RESEARCH ARTICLE

Evaluation of the convalescent plasma therapy effectiveness and the factors that influence the therapeutic outcome in hospitalized COVID-19 patients: A retrospective cohort study. [version 1; peer review: 1 approved with reservations]

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Abstract

Background: As an effective antiviral therapy is not available for the treatment of the current rapidly and continuously spreading coronavirus disease (COVID-19), it is very crucial to find an alternative treatment strategy. Convalescent plasma (CP) therapy has been used for prevention and treatment of many emerging infectious diseases, however, the results of current studies on CP in COVID-19 are not consistent. Therefore, this study aimed to evaluate the effectiveness of CP therapy in hospitalized patients with COVID-19, while evaluating patient and donor-related factors that might influence the therapeutic outcome. **Methods:** We conducted a retrospective cohort study on 312 patients with either severe or critical COVID-19, who were admitted to Al-Hakeem and Al-Amal hospitals in Al-Najaf city, Iraq from June to August 2020. The patients were allocated to either the plasma therapy group (152 patients) who received CP combined with standard therapy or the standard therapy group (160 patients). The outcome measures were the 21-day mortality rate and time to clinical improvement. **Results:** The overall cumulative survival rate was significantly higher in patients who received CP compared to standard therapy alone at 21 days (68.3% vs. 46.8%, p-value = 0.010), with mean survival at 17.6 vs. 15.3 days, (p-value = 0.010). In multivariate analysis, the plasma therapy effect was an independent predictor of survival (adjusted hazard ratio, 95% confidence interval: 0.368, 0.177 – 0.765). In terms of clinical improvement, the use of CP resulted in shorter clinical improvement (median duration of

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improvement: 8 vs. 11 days, p -value = 0.007), with 74.3% improvement rate after 21 days in CP compared to 65.0% in standard therapy.

Conclusions: Therapy with CP in combination with standard therapy, independently improved survival in hospitalized patient with severe or critical COVID-19.

Keywords

COVID-19, SARS-CoV-2, Convalescent plasma, mortality, clinical improvement

This article is included in the **Emerging Diseases and Outbreaks** gateway.

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Introduction

Since the emergence of the new coronavirus COVID-19 outbreak in late 2019, the outbreak has continued to spread exponentially across the world. As of early April 2021, the global cumulative incidence has exceeded 130 million reported cases, with approximately three million associated deaths.¹ To date, an effective antiviral therapy for this disease does not exist. Therefore, it is imperative to find an alternative treatment strategy, especially for severe COVID-19 patients.^{2,3} For more than a century, convalescent plasma (CP) therapy, as a classic adoptive immunotherapy, has been used to effectively prevent and treat many infectious diseases. CP therapy has been successfully used in the treatment of severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and the 2009 H1N1 pandemic with adequate effectiveness and protection over the past two decades.^{4,5} For patients with serious or life-threatening COVID-19, the United States of America (USA) Food and Drug Administration (FDA) approved the emerging use of CP at the end of March 2020. While the use of CP might be a promising therapeutic approach, the results from previous studies are not consistent and the evidence supporting its use for the treatment of COVID-19 are not clear, therefore there is a need for further investigations.^{2,6}

Many factors might influence the therapeutic effectiveness of CP, such as patients' age, comorbidities, disease stage, and concomitant treatment.^{7,8} Other factors are related to the plasma donor, most importantly titer of the antibody. Additional factors are associated with the plasma administration protocol such as the time of administration and volume of plasma.^{9,10}

Based on the high number of patients that were treated with CP in AL Najaf, Iraq during the first wave of this pandemic, we designed this study to evaluate the effectiveness of CP therapy in hospitalized patients with COVID-19, by analyzing the variables related to the patients, donors and the plasma administration practice.

Methods

Study design

A multicenter, retrospective cohort study was conducted on adult patients that were diagnosed with severe or critical COVID-19. The study involved a retrospective assessment of the medical records of patients who were admitted to tertiary specialized hospitals (Al-Hakeem and Al-Amal hospitals). Based on the treatment protocol whether it included CP therapy or not, the patients were allocated into two groups; the standard therapy group, that consisted of patients who received the standard therapy which mainly included antiviral agents, antibiotics, steroids and anticoagulants, according to the Iraqi ministry of health (MOH) approved guidelines.¹¹ The second group was the plasma therapy group that consisted of patients who received CP combined with the standard therapy.

Study setting

The study included patients that were admitted to Al-Hakeem and Al-Amal hospitals from June 1, 2020 till August 31, 2020, in Al-Najaf Province, Iraq. Al-Hakeem hospital is the first center for the admission of COVID-19 patients in Najaf, and it contains 264 beds. Al-Amal hospital has 170 beds, including 50 intensive care unit (ICU) beds, and it has been assigned as a referral center for severe and critical cases of COVID-19.

Ethical consideration

The Scientific Research Committee at Al-Najaf Health Directorate approved this study which involved Al-Hakeem hospital and the main blood bank with the approval number (19421), and Al-Amal hospital with approval number (30418). This study was also granted approval by the ethics and scientific committee of faculty of pharmacy/the University of Kufa with approval number (2403). All participants gave written informed consent to participate in this study. The current study is registered at Clinical Trials.gov (<https://clinicaltrials.gov/ct2/show/NCT04764747>) with the registration number (NCT04764747).¹²

Eligibility criteria

Eligible participants were 18 years of age or older, with COVID-19 infection confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) test, who were hospitalized with severe or critical case of COVID-19. We excluded patients who did not require oxygen therapy, patients that were discharged or died within 48 hours of admission, patients with a history of allergy to plasma transfusion, and those with incomplete data on their medical records.

The study participants with severe COVID-19 were defined as patients who had oxygen saturation of less than or equal to 93%, therefore, they needed oxygen therapy. Patients with critical cases of COVID-19 were defined as patients who needed mechanical ventilation and ICU observation.^{2,13}

Data sources

The medical records of patients diagnosed with COVID-19 were taken from the archive unit of the tertiary specialized public hospital and reviewed retrospectively. Data collection period was from September 2020 to February 2021. Data was collected by using a chart extraction sheet which is used to collect information from patients' medical records. These medical records were selected based on chronological categorization in the statistical unit according to admission date. Blind data abstraction was performed for this study. Also, two senior physicians reviewed the data extracted from the medical records and approved the abstraction process. The chart extraction sheet consists of patients' demographics (age, gender, occupation, address), comorbidities (hypertension, coronary artery disease, type 2 diabetes mellitus (T2DM), obstructive airway disease, and chronic kidney disease), date of admission, date of discharge, length of stay in the hospital, symptoms (fever, cough, shortness of breath, fatigue, headache, sore throat, nausea and vomiting, oxygen-support categories were defined either as ambient air, low-flow oxygen, high-flow oxygen, and mechanical ventilation,¹⁴ vital signs on admission (temperature, heart rate, oxygen saturation (SpO₂%)). Additionally, laboratory parameters such as white cell counts, lymphocytes count, serum creatinine, D-dimer, ferritin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), were included. Lastly, type of medications, and outcomes, which was defined as in-hospital mortality and clinical improvement (according to the modified World Health Organization (WHO) ordinary scale),^{13,14} were considered in the chart sheet. Information of plasma donor that was obtained from the plasma unit of the main blood bank consisting of donors' demographics, ID code of plasma bottle, and immunoglobulin G (IgG) titer (*See Underlying data: <http://doi.org/10.5281/zenodo.4982052>*¹⁵) was also included.

Outcomes measures

In this study the primary outcome was the in-hospital mortality rate (MR) (number of deaths with a 21-day time frame). The secondary outcome was the association with various predictors (sociodemographic, clinical, laboratory variables and medications). Both these outcomes were examined with uni- and multivariate analysis.

The time to clinical improvement was also assessed. Clinical improvement for COVID-19 was defined as a reduction of two-points in a modified six-point scale, discharged or achieved criteria of discharge, which was defined as clinical recovery (i.e., SpO₂ equal to 94% on room air, fever subsided, and relief of cough, all continued for at least 72 hours) (one-point); hospitalized without oxygen therapy (two-points); hospitalized on low-flow oxygen therapy (three-points); hospitalized on high-flow oxygen therapy (four-points); hospitalized and required mechanical ventilation (five-points); death (six-points).^{14,16}

Sample size

The sample size was based on all medical records available in the archive unit for patients admitted to these public hospitals during June, July, and August 2020. Total of 312 patients included in the statistical analysis as illustrated in (Figure 1). Post hoc power analysis of sample size based on mortality outcome and level of significance at alpha = 0.05 (type I error) yielded statistic power of 97.3% (1- type II error) in detecting the difference between the two group of the study.

Statistical analysis

Normality test was performed for all variables. Normally distributed mean was used to present the data, while for variables with non-normal distribution median and interquartile range (IQR) (25% to 75% percentile range) were used. Chi-square test or Fisher exact test was used to analyze the discrete variable. To assess the difference in continuous variables; two-samples t-test (in normally distributed variables), and Mann-Whitney U test was used in variables with non-normal distribution. Kaplan–Meier analysis¹⁷ was used to estimate the median time of the cumulative percentage of survival or clinical improvement, the Log-rank test was used to calculate the p-value and to compare the significance between the two groups. Lack of clinical improvement at day 21 and death before day 21 was considered as right censored for that day.

Univariate analysis was performed using Cox regression for all patients' variables, and if p-value < 0.1, the variables were included in the multivariate Cox proportional hazard model to allow adjustment of certain confounder variables. The hazard ratio (HR) was calculated by using the Cox proportional hazard regression analysis, to find the time-dependent association of the model, in order to calculate the 95% confidence interval. Missing data were excluded from the final analysis.

SPSS 22.0.0 (Chicago, IL), GraphPad Prism version 8.1.0 for Windows (<https://www.graphpad.com/>) was used for the statistical analysis. P-value was considered statically significant if less than 0.05.

Figure 1. Flowchart of the study population.

Results

Baseline patient demographic and clinical characteristics

In this cohort the mean age of the patients was $55.1(\pm 13.6)$ years, and 70.2% were male. Overall, 82% of the hospitalized patients had cough and 81.4% had shortness of breath (SOB). The mean SpO_2 was 82.7 % (which is consistent with the disease severity stage of the patients included in the study). All baseline characteristics of patients' demography, comorbidities and clinical parameters of the two groups were not statistically significant, except for azithromycin and lopinavir/ritonavir that were significantly higher in patients treated with plasma therapy, while acetaminophen and favipiravir were significantly higher in patients treated with the standard therapy (Table 1). Plasma characteristics are illustrated in Table.

Effect of plasma therapy on mortality rate

The survival rate was 90.2% in the plasma therapy group compared to 84.2% in the standard therapy group, after 7 days. Additionally, the survival rate in the plasma therapy group was significantly higher (77.7%) compared to the standard group (60.5%) after 14 days ($p\text{-value} = 0.010$). This trend continued after 21 days in the plasma group (68.3%) vs. (46.8%) in the standard group, with a mean survival time of 17.6 in the plasma group and 15.3 in the standard therapy group (Table 3).

Table 1. Baseline patients' demographic and clinical characteristics.

Variables	All	Standard therapy	Plasma therapy	p-value
Number (n)	312	160	152	-
Age (y), mean ($\pm$ SD)	55.1 ($\pm$ 13.6)	56.0 ($\pm$ 14.4)	54.1 ($\pm$ 12.6)	0.219
Gender				0.939
Female n (%)	93 (29.8%)	48 (30%)	45 (29.6%)	
Male n (%)	219 (70.2%)	112 (70%)	107 (70.4%)	
Employed, n (%)	59 (18.9%)	27 (16.9%)	32 (21.1%)	0.346
Residence				0.731
Rural	20 (6.4%)	11 (6.9%)	9 (5.9%)	
Urban	292 (93.6%)	149 (93.1%)	143 (94.1%)	
Comorbidities				
Hypertension	126 (40.4%)	66 (41.3%)	60 (39.5%)	0.749
T2DM	122 (39.1%)	65 (40.6%)	57 (37.5%)	0.572
Smoking	56 (17.9%)	28 (17.5%)	28 (18.4%)	0.832
IHD	46 (14.7%)	25 (15.6%)	21 (13.9%)	0.652
Asthma or COPD	12 (3.8%)	9 (5.6%)	3 (2.0%)	0.094
CKD	9 (2.9%)	4 (2.5%)	5 (3.3%)	0.745
Clinical Presentation				
Cough	257 (82.4%)	133 (83.1%)	124 (81.6%)	0.720
SOB	254 (81.4%)	128 (80%)	126 (82.9%)	0.511
Fever	87 (27.9%)	39 (24.4%)	48 (31.6%)	0.156
Headache	49 (15.7%)	27 (16.9%)	22 (14.5%)	0.560
Sore throat	25 (8%)	16 (10%)	9 (5.9%)	0.185
Fatigue	24 (7.7%)	16 (10%)	8 (5.3%)	0.117
N and V	7 (2.2%)	4 (2.5%)	3 (2.0%)	0.999
Temperature	37.1 ($\pm$ 0.7)	37.1 ($\pm$ 0.7)	37.1 ($\pm$ 0.7)	0.720
HR	89.0 ($\pm$ 15.8)	90.1 ($\pm$ 16.8)	88.0 ($\pm$ 14.7)	0.238
SpO ₂ (%)	82.7 ($\pm$ 6.8)	82.3 ($\pm$ 7.3)	83.1 ($\pm$ 6.2)	0.310
WBC	10.6 ($\pm$ 5.0)	10.8 ($\pm$ 4.8)	10.4 ($\pm$ 5.2)	0.487
Lymphocyte count	1.1 ($\pm$ 0.6)	1.1 ($\pm$ 0.7)	1.0 ($\pm$ 0.6)	0.503
Platelet count	238.4 ($\pm$ 89.4)	235.8 ($\pm$ 84.0)	241.1 ($\pm$ 95.0)	0.626
Creatinine (IQR)	0.7 (0.6-0.9)	0.7 (0.6-0.9)	0.73 (0.6-0.9)	0.999
D-dimer (IQR)	921 (322-2399)	960 (363-3121)	664 (284-2198)	0.200
Ferritin	682.0 ($\pm$ 429.6)	668.3 ($\pm$ 473.6)	698.9 ($\pm$ 370.7)	0.665
AST (IQR)	40.4 (30.5-55.9)	37.1 (28.3-52.2)	47 (31.8-66)	0.062
ALT (IQR)	36 (26-72.6)	33.9 (26.0-58.0)	43.2 (24.2-73.4)	0.145
Oxygen Therapy				
Invasive mechanical ventilation				0.755
Negative	269 (86.2%)	137 (85.6%)	132 (86.8%)	
Positive	43 (13.8%)	23 (14.4%)	20 (13.2%)	
High flow oxygen				0.732
Negative	62 (19.9%)	33 (20.6%)	29 (19.1%)	
Positive	250 (80.1%)	127 (79.4%)	123 (80.9%)	

Table 1. *Continued*

Variables	All	Standard therapy	Plasma therapy	p-value
Low flow oxygen				0.903
Negative	293 (93.9%)	150 (93.8%)	143 (94.1%)	
Positive	19 (6.1%)	10 (6.3%)	9 (5.9%)	
Medications				
Enoxaparin	292 (93.6%)	150 (93.8%)	142 (93.4%)	0.906
Acetaminophen	278 (89.1%)	150 (93.8%)	128 (84.2%)	0.007 *
Bromhexine	272 (87.2%)	145 (90.6%)	127 (83.6%)	0.062
Dexamethasone	256 (82.1%)	135 (84.4%)	121 (79.6%)	0.272
Meropenem	197 (63.1%)	93 (58.1%)	104 (68.4%)	0.060
Famotidine	126 (40.4%)	67 (41.9%)	59 (38.8%)	0.582
Ceftriaxone	120 (38.5%)	66 (41.3%)	54 (35.5%)	0.299
Methylprednisolone	89 (28.5%)	46 (28.7%)	43 (28.3%)	0.928
Favipravir	76 (24.4%)	49 (30.6%)	27 (17.8%)	0.008 *
Hydroxychloroquine	71 (22.8%)	34 (21.3%)	37 (24.3%)	0.515
Ivermectin	68 (21.8%)	33 (20.6%)	35 (23.0%)	0.608
Azithromycin	62 (19.9%)	24 (15.0%)	38 (25.0%)	0.027 *
Lopinavir/Ritonavir	59 (18.9%)	18 (11.3%)	41 (27.0%)	<0.001*
Tocilizumab	24 (7.7%)	10 (6.3%)	14 (9.2%)	0.327
Rivaroxaban	20 (6.4%)	8 (5.0%)	12 (7.9%)	0.297

This table indicates the demographics and clinical characteristics of the hospitalized patients treated with either standard or plasma therapy. Mass-Whitney test was used for the evaluation of creatinine, D-dimer, AST and ALT. IHD: ischemic heart disease; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; SOB: shortness of breath; N and V: nausea/vomiting; HR: heart rate; SpO₂: oxygen saturation; WBC: white blood cells; AST: aspartate aminotransferase; ALT: alanine transaminase. IQR: interquartile range; SD (standard deviation). *Represents p-value: *p ≤ 0.05.

Table 2. Assessment of plasma related parameters in patients who received plasma therapy.

Variable	Value
Total daily dose, mean (±SD)	376.6 (±79.7)
Time before plasma transfusion, median (IQR)	2 (2-4)
Donor age, mean (±SD)	36.5 (±10.4)
Donor gender, n (%)	
Female	9 (6.6%)
Male	128 (93.4%)
Antibodies titer (IgG), mean (±SD)	16.7 (±10.8)

This table shows factors such as donor characteristics and the titer of the antibody that can influence the plasma treatment. SD: standard deviation; IQR: interquartile range.

Table 3. Kaplan Meir analysis of the effect of plasma therapy on mortality rate.

	7 days survival	14 days survival	21 days survival	Mean survival rate (95%CI)	p-value
Overall	87.1%	69.6%	58.8%	16.5 (15.6-17.3)	0.010*
Therapy Plasma	90.2%	77.7%	68.3%	17.6 (16.5-18.6)	
Therapy Standard	84.2%	60.5%	46.8%	15.3 (14.0-16.5)	

This table indicates the effect of the plasma therapy and standard therapy on mortality rate. Log-rank analysis was used for the data evaluation. The median survival rate could not be calculated, instead mean survival rate was considered. CI: confidence interval. *Represents p-value: *p ≤ 0.05.

Kaplan-Meier survival analysis revealed statistically significant improvement in the survival in the plasma therapy group, compared with the standard therapy group (Figure 2).

Univariate and multivariate analysis

The univariate analysis showed that the use of plasma compared to standard therapy resulted in a reduced risk of death by 54.7%. The results from the overall study population included in the multivariate model showed that plasma therapy has a

Figure 2. Kaplan Meir curve of overall mortality rate for plasma therapy vs. standard therapy.

Table 4. Cox-proportional hazard analysis for predictors of survival rate.

Predictors	Univariate		Multivariate	
	HR (95%CI)	p-value	HR (95%CI)	p-value
Plasma therapy	0.557 (0.352-0.883)	0.013*	0.368 (0.177-0.765)	0.007*
T2DM	1.52 (0.975-2.371)	0.065*	3.189 (1.468-6.928)	0.003*
CKD	2.193 (0.886-5.430)	0.090*	1.420 (0.229-8.812)	0.707
Heart rate	1.016 (1.001-1.031)	0.042*	1.023 (0.999-1.047)	0.060
SpO ₂	0.940 (0.917-0.964)	<0.001*	0.988 (0.944-1.035)	0.618
WBC	1.076 (1.04-1.113)	<0.001*	1.096 (1.027-1.170)	0.006*
Creatinine	1.197 (1.059-1.365)	0.004*	1.388 (0.915-2.106)	0.123
D-dimer	1.001 (1.001-1.002)	0.005*	1.000 (1.000-1.000)	0.018*
Invasive mechanical ventilation	4.362 (2.769-6.87)	<0.001*	1.140 (0.108-12.009)	0.913
High flow O ₂	0.303 (0.193-0.476)	<0.001*	0.813 (0.092-7.164)	0.852
Azithromycin	0.427 (0.213-0.857)	0.017*	0.748 (0.234-2.393)	0.624
Tonics	0.380 (0.174-0.827)	0.015*	1.124 (0.219-5.772)	0.889
Bromhexin	0.555 (0.316-0.975)	0.041*	0.802 (0.261-2.464)	0.700
Hydroxychloroquine	0.409 (0.188-0.891)	0.024*	0.604 (0.100-3.637)	0.582
Rivaroxaban	0.109 (0.015-0.785)	0.028*	0.112 (0.013-0.930)	0.043*
Meropnam	2.415 (1.326-4.398)	0.004*	2.374 (0.710-7.933)	0.160
Methylprednisolone	2.065 (1.322-3.226)	0.001*	0.727 (0.303-1.745)	0.476

This table shows the cox-proportional hazard analysis for the predictors of survival rate. T2DM: type 2 diabetes mellitus, CKD: chronic kidney disease; SpO₂: oxygen saturation; WBC: white blood cells; HR: hazard ratio; CI: confidence interval. *Represents p-value: *p ≤ 0.05.

Table 5. Cox-proportional hazard analysis of predictors for mortality in patients who received plasma therapy.

Variables	Univariate		Multivariate	
	HR (95%CI)	p-value	HR (95%CI)	p-value
T2DM	1.541 (0.988-2.403)	0.057*	75.558 (1.130-5,051.332)	0.044*
HR [®]	1.013 (0.998-1.028)	0.079	0.801 (0.602-1.065)	0.127
SpO ₂	0.937 (0.915-0.959)	<0.001*	2.451 (0.996-6.031)	0.051
WBC	1.078 (1.044-1.114)	<0.001*	1.677 (0.957-2.940)	0.071
Creatinine	1.190 (1.050-1.348)	0.006*	2.999 (0.036-248.355)	0.626
D-dimer	1.000 (1.000-1.000)	0.005*	1.000 (1.000-1.001)	0.017*
Invasive mechanical ventilation	4.823 (3.063-7.597)	<0.001*	0.014 (UD-UD)	0.976
High flow oxygen	0.286 (0.182-0.448)	<0.001*	0.001 (UD-UD)	0.956
Azithromycin	0.434 (0.217-0.870)	0.019*	0.075 (0.000-22.105)	0.372
Tonics	0.417 (0.191-0.909)	0.028*	10.630 (UD-UD)	0.975
Tocilizumab	1.896 (1.000-3.596)	0.050*	4.496 (0.183-110.492)	0.358
Hydroxychloroquine	0.384 (0.176-0.836)	0.016*	2.212 (0.036-135.899)	0.705
Rivaroxaban	0.142 (0.020-1.024)	0.053	0.001 (UD-UD)	0.805
Meropenem	2.663 (1.463-4.848)	0.001*	0.001 (0.000-7.757)	0.135
Lag time	0.729 (0.575-0.924)	0.009*	0.047 (0.002-1.208)	0.065
Plasma amount	0.999 (0.997-1.000)	0.031*	0.993 (0.986-1.000)	0.051
Antibody titer	0.951 (0.912-0.992)	0.021*	0.457 (0.233-0.898)	0.023*

This table indicates the cox-proportional hazard analysis for mortality in the plasma therapy group. T2DM: type 2 diabetes mellitus, HR[®]: heart rate; SpO₂: oxygen saturation; WBC: white blood cells; HR: hazard ratio; CI: confidence interval. *Represents p-value: *p ≤ 0.05.

Table 6. Kaplan Meir analysis of the effect of plasma therapy on clinical improvement rate.

	Seven days improvement	14 days improvement	21 days improvement	Medium duration of improvement (95%CI)	p-value
Overall	21.8%	62.8%	69.6%	10 (9.1-10.9)	
Therapy Plasma	44.1%	67.1%	74.3%	8 (6.3-9.7)	0.007*
Therapy Standard	18.1%	58.8%	65.0%	11 (9.9-12.1)	

This table indicates the effects of plasma therapy on clinical improvement rate analyzed by Kaplan-Meier. Log-rank test was used to obtain these results. CI: confidence interval.

statistically significant effect on improving the survival rate and it can be considered as an independent predictor of mortality. This adjusted analysis revealed a further reduction in the HR of the plasma therapy group from 0.557 (0.352-0.883) in unadjusted analysis to 0.368 (0.177-0.765). This meant that the reduction in the risk of death reached 63.2%, thus indicating that plasma therapy is more effective in improving survival rates. The increase in white blood cells (WBC), D-Dimer, and T2DM were independent predictors of mortality rate, while both the use of plasma and rivaroxaban reduced the risk of MR independently, as shown in [Table 4](#).

In the multivariate analysis for the plasma therapy group, the result showed that as independent predictors of mortality, T2DM and D-Dimer are associated with increased mortality, while high antibody titer is associate with decrease mortality as illustrated in [Table 5](#).

Effect of plasma therapy on clinical improvement

Interestingly, the median time to improvement was three days faster in plasma therapy than standard therapy (8 days vs. 11 days). Kaplan-Meier analysis showed a significant statistical difference between the two groups. The cumulative

Figure 3. Kaplan Meir curve of cumulative incidence of clinical improvement.

incidence of clinical improvement was significantly higher in patients who received plasma therapy (44.1%) than those who received standard treatment (18.1%), after 7 days. Treatment after 14 days indicated that the cumulative incidence of clinical improvement was higher in the plasma therapy (67.1%) vs. standard therapy group (58.8.9%). Additionally, 21 days post-treatment the cumulative incidence of clinical improvement was still significantly higher in plasma therapy (74.3%) compared to standard therapy group (65.0%) (Table 6 and Figure 3)

Discussion

COVID-19 is a rapidly evolving infection that lacks an effective antiviral treatment. CP therapy as an available treatment can potentially be an effective and lifesaving treatment for this disease.⁹ Several previous outbreaks of respiratory viral infection have been treated by CP such as SARS-CoV and MERS-CoV¹⁸. However, in patients with COVID-19, the effectiveness of CP is not consistent, and it is dependent on many prognostic factors,^{9,19} therefore, we designed this study to evaluate the effectiveness of CP in hospitalized patients with COVID-19 to explore the factors related to the patients, donors and CP administration practice that might influence the therapeutic outcome.

In this retrospective cohort study, the plasma therapy showed considerable survival improvement as evident by a reduction in the risk of in-hospital mortality after 21 days, compared to the patients who received standard therapy. Also, the time to clinical improvement was significantly faster in patients on CP combined with standard therapy, than those on standard therapy alone. The plasma therapy had three days shorter median time to clinical improvement compared to the standard therapy group. Additionally, the cumulative incidence of clinical improvement was 74.3% in the plasma therapy group vs. 65% in the standard therapy group.

These positive effects of plasma therapy on survival rate and clinical improvement in the present study are in line with the findings from a retrospective cohort study by Xinyi Xia et al.²⁰ In this study, 1568 patients with severe and critical COVID-19 were grouped into 1430 patients who received standard therapy and 138 patients who received plasma therapy.²⁰ The results indicated that the patients had improved clinical symptoms and mortality after the transfusion with CP.²⁰

Similarly, a prospective study conducted on 316 patients with severe and/or critical COVID-19 infection, showed that the administration of CP significantly reduced mortality and improved clinical symptoms.²¹ Additionally, improved clinical symptoms and mortality after administration of CP have been recently reported by a multicenter non-randomized prospective interventional cohort study on patients with a moderate or severe stage of COVID-19.²²

Strong evidence supporting these beneficial effects of plasma therapy on survival and clinical improvement was also reported in several SARS and COVID-19 meta-analysis studies.^{10,23,24}

The positive effects of CP on patient survival and clinical improvement may be attributed to the antiviral mechanism of CP via neutralizing antibodies that enhance the viral clearance and provides immunomodulation via the anti-inflammatory

effect. Furthermore, the control of overactive immune response by preventing complement activation and blocking autoantibodies, as well as regulating the hypercoagulable state, can prevent lung damage and bad prognosis.²⁵

However, the results from plasma therapy are not always consistent, as indicated by the results of a particular systematic review and meta-analysis, which included 10 randomized control trials (RCTs) with over 10,000 patients.²⁶ Simonovich *et al.*, demonstrated that CP therapy was not beneficial for mortality and improvement rate in severe patients with COVID-19, however the time of plasma transfusion was considered to be the limitation of their study.²⁷ In another RCTs, CP therapy did not reduce mortality or the progress in disease severity, however, about 2/3 of patients received plasma with low antibodies titer, and the remaining patients receiving plasma without antibody detections.²⁸ Also, the preliminary analysis from a very recent RTCs did not show survival improvement in hospitalized patients with either confirmed or suspected COVID-19. The possibility of different virus variants between the donor and recipient and the time of CP administration, could explain the non-significant findings of CP in COVID-19 in this study.²⁹ In general, these discrepancies and mixed results regarding the benefits of CP in COVID-19 mainly is dependent on many patients related factors such as age, comorbidities, clinical characteristics, degrees of disease severity, as well as variations in medication use in standard therapy. Most importantly the donors' related factors such as antibody titers must be considered, along with the plasma administration protocol including the volume administered and the time of administration.^{9,10,19}

In the present study, the confounding effects of these variables on the primary outcome were explored by multivariate analysis which confirmed the beneficial effect of plasma in reducing the risk of mortality independent of other variable effects. It is worth mentioning that most patients in this study were administered plasma therapy within the first two days of admission to the hospital. Also, the plasma average antibody IgG index was high (16.7 ± 10.8), which is considerably associated with a reduced risk of death. Consistently, a retrospective study in the USA on 3082 hospitalized patients with COVID-19 has revealed that the transfused plasma with high IgG antibody levels were correlated with a lower risk of mortality, compared to the transfused plasma with low antibody titer.³⁰ Regarding the time of administration, RCTs in Argentina that included 160 elderly patients, showed that the early administration of CP within 72 hours of the onset of symptoms was associated with a lower risk of progression to severe COVID-19 and a lower risk of death, in comparison to the control group.³¹ T2DM patients and individuals with a high level of D-dimer and WBC were associated with an increased risk of death. Comparable findings were also reported from previous studies.^{32,33}

Our study has some limitations. Firstly, the study design was retrospective, which was subjected to high effect of the cofounders. We tried to reduce that risk by increasing the sample size (reduce type II error); in addition adjusted analysis (multivariate regression) was used, in order to reduced the effect of cofounders. Second, the time from onset of symptoms to hospital admission was not known, however at the beginning of the pandemic in Iraq, most of the patients were referred to the hospital, once their PCR test was positive.

Conclusion

Therapy with PC in combination with standard therapy independently improved survival in hospitalized patient with severe or critical COVID-19. We recommend a large double-blind randomized trial with emphasis on controlling the factors related to the plasma administration protocols.

Data availability statement

Underlying data

Zenodo: Evaluating the effectiveness of convalescent plasma therapy and the factors that influence the therapeutic outcome in hospitalized COVID-19 patients: A retrospective cohort study.

<http://doi.org/10.5281/zenodo.4982052>.³¹

The project contains the following underlying data:

Database: Data for CP in COVID-19 patients.

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

Acknowledgments

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This is a non-randomized multicenter retrospective cohort trial in Iraq. It was conducted at the time of the wild-type variants, so convalescent plasma was collected from unvaccinated donors.

The Methods section is lacking information about anti-Spike IgG assay (the authors report outputs in Table 2 without unit of measurement), which leaves the doubt about potency. The time before plasma transfusion (median 2 days) should be better specified if calculated from the onset of symptoms or (more likely) from hospitalization. This is an important parameter that, together with the undisclosed serostatus before transfusion, could let us better understand whether the patients were still in the time window in which benefit from convalescent plasma is expected.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: COVID-19 convalescent plasma; emerging pathogens

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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