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## Convalescent plasma therapy for severe Covid-19 in patients with hematological malignancies

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### ABSTRACT

**Background:** Data on convalescent plasma therapy (CPT) in patients of hematological malignancies with severe Covid-19 is scarce.

**Objective:** To study 14-day mortality in patients who received CPT.

**Patients & methods:** Retrospective multicentre observational study conducted in 4 centres treating haematological malignancies across Delhi-national capital region. Total 33 haematological malignancies patients with severe Covid-19 who received CPT were analysed.

**Results:** The median age of the study cohort was 62 years (18–80 years). Twenty one percent patients had 1 comorbidity, 18 % had 2 comorbidities and 6% patients had 3 and 5 comorbidities each. Twenty four patients were on active therapy. Sixty nine percent of patients required ICU stay. Twenty five patients received plasma therapy within 7 days (early) of diagnosis of Covid-19 infection. Median day of plasma infusion from date of diagnosis of Covid-19 infection was 4 days (range: 2–25 days). Patient who had early initiation of plasma therapy had shorter duration of hospitalisation (12.7 vs 24.3 days,  $p = 0.000$ ). Overall mortality in the cohort was 45.5%. There was no effect of disease status, active therapy, presence of comorbidity on mortality. There was no difference in the mortality in patients receiving early vs late initiation of plasma therapy or in patients receiving one versus two plasma therapy.

**Conclusions:** We provide a large series of patients with hematological malignancies and role of CPT in this group.

### 1. Introduction

The coronavirus (Covid-19) pandemic, with its origin in Wuhan, China, has ravaged the global population with 1.57 million deaths globally so far [1]. Various drugs starting from hydroxychloroquine (HCQs) and ivermectin to antiretrovirals like remdesivir and favipiravir have been tried with variable results and WHO has repeatedly pointed out on the lack of effectiveness of these repurposed drugs [2].

In the absence of an effective antiviral drug, and taking a clue from the effectiveness of convalescent plasma therapy (CPT) in treating other viral diseases like influenza [3], H1N1 [4], Ebola [5] convalescent plasma was tried in moderate to severe Covid-19 infections. The proposed mechanism of convalescent plasma is primarily through transfer

of virus-neutralizing antibodies against Covid -19 [6]. The adverse effects of plasma transfusion has been well studied and reported in the literature and are mostly non-lethal and rare but need close monitoring [7]. The ministry of health and family welfare (MoHFW), India approved convalescent plasma in June 2020 for off-label use in moderate and severe Covid-19 infections [8].

Patients with haematological malignancy pose specific issues like impairment of humoral immunity, defects in myeloid and lymphoid maturation, and increased susceptibility to cytokine storm, predisposing them to more severe disease and possibly increased morbidity and mortality [9]. These patients are also at increased risk of transmission due to frequent visits to the health care centres and their immunocompromised status [10]. Data on usefulness of convalescent plasma therapy

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in patients with hematological malignancies is scarce. Herein, we describe the outcomes of 33 haematological malignancies patients who received convalescent plasma.

## 2. Patients and methods

**Patients:** This was a retrospective multicentre observational study conducted in 4 centres treating haematological malignancies across Delhi-national capital region. Patients with malignant hematological disorders either newly diagnosed, or on ongoing therapy or follow-up at any of the participating centres were included. Patients diagnosed with Covid -19 infection from 27 June 2020 to 28 Nov 2020 were enrolled in the study. Criteria for classifying patients into severe category were as per the clinical management protocols of government of India [8].

**Severe disease:** patient having one or more of the following conditions:

- Clinical signs of pneumonia plus one of the following: respiratory rate > 30/min or severe respiratory distress requiring ventilation or SPO<sub>2</sub> < 90% on room air.
- ARDS (new onset bilateral opacities & SpO<sub>2</sub> / FiO<sub>2</sub> ≤ 315)
- Sepsis
- Septic shock

### 2.1. Laboratory analysis

A diagnosis of SARS-CoV-2 infection was based on quantitative real-time reverse transcriptase-polymerase chain reaction (qRT-PCR) of nasal and/or oropharyngeal swabs. Baseline demographic data including comorbidities, severity of illness, remission status, ongoing therapy were extracted from electronic/manual health records and entered in common Microsoft Excel spreadsheet format. MoHFW allowed CPT as off-label if with donor plasma IgG titer (against S-protein RBD) were above 1:640 [8]. The first 200 mL (one unit) plasma was infused over one to one and half hours and if the patient did not show any improvement after 24 h, based on the decision of responsible physician, another unit of plasma was administered.

### 2.2. Treatment details

Patients received various treatment regimens as per physician discretion or institutional protocol in accordance with the national guidelines for the management of Covid-19, issued by the government from time to time [11]. A variety of medicines were used in these patients and included HCQ, remdesivir, favipiravir, other broad spectrum antibiotics, steroids (methylprednisolone or dexamethasone), tocilizumab and oxygen support/ventilation [12].

### 2.3. Inclusion criteria

Patients with hematological malignancies with Covid-19 infection confirmed with RT-PCR were included. Patients were required to have at least 14 days follow-up from first positive test.

### 2.4. Exclusion criteria

Patients with benign hematological disorders were excluded. Any patient lacking sufficient clinical information or less than 14 days follow-up was excluded. Patients diagnosed Covid -19 based on only radiological criteria or with indeterminate Covid -19 status were excluded. Pregnant and lactating mothers were also excluded.

## 3. Objectives

Primary objective of the study was to study 14-day mortality in

patients who received convalescent plasma therapy.

This retrospective study was approved by institutional review board and conducted as per Helsinki declaration.

## 4. Statistical analysis

Data was described in percentages for categorical variables and as the mean ± standard deviation and median in case of continuous variables. For categorical data, comparisons were made by using the Chi square/Fisher exact test, for quantitative data by *t* test/F-test and for non-normally distributed quantitative variables by the Mann-Whitney/Kruskal Wallis test. Data was analysed with SPSS v 23 software. *P* value ≤ 0.05 was considered significant in all statistical evaluations.

## 5. Results

A total of 33 patients from 4 centres were included in the study. The median age of the study cohort was 62 years (18–80 years). Sixty percent of patients were above the age of 60 years. Majority of patients were males (69.7%). Nearly half the cohort (48.5%) did not have any comorbidities. Hypertension and diabetes were most common comorbidities (Table 1). Eight patients (24.2%) were newly diagnosed

**Table 1**  
Demographic profile of study cohort.

Patient characteristics	N (%), N = 33
Median age (Range)	62 years (17–80 years)
Elderly (≥ 60 years)	20 (60.6%)
Child (17 years)	1(3%)
Gender	
Male	23 (69.7%)
Female	10 (30.3%)
Comorbidities	
Median number of comorbidities (range)	1 (0–5)
Hypertension	14 (42.4%)
Diabetes Mellitus	9 (27.3%)
Ischemic heart disease	2 (6.1%)
Hypothyroidism	3 (9.1%)
Chronic Liver disease	1 (3.0%)
Pulmonary tuberculosis	1 (3.0%)
Others	4 (12.1%)
Number of comorbidities	
0	16 (48.5%)
1	7 (21.2%)
2	6 (18.25%)
3	2 (6.1%)
5	2 (6.1%)
Diagnosis	
Acute leukemia	4 (12.1%)
Acute myeloid leukemia	3 (9.1%)
Acute lymphoblastic leukemia	1 (3%)
Myelodysplastic syndrome-Excess Blasts	2 (6%)
Chronic myeloid leukemia	2 (6%)
Non-hodgkin lymphoma	18 (54.5%)
Chronic lymphocytic leukemia	7 (21.2%)
Diffuse large B-cell lymphoma	8 (24.2%)
Mantle cell lymphoma	1(3%)
Hairy cell leukemia	1(3%)
Angioimmunoblastic T-cell lymphoma	1(3%)
Multiple myeloma	7 (21.2%)
Status of disease	
Newly diagnosed	8 (24.2%)
Yet to be assessed (on treatment before assessment)	1 (3%)
Remission (Complete, very good or partial)	9(27.3%)
Stable disease (Observation)	5 (15.15%)
Relapse/Refractory	10 (30.3%)
Active treatment	24 (72.7%)
Not started therapy/ follow up/observation	9 (27.3%)
Chemotherapy (C)	5 (15.2%)
Immunotherapy (I)	2 (6.1%)
Oral targeted (O)	4 (12.1%)
C + I	6 (18.2%)
C + O / C + I+O	7 (21.2%)

and not on any therapy, 9 patients were in remission [Complete, very good or partial) CR/PR/VGPR], 10 patients had relapsed/refractory disease. Five patients had stable disease (SD) or were on observation. One patient was on observation post autologous stem cell transplant for multiple myeloma. Twenty four patients were on active therapy at the time of Covid-19 infection.

All patients who received convalescent plasma therapy had severe disease. All 33 patients had fever. Cough was present in 60.6% and breathlessness was present in 66.7%. Median duration of hospital stay was 14 days. Sixty nine percent of patients required ICU stay. Eighty one percent of patients required oxygen by mask, 48.5% required non-invasive ventilation (NIV) and 42.4% required invasive mechanical ventilation. Forty five percent of patients required vasopressor support of which 5 patients required double vasopressor support (Table 2).

Twenty five patients received plasma therapy within 7 days (early) of diagnosis of Covid -19 infection. Median day of plasma infusion from date of diagnosis of Covid -19 infection was 4 days (range: 2–25 days). Eighteen patients received 1 plasma infusion and 15 patients received 2 plasma infusion. Patient who had early initiation of plasma therapy had shorter duration of hospitalisation as compared to patients who had late initiation (12.7 ± 6.5 days vs 24.3 ± 9.5 days, p = 0.000). Patients receiving plasma within 3 days had shorter ICU stay (p = 0.026). Overall mortality in the cohort was 45.5% (14-day mortality 24.2% and 28-day mortality 33.3%). Overall mortality was higher in patients older than 60 years (13 vs 2, p = 0.005). There was no effect of disease status, active therapy, presence of comorbidity on mortality. There was no difference in the mortality in patients receiving early vs late initiation of plasma therapy or in patients receiving one versus two plasma therapy (Table 3).

No severe adverse effect was reported.

## 6. Discussion

We report a real-life experience of severe Covid-19 patients with hematological malignancies treated with convalescent plasma therapy. Studies evaluating the efficacy of CPT in haematological malignancies are scarce.

Wright et al. reported a case of follicular lymphoma on maintenance rituximab with prolonged course of Covid-19 who responded in 3–5 days after CPT [13]. A 63-year-old female with non-hodgkin lymphoma

**Table 2**  
Clinical profile of COVID-19 infection and convalescent plasma therapy.

Characteristics	N = 33
Fever	33 (100%)
Cough	20 (60.6%)
Breathlessness	22 (66.7%)
Severe Covid-19 infection	33 (100%)
Median duration of hospital stay (range)	14 days (2–39)
Need for ICU stay	23 (69.7%)
Oxygen support	
Oxygen by mask	27 (81.8%)
Non-invasive ventilation	16 (48.5%)
Invasive ventilation	14 (42.4%)
Need for vasopressor support	15 (45.5%)
Single inotrope support	10 (30.3%)
Double inotrope support	5 (15.2%)
Median day of plasma infusion from date of diagnosis (range)	4 (1 to 25)
Plasma infusion < 7 days	25 (75.8%)
Plasma infusion ≥ 7 days	8 (24.2%)
Plasma infusion ≤ 3 days	16 (48.5%)
Plasma infusion > 3 days	17 (51.5%)
Median number of times plasma was infused (range)	1 (1 to 2)
1 plasma infusion	18 (54.5%)
2 plasma infusion	15 (45.5%)
Mortality	
14-day mortality	8 (24.2%)
28-day mortality	11 (33.3%)
42-day mortality (overall mortality)	15 (45.5%)

**Table 3**  
Outcome analysis of study cohort.

Overall mortality	N = 15	P value
Remission (Complete/partial)	3	0.392
Not in remission (stable disease/relapse-refractory/not assessed)	12	
Age <60 Years	2	0.005
Age ≥60 Years	13	
Active treatment	11	0.943
Not on active treatment	4	
Comorbidities present	10	0.112
Comorbidities absent	5	
Early plasma initiation < 7 days	9	0.101
Late plasma initiation ≥ 7 days	6	
Plasma infusion ≤ 3 days	6	0.373
Plasma infusion > 3 days	9	
One plasma infusion	7	0.407
Two plasma infusion	8	
<b>Relationship of duration of hospital stay and timing of plasma therapy infusion</b>		
Early plasma initiation < 7 days	12.7 ± 6.5 days	0.000
Late plasma initiation ≥ 7 days	24.3 ± 9.5 days	

in remission and on maintenance therapy with Obinutuzumab had a persistent positive PCR for Covid-19 over 12 weeks with negative antibody response. Her symptoms resolved rapidly after the administration of convalescent plasma [14]. Another 55-year-old female with B cell acute lymphoblastic leukemia(ALL) has been reported who developed reactivation of Covid-19 after receiving rituximab, cytarabine, and dasatinib. A dramatic response within 48 h of CPT was observed [15]. Shankar et.al. reported a 4 year female with case of Covid-19 pneumonia and ALL who was treated with CPT, IVIG and steroids [16]. These few case reports mostly highlight good outcome with CPT. It is possible that CPT has been used in lot many situations but only positive reports are published. In a study of 24 cancer patients (including 14 hematological malignancies) receiving CPT by Tremblay et al., a mortality rate of 41.7% was observed, similar to our results [17]. A significant decrease in C-reactive protein and rise in lymphocyte count were observed.

Altuntas et al. have documented benefit of CPT in large series of 1776 community (non-cancer) patients where CPT was shown to reduce duration in the ICU, the rate of mechanical ventilation support and vasopressor support. There was no difference in mortality [18]. A large randomised phase II trial of CPT in moderate Covid-19 documented 15% mortality in moderate subgroup with no benefit of CPT in general population [12]. We have earlier shown benefit of CPT in patients with severe Covid-19 in general population with reduction in mortality [19]. Yigenoglu et al. have reported a large database of 740 patients with hematological malignancy. This study revealed an increased risk of need for ICU admission, mechanical ventilation and death compared with Covid-19 patients without cancer [20]. We have earlier documented a high 60% mortality rate in patients with hematological malignancies with severe Covid-19 [21]. Mortality in present study with use of CPT is 45.5%. This difference may be due to benefit of CPT or could be due to present study being limited to 4 larger centres with better infrastructure to manage Covid-19 complications compared to previous study which was spread-out in 11 centres across India [21]. Lack of control arm in present study makes it difficult to evaluate efficacy of CPT in this group. However, it was difficult to deny benefit of convalescent plasma to this high-risk subgroup of patients for a disease where treatment is still evolving.

Thirteen of the 15 patients who died were on invasive mechanical ventilation and only 2 were not (p = 0.000). This is similar to the results observed by another study [22]. This suggests that patients with advanced respiratory involvement may not benefit much out of plasma therapy.

Timing of initiation of plasma therapy is critical for its efficacy. In a

multicentre study of 35,322 patients, mortality was lower in patients receiving plasma therapy within 3 days of diagnosis [23]. Most of the patients in our study received plasma therapy within 7 days of diagnosis (75%). We did not find any difference in mortality in patients receiving early versus late plasma therapy. Similarly, there was no difference in mortality if patients received plasma within 3 days or later in our study. The median duration of hospital stay in our study was 11 days similar to Tremblay et al. [17]. We did notice a shorter duration of hospital stay on patients receiving early plasma (<7 days) therapy. Patients receiving plasma within 3 days had shorter ICU stay in our study. This has not been reported in literature.

Covid-19 related mortality in elderly patients and/or patients with co-morbidities can be 15% higher than in general younger population [19,21,24]. The median age of patients included in our study was 62 years and > 60% of patients were above the age of 60 years. More than half these patients had concomitant comorbidities. Of the 15 patients who died only 2 were less than 60 years ( $p = 0.005$ ). This could be one of the reasons for high mortality in our study. Adverse effect of age and comorbidity in patients with haematological malignancy was previously demonstrated by our group [21].

In this cohort of patients, disease status, active therapy and presence of comorbidity did not impact mortality. Also, no difference in the mortality was noted in patients who received early vs late initiation of CPT or in patients receiving one versus two CPT. This may be due to relatively smaller sample size in our study (despite being largest till date) and study may not be adequately powered to address these issues.

## 7. Limitations

This is a retrospective study. Therefore, complete data was not available for all patients. There was no control arm due to rarity of disease. Covid -19 being a new disease, national treatment guidelines were dynamic over relatively wider study duration. We also do not have information if some of the patients had already developed adequate antibodies when CPT was administered. These limitations notwithstanding, we report largest series till date on utility of CPT in this high risk population and add to literature of growing knowledge in this subject.

### 7.1. Conclusions

We provide a large series of patients with hematological malignancies and role of CPT. Elderly patients with hematological malignancy and severe Covid-19 have worst outcomes.

### Author contributions

RN conceptualised the project. PJ, PB, NA, SB, NR, DB were involved in data curation. PJ analysed the data. All authors were involved in clinical care of these patients. RB, RA, DB validated the data. DB, PJ, RN, NA were involved in writing the manuscript. All authors reviewed the manuscript, critically analysed and agreed to content.

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### Declaration of Competing Interest

The authors report no declarations of interest.

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