Research article

Efficacy of Convalescent Plasma Therapy in Hospitalized COVID-19 Patients: A Single Center Retrospective Analysis of 190 Cases in Lebanon

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Abstarct

Introduction: Till date, there is still no specific therapeutic agent against Corona Virus Infectious Disease 2019 (COVID-19). Convalescent plasma (CP) from recently recovered patients has emerged as a potential treatment. In front of conflicting results reported by recently published articles regarding benefits of CP, we sought in this study to investigate its efficacy in COVID-19 patients.

Methods: We performed a retrospective study that enrolled 190 patients confirmed SARS-CoV-2 positive at Lebanese Hospital Geitaoui-University Medical Center, between 1st of December 2020 and 1st of March 2021. Patients were divided into CP and non-CP groups. Clinical characteristics, laboratory and respiratory parameters

were compared between both groups. We assessed the benefit of CP by evaluating the survival rate, the improvement in laboratory parameters and the need for oxygen on discharge.

Results: Out of 190 patients, 35.2% received CP transfusion. When compared to non-CP group, CP patients were more likely to require Mechanical Ventilation and oxygen during hospitalization (p=0.027), and to be discharged on oxygen (p=0.033). After transfusion, only WBC count and ferritin levels significantly increased (p=0.048 and p=0.022 respectively).As for survival rate, it was significantly lower in CP group than non-CP group (51% vs. 67%, p=0.024). Even in mild diseased patients, survival rate of CP individuals was also significantly less than non-CP individuals (p=0.004). In addition, level of LDH (p=0.001) and ferritin (p=0.001) post transfusion were found to be higher in deceased patients.

Conclusion: Our study failed to prove that Convalescent Plasma is effective in the treatment of COVID-19 patients. Our findings require further research.

Keywords: convalescent plasma; hyperimmune plasma; neutralizing antibody COVID-19; SARS-CoV-2; Lebanon;

Abbreviation:

CP: Convalescent plasma
CRP: C-reactive protein
FDA: Food and Drug Administration
F_iO2: Inspiratory oxygen fraction
ICU: Intensive Care Unit
LDH: Lactate Dehydrogenase
MERS: Middle East Respiratory Syndrome
MV: Mechanical Ventilation
NIV: Non-Invasive Ventilation
P_aO2: Arterial oxygen pressure
RT-PCR: Reverse transcription polymerase chain reaction
SARS-CoV-1: Severe Acute Respiratory Syndrome Corona virus 1
SARS-CoV-2: Severe Acute Respiratory Syndrome Corona virus 2
WBC: White Blood Cells

1. Introduction

Corona virus infectious disease 2019 (COVID-19) has put the world in a pandemic mode for more than a year and a half. As of 24th of June 2021, multiple vaccines were approved for usage and 22.4% of the world population had already received at least one dose of the COVID-19 vaccine [1]. Unfortunately, there is still no specific therapeutic agent available and current treatment consists of supportive care, and critical care when needed [2]. Furthermore,

many treatment strategies are being evaluated to identify the potential effective drug or combination of drugs against the disease. Particularly, convalescent plasma (CP), also called hyperimmune plasma, has been the subject of increasing attention as it is showing promising results [2].

Hyperimmune plasma involves collecting plasma from a recently recovered patient to passively transfer instantaneous immunity to an infected patient. Throughout the years, it has proved its efficacy in the treatment of various infections [3], including Severe Acute Respiratory syndrome (SARS) [4] and Middle Eastern Respiratory Syndrome (MERS) [5] outbreaks. In fact, it is well documented that neutralizing antibodies provided by CP could bind to many antigens on the surface of the virus preventing cellular entry and reducing infectivity [6,7]. Other proposed mechanisms that play an important role in prophylaxis and recovery include antibody-dependent cellular toxicity as well as non-immune mechanisms such as complements activation and cytokines [6,7].Moreover, two to three weeks after COVID-19 infection, majority of recovered patients develop antibodies against Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) proteins, which could provide immunity against the virus for several months[8], and these antibodies constitute the basis of COVID-19 CP therapy.

Many studies proved that CP administration in COVID-19 patients could improve their clinical outcome, laboratory markers and survival rate [9–11], while others demonstrated neither clinical improvement nor amelioration of laboratory parameters, nor a reduction in mortality rate [12–14]. In addition, some scholars could not draw conclusive results regarding the efficacy of CP application [15,16]. In the presence of such conflicting findings, the Food and Drug Administration (FDA) still considers CP as an investigational product for COVID-19 treatment [17]. Therefore, in this study, we aimed to determine the efficacy of CP in the treatment of Lebanese COVID-19 patients by evaluating whether CP administration is associated with a better clinical outcome, an improvement in laboratory markers and/or an increase in survival rate.

2. Methods

2.1 Study design and population

This study was conducted retrospectively at Lebanese Hospital Geitaoui-University Medical Center, between 1st of December 2020 and 1st of March 2021. All enrolled patients identified from the hospital electronic database were above 18 years old and were confirmed to be COVID-19 positive by a reverse transcription polymerase chain reaction (RT-PCR) of a nasopharyngeal sample. Participants were separated into two groups: CP group who received CP treatment and non-CP group who represented the control one. Based on CURB 65 score [18], we classified patients according to disease severity at admission to three categories: mild, moderate and severe cases. Since we wanted to test the effect of CP on all categories of patients, all participants were hospitalized and admitted to regular floor or ICU.

2.2 Data collection

We retrieved from patients' electronic medical records demographic data (age and gender), underlying comorbidities, symptoms at admission, laboratory values before and after transfusion (White Blood Cell (WBC)

count, lymphocyte count, D-Dimer, Lactate Dehydrogenase (LDH) and Ferritin), and need for oxygen upon discharge. We also reported the following variables: need for regular floor, ICU, oxygen, non-invasive ventilation (NIV), or mechanical ventilation (MV) during hospital stay. The main criteria used to evaluate the efficacy of CP were the increase in survival rate, the improvement in laboratory parameters and the need for oxygen on discharge.

2.3 Ethical considerations

According to the principles of the Declaration of Helsinki (7th revision), this retrospective work was waived the need for ethical approval and informed consent; instead, access letter to patients' medical files was received.

2.4 Statistical analysis

We reported categorical data as frequencies or percentages, while continuous variables were represented as Mean ± SD and median. We also calculated mortality rate, time from onset of symptoms till diagnosis, time from onset of symptoms till admission, time from onset of symptoms till transfusion, time from admission till transfusion and length of stay in the hospital. Furthermore, as the data was non-parametric according to Shapiro-Wilk test of normality, we compared between CP and non-CP groups using Mann-Whitney U test for continuous variables and Chi-squared test for categorical variables. We also performed Wilcoxon signed rank test to compare laboratory values before and after transfusion. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) Version 22 and p-value < 0.005 was considered statistically significant.

3. Results

3.1 General characteristics of enrolled participants

In total, 190 patients with COVID-19 were included in this study. Only 67 (35.2%) participants received CP. General Characteristics of this cohort are reported in **Table 1.** The mean age among all patients was 66.98 ± 16.40 years and 66.3% were men. The leading underlying chronic disease was hypertension (60.0%) followed by diabetes (41.6%) and cardiac diseases (31.1%). Patients' demographic characteristics and co morbidities were not significantly different between CP and non-CP groups. In addition, mortality rate in our population reached 38.5%.

Table 1: Comparison of demographic characteristics, medical history, clinical characteristics, laboratory and respiratory parameters between CP and non-CP groups

		Total (N=190)	**CP group (N=67)**	**Non-CP group (N = 123)**	***p*-value**
Demographic Characteristics					
Gender	**Male**	126	47	79	0.409
		66.3%	70.1%	64.2%	
	Female	64	20	44	
		33.7%	29.9%	35.8%	
Age	**Mean (SD)**	66.98 (16.40)	67.52 (15.92)	66.68 (16.71)	0.666
	Median	67.00	69.00	67.00	
	Min - Max	21.00 - 95.00	27.00 - 90.00	21.00 - 95.00	

Medical History					
Diabetes	**No**	111	37	74	0.509
		58.4%	55.2%	60.2%	
	Yes	79	30	49	
		41.6%	44.8%	39.8%	
Hypertension	**No**	76	24	52	0.385
		40.0%	35.8%	42.3%	
	Yes	114	43	71	
		60.0%	64.2%	57.7%	
Cardiac	**No**	131	45	86	0.695
		68.9%	67.2%	69.9%	
	Yes	59	22	37	
		31.1%	32.8%	30.1%	
Kidney	**No**	169	56	113	0.082
		88.9%	83.6%	91.9%	
	Yes	21	11	10	
		11.1%	16.4%	8.1%	
Pulmonary	**No**	181	64	117	0.901
		95.3%	95.5%	95.1%	
	Yes	9	3	6	
		4.7%	4.5%	4.9%	
Cancer	**No**	177	60	117	0.146
		93.2%	89.6%	95.1%	
	Yes	13	7	6	
		6.8%	10.4%	4.9%	
Symptoms					
Dyspnea	**No**	46	11	35	0.064
		24.2%	16.4%	28.5%	
	Yes	144	56	88	
		75.8%	83.6%	71.5%	
Cough	**No**	87	24	63	0.042
		45.8%	35.8%	51.2%	
	Yes	103	43	60	
		54.2%	64.2%	48.8%	
Fever	**No**	134	43	91	0.157
		70.5%	64.2%	74.0%	
	Yes	56	24	32	

		29.5%	35.8%	26.0%	
Disease severity					
Disease Severity at Admission	**Low Risk/outpatient**	71	20	51	0.009
		39.0%	30.3%	44.0%	
	Hospitalizedvs. Supervised outpatient	81	28	53	
		44.5%	42.4%	45.7%	
	Severe	30	18	12	
		16.5%	27.3%	10.3%	
Hospitalization					
Regular Floor	**No**	67	29	38	0.088
		35.3%	43.3%	30.9%	
	Yes	123	38	85	
		64.7%	56.7%	69.1%	
ICU	**No**	97	26	71	0.013
		51.1%	38.8%	57.7%	
	Yes	93	41	52	
		48.9%	61.2%	42.3%	
Respiratory parameters					
Oxygen	**No**	74	19	55	0.027
		38.9%	28.4%	44.7%	
	Yes	116	48	68	
		61.1%	71.6%	55.3%	
NIV	**No**	151	51	100	0.398
		79.5%	76.1%	81.3%	
	Yes	39	16	23	
		20.5%	23.9%	18.7%	
MV	**No**	132	39	93	0.013
		69.5%	58.2%	75.6%	
	Yes	58	28	30	
		30.5%	41.8%	24.4%	
P_aO2/F_io2	**Mean (SD)**	166.21 (122.13)	136.44 (107.72)	189.85 (129.13)	0.045
	Median	120.00	96.00	131.00	
	Min - Max	51.00 - 440.00	51.00 - 400.00	58.00 - 440.00	
Laboratory parameters					
WBC Count (x-10^9cell/L)	**Mean (SD)**	9669.42(11515.99)	10485.07(17595.42)	9221.48 (6050.48)	0.393
	Median	7400.00	6300.00	7900.00	

	Min - Max	500.00 - 145000.00	500.00 - 145000.00	800.00 - 34700.00	
LDH(U/L)	**Mean (SD)**	512.74(293.73)	540.44(308.02)	496.71(285.29)	0.626
	Median	438.50	421.00	438.50	
	Min - Max	49.00 - 2415.00	49.00 - 1345.00	105.00 - 2415.00	
Ferritin (µg/L)	**Mean (SD)**	772.71(1098.13)	1131.05(1480.71)	541.37(671.38)	<0.001
	Median	406.00	606.00	319.00	
	Min - Max	0.05 - 9964.00	0.12 - 9964.00	0.05 - 2000.00	
D-dimers (ng/ml)	**Mean (SD)**	876.88(1587.00)	1047.01(1815.25)	764.30(1419.10)	0.703
	Median	266.00	244.00	288.50	
	Min - Max	0.23 - 5250.00	0.23 - 5250.00	0.28 - 5250.00	
Lymphocytes count (lymphocyte/mcL)	**Mean (SD)**	1024.54 (9478.67)	1145.88 (1277.06)	955.35 (691.16)	1.664
	Median	768.00	790.00	738.50	
	Min - Max	220.0 - 10150.0	220.0 - 10150.0	294.0 - 3636.0	
Clinical outcome on discharge					
Discharge on Oxygen	**No**	108	29	79	0.033
		93.1%	85.3%	96.3%	
	Yes	8	5	3	
		6.9%	14.7%	3.7%	

Data are expressed as mean (SD) and median with range or frequency with percentage. Total counts are presented for each cell. Comparisons between CP and non-CP groups have been performed by non-parametric tests: Mann-Whitney U test for continuous variable and Chi-square test for categorical variables. $p<0.005$ was considered statistically significant. For abbreviations: CP group: Convalescent Plasma group; ICU: intensive care unit; LDH: Lactate Dehydrogenase; MV: Mechanical Ventilation; NIV: Non-invasive Ventilation; Non-CP group: non-convalescent plasma group; WBC: White Blood Cell.

3.2 Comparison of clinical, laboratory and respiratory characteristics between CP and non-CP groups

Among all participants, the most common reported symptom was dyspnea (75.8%). Particularly, CP patients were more likely to experience cough (p=0.042). Furthermore, 44.5% of the total participants had moderate illness. When compared to non-CP patients, CP individuals were more likely to have severe COVID-19 pneumonia (p=0.009) and to require ICU admission (p=0.013).Besides, 30.3% of patients with mild illness received CP transfusion (**Table 1**).

The mean time between symptoms onset to diagnosis and the mean time between symptoms onset to admission were 2.70±4.05 (range:- 0-36 days) and 5.70 ± 6.10 days (range, 0-45days) respectively. Moreover, the mean time from symptoms onset to CP transfusion and the mean time from admission to CP transfusion were 7.21 ± 4.45 (range:- 0-21 days) and 3.06 ± 2.42 (range:- 0-13 days) days respectively. The median length of stay in the hospital (regular floor or ICU) was 10 days (range, 1-50 days). There were no significant differences in previously mentioned time intervals between CP and non-CP groups. (**Figure 1**)

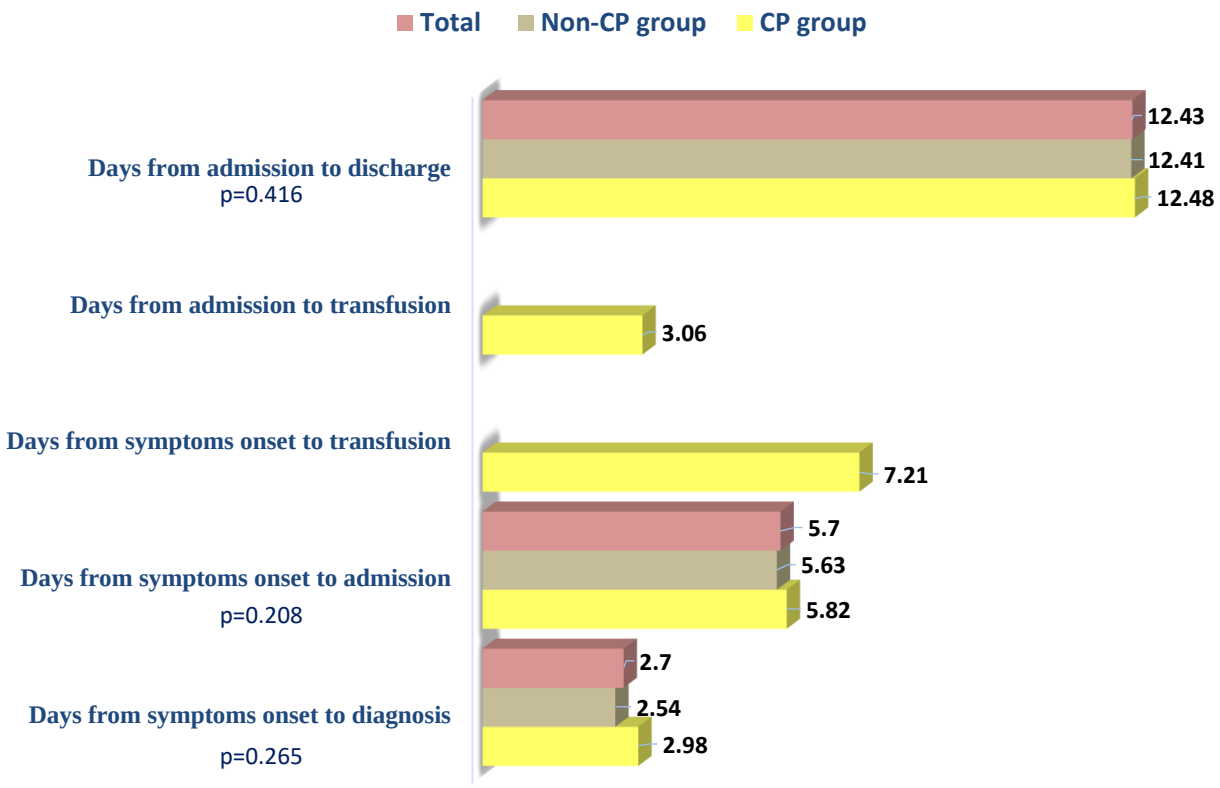

Figure 1: Comparison of time intervals in days between CP and non-CP groups.

Data are expressed as mean. Comparisons between CP and non-CP grosups have been performed by non-parametric Mann-Whitney U test. $p<0.005$ was considered statistically significant. For abbreviations: CP group: convalescent Plasma group; Non-CP group: non-convalescent Plasma group.

As for respiratory parameters, out of 190 patients, 61.1% required oxygen therapy, 20.5% needed NIV, and 30.5% were mechanically ventilated. Compared to non-CP group, CP group had a significantly higher need for MV ($_p$=0.0013) and oxygen during hospitalization ($_p$=0.027).In addition, at admission, CP group had a significantly lower PaO2/FiO2 ratio than non-CP group ($_p$=0.045). There were no significant differences between the two groups laboratory values at admission except for ferritin, which was significantly higher in CP group ($p<0.001$). (Table 1)

3.3 Effect of CP transfusion on the need for oxygen at discharge

Only 6.9% of all patients were discharged on oxygen and CP individuals were the ones to more likely require oxygen on discharge ($p=0.033$). (Table 1) When distributed according to CURB-65, CP patients in the mild category were more likely to need oxygen upon discharge ($p=0.001$) if compared to non-CP individuals. Only 1 patient who received CP in the severe category was discharged on oxygen. There was no significant difference between both groups in the moderate disease category. (Figure 2)

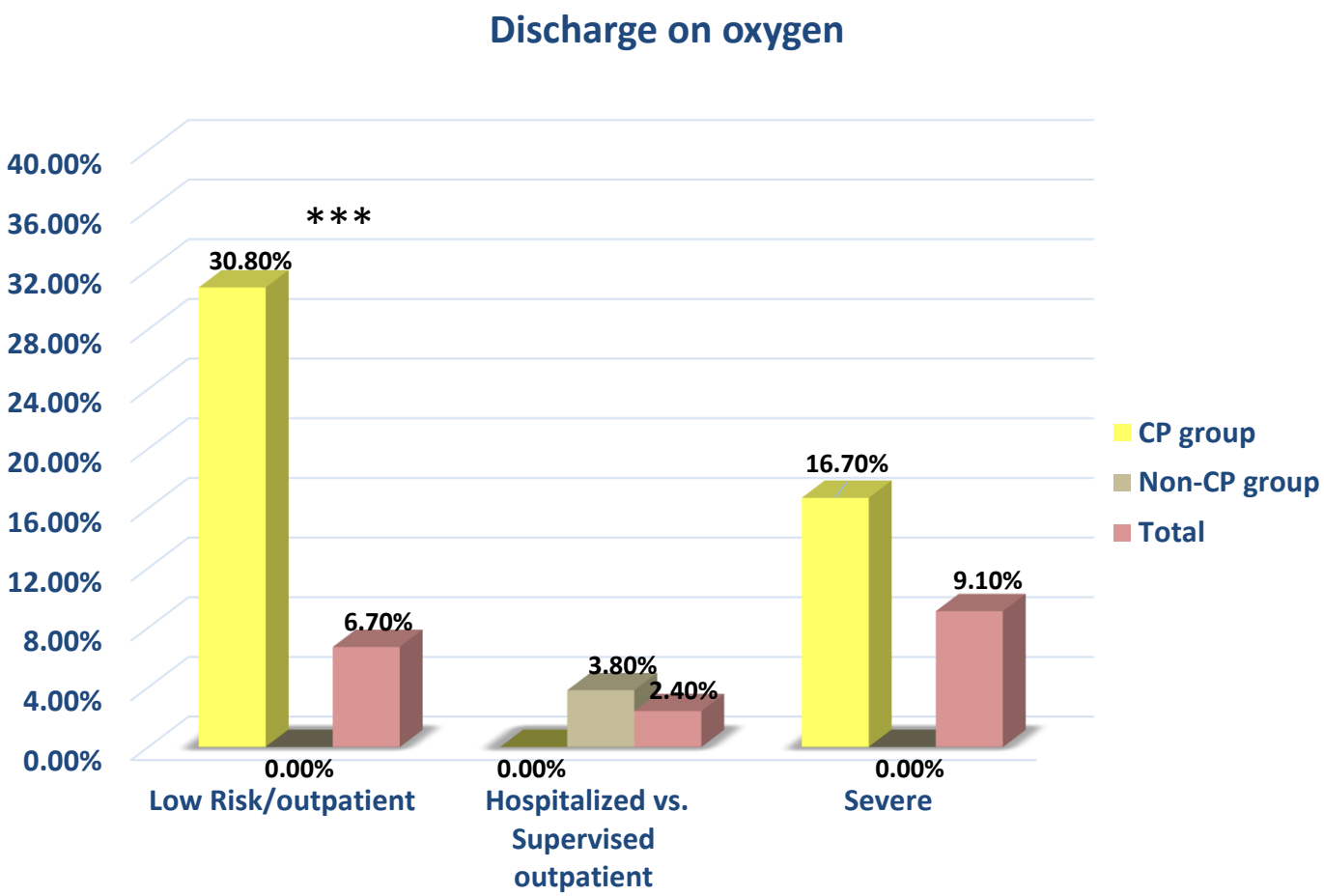

Figure 2: Comparison of the percentage of patients discharged on oxygen between CP and Non-CP groups in each category of disease severity.

Data are expressed as mean. Comparisons between CP and non-CP groups have been performed by non-parametric Chi-square test. $p<0.005$ was considered statistically significant with ***$p\leq0.001$. For abbreviations: CP group: convalescent plasma group; non-CP group: non-convalescent plasma group.

3.4 Effect of CP transfusion on laboratory markers

Among CP patients, the median level of WBC count significantly increased after transfusion (8400 x 10^9 cell/L vs. 6400 x 10^9 cell/Lp=0.048) but without reaching clinical significance. The median level of LDH and lymphocyte counts increased after transfusion, while D-dimer levels decreased, however, these variations did not achieve any statistical significance. As for Ferritin, after receiving CP transfusion, CP participants had statistically and clinically significant higher levels (802 µg/L vs. 790 µg/Lp=0.022). (Table 2)

Table 2: Comparison of laboratory markers at admission and 24 hours post transfusion. Data are expressed as mean (SD) and median with range.

Population: Patients who received Plasma (N = 67)				
		Upon admission	**24hours after transfusion**	***p*-value**

WBC count(x 10^9 cell/L)	**Mean (SD)**	10485.07 (17595.42)	11454.15 (17737.49)	0.048
	Median	6300.00	8400.00	
	Min - Max	500.00 - 145000.00	828.00 - 148400.00	
LDH (U/L)	**Mean (SD)**	540.44 (308.02)	871.19 (1544.75)	0.140
	Median	421.00	528.00	
	Min - Max	49.00 - 1345.00	84.00 - 10280.00	
Ferritin (µg/L)	**Mean (SD)**	1131.05 (1480.71)	1228.60 (854.84)	0.022
	Median	606.00	1266.00	
	Min - Max	0.12 - 9964.00	81.00 - 5000.00	
D-dimers (ng/ml)	**Mean (SD)**	1047.01 (1815.25)	685.45 (1565.96)	0.127
	Median	244.00	4.14	
	Min - Max	0.23 - 5250.00	0.04 - 5250.00	
Lymphocytes count (lymphocyte/mcL)	**Mean (SD)**	1145.88 (1277.06)	964.84 (683.57)	0.255
	Median	790.00	802.00	
	Min - Max	222.0 - 10150.0	120.0 - 4400.0	

Comparisons between laboratory values have been performed by Wilcoxon signed-rank test. $p<0.005$ was considered statistically significant. For abbreviations: LDH: Lactate Dehydrogenase; WBC: white blood cell.

3.5 Effect of CP transfusion on survival rate

Survival rate in CP group reached 51% which was significantly lower than non-CP group (67%, $p=0.024$). Vice versa, mortality rate was significantly higher among CP group. (Figure 3) When distributed according to disease severity, survival rate of CP patients in mild category was 65% which was also significantly lower than non-CP individuals ($p=0.004$). As for the moderate and severe category, survival rates were lower in CP group but differences between both groups were not statistically significant. (Table 3) Among individuals who received CP, the time from symptoms onset till transfusion and the time from admission till transfusion did not significantly vary between deceased and alive patients. When separated into two subgroups (early CP transfusion received after 7 days or less of symptoms onset and late CP transfusion received after more than 7 days of symptoms onset), we found

that 56.8% of patients who received early plasma survived, whereas 43.3% of late CP transfusion subgroup survived. However, this difference was not statistically significant. (Table 4) In addition, significant mean differences between deceased and alive patients were identified for LDH (p=0.001) and ferritin (p=0.001) levels post- transfusion. Both of them were higher in deceased patients. (Table 4)

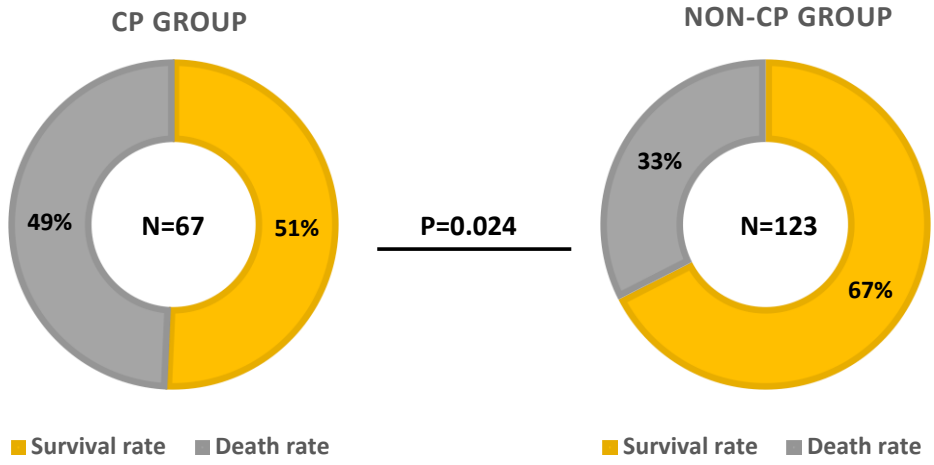

Figure 3: Comparison of survival and death rates between CP and non-CP groups.

Data are expressed as percentage. Comparisons between CP and non-CP groups have been performed by non-parametric Chi-square test. $p<0.005$ was considered statistically significant. For abbreviations: CP group: convalescent plasma group; Non-CP group: non-convalescent plasma group.

Table 3: Comparison of survival and death rates between CP and Non-CP groups in each category of disease severity.

Disease Severity At Admission		**Total (N=190)**	**CP group (N=67)**	**Non-CP group (N=123)**	***p*-value**
Low Risk/out patient	**Death**	10	7	3	0.004
		14.1%	35.0%	5.9%	
	Alive	61	13	48	
		85.9%	65.0%	94.1%	
Hospitalized vs. Supervised outpatient	**Death**	40	13	27	0.699
		49.4%	46.4%	50.9%	
	Alive	41	15	26	
		50.6%	53.6%	49.1%	
Severe	**Death**	19	12	7	0.643
		63.3%	66.7%	58.3%	
	Alive	11	6	5	

		36.7%	33.3%	41.7%	

Data are expressed as frequency and percentage. Comparisons between CP and non-CP groups have been performed by Chi-square test. $p<0.005$ was considered statistically significant. For abbreviations: CP group: convalescent plasma group; non-CP group: non convalescent Plasma group.

Table 4. Comparison of time intervals in days and laboratory markers post transfusion in deceased and alive patient among CP group.

CP group (N = 67)					
		N	**Mean**	**SD**	***p*-value**
Days from symptoms onset to transfusion	Death	33	8.1	4.0	0.058
	Alive	34	6.4	4.7	
	Total	67	7.2	4.5	
Days from admission to transfusion	Death	33	2.7	1.7	0.700
	Alive	34	3.4	2.9	
	Total	67	3.1	2.4	
WBC count (post transfusion)	Death	33	14697.8	24708.8	0.086
	Alive	34	8305.9	4059.5	
	Total	67	11454.1	17737.5	
LDH (post transfusion)	Death	32	1253.9	2102.5	0.001
	Alive	31	476.1	214.7	
	Total	63	871.2	1544.7	
Ferritin (post transfusion)	Death	26	1476.5	640.8	0.001
	Alive	27	989.9	972.7	
	Total	53	1228.6	854.8	
D-dimer (post transfusion)	Death	13	585.2	1538.4	0.912
	Alive	20	750.6	1619.8	
	Total	33	685.5	1566.0	
Lymphocytes count (post transfusion)	Death	31	956.9	882.2	0.928
	Alive	31	972.8	414.5	
	Total	62	964.8	683.6	

Data are expressed as frequency and mean with SD. Comparisons between mean shave been performed by Mann-Whitney U test. $p<0.005$ was considered statistically significant. For abbreviations: LDH: Lactate Dehydrogenase; WBC: White Blood Cell; CP group: convalescent plasma group.

4. Discussion

Standard treatment for COVID-19 is presently lacking and many repurposed new therapeutic agents, including CP therapy, are still under investigation. In this study, we sought to evaluate the efficacy of CP transfusion in patients with mild, moderate and severe COVID-19 illness. We retrospectively examined 190 COVID-19 infected patients of whom 35.2% received a CP transfusion. The mean time from symptoms onset to CP transfusion and the mean time from admission to CP transfusion were around 7 days and 3 days respectively with no significant difference in survival rate between early and late transfusion. Furthermore, there was no statistically significant difference in the duration of hospitalization between both groups. We identified that CP patients were more likely to be discharged on oxygen. In addition, the mortality rate reported in CP group was significantly higher than non-CP group. Although not clinically significant, we observed a statistically relevant rise in WBC count after post transfusion associated with a non-significant elevation in lymphocyte counts. Regarding ferritin, it had significantly further increased after transfusion accompanied by a non-statistical upward trend in LDH level post transfusion.

4.1 Comparison with other studies

In contrast to our findings, a large observational cohort study of 35,000 patients with COVID-19 demonstrated a reduced 7 days and 30days mortality in individuals who received CP [19]. In addition, an aggregate of various randomized controlled trials, matched-control, case series and case reports studies found a 57% decrease in death rate among CP patients [20]. Salazar et al, in his prospective propensity matched study, also reported a significantly lower mortality rate at day 28 in CP group particularly when transfusion was received within 72 hours of admission [21]. In addition, an Indian multi centric retrospective research on 1079 patients found that the decrease in mortality rate among CP group was significantly noticed among patients admitted to the ICU, with underlying chronic diseases, as well as female individuals and participants of increased age, particularly above 60 years [22]. As for clinical outcomes, many scholars reported improvement in clinical symptoms among CP patients, including two Chinese studies respectively realized on5 critically ill patients [23]and 1568 patients with severe or critical illness from whom 138 patients received CP [24]. Altuntas et al proved as well that CP could also shorten the duration of ICU stay and reduce the need for MV and vasopressors [25]. In contrast to our findings where CP group was more likely to be discharged on oxygen, symptomatic recovery after CP transfusion was also associated with an increase in oxygen saturation [26,27]. Regarding laboratory markers, a Mexican study conducted retrospectively on 8 patients with severe respiratory failure identified a decrease in C-reactive protein (CRP), LDH, procalcitonin, cardiac tropon in I and Brain Natriuretic Peptide (BNP) [28]. Duan et al additionally reported an increase in lymphocyte counts after transfusion [27]. Concerning viral clearance which underlines the neutralizing effect of CP, the PLACID trial conducted in India, and an early terminated RCT in China, both showed an early and higher rate of negative PCR conversion among CP patients [12,29]. Even in patients with prolonged SARS-CoV-2 positivity, CP therapy was able to eliminate virus and reduce the duration of hospitalization [30].

In accordance with our results, a study conducted in Abu Dhabi on 110 critically ill patients found that CP was not associated with time to clinical improvement. In this same study, mortality rate, ICU admission, and duration of hospitalization and MV did not statistically vary between CP and non-CP groups [13]. Another retrospective cohort

realized in Qatar on severe COVID-19 patients revealed no statistical differences in both groups regarding respiratory support status, mortality and viral clearance within 28 days of follow-up [31].Furthermore, the PLACID trial, conducted on moderate COVID-19 patients, demonstrated no significant differences in inflammatory markers such as ferritin, LDH, D-dimers and CRP between both groups [29]. This same trial reported a significant clinical improvement after transfusion accompanied by a negative PCR test at day 7 after enrollment, but, no reduction in mortality or progression to severe disease was seen in CP group compared to non-CP group [29]. Moreover, recently published Cochrane reviews reported uncertainties regarding the effectiveness of CP transfusion [32,33], while a meta-analyses found no significant effect of CP on mortality and clinical outcome [14].

4.2 Possible causes for lack of clinical benefits

Various causes could possibly explain the apparent lack of clinical benefit of CP in our study. First, sample size in both groups was not balanced (67 CP patients vs. 123 non-CP patients). Besides, enrolled individuals were heterogeneous with regard to their age (range:- 21-95 years), underlying co morbidities, duration of symptoms (range, 0-45 days), and severity of illness. In attempt to reduce this heterogeneity, our analysis took into consideration severity of COVID-19 and categorized patients according to CURB-65. (Table 3) Despite that, mortality rate was still significantly lower among mild diseased non-CP patients and no statistical differences in death rate in CP and non-CP patients was seen in moderate and severe categories. These latter findings could be explained by the fact that patients with moderate to severe COVID-19 illness have higher inflammatory state that neutralizing antibodies might not be able to overcome it. Indeed, levels of LDH and ferritin after transfusion in CP patients were both significantly higher in deceased patients than alive ones. (Table 4) Second, we were not in control of the selection process for plasma donor's and we were neither able to measure nor evaluate the nature of antibodies present in CP units. And since high level of neutralizing immunoglobulin is a prerequisite for effectiveness[34], we suggest that plasma units in our study might have inadequate levels of SARS-CoV-2 neutralizing antibody titers. Third, timing of CP administration varied in our sample (range 0-21 days from symptoms onset and 0-13 days from admission). It is true that till date there is no specific timing for CP administration, however, studies proved that early administration within 72 hours of admission could improve survival rate[21] and higher rates of MV was reported when CP administered after 20 days of onset of symptoms [25]. Nonetheless, when we took into account the time of CP administration in our analysis of CP patients, it had no statistically significant effect on mortality and early transfusion was not significantly associated with better survival rate. (Table 4) Fourth, patients in both groups were receiving non standardized supportive care, this might have affected our findings as some treatment might antagonize the effect of CP or influence the course of the disease. Fifth, missing data in certain inflammatory markers post transfusion might have concealed the proof of an improvement in laboratory parameters.

4.3 Limitations

There are several limitations to our present study. First, the retrospective mono centric nature of the research and the small number of enrolled participants both limited the ability to generalize our results and to settle the differences between conflicting findings in the current literature regarding the benefit of CP. Second, we were unable to report

CP procurement methodology and transfusion related adverse events. Third, CP was administered empirically by physicians. Fourth, the level of neutralizing antibodies was not determined neither in donors' plasma nor in CP individuals due to lack of tests in Lebanon during the time of the study. Fifth, given the lack of unified management protocol for this illness in Lebanon and around the world, our findings should be interpreted with caution.

4.4 Perspectives and Recommendations

To our knowledge, this is the first study in Lebanon that evaluates the efficacy of CP therapy. Our findings are of clinical importance and provide useful insight for physician regarding CP administration. This study added more data to the existing literature regarding the benefits of CP in COVID-19 treatment. Our research also addresses the impact of CP usage in mild to moderate COVID-19 pneumonia. Due to previously mentioned limitations, further research through randomized double-blind trials with proper measurement of neutralizing antibodies in donors' plasma and receivers are warranted to better assess the potential therapeutic role of CP transfusion and evaluate its safety in COVID-19 patients. Future research should focus on the appropriate dosage and time for CP transfusion, as well as its specific underlying mechanism of action. Administration of CP in mild to moderate COVID-19 cases merits to be studied also.

5. Conclusion

In conclusion, in this retrospective cohort study of 190 patients with COVID-19, CP transfusion was not associated with therapeutic benefits. However, our study limitations might have underpowered the efficacy of CP, hence, more research are required to address this matter.

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Declaration of Competing Interest

All authors declare that they do not have any conflict of interest that could inappropriately influence the present study.

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References

1. Our World in Data. Corona virus (COVID-19) Vaccinations. Retrieved June 24 (2021).
2. Bartoli A, Gabrielli F, Alicandro T, Nascimbeni F AP. COVID-19 treatment options: a difficult journey between failed attempts and experimental drugs. Intern Emerg Med 16 (2021): 281-308.
3. Marano G, Vaglio S, Pupella S, Facco G, Catalano L, Liumbruno GM GG. Convalescent plasma: new evidence for an old therapeutic tool? Blood Transfus 14 (2016): 152-7.

4. Soo YO, Cheng Y, Wong R, Hui DS, Lee CK, Tsang KK, Ng MH, Chan P, Cheng G SJ. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clin Microbiol Infect 10 (2004): 676-8.
5. Arabi YM, Hajeer AH, Luke T, Raviprakash K, Balkhy H, Johani S, Al-Dawood A, Al-Qahtani S, Al-Omari A, Al-Hameed F, Hayden FG, Fowler R, Bouchama A, Shindo N, Al-Khairy K, Carson G, Taha Y, Sadat M AM. Feasibility of Using Convalescent Plasma Immunotherapy for MERS-CoV Infection, Saudi Arabia. Emerg Infect Dis 22 (2016): 1554-61.
6. Al-Riyami AZ. COVID-19 convalescent plasma: mechanisms of action and rationale for use: a narrative review.Ann Blood 6 (2021): 16.
7. Rojas M, Rodríguez Y, Monsalve DM, Acosta-Ampudia Y, Camacho B, Gallo JE, Rojas-Villarraga A, Ramírez-Santana C, Díaz-Coronado JC, Manrique R, Mantilla RD, Shoenfeld Y AJ. Convalescent plasma in Covid-19: Possible mechanisms of action. Autoimmun Rev 19 (2020): 102554.
8. Kirkcaldy RD, King BA BJ. COVID-19 and Postinfection Immunity: Limited Evidence, Many Remaining Questions. JAMA 323 (2020): 2245-2246.
9. Hatzl S, Posch F, Sareban N, Stradner M, Rosskopf K, Reisinger AC, Eller P, Schörghuber M, Toller W, Sloup Z, Prüller F, Gütl K, Pilz S, Rosenkranz AR, Greinix HT, Krause R, Schlenke P SG. Convalescent plasma therapy and mortality in COVID-19 patients admitted to the ICU: a prospective observational study. Ann Intensive Care 11 (2021): 73.
10. Bansal V, Mahapure KS, Mehra I, Bhurwal A, Tekin A, Singh R, Gupta I, Rathore SS, Khan H, Deshpande S, Gulati S, Armaly P, Sheraton M KR. Mortality Benefit of Convalescent Plasma in COVID-19: A Systematic Review and Meta-Analysis. Front Med (Lausanne) 8 (2021): 624924.
11. Huang S, Shen C, Xia C, Huang X, Fu Y, Tian L. A Retrospective Study on the Effects of Convalescent Plasma Therapy in 24 Patients Diagnosed with COVID-19 Pneumonia in February and March 2020 at 2 Centers in Wuhan, China. Med Sci Monit 26 (2020): e928755.
12. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, Kong Y, Ren L, Wei Q, Mei H, Hu C, Tao C, Yang R, Wang J, Yu Y, Guo Y, Wu X, Xu Z, Zeng L, Xiong N, Chen L, Wang J, Man N, Liu Y, Xu H, Deng E, Zhang X, Li C, Wang C, Su S, Zhang L, Wang J, Wu Y LZ. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial JAMA 324 (2020): 460-470.
13. Abuzakouk M, Saleh K, Algora M, Nusair A, Alameri J, Alshehhi F, Alkhaja S, Badr M, Abdallah K, De Oliveira B, Nadeem A, Varghese Y, Munde D, Salam S, Abduljawad B, Elkambergy H, Wahla A, Taha A, Dibu J, Bayrlee A, Hamed F, AbdelWareth L, Rahman N, Guzman MJ. Convalescent Plasma Efficacy in Life-Threatening COVID-19 Patients Admitted to the ICU: A Retrospective Cohort Study. J Clin Med 10 (2021): 2113.
14. Janiaud P, Axfors C, Schmitt AM, Gloy V, Ebrahimi F, Hepprich M, Smith ER, Haber NA, Khanna N, Moher D, Goodman SN, Ioannidis JPA HL. Association of Convalescent Plasma Treatment with Clinical Outcomes in Patients with COVID-19: A Systematic Review and Meta-analysi JAMA 325 (2021):1185-1195.

15. O'Donnell MR, Grinsztejn B, Cummings MJ, Justman JE, Lamb MR, Eckhardt CM, Philip NM, Cheung YK, Gupta V, João E, Pilotto JH, Diniz MP, Cardoso SW, Abrams D, Rajagopalan KN, Borden SE, Wolf A, Sidi LC, Vizzoni A, Veloso VG, Bitan ZC, Scotto DE, Meyer BJ, LW. A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19 J Clin Invest 11 (2021): 150646.
16. Rejeki MS, Sarnadi N, Wihastuti R, Fazharyasti V, Samin WY, Yudhaputri FA, Johar E, Nurainy N, Bachtiar NS MD. Convalescent plasma therapy in patients with moderate-to-severe COVID-19: A study from Indonesia for clinical research in low- and middle-income countries. E Clinical Medicine. 4 (2021): 100931.
17. Food and Drugs Administration (FDA). Recommendations for Investigational COVID-19 Convalescent Plasma. Retrieved June 24 (2021).
18. Liu JL, Xu F, Zhou H, Wu XJ, Shi LX, Lu RQ, Farcomeni A, Venditti M, Zhao YL, Luo SY, Dong XJ FM. Expanded CURB-65: a new score system predicts severity of community-acquired pneumonia with superior efficiency. Sci Rep 6 (2016): 22911.
19. Joyner MJ, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, Wiggins CC, Bruno KA, Klompas AM, Lesser ER KK. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience MedRxiv (2020).
20. Joyner MJ, Klassen SA, Senefeld J, Johnson PW, Carter RE, Wiggins CC, Shoham S, Grossman BJ, Henderson JP, Musser JM SE. Evidence favouring the efficacy of convalescent plasma for COVID-19 therapy. medRxiv (2020).
21. alazar E, Christensen PA, Graviss EA, Nguyen DT, Castillo B, Chen J, Lopez BV, Eagar TN, Yi X, Zhao P, Rogers J, Shehabeldin A, Joseph D, Leveque C, Olsen RJ, Bernard DW, Gollihar J MJ. Treatment of Coronavirus Disease 2019 Patients with Convalescent Plasma Reveals a Signal of Significantly Decreased Mortality. Am J Pathol 190 (2020): 2290-2303.
22. Budhiraja S, Dewan A, Aggarwal R, Singh O, Juneja D, Pathak S, Singh YP, Gupta A, Rai R, Indrayan A, Jha V NR. Effectiveness of convalescent plasma in Indian patients with COVID-19. Blood Cells Mol Dis 88 (2021): 102548.
23. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, Wang F, Li D, Yang M, Xing L, Wei J, Xiao H, Yang Y, Qu J, Qing L, Chen L, Xu Z, Peng L, Li Y, Zheng H, Chen F, Huang K, Jiang Y, Liu D, Zhang Z, Liu Y LL. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma JAMA 323 (2020): 1582-1589.
24. Xia X, Li K, Wu L, Wang Z, Zhu M, Huang B, Li J, Wang Z, Wu W, Wu M, Li W, Li L, Cai Y, Bosco B, Zhong A, Liu X, Lv T, Gan Z, Chen G, Pan Y, Liu C, Zhang K, Xu X, Wang C WQ. Improved clinical symptoms and mortality among patients with severe or critical COVID-19 after convalescent plasma transfusion. Blood 136 (2020): 755-759.
25. Altuntas F, Ata N, Yigenoglu TN, Bascı S, Dal MS, Korkmaz S, Namdaroglu S, Basturk A, Hacıbekiroglu T, Dogu MH, Berber İ, Dal K, Kınık K, Haznedaroglu İ, Yılmaz FM, Kılıç İ, Demircioğlu S, Yosunkaya A, Erkurt MA, Turgut B, Caglayan M CO. Convalescent plasma therapy in patients with COVID-19. Transfus Apher Sci 60 (2021): 102955.

26. Alsharidah S, Ayed M, Ameen RM, Alhuraish F, Rouheldeen NA, Alshammari FR, Embaireeg A, Almelahi M, Adel M, Dawoud ME, Aljasmi MA, Alshammari N, Alsaeedi A, Al-Adsani W, Arian H, Awad H, Alenezi HA, Alzafiri A, Gouda EF, Almehanna M, Alqahtani S, Alshamma AM. COVID-19 convalescent plasma treatment of moderate and severe cases of SARS-CoV-2 infection: A multicenter interventional study. Int J Infect Dis 103 (2021): 439-446.
27. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, Zhou M, Chen L, Meng S, Hu Y, Peng C, Yuan M, Huang J, Wang Z, Yu J, Gao X, Wang D, Yu X, Li L, Zhang J, Wu X, Li B, Xu Y, Chen W, Peng Y, Hu Y, Lin L, Liu X, Huang S, Zhou Z, Zhang L, Wang Y, Zhang Z, Deng K, Xia YX. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A 117 (2020): 9490-9496.
28. Martinez-Resendez MF, Castilleja-Leal F, Torres-Quintanilla A, Rojas-Martinez A, Garcia-Rivas G, Ortiz-Lopez R, Trevino V, Lara-Medrano R, Villanueva-Lozano H, Ramirez-Elizondo T S-N V. Initial experience in Mexico with convalescent plasma in COVID-19 patients with severe respiratory failure, a retrospective case series Med Rxiv (2020).
29. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T MP. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial) bmj 22 (2020): 371.
30. Wu Y, Hong K, Ruan L, Yang X, Zhang J, Xu J, Pan S, Ren L, Chen L, Huang C SY. Patients with Prolonged Positivity of SARS-CoV-2 RNA Benefit from Convalescent Plasma Therapy: A Retrospective Study. Virol Sin 35 (2020): 768-775.
31. Omrani AS, Zaqout A, Baiou A, Daghfal J, Elkum N, Alattar RA, Bakdach D, Abusriwil H, Mostafa AM, Alhariri B AN. Convalescent plasma for the treatment of patients with severe coronavirus disease 2019: A preliminary report. Journal of Medical Virology (2020).
32. Piechotta V, Chai KL, Valk SJ, Doree C, Monsef I, Wood EM, Lamikanra A, Kimber C, McQuilten Z, So-Osman C, Estcourt LJ SN. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev 7 (2020): CD013600.
33. Chai KL, Valk SJ, Piechotta V, Kimber C, Monsef I, Doree C, Wood EM, Lamikanra AA, Roberts DJ, McQuilten Z, So-Osman C, Estcourt LJ SN. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev 12 (2020): CD013600.
34. Salazar E, Christensen PA, Graviss EA, Nguyen DT, Castillo B, Chen J, Lopez BV, Eagar TN, Yi X, Zhao P, Rogers J, Shehabeldin A, Joseph D, Masud F, Leveque C, Olsen RJ, Bernard DW, Gollihar J MJ. Significantly Decreased Mortality in a Large Cohort of Corona virus Disease 2019 (COVID-19) Patients Transfused Early with Convalescent Plasma Containing High-Titer Anti-Severe Acute Respiratory Syndrome Corona virus 2 (SARS-CoV-2) Spike Proteins IgG. Am J Pathol 191 (2021): 90-107.