out-patient treatment for prevention of progression of disease and in-patient treatment for severe/critical cases particularly immune compromised patients.

## Conclusions

Although the severity criteria in entry point was the same, severe or critical by WHO, patients in CPT group were having some factors favouring poor prognosis than Standard treatment group in both clinical and laboratory aspects: old age, heavier body weight and co-morbidities, higher CRP and AST, and lower absolute lymphocyte count. Convalescent plasma therapy plus Remdesivir (CPT group) was not better than Standard treatment group (Remdesivir) in treating patients with severe or critical COVID-

19 infection. Among the survivors, the duration of hospital stay was shorter in CPT group; moreover, the improvement in oxygen requirement by Day 7 was better in them too. Older age and larger body weight in CPT group may alter treatment outcome. The immune status did not determine the survival in Standard treatment group; however, eighty percent of immune compromised patients were significantly saved by CPT. The outcome of immune compromised patients with severe or critical COVID-19 infection would be better with CPT.

## Recommendation

Randomized control trial with large number of cases particularly with immune compromised state are required for better information. CPT may save lives in severe/critical cases if they do not respond to anti-viral drugs and IL 6 antagonist. If the donors for CPT are easily available, CPT should be given early to immune compromised patients with moderate to severe COVID-19 infection.

## Acknowledgements

The authors would like to thank all the candidates for giving informed consent to this study. The authors also acknowledged Prof Ko Ko Lwin, Prof Kyaw Zay Ya, Prof Myint Zaw, Prof Aung Myat Kyaw and Dr Zaw Myo Han for administrative support, Professor Yu Aye Latt and team for intensive care, Professor Ohmar Hlaing for radiological support, and Professor Tin Moe Mya, Professor Tin Tin San, Professor Khine Khine Su and Dr Kyaw Wunna for laboratory support.

## Declaration of Conflict of Interest

The authors declared no potential conflicts of interests with respect to authorship and publication of this article.

## Ethical Approval

This study was approved by Hospital Research and Ethic Committee from Defence Services General Hospital (1000-Bedded) Mingaladon, Myanmar. Informed consent was also taken from each patient.

## Funding

The authors received no financial support for publication of this article.

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**Citation:** Phyu Pyar K, Phyo Kyaw A, Lin Maung N, Htet Aung ZN, Min Aung S, Aung Aung, et al. (2022). Efficacy of Convalescent Plasma Therapy (CPT) plus Remdesivir versus Standard Therapy (Remdesivir) In Patients with Severe or Critical COVID-19 Infection in Second and Third Wave of Epidemics in Myanmar: Non-Randomized Interventional Study. *SunText Rev Virol* 3(1): 128.

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