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Convalescent plasma for the treatment of patients with severe coronavirus disease 2019: A preliminary report

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Abstract

Background: The role of convalescent plasma therapy for patients with coronavirus disease 2019 (COVID-19) is unclear.

Methods: We retrospectively compared outcomes in a cohort of critical COVID-19 patients who received standard care (SC Group) and those who, in addition, received convalescent plasma (CP Group).

Results: In total, 40 patients were included in each group. The median patient age was 53.5 years (interquartile range [IQR] 42–60.5), and the majority of patients required invasive ventilation (69, 86.2%). Plasma was harvested from donors after a median of 37 days (IQR 31–46) from the first positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) result and 26 days (IQR 21–32) after documented viral clearance; it was administered after a median of 10 days (IQR 9–10) from the onset of symptoms and 2.5 days (IQR 2–4) from admission to intensive care unit. The primary endpoint of improvement in respiratory support status within 28 days was achieved in 26 patients (65%) in the SC Group and 31 patients (77.5%) in the CP Group (p = .32). The 28-day all-cause mortality (12.5% vs. 2.5%; p = .22) and viral clearance (65% vs. 55%; p = .49) were not significantly different between the two groups. Convalescent plasma was not significantly associated with the primary endpoint (adjusted hazard ratio 0.87; 95% confidence interval 0.51–1.49; p = .62). Adverse events were balanced between the two study groups.

Conclusion: In severe COVID-19, convalescent plasma therapy was not associated with clinical benefits. Randomized trials are required to confirm our findings.

KEYWORDS
convalescent plasma, coronavirus, COVID-19, passive immunotherapy, SARS-CoV-2

1 | INTRODUCTION

The total global number of individuals diagnosed with coronavirus disease 2019 (COVID-19), caused by the novel betacoronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has surpassed 10 million, with more than 500,000 associated deaths.[1] Up to 10% of COVID-19 patients may develop organ failure and may require admission to an intensive care unit (ICU).[2] Several investigational antiviral agents are currently being evaluated for the treatment of patients with severe and critical COVID-19.[2] Thus far, hydroxychloroquine, with or without azithromycin, lopinavir–ritonavir, and remdesivir have not been shown to be associated with a clear clinical benefit in patients with severe COVID-19.[3–5]

In patients with severe influenza, convalescent plasma was associated with improved viral clearance and reduced mortality.[6] Similarly, convalescent plasma therapy for patients with severe acute respiratory syndrome (SARS) shortened hospital stays and lowered overall mortality.[7] Convalescent plasma may be useful in the treatment of severe COVID-19. However, peer-reviewed clinical data are limited.[8] Using a cohort of patients with severe COVID-19, we aimed to assess the clinical benefits of convalescent plasma over and above standard care.

2 | METHODS

2.1 | Study design and patients

Hamad Medical Corporation (HMC) provides medical care for all COVID-19 patients in Qatar. SARS-CoV-2 infection was confirmed on respiratory samples using reverse transcription polymerase chain reaction (RT-PCR) assays TaqPath COVID-19 Combo Kit (Thermo Fisher Scientific) or Cobas SARS-CoV-2 Test (Roche Diagnostics).

COVID-19 is classified as severe if any one or more of the following is present: respiratory rate >30/min, oxygen saturation ≤90% while in ambient room air, partial pressure of oxygen–oxygen concentration (PaO_2/FiO_2) ≤ 300 mmHg, hypotension, or any organ failure.[2] Standard care for patients with severe COVID-19 in HMC involved supportive care and antiviral therapy with hydroxychloroquine, azithromycin, and/or lopinavir–ritonavir. Tocilizumab could be added for those with evidence of significant systemic inflammation and methylprednisolone for acute respiratory distress syndrome (ARDS). Individual regimens were selected by the attending clinical teams based on patients' characteristics and needs.

From April 13, 2020, convalescent plasma derived from recovered COVID-19 patients was available for clinical use for patients with severe COVID-19. Plasma donors are adults whose COVID-19 symptoms have resolved more than 2 weeks ago, with documented negative upper airway SARS-CoV-2 RT-PCR and negative serological tests for syphilis and blood-borne viruses.

We retrospectively included patients from HMC COVID-19 database. The convalescent plasma group (CP Group) included patients who received SARS-CoV-2 convalescent plasma therapy within the first 7 days of admission to ICU, required mechanical ventilation, and completed 28 days of follow-up by June 1, 2020. Criteria for inclusion in the comparator group, the standard care (SC Group), included laboratory-confirmed SARS-CoV-2 infection, need for mechanical ventilation in ICU, and completion of 28 days of follow-up by June 1, 2020. Starting from the earliest case of SARS-CoV-2 in Qatar, consecutive patients eligible for inclusion in the SC Group were selected until one control was identified for each individual in the CP Group.

2.2 | Procedures

Donor apheresis was performed using Trima Accel Automated Blood Collection System (Terumo BCT) and inactivated using Mirasol PRT System (Terumo BCT). Each recipient received a total of 400 ml of ABO-compatible convalescent plasma. Donation and receipt of plasma were subject to HMC standard clinical policies. SARS-CoV-2 antibody titers in the donated plasma were not available. The date on which a patient was admitted to ICU was designated as study day 1. All outcomes were recorded on the basis of the patients' disposition up to study day 28. Data including outcomes and adverse events were retrieved retrospectively from the electronic healthcare records. Radiological findings were reviewed and reported by a single radiologist who was blinded to the group allocation.

The results are reported according to the recommendations of STROBE initiative.[9] The study was approved by HMC's Institutional Review Board (MRC0120191), with a waiver of informed consent.

2.3 | Outcomes

The primary outcome was improvement in the respiratory status, defined as two-category improvement on a six-level ordinal scale.[4] The scale in a descending order was death, invasive mechanical ventilation, noninvasive ventilation (NIV) or high-flow nasal oxygen (HFNO) therapy, oxygen therapy other than NIV or HFNO, hospitalization without need for oxygen therapy, and discharge home or a community isolation facility. Secondary outcomes were as follows: discharged alive from ICU by study day 28 and viral clearance, defined as two consecutive negative RT-PCR tests on airway samples taken within a gap of more than 24 hours.

2.4 | Statistical analysis

In the absence of data on treatment effect, the sample size for the study was arbitrarily set at 40 patients in each group. This sample size provides approximately 80% power to detect an increase in the primary endpoint from 30% in the SC Group to 65% in the CP Group, at a two-sided significance level of .05.

Categorical data were summarized as numbers (percentages) and compared using Fisher's exact test, whereas continuous data were presented as medians and interquartile ranges (IQR), and

compared using Wilcoxon rank-sum test. Cox proportional hazard was used to identify covariables associated with time to improvement in respiratory support status. To avoid overfitting the model, given the sample size and the number of events in the study, the number of variables included in the multivariate model was limited to four. In addition to receipt of convalescent plasma therapy and need for invasive mechanical ventilation, Acute Physiology and Chronic Health Evaluation (APACHE II) score was included due to its established role as a prognostic tool in critically ill patients.[10] The fourth variable in the multivariable Cox model was receipt of systemic corticosteroid therapy, which was recently reported to be associated with survival benefit in patients with severe COVID-19.[11] Kaplan–Meier survival curve with log-rank p value was used to compare time to improvement in respiratory status between the two study groups.

All p values were two-sided with a threshold of <.05 for statistical significance. Statistical analyses were performed using Stata Statistical Software Release 15.1 (StataCorp LLC).

3 | RESULTS

Eighty individuals were included, with 40 in each group. The majority were males (69, 86.3%) and the median age was 53.5 years (IQR 42–60.5). Diabetes mellitus (40, 50%) and hypertension (32, 40%) were common, and median body mass index (BMI) was 27.4 kg/m^2 (IQR 25–32.4). The median duration between the onset of symptoms and admission to ICU was 7 days (IQR 6–9). Cough (73, 91.2%) and fever (68, 85.0%) were the most frequent presenting symptoms. The median APACHE II score was 12 (IQR 9–12), and all patients had pulmonary infiltrates on their chest radiographic images (Table 1).

During their ICU stay, the majority of patients required invasive mechanical ventilation (69, 86.2%), and/or vasopressor support (42, 52.5%). All patients received hydroxychloroquine, azithromycin, and lopinavir–ritonavir, whereas tocilizumab was given to 73 patients (91.2%) and intravenous methylprednisolone to 66 patients (82.5%). Compared with the CP Group, the SC Group had higher median serum creatinine at admission to ICU (90 vs. 81 µmol/L, $p = .009$). There were no other significant baseline differences between the two groups (Table 1).

The median donor age was 36.5 years (IQR 26.3–41). All donors had infiltrates in their chest X-rays. Seventeen donors (42.5%) required oxygen via nasal canulae, nine (22.5%) required noninvasive ventilation, and three (7.5%) required invasive mechanical ventilation. Plasma was harvested after a median of 37 days (IQR 31–46, range 26–56) from the first positive SARS-CoV-2 PCR result and 26 days (IQR 21–32, range 14–45) after documented viral clearance; it was administered after a median of 10 days (IQR 9–10) from the onset of symptoms and 2.5 days (IQR 2–4, range 1–7) from admission to ICU.

Adverse events occurred in 77 patients (96.3%), including grade 4 in eight, seven of which were from the SC Group. The frequency of adverse events was comparable between the two groups (Table 1).

Overall, the primary endpoint of improvement in respiratory support status was achieved in 57 patients (71.3%): 26 (65%) in the SC Group and 31 (77.5%) in the CP Group ($p = .32$). There were no significant differences between the SC Group and CP Group in the proportions of patients who were discharged alive from ICU within 28 days (65% for both groups; $p > .99$), viral clearance (65% vs. 55%; $p = .49$), or the 28-day all-cause mortality (12.5% vs. 2.5%; $p = .22$; Table 1).

Compared with patients in whom improvement in respiratory status was documented within 28 days, patients in whom it was not achieved were significantly older (median age 60 vs. 48 years; $p < .001$), had higher APACHE II scores (13 vs. 11; $p = .017$), and were more likely to have required hemodialysis (21.7% vs. 2 (3.5%; $p = .019$). Convalescent plasma recipients constituted 54.4% of those patients in whom the primary endpoint was achieved, compared with 39.1% of those in whom it was not achieved ($p = .32$; Table 2).

Time to improvement in the respiratory support status was not significantly different between the two study groups ($p = .99$; Figure 1). In the multivariable Cox model, higher APACHE II score (adjusted hazard ratio [aHR], 0.89; 95% confidence interval [CI], 0.83–0.95; $p = .001$) and receipt of methylprednisolone (aHR, 0.23; 95% CI 0.11–0.50; $p < .001$) were independently associated with a lower likelihood of achieving improvement in respiratory support status within 28 days. Receipt of convalescent plasma was not associated with time to improvement in the respiratory support status (aHR, 0.87; 95% CI, 0.51–1.49; $p = .622$; Table 3).

4 | DISCUSSION

We report 28-day outcomes for patients with severe COVID-19 requiring mechanical ventilation in ICU. The administration of convalescent plasma after a median of 10 days from the symptom onset was not associated with an increased likelihood of improvement in the respiratory support status. Our results are consistent with those recently reported in an underpowered randomized clinical trial where the administration of convalescent plasma did not improve time to clinical improvement in patients with critical COVID-19.[12]

There are several possible explanations for our findings. First, the majority of patients in this study (86.2%) required invasive ventilation. Severe COVID-19 is largely driven by a dysregulated inflammatory response.[13] SARS-CoV-2-neutralizing antibodies may not be adequate to reverse the immunological cascade and result in clinical improvement.[14] Indeed, earlier administration of convalescent plasma for patients with SARS was associated with favorable clinical outcomes.[7] Furthermore, a meta-analysis of eight studies (1703 patients) found that convalescent plasma for severe influenza within less than 4 days of pneumonia complications was associated with all-cause mortality rate of 19%, as opposed to 59% in those who started treatment at a later point in their illness.[15] However, five out of six patients with critical COVID-19 who received convalescent plasma after a median of 21.5 days from

TABLE 1 Baseline characteristics of study groups

Variable	Total (n = 80)	Standard care group (n = 40)	Convalescent plasma group (n = 40)	p value
Demographics and comorbidities				
Male sex	69 (86.3%)	35 (87.5%)	34 (85%)	>.99
Arab ethnicity	22 (27.5%)	15 (37.5%)	7 (17.5%)	.078
Age (years)	53.5 (42–60.5)	55.5 (46.5–60.5)	47.5 (39–60.5)	.073
Body mass index (kg/m^2)	27.4 (25–32.4)	28.5 (24.7–32.4)	27.2 (25.6–29.3)	.68
Diabetes mellitus	40 (50%)	20 (50%)	20 (50%)	>.99
Hypertension	32 (40%)	19 (47.5%)	13 (32.5%)	.25
Chronic kidney disease	6 (7.5%)	4 (10%)	2 (5%)	.68
Chronic lung disease	5 (6.2%)	2 (5%)	3 (7.5%)	>.99
Current or past smoker[a]	12 (15%)	9 (22.5%)	3 (7.5%)	.12
Presenting symptoms				
Symptoms at ICU admission (days)	7 (6–9)	7 (5.5–9)	7 (6–8.5)	.85
Fever	68 (85%)	36 (90%)	32 (80%)	.35
Cough	73 (91.2%)	35 (87.5%)	38 (95%)	.43
Sore throat	20 (25%)	9 (22.5%)	11 (27.5%)	.80
Dyspnea	58 (72.5%)	26 (65%)	32 (80%)	.21
Oxygen saturation at admission to ICU	91% (85–95%)	94% (85–96%)	89% (86–94%)	.059
APACHE II Score	12.0 (9.0–14.0)	12.0 (9.0–15.0)	11.5 (9.0–13.0)	.23
Laboratory results at admission to ICU				
Peripheral white cell count (×10^9/L)	8.0 (5.3–10.4)	8.0 (6.3–11.5)	7.2 (5.0–9.6)	.28
Lymphocyte count (×10^9/L)	0.9 (0.6–1.2)	0.90 (0.7–1.3)	0.9 (0.6–1.1)	.43
Platelet count (×10^9/L)	234 (190–300)	248.5 (200–300)	219.5 (185–281.5)	.34
Serum creatinine (µmol/L)	86 (70.5–106)	90 (80–119)	81.0 (63.5–91.5)	.009
CRP (mg/L)	180 (103–259)	180 (110.0–300.0)	172.5 (93–231.4)	.16
Serum ferritin (µg/L)[b]	940 (671–1484)	1200 (595.5–1571.5)	920.5 (697.5–1288)	.61
ALT (IU/L)	38.5 (24–60)	40 (24–69)	37 (21.5–55)	.48
Management				
Invasive mechanical ventilation	69 (86.2%)	36 (90%)	33 (82.5%)	.52
Vasopressor support	42 (52.5%)	22 (55%)	20 (50%)	.82
Hemodialysis	7 (8.7%)	5 (12.5%)	2 (5.0%)	.43
Methylprednisolone	66 (82.5%)	31 (78%)	35 (88%)	.38
Tocilizumab	73 (91.2%)	34 (85%)	39 (98%)	.11
Adverse events				
Acute kidney injury	29 (36.2%)	16 (40%)	13 (32.5%)	.64
Anemia	48 (60.0%)	20 (50%)	28 (70%)	.11
ALT rise	66 (82.5%)	35 (87.5%)	31 (77.5%)	.38
Bilirubin rise	28 (35.0%)	13 (32.5%)	15 (37.5%)	.81
Hypernatremia	31 (38.7%)	13 (32.5%)	18 (45.0%)	.36
Hypokalemia	16 (20%)	7 (17.5%)	9 (22.5%)	.78
QTc prolongation	13 (16.2%)	5 (12.5%)	8 (20%)	.55
Outcomes				
Improvement in respiratory support status	57 (71.3%)	26 (65%)	31 (77.5%)	.32
Discharged alive from ICU within 28 days	52 (65%)	26 (65%)	26 (65%)	>.99
The 28-day all-cause mortality	6 (7.5%)	5 (12.5%)	1 (2.5%)	.22
Viral clearance	48 (60%)	26 (65%)	22 (55%)	.49

(Continues)

TABLE 1 (Continued)

Variable	Total (n = 80)	Standard care group (n = 40)	Convalescent plasma group (n = 40)	p value
Respiratory support at outcome				.42
Ambient room air	9 (11.3%)	3 (7.5%)	6 (15%)	
Supplemental oxygen	50 (62.5%)	25 (62.5%)	25 (62.5%)	
Noninvasive ventilation	1 (1.3%)	0	1 (2.5%)	
Invasive ventilation	20 (25%)	12 (30%)	8 (20%)	

Note: Data are presented as numbers (percentages) or median (interquartile range). *p* values are based on Fisher's exact or Wilcoxon rank-sum tests.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; ICU, intensive care unit; IQR, interquartile range; LDH, lactate dehydrogenase.

[a]Data missing for three patients.

[b]Data missing for eight patients.

TABLE 2 Baseline characteristics with respiratory status improvement at day 28 of admission to ICU

Variable	No improvement (n = 23)	Improvement (n = 57)	p value
Demographics and comorbidities			
Male sex	20 (87%)	49 (86%)	>.99
Arab ethnicity	6 (26.1%)	16 (28.1%)	>.99
Age (years)	60 (55–66)	48 (41–59)	<.001
Body mass index (kg/m^2)	27 (25–32)	27.8 (24.91–32.87)	.84
Diabetes mellitus	14 (60.9%)	26 (45.6%)	.32
Hypertension	12 (52.2%)	20 (35.1%)	.21
Chronic kidney disease	1 (4.3%)	5 (8.8%)	.67
Chronic lung disease	1 (4.3%)	4 (7.0%)	>.99
Current of past smoker[a]	4 (17.4%)	8 (14.0%)	.73
Onset of symptoms at ICU admission (days)	7 (4–8)	7 (6–9)	.085
Oxygen saturation at admission to ICU	90% (85%–95%)	90% (86–95%)	.77
APACHE II Score	13 (10–20)	11 (8–13)	.017
Laboratory results on the day of admission to ICU			
Peripheral white cell count (×10^9/L)	8.8 (6.4–13.8)	7.2 (5.10–9.6)	.079
Lymphocyte count (×10^9/L)	1.0 (0.6–1.5)	0.9 (0.6–1.0)	.39
Platelet count (×10^9/L)	238 (190–300)	233 (190–300)	.86
Serum creatinine (µmol/L)	103 (73–130)	84 (70–95)	.10
CRP (mg/L)	186.3 (129.1–300)	175 (92.8–240.9)	.11
Serum ferritin (µg/L)[b]	1293 (858.5–1847)	842 (657.5–1304)	.025
ALT (IU/L)	31.5 (20–59)	39 (29.5–60)	.52
Management			
Convalescent plasma	9 (39.1%)	31 (54.4%)	.32
Invasive mechanical ventilation	21 (91.3%)	49 (86.0%)	.72
Vasopressor support	14 (60.9%)	28 (49.1%)	.46
Hemodialysis	5 (21.7%)	2 (3.5%)	.019
Methylprednisolone	21 (91.3%)	45 (78.9%)	.33
Tocilizumab	21 (91.3%)	52 (91.2%)	>.99

Note: Data are presented as numbers (percentages) or median (interquartile range). *p* values are based on Fisher's exact or Wilcoxon rank-sum tests.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; ICU, intensive care unit; LDH, lactate dehydrogenase.

[a]Data missing for three patients.
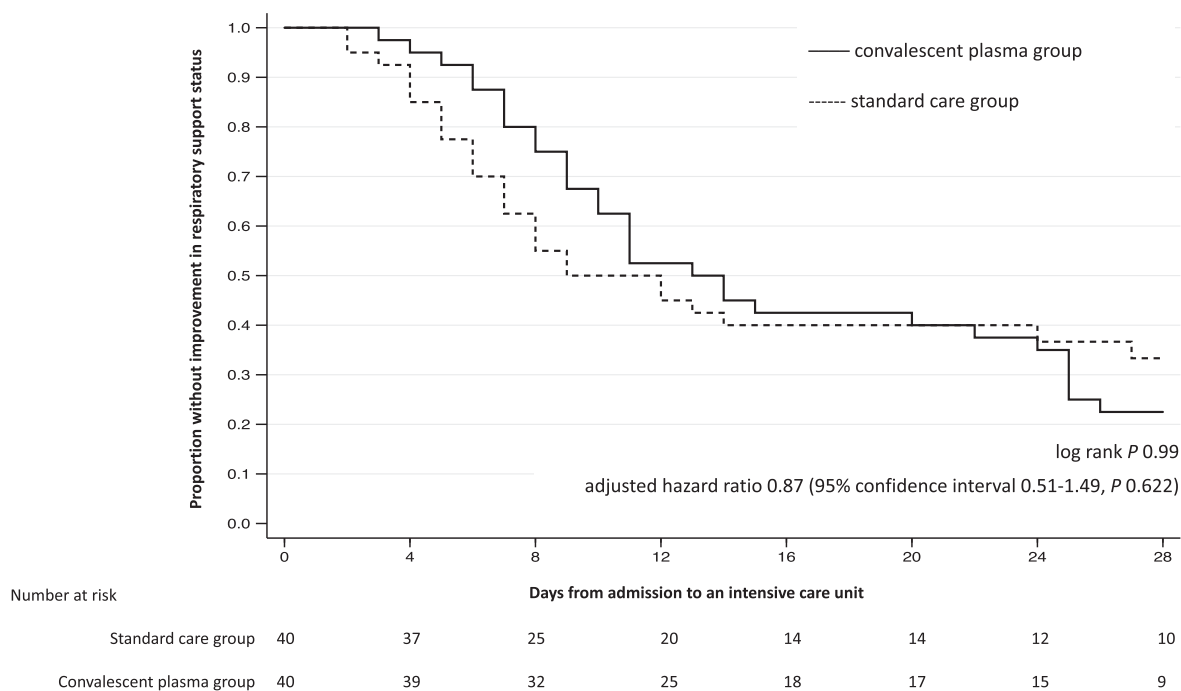
[b]Data missing for eight patients.

Number at risk

	0	4	8	12	16	20	24	28
Standard care group	40	37	25	20	14	14	12	10
Convalescent plasma group	40	39	32	25	18	17	15	9

FIGURE 1 The Kaplan–Meier survival curve for time to improvement in the respiratory support status

molecular confirmation could not survive.[16] To maximize potential clinical benefit, SARS-CoV-2 convalescent plasma may need to be administered earlier in the clinical course. To facilitate patient selection, robust COVID-19 severity prediction tools are required. Examples exist, but none of them have been widely validated.[17]

A second possible explanation for the apparent lack of clinical benefit in association with SARS-CoV-2 convalescent plasma in this study is the patients' characteristics. The median patient age in this study was 53.5 years, and only 7.5% of patients died within 28 days of follow-up. This contrasts with experiences reported elsewhere. For example, an Italian report described 1591 patients with critical COVID-19. The median age was 63 (IQR 56–70) and the overall ICU mortality was 26%.[18] Another study from the United States reported 50% all-cause mortality in 24 patients with critical COVID-19 who had a mean age of 64 years.[19] Our substantially lower mortality rate suggests that any clinical benefit with convalescent plasma, if one exists, may be too small to be detected in our setting using our relatively small sample size.

Third, we were unable to establish that our donors' plasma contained adequate SARS-CoV-2-neutralizing antibody titers, a prerequisite for effective convalescent plasma therapy.[20] However, donations were obtained after a median of 37 days (IQR 31–46) after the date of COVID-19 confirmation by RT-PCR. It has been shown that immunoglobulin M (IgM) and IgG antibodies against the receptor-binding domain (anti-RBD) of SARS-CoV-2 are detectable in nearly all COVID-19 patients after 14 days of the clinical onset.[21] Moreover, the presence of such antibodies strongly correlated with SARS-CoV-2-neutralizing antibody titers.[21,22] In one study,

SARS-CoV-2-neutralizing antibodies were undetectable in only 5.7% of 175 individuals who recovered from mild COVID-19.[22] Considering this low percentage and the extended time frame between infection and donation in our study, it is reasonable to suggest that the probability that our donors did not have adequate neutralizing SARS-CoV-2 antibodies is low. However, this possibility was not fully excluded.

In this study, the baseline APACHE II score, a well-established prognostic tool for critically ill patients, was negatively associated with the primary endpoint. In addition, the use of methylprednisolone was independently associated with a lower likelihood of treatment success. Current COVID-19 management guidelines do not recommend the routine use of systemic corticosteroids.[2] This recommendation is the result of consistent evidence of lack of clinical benefit in settings of viral pneumonia and possible harm including delayed viral clearance and increased mortality.[23] However, dexamethasone at a dose of 6 mg daily for up to 10 days was recently reported to be associated with significant survival benefit in patients with moderate-to-severe COVID-19.[11] It has been suggested that systemic steroids are probably beneficial in severe COVID-19 when administered at lower doses, but are potentially harmful at higher doses.[24] Our finding emphasizes the importance of carefully selecting COVID-19 patients for systemic steroid therapy and the need for judicious selection of the specific treatment agent and dosing regimen.

Adverse events occurred in the majority of patients in this study. This is not surprising, given their critical status and the multitude of medical interventions employed for both groups.

TABLE 3 Cox proportional hazard for associations with improvement in the respiratory support status

Variable	Unadjusted hazard ratio (95% confidence interval; p value)	Adjusted hazard ratio (95% confidence interval; p value)
Convalescent plasma therapy	0.99 (0.59–1.68; >.999)	0.87 (0.51–1.49; .622)
Male sex	1.12 (0.53–2.38; .749)	
Non-Arab ethnicity	1.02 (0.57–1.83; .936)	
Body mass index (kg/m^2)	1.00 (0.96–1.04; .856)	
Diabetes mellitus	0.75 (0.44–1.26; .276)	
Hypertension	0.71 (0.41–1.22; .217)	
Current or past smoker	1.09 (0.52–2.32; .808)	
Onset of symptoms at ICU admission (days)	1.08 (0.99–1.18; .083)	
Oxygen saturation	5.11 (0.9–299.44; .432)	
APACHE II Score	0.92 (0.87–0.98; .006)	0.89 (0.83–0.95; .001)
Invasive mechanical ventilation	0.99 (0.47–2.11; .995)	2.37 (1.01–5.57; .048)
Methylprednisolone	0.41 (0.21–0.79; .007)	0.23 (0.11–0.50; <.001)
Tocilizumab	0.63 (0.25–1.59; .331)	
Lymphocyte count (×10^9/L)	0.74 (0.48–1.12; 153)	
Platelet count (×10^9/L)	1.00 (0.99–1.00; .506)	
CRP (mg/L)	0.99 (0.99–1.00; .351)	
ALT (IU/L)	1.00 (0.99–1.01; .798)	
LDH	1.00 (0.99–1.00; .576)	
D-dimer	0.99 (0.97–1.01; .494)	
Serum ferritin	0.99 (0.99–1.00; .991)	
Vasopressor support	0.98 (0.58–1.65; .932)	

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; ICU, intensive care unit; IQR, interquartile range; LDH, lactate dehydrogenase.

However, convalescent plasma appeared to be safe and was not associated with excess adverse events. Modern transfusion medicine techniques have substantially improved the safety of blood product therapies. However, there remain some potential risks with convalescent plasma therapy that require careful weighing against any possible benefits. It remains unexplored whether passive immunotherapy for COVID-19 results in an attenuated natural SARS-CoV-2 immune response and post-recovery susceptibility to SARS-CoV-2 re-infection, and the potential risk of antibody-dependent enhancement, a detrimental immunological phenomenon previously described with other viral infections.[20,25] In addition, the risk of blood product-derived infections, including currently unrecognized agents, can never be completely eliminated.[26]

The limitations of this study include its observational nature. We used multivariate analyses to assess independent associations with the study endpoints, but the risk of residual confounding by indication cannot be eliminated. Nonetheless, existing peer-reviewed data in this area are mostly limited to uncontrolled case series of two to ten patients and a single prematurely halted randomized trial.[12,27–31]

We, therefore, believe that our report, despite the limitations discussed above, provides useful insight for physicians considering the use of SARS-CoV-2 convalescent plasma for the treatment of patients with COVID-19.

In conclusion, in this retrospective cohort study of critically ill COVID-19 patients, convalescent plasma therapy was not associated with clinical benefit in terms of improvement in the respiratory support status within 28 days. It is not clear if the administration of convalescent plasma at an earlier stage may prevent the clinical progression of COVID-19 and result in better clinical outcomes. Randomized clinical trials are urgently required to address these questions.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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