Convalescent Plasma Therapy in Filipino Patients with Confirmed COVID-19 Infection in a Tertiary Hospital in Cebu City: A Retrospective Cohort Single Center Study

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Abstract

Introduction: Convalescent plasma therapy (CPT) is a type of experimental passive immunotherapy with a sizable background in viral outbreaks. Although there has been documented favorable outcomes in using CPT in the treatment of viral illnesses, its use in COVID-19 is still experimental.

Objectives: To determine if adding convalescent plasma to standard of care is associated with better clinical outcomes than giving standard of care alone to severe and critical COVID-19 patients admitted in a tertiary hospital in Cebu City.

Methods: This is a retrospective cohort study conducted in a tertiary hospital in Cebu between March to September 2020. The data of a total of 22 COVID-19 patients who received convalescent plasma therapy plus standard treatment regimen based on the institution's interim guideline were identified by chart review. The demographic information, laboratory results, management and outcome data from this group were collated, matched with and compared to 43 critically ill COVID-19 patients who received COVID-19 standard treatment regimen only.

Results: Both the CPT and non-CPT groups are comparable in terms of the socio-clinical variables, inflammatory marker levels, laboratory test results and therapeutic interventions. However, there is no relationship between the level of inflammatory markers and the illness day to which CPT was given. Additionally, the outcomes also differ significantly in terms of duration of admission, severity of illness, critical care support and mortalities. The control group has shorter hospital admissions, more patients with critical illness and more mortalities. The intervention arm, however, has more recoveries but longer duration of critical care.

Conclusion: Convalescent Plasma Therapy added to standard treatment is not associated with improved clinical outcomes among Filipino patients with severe or life-threatening COVID-19 infection admitted in a tertiary hospital in Cebu City.

Keywords: COVID-19, convalescent plasma, outcomes, retrospective study

Introduction

Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), the causative agent of Coronavirus Disease 2019 (COVID-19), propelled an unprecedented international health crisis. As of May 10, 2021, there are already 158 million confirmed cases worldwide including 3.29 million mortalities[1], making it one of the biggest killers of 2020 as its global death toll.

In the Philippines, the number of COVID-19 cases has already breached the one million mark with more than 18,000 deaths as of May 10, 2021 based on official local data provided by the Department of Health[3]. Although, majority of the cases exhibit mild, self-limited respiratory illness, approximately 18% will have severe to critical disease affecting mostly the higher risk population[5].

This recent emergence of COVID-19 pandemic has spurred the discussion related to the usefulness of passive immunization therapy particularly the historic Convalescent Plasma Therapy (CPT). Convalescent Plasma Therapy is a classic adaptive immunotherapy used in the prevention and treatment of infectious disease. It involves administration of immunoglobulin-

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containing plasma from a recently recovered individual who was infected with a specific disease for the purpose of prophylaxis and treatment. The transfusion of convalescent blood products is able to neutralize the pathogen and eventually leads to its eradication from the peripheral circulation.[7] Although, several case studies showed consistent evidence for reduction in mortality especially with early administration of convalescent plasma, use of CPT is still experimental as studies were commonly uncontrolled, of low quality, and at moderate or high risk of bias.

To date, there are multiple ongoing clinical trials being conducted internationally with the aim of evaluating the clinical effectiveness of Convalescent Plasma Therapy in COVID-19 patients. In the Philippines, there is very scarce literature available regarding the use of CPT on admitted Filipino COVID-19 patients. More hospitals are launching their own convalescent plasma therapy programs under the guidance of the Department of Health which issued a guideline on the Collection of Convalescent Plasma (CP) and Networking for Therapeutic Strategy for COVID19.[11]

In Cebu, after an alarming rise in the number of critical cases of COVID-19 infections particularly between May to September 2020, medical practitioners have adapted the use of convalescent plasma transfusion as an adjunct to standard therapy. Although its effectiveness as a therapy is still being evaluated and not yet part of the standard of care, our institution approved the use of Convalescent Plasma Therapy as an adjunct to COVID-19 management to help and improve the clinical outcomes of our critical COVID 19 patients.

Significance of the Study

Despite the outbreak of COVID-19 causing public health emergency, its therapies are rather limited and unproven. Clinicians and investigators have been relying heavily on experimental, supportive, and in several occasions, off-label drugs to combat this disease. The use of Convalescent Plasma Therapy (CPT) is a welcome addition to the several experimental therapies that are undergoing extensive clinical trials worldwide. The aim of the study is to add to the scant literature on CPT and assess retrospectively the association of Convalescent Plasma Therapy added to standard care to clinical outcomes hospitalized COVID-19 Filipino patients in our institution.

Objectives

General Objective:

To determine if adding convalescent plasma to standard of care associated with better clinical outcomes than giving standard of care alone to severe and critical COVID-19 patients admitted in Perpetual Succour Hospital.

Specific Objectives:

1. To determine the sociodemographic characteristics and clinical profile of COVID19 confirmed patients who received CPT and standard of care compared to the standard of care alone in terms of the following:
2. To determine the therapeutic intervention of COVID19 confirmed patients who received CPT and standard of care compared to the standard of care alone in terms of the following:
3. To determine the relationship between illness day on which convalescent plasma transfusion was given and levels of inflammatory markers before and after treatment.
4. To determine the outcomes of COVID19 confirmed patients who received CPT plus standard of care compared to standard of care alone in terms of the following:

Methodology

Definition of Terms

1. Convalescent Plasma Therapy - is a form of passive antibody therapy that involves the administration of the liquid part of blood that is collected from patients who have recovered from the novel coronavirus disease, COVID-19, caused by the virus SARS-CoV-2, to susceptible individuals or infected patients
2. Inflammatory markers - are a disparate set of biomarkers used clinically to asses a patient for the presence or absence of an active inflammatory disease
3. Standard of care - is the minimum level of care that was provided to the control group including giving of oxygen supplementation and administration of available antibacterial, antiviral, anti-thrombotic and anti-inflammatory therapies as deemed appropriate.

Study Design and Setting. The researchers used a single center retrospective cohort study of adult Filipino patients diagnosed with severe to critical COVID-19 infection admitted between March 2020 to September 2020 at Perpetual Succour Hospital.

Study Population. A total of 68 patients were included in the study and were divided into two groups. For the intervention arm, all 22 adult patients with confirmed COVID-19 infection regardless of severity who received convalescent plasma therapy in addition to standard of care therapy were included. For the control arm, 46 severe to critically ill COVID-19 confirmed patients who only received standard COVID-19 therapy were enrolled.

The inclusion and exclusion criteria of this study are as follows:

Inclusion Criteria. The study included patients who are 18 years old and above with confirmed COVID-19 laboratory results based on a positive reverse transcriptase polymerase chain reaction (RT-PCR) result for SARS-CoV-2 and admitted at Perpetual Succour Hospital from March 2020 to September 2020

Exclusion Criteria. The study excluded patients with incomplete charts.

Data Collection. After receiving Institutional Ethics Review Board (IERB) approval to conduct the study, the

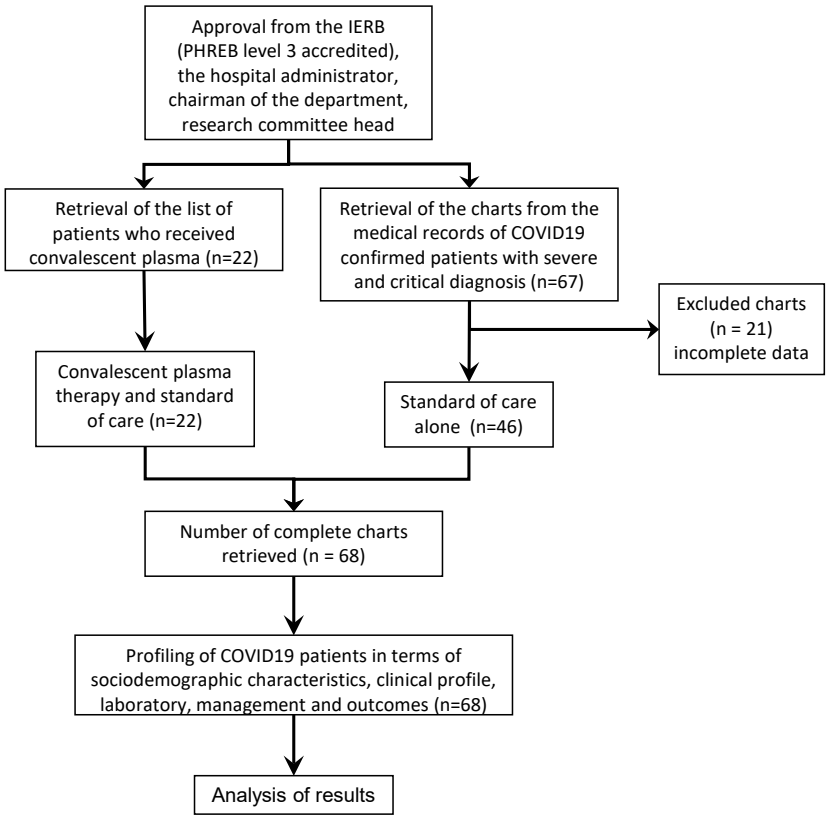

Figure 1. Flow Diagram of Data Collection

Table Ia. Patients' Baseline Characteristics-Socio-clinical Categorical Variables

Patients' Baseline Characteristics	CPT and standard of care n=22		Standard of care alone n=46		P-value*
Sex	f	(%)	f	(%)	0.615
Female	9	(40.91)	22	(47.83)	
Male	13	(59.09)	24	(52.17)	
Residence					0.758
Cebu City	18	(81.82)	35	(76.09)	
Outside Cebu City	4	(18.18)	11	(23.91)	
Smokers	2	(9.09)	5	(10.87)	1.000
With comorbidities	21	(95.45)	39	(84.78)	0.260
Serology					
IgM reactive	8	(36.36)	16	(34.78)	0.152
IgG reactive	8	(36.36)	14	(30.43)	0.162
Chest X-ray results					
With infiltrates	21	(95.45)	29	(63.04)	0.007
With consolidation	15	(68.18)	30	(65.22)	1.000
With effusion	4	(18.18)	7	(15.22)	0.738
Chest CT Scan results					
With ground glass opacities	22	(100)	24	(52.17)	<0.001
With consolidation	18	(81.82)	34	(73.91)	0.554
With effusion	5	(22.73)	8	(17.39)	0.743

* Value computed using Fisher's Exact Test (2x2 variables); significant at $p<0.05$

electronic records of all COVID-19 patients admitted in this institution were reviewed. The researchers identified which patients have received convalescent plasma therapy and those who have not. The electronic records of twenty-two (22) patients who received Convalescent Plasma was then retrieved and reviewed to be included as a part of the intervention arm. For the control arm, confirmed COVID-19 patients with severe to critical infection who received standard of care but were not able to receive convalescent plasma therapy were included. Out of the sixty-seven (67) charts that were initially retrieved after fulfilling the aforementioned criteria, twenty-one (21) charts were excluded due to incomplete data rounding up a total of forty-six (46) patients for the control group. Profiling was done with respect to the sociodemographic characteristics, clinical profile, laboratory, management and outcomes (Figure 1).

Statistical Analysis. For categorical data, frequency and simple percentage were recorded. For the continuous variables, the mean, Median, interquartile range and standard deviation were computed. Differences within categories of selected demographic and clinical variables was assessed by Chi square test or Fisher's Exact Test (2x2 variables). For continuous data of patient characteristics, comparison was done with Mann-Whitney U Test where values for each group shown as median. Comparison for significant differences of vital signs and laboratory parameters before and after convalescent plasma therapy was tested using Wilcoxon Signed-Rank test. All test used 0.05 level of significance with $p<.05$ indicating a significant factor. All analysis will be performed using IBM-SPSS v.21.

Statement of Confidentiality. All patients were labeled according to numbers instead of their names and data will be collated with utmost confidentiality.

Results

The study aimed to determine if convalescent plasma with standard of care is associated with better clinical outcomes of severe to critical COVID-19 Filipino patients who were admitted in Perpetual Succour Hospital from March 2020 to September 2020. The results from the analysis of 68 medical records from COVID19 confirmed patients who received convalescent plasma transfusion and standard of care compared to standard of care alone are shown in Table Ia and !b.

Patients in the intervention arm and the control arm are comparable in terms of most of the socio-clinical

Table Ib. Patients' baseline characteristics - Socio-clinical numerical variables

Patients' Baseline Characteristics	CPT and standard of care n=22			Standard of care alone n=46			P-value [b]
	Median	IQR (Q1-Q3)		Median	IQR (Q1-Q3)		
Age	70.50	54.50	83.25	67.00	59.75	76.00	0.495
Illness day on admission	5.00	3.75	7.00	6.00	3.00	7.25	0.806
APACHE II Score	11.50	8.50	14.25	14.00	9.00	18.25	0.214
Vital signs upon admission							
Temperature in °C	36.90	36.58	38.05	37.00	36.40	37.80	0.577
Systolic BP in mmHg	130.00	120.00	140.00	130.00	110.00	140.00	0.827
Diastolic BP in mmHg	80.00	70.00	80.00	70.00	70.00	80.00	0.627
Mean arterial pressure	93.30	89.17	98.35	93.30	83.30	103.30	0.644
Heart rate (BPM)	98.00	82.75	112.50	95.50	82.00	112.00	0.768
Respiratory rate (CPM)	26.50	21.00	33.25	28.00	23.75	34.25	0.572
O2 Sat (%)	86.50	67.00	95.00	88.50	75.25	94.00	0.773
FiO2	21.00	21.00	21.00	21.00	21.00	21.00	0.631

* Comparison done with Mann-Whitney U Test; values for each group shown as median; significant at *p<0.05*

variables given above. Since the p-values for most of the variables specified above are greater than the significance level (*p<0.05*), the differences between the proportions are not statistically significant.

However, it must be noted that the p-values for infiltrates noted on chest radiographs (p-value=0.007) and chest CT Scan ground glass opacities (p-value <0.001) are noted to be statistically significant. This means that the proportions of those with noted infiltrates and ground glass opacities differ significantly between the two groups. There are significantly more patients in the intervention group who have infiltrates according to their X-ray results. The same thing can be said for the presence of ground glass opacities in CT Scan results. The proportions differ significantly, as a matter of fact, all the patients under the intervention group have ground glass opacities compared to only about 50% of those in the control group.

Patients in both groups are comparable in terms of socio-clinical numerical variables and vital signs upon admission. Since the p-values are greater than the significance level (0.05), the differences between the population medians for these clinical parameters are not

Table IIa. Patients' diagnostic test results-CBC, ABG and other tests

Diagnostics	CPT and standard of care N=22			Standard of care alone N=46			P-value*
	Median	IQR (Q1-Q3)		Median	IQR (Q1-Q3)		
CBC upon admission							
WBC	9.29	7.21	15.00	9.79	7.03	15.23	0.723
Neutrophils	84.50	77.50	90.00	85.00	74.00	91.00	0.699
Lymphocytes	8.50	4.00	16.00	11.00	5.00	17.00	0.769
Absolute Neutrophil Count	1071.00	619.00	5644.00	984.00	629.00	2488.00	0.875
Absolute Lymphocyte Count	91.10	58.60	389.20	106.00	69.00	256.00	0.836
Hemoglobin	13.30	11.85	14.63	13.10	11.43	14.15	0.577
Hematocrit	39.80	34.50	44.17	38.90	33.20	42.30	0.637
MCV	87.25	86.22	91.65	84.95	82.50	88.85	0.048
MCH	29.45	28.00	31.00	28.40	27.00	29.92	0.142
Platelet	170.00	141.50	248.80	189.50	133.30	228.00	0.937
ABG upon admission							
pH	7.42	7.34	7.46	7.40	7.32	7.46	0.984
pCO2 (mmHg)	25.00	22.90	36.55	26.15	24.00	35.30	0.427
HCO3(mmol/L)	16.90	14.75	19.63	17.60	14.43	19.30	0.758
SO2 (%)	90.20	78.90	94.90	90.50	79.50	96.00	0.604
paO2 (mmHg)	63.90	45.25	78.13	62.00	46.00	79.00	1.000
FiO2(%)	21.00	21.00	65.00	21.00	21.00	48.00	0.530
PFR	212.50	125.90	307.30	198.50	134.90	301.00	0.758
A-a (mmHg)	56.50	18.60	79.00	86.50	48.30	237.10	0.064
Other tests upon admission							
SGPT (U/L)	45.00	30.00	61.00	51.00	32.00	76.00	0.976
Creatinine (mg/dL)	1.08	1.01	1.35	1.12	0.97	1.41	0.655
eGFR	58.00	47.00	79.00	57.30	46.90	72.80	0.805
BUN (mg/dL)	22.00	15.00	37.00	21.50	13.17	38.00	0.950
BCR	14.90	11.25	21.00	15.71	10.50	25.00	0.973
Sodium (mmol/L)	135.00	130.00	141.00	135.00	131.75	139.25	0.973
Potassium (mmol/L)	3.80	3.55	4.15	3.65	3.28	4.20	0.336
HbA1c(%)	7.00	6.50	7.45	6.40	5.90	7.64	0.146
PROTIME (INR)	0.95	0.92	1.05	0.98	0.91	1.08	0.925

* Comparison done with Mann-Whitney U Test; values for each group shown as median; significant at *p<0.05*

Table IIb. Patients' diagnostic test results-Inflammatory markers and other tests

Inflammatory markers and Clinical Chemistries	CPT and standard of care N=22			Standard of care alone N=46			P-value [b]
	Median	IQR (Q1-Q3)		Median	IQR (Q1-Q3)		
Inflammatory Markers on admission							
LDH	510.00	280.00	609.00	496.00	345.50	694.50	0.243
CRP	9.80	3.83	16.22	12.48	7.81	18.63	0.193
Ferritin	1150.00	873.00	2875.00	1397.00	710.00	2126.00	0.798
D-dimer	1163.00	760.00	2250.00	1832.00	1044.00	4563.00	0.138
Procalcitonin	0.30	0.10	2.00	0.37	0.21	2.35	0.344

Table III. Patients' Therapeutic Interventions

Therapeutic Management	CPT and standard of care n=22		Standard of care alone n=46		P-value*
	f	(%)	f	(%)	
Antibiotics	22	(100)	45	(97.83)	1.000
Antivirals	21	(95.45)	36	(78.26)	0.089
Hydroxychloroquine	0	(0.00)	8	(17.39)	**0.047**
Anticoagulants	21	(95.45)	43	(93.48)	1.000
Antiplatelets	7	(31.82)	13	(28.26)	0.782
Antipyretics	15	(68.18)	32	(69.57)	1.000
Anti-inflammatory drugs	17	(77.27)	23	(50.00)	**0.039**
Supplements	12	(54.55)	15	(32.61)	0.113
Dyslipidemic drugs	4	(18.18)	12	(26.09)	0.554
With SUPPLEMENTAL OXGEN THERAPY	19	(86.36)	38	(82.61)	1.000
Nasal cannula	14	(63.64)	29	(63.04)	1.000
High flow nasal cannula	15	(68.18)	10	(21.74)	**<0.001**
Intubation	10	(45.45)	29	(63.04)	0.198
IMMUNOMODULATORS	20	(90.9)	29	(63.04)	**0.021**
Tocilizumab	20	(90.9)	29	63.04	**0.021**
Steroids	20	(90.91)	27	(58.70)	**0.010**
IV Ig	0	(0.00)	6	(13.04)	0.166
Hemoperfusion	6	(27.27)	4	(8.70)	0.066
OTHERS					
Proning	11	(50.00)	32	(69.57)	0.178
Sedation	5	(22.73)	20	(43.48)	0.114
Initiation Hemodialysis	5	(22.73)	12	(26.09)	1.000

*Value computed using Fisher's Exact Test (2x2 variables); significant at $p<0.05$

statistically significant. The two groups do not differ significantly when it comes most of the tests listed above, making them similar in terms of numerical baseline characteristics.

Table IIa and IIb present the patients' diagnostic test results in both groups. Comparatively, all tests in CBC, ABG and other tests upon admission were statistically equal between the two cohorts except MCV upon admission. There was a significantly higher mean corpuscular volume recorded from the intervention arm than the control arm.

Only C-reactive protein upon discharge recorded a significant median difference between the two groups (p-value = 0.01). It can be observed that the intervention group had a relatively lower median value (1.80) than the control group (5.41).

Table III illustrates the comparability of the intervention group and the control group in terms of the use of therapeutic interventions. The Fisher's test also revealed that there was a significantly higher number of CPT patient proportions who were medicated using immunomodulators, steroids, anti-inflammatory drugs and high flow nasal cannula compared to its non-CPT counterpart. However, sufficient statistical evidence indicated higher proportions of non-CPT patients in terms of hydroxychloroquine treatment.

The p-values for heart rate (0.009), CRP (0.004), Creatinine (0.017) and eGFR (0.023) are all less than the significance level. This means that the differences between the population medians of the aforementioned variables are statistically significant, i.e., these diagnostic parameters differ significantly pre- and post-therapy.

There is a notable reduction in the heart rate of patients after CPT. The same is true for CRP as inflammatory marker, and the creatinine level. On the other hand, a significantly higher eGFR can be noted among patients after their convalescent plasma therapy.

However, there is no significant difference in the rest of the vital signs and most of the laboratory test results prior to and 24 hours after giving convalescent plasma.

Since all the p-values above are greater than the significance level (0.05), the decision is failure to reject the null hypotheses. There is not enough evidence to conclude that illness day initiation of CPT of COVID-19 patients is associated with level of inflammatory markers.

Upon discharge, most vital signs are again noted to be comparable in both groups. Since the p-values are greater than the significance level (0.05), the differences between the population medians for these clinical parameters are not statistically significant.

In terms of the patients' diagnostic inflammatory markers and other test results, only C-reactive protein upon discharge recorded a significant median difference between the two groups (p-value = 0.01). It can be clearly observed that the CPT group had a relatively lower median value (1.80) than the non-CPT group (5.41).

Since all the p-values above are greater than the significance level (0.05), the decision is failure to reject

Table IV. Relationship between illness day of convalescent plasma therapy and inflammatory markers

Variables	Computed Values*	P-value*	Interpretation
Illness day of CPT treatment and inflammatory markers BEFORE treatment			
LDH	0.162	0.482	NS
CRP	-0.354	0.137	NS
Ferritin	-0.226	0.325	NS
D-dimer	0.182	0.442	NS
Procalcitonin	0.195	0.505	NS
Illness day of CPT treatment and inflammatory markers AFTER treatment			
LDH	0.007	0.978	NS
CRP	0.402	0.088	NS
Ferritin	-0.116	0.637	NS
D-dimer	0.357	0.134	NS
Procalcitonin	-0.393	0.383	NS

*Spearman's rho; value computed using Spearman's Rank Correlation; significant at $p<0.05$

the null hypotheses. The relationship between IgG titer of donor and level of inflammatory markers is not statistically significant. The same is true for amount of plasma given and level of inflammatory markers.

As to patients' outcomes, there was a significant difference in the number of days spent in terms of overall duration of admission, ICU and critical care support duration (p-value < 0.05) in favor with the non-CPT patients. However, the number of days in the ward between two groups did not statistically differ (Table VIIa).

In terms of severity upon discharge, the p-values for both critical cases (0.004) and severe cases (<0.010) are less than the significance level (0.05). There are significantly more patients in the control group who were classified critical in their final disposition.

Table Va. Patient's vital signs after discharge

Vital signs upon discharge							
Temperature in °C	36.60	36.48	37.00	36.35	36.08	36.53	**0.014**
Systolic BP in mmHg	115.00	100.00	130.00	110.00	110.00	122.50	1.000
Diastolic BP in mmHg	75.00	67.50	80.00	75.00	70.00	80.00	0.750
Heart rate (BPM)	83.50	69.75	90.00	80.00	76.00	84.50	0.475
Respiratory rate (CPM)	21.50	20.00	23.25	20.00	20.00	20.25	**0.030**
O2 Sat (%)	96.50	95.00	98.00	98.00	97.00	98.00	0.021

Table Vb. Patient's inflammatory markers and chemistry tests upon discharge

Inflammatory Markers upon discharge							
LDH	402.50	321.80	643.50	538.50	369.50	796.50	0.269
CRP	1.80	0.08	6.45	5.41	2.34	11.67	**0.013**
Ferritin	1546.00	1214.00	2366.00	1839.00	1059.00	2892.00	0.950
D-dimer	2699.00	1508.00	6284.00	2043.00	1279.00	5818.00	0.551
Procalcitonin	0.50	0.10	12.50	0.41	0.20	2.58	0.675
Other tests upon discharge							
Creatinine (mg/dL)	1.47	0.91	2.75	1.60	0.88	5.18	0.795
eGFR	48.00	20.50	62.13	40.00	11.20	76.90	0.668
BUN (MG/DL)	54.00	21.50	117.50	46.50	20.50	81.00	0.792
BCR	24.00	18.50	33.50	19.00	9.00	25.00	0.257
SGPT (U/L)	67.00	51.30	132.30	54.00	43.00	95.75	0.407

*Comparison done with Mann-Whitney U Test; values for each group shown as median; significant at $p<0.05$

Also, with a p-value of 0.018, the two groups differ significantly terms of proportions in the final disposition. More patients recovered in the CPT group (68.18%) than in the non-CPT (34.78%) (Table VIIb).

Discussion

Due to the pressing need to find a cure for COVID-19, the use of Convalescent Plasma Therapy has once again sparked interest among the medical community. Chenguang S. et al (2020) reported in a case series in China about five critically-ill patients with COVID 19 who were given 2 consecutive transfusions of 200-250 ml of ABO-compatible convalescent plasma together with standard anti-viral treatment. Following transfusion, there was a noted improvement in terms of body temperature, CT scan findings, inflammatory markers, Pao2/Fio2 and ventilator support. Three patients were weaned from mechanical ventilation within 12 days. However, in spite of encouraging results, this study is limited by its small sample size, non-uniform protocols in the treatment of control group, and the herculean task of determining whether the improvement observed is related to therapies other than the CPT.[15]

A much larger randomized clinical trial by Ling Li et al. (2020) was recently published involving 103 COVID 19 patients with severe and life-threatening disease. In this trial, convalescent plasma therapy was added to standard treatment and was compared to standard of treatment alone. The result showed clinical improvement within 28 days in 51.9% vs 43.1% respectively. CP also improved the rate of nasopharyngeal viral RNA clearance at 72 hours compared to standard treatment. However, despite the promising results, it did not reach statistical significance and the trial was prematurely terminated due to poor enrollment.[16]

Conversely, Valk SJ et al, in a Cochrane rapid review of one randomized clinical trial and three non-randomized studies on the effectiveness of CPT, showed no significant differences in all-cause mortality, improvement of clinical symptoms and length of ICU stay. Studies involved in these reviews possess high risk of bias due to poor study design, limited population and poor reporting within the studies.[17]

Just recently, however, Bakhtawar N. et al (2020) completed an open label, phase II

Table VI. Relationship between IgG titer of donor, amount of plasma given, and inflammatory markers

Variables	Computed Values*	P-value*	Interpretation
IgG Titer of Donor and			
Severity, discharge	0.106	0.667	NS
Over-all duration of admission	0.186	0.445	NS
ICU duration	0.149	0.555	NS
LDH-after CPT	-0.024	0.926	NS
CRP-after CPT	-0.038	0.888	NS
Ferritin-after CPT	-0.397	0.128	NS
D-dimer-after CPT	0.393	0.106	NS
Procalcitonin-after CPT	-0.371	0.468	NS
Amount of Plasma Given and			
Severity, discharge	0.067	0.766	NS
Over-all duration of admission	0.034	0.879	NS
LDH-after CPT	-0.183	0.426	NS
CRP-after CPT	0.425	0.055	NS
Ferritin-after CPT	-0.061	0.805	NS
D-dimer-after CPT	-0.033	0.895	NS
Procalcitonin-after CPT	-0.034	0.889	NS
LDH-after CPT	-0.360	0.427	NS

* Spearman's rho; value computed using Spearman's Rank Correlation; significant at $p<0.05$

Table VIIa. Patients' outcomes

Patients' Outcomes	CPT and standard of care N=22			Standard of Care Alone N=46			P-value [b]
Numerical variables	Median	IQR (Q1-Q3)		Median	IQR (Q1-Q3)		
Over-all duration of admission, in days	**16.00**	11.75	24.25	**10.00**	5.75	13.25	**0.000**
Ward Duration, in days	7.00	1.00	12.25	3.50	0.00	10.00	0.221
ICU Duration, in days	**7.00**	3.50	14.50	**3.50**	0.00	8.25	**0.013**
Critical Care Support Duration, in days	**7.00**	3.00	12.50	**3.00**	0.75	6.00	**0.006**

*Comparison done with Mann-Whitney U Test; values for each group shown as median; significant at $p<0.05$

Table VIIb. Patients' outcomes- categorical variables

Patients' Outcomes	CPT and standard of care N=22		Standard of care alone N=46		P-value [a]
Categorical variables	**no.**	**(%)**	**no.**	**(%)**	0.615
With Pressors	12	(54.55)	32	(69.57)	0.282
COVID-19 Severity upon admission					
Critical	7	(31.82)	22	(47.83)	0.296
Severe	13	(59.09)	17	(36.96)	0.118
Moderate	2	(9.09)	7	(15.22)	0.707
COVID-19 Severity, discharge					
Critical	14	(63.64)	43	(93.48)	**0.004**
Severe	7	(31.82)	3	(6.52)	**0.010**
Moderate	1	(4.55)	0	(0.00)	0.324
Final Disposition					
Died	7	(31.82)	30	(65.22)	**0.018**
Recovered	15	(68.18)	16	(34.78)	

* Value computed using Fisher's Exact Test (2x2 variables); significant at p<0.05

multicenter randomized controlled trial of CPT use on COVID-19 adult infections (PLACID Trial) in India. 464 adult Indian patients with confirmed moderate COVID-19 infection were enrolled in the study. 234 patients were assigned to the convalescent plasma with best standard of care (intervention arm) and 229 to best standard of care only (control arm). Participants in the intervention arm received two doses of 200mL of convalescent plasma. The study concluded that convalescent plasma was not associated with a reduction in the progression to severe COVID-19 or all-cause mortality. As a potential therapy, the use of convalescent plasma only showed limited effectiveness. [25]

In the Philippines, the Philippine College of Physicians (PCP) through the Philippine Society for Microbiology and Infectious Disease (PSMID) has approved the use of CPT for compassionate use among severe COVID-19 patients. An ongoing clinical trial is underway to investigate the efficacy and safety of CP in preventing disease progression and ICU admission among hospitalized COVID-19 patients. Donor Protocols have already been made to meet specific criteria for eligible individuals who recovered from COVID-19.[14]

In this study, the population between the two groups has comparable socio-clinical categorical variables. However, it should be worth noting that a greater proportion of the intervention group has more significant baseline imaging findings of infiltrates and ground glass opacities on both radiographic and chest CT scans compared to the control group. This is in contrast to a nonrandomized multicenter study done by H. A, et al., (2020) wherein both groups have statistically significant chest CT scan scores indicating similar clinical condition prior to giving the CP, although this study demonstrated a statistically

significant finding in terms of reduced hospitalization duration and intubation in comparison to the control group.[19]

In terms of socio-clinical variables, both groups are comparable. Numerical variables such as vital signs upon discharge particularly temperature and respiratory rate in both groups were noted to be statistically significant. Duan et al. (2020) showed that a small sample of 10 patients with severe COVID-19 infection had clinical improvement of symptoms and vital signs noted within 1 to 3 days upon convalescent plasma transfusion and all patients were weaned from invasive or non-invasive ventilation. [21]

In terms of diagnostic values, there was marked improvement in C-reactive protein (CRP) levels in the intervention group. However, reduction of CRP levels alone is not an indication of clinical outcome as indicated by a study by Ercurt (2020) wherein a collective diagnostic marker such as difference in differential counts, inflammatory markers, liver function tests and oxygen saturation did not show statistical improvement after 1 week of CPT.[22] Additionally, the relationship between illness day of CPT and inflammatory markers also did not show significant relationship between before and after CP.

In terms of outcome, the intervention showed longer duration of hospitalization, duration of ICU stay and critical care compared to the control group. This is in contrast to a study done by H. Abolghasemi (2020) wherein CPT significantly reduced patients' hospitalization period from 12 to 9 days and interestingly, 28% of patients was discharged within 5 days after receiving CPT.[19]

In terms of severity, a significant proportion of patients was classified with critical illness in the control group compared to the intervention group upon discharge. Furthermore, more patients recovered in the intervention group compared to the control group. This can be supported by a systemic review by K. Rajendra, et al (2020) revealing that more recoveries were recorded in patients who received convalescent plasma. He postulated that CP antibodies can limit viral reproduction and help clear the infection, which is beneficial in the recovery of the disease.

Conclusion

In conclusion, convalescent plasma therapy added to standard treatment, compared with standard treatment alone is not associated with improved clinical outcomes among patients with severe or life threatening COVID-19 infection among hospitalized adult Filipino patients admitted at Perpetual Succour Hospital, Cebu City.

Limitations

This study has several limitations:

- The sample size is small and only limited to admitted patients in one tertiary hospital.
- Not all variables are uniformly present between the two groups especially the results of inflammatory markers, use of immunomodulators, and availability of hematologic and clinical chemistry results.
- The primary outcome is based partially on the physician's clinical decisions.
- The study findings should be evaluated with caution due to differences in practice among different hospitals, regions and countries.
- The outcomes of this study may be affected by presence of confounding variables in both groups that the researchers have failed to eliminate during the sampling process.

Recommendations

The limitations met during the conduct of this study are well noted by the researchers and despite the surmounting challenges brought upon by this pandemic, careful and meticulous collection and analysis of data were done. As this study aims to bridge and understand the gap related to COVID-19 and the use of convalescent plasma therapy, the researchers suggest the following recommendations for future research:

1. Conduct the study in a multi-centre approach to address the issue of small number of patients enrolled in the study.
2. Eliminate confounding variables such as presence of infiltrates on baseline chest x-ray, presence of ground glass opacities on CT scan of the chest, difference in the additional medications or interventions given to either group (Hydroxychloroquine, anti-inflammatory, immunomodulators, supportive oxygen therapy).
3. Emphasize the relationship between interventions concurrent with convalescent plasma use.
4. Include antibody titers and investigate their association with the degree of all-cause mortality in the locality.

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Conflict of Interest

The authors declared that there is no conflict of interest.

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