RESEARCH ARTICLE

Therapeutic plasma exchange: A potential therapeutic modality for critically ill adults with severe acute respiratory syndrome coronavirus 2 infection

Sabria Al-Hashami[1] [ORCID] | Faryal Khamis[2] | Maha Al-Yahyay[1] |
Samata Al-Dowaiki[2] | Louza Al-Mashaykhi[1] | Huda Al-Khalili[3] |
Juhi Chandwani[3] | Issa Al-Salmi[4] | Ibrahim Al-Zakwani[5]

[1]Department of Clinical Hematology, Royal Hospital, Muscat, Oman

[2]Infection Diseases Unit, Royal Hospital, Muscat, Oman

[3]Department of Anesthesia and Critical Care, Royal Hospital, Muscat, Oman

[4]Department of Nephrology, Royal Hospital, Muscat, Oman

[5]Department of Pharmacology & Clinical Pharmacy, College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Oman

Correspondence
Sabria Al-Hashami, Department of Clinical Hematology, Royal Hospital, Muscat, Oman.
Email: sabria.alhashami@gmail.com

Abstract

Background: Severe acute respiratory syndrome coronavirus 2 infection can be severe and fatal due to cytokine storm. Therapeutic plasma exchange (TPE) potentially mitigates the harmful effects of such cytokines. We investigated the use of TPE, as rescue therapy, in patients with severe Coronavirus disease 2019 (COVID-19) infection.

Study Design and Methods: A retrospective analysis on COVID-19 patients admitted to the intensive care unit and treated with TPE from April 17, 2020 to July 2, 2020. This group was compared with COVID-19 patients who received standard therapy without TPE. The following outcomes were analyzed: changes in laboratory parameters, length of hospital stay (LOS), days on mechanical ventilation, mortality at days 14 and overall mortality.

Results: A total of 95 patients were included, among whom 47% (n = 45) received TPE. Patients who received TPE had reductions in C-reactive protein ($P = .002$), ferritin ($P < .001$) and interleukin-6 ($P = .013$). After employing entropy-balancing matching method, those on TPE were also more likely to discontinue inotropes (72% vs 21%; $P < .001$). However, they were more likely to be associated with longer LOS (23 vs 14 days; $P = .002$) and longer days on ventilatory support (14 vs 8 days; $P < .001$). Despite marginal mortality benefit at 14-days (7.9% vs 24%; $P = .071$), there was no significant differences in overall mortality (21% vs 31%; $P = .315$) between the groups.

Conclusions: TPE was effective in reducing inflammatory markers in patients with severe COVID-19 infection, however, further research is warranted.

KEYWORDS

acute respiratory distress syndrome, blood purification, COVID-19, plasma exchange, pneumonia, severe acute respiratory syndrome coronavirus 2

1 | INTRODUCTION

The COVID-19 pandemic perpetuated since the first reported case on December 2019 in Wuhan-China. Globally, the number of confirmed cases with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection reached 214 468 601 with case fatalities of 4 470 969 (WHO Coronavirus Disease; COVID-19, Dashboard, as of August 27, 2021). In the absence of a specific treatment modality, management of patients with SARS-CoV-2 is challenging, particularly in patients with severe illness requiring intensive care unit (ICU) admission and mechanical ventilation (MV).[1,2] Majority of patients infected with SARS-CoV-2 have mild symptoms but some rapidly progress to acute respiratory distress syndrome (ARDS), multiorgan failure and death.[1-3]

SARS-CoV-2 virus binds angiotensin converting enzyme 2 receptor (ACE2 receptor) via its S protein and infects the alveolar epithelial cells. ACE2 receptors are expressed on endothelial cells (ECs), in the lung, heart, kidney, and intestine.[4,5] Recent studies indicate that vascular endothelial cells are resistant to SARS-CoV-2 infection and indirectly injured by the immune response elicited by infected nonendothelial cells.[4] The tissue damage in severe COVID-19 occurs secondary to (ECs) injury, complement activation, degradation of the glycocalyx layer, hypercoagulable state, and impaired hyperfibrinolysis.[4]

The binding of the virus to the pulmonary epithelium activates the complement system causing the release of pro-inflammatory cytokines, specifically, tumor necrosis factor-α (TNFα), interleukin-1 (IL-1β), interleukin-6 (IL-6), and interleukin-8 (IL-8), and the recruitment of phagocytic cells.[4,6,7] Impaired type I/III interferon (IFN) response in severe COVID-19 results in delayed viral clearance and exacerbate the host immune response leading to a cytokine storm.[4] TNF-α and IL-1 bind to the surface of ECs fostering the expression of adhesion molecules like selectins (E-selectin and P-selectin) and integrins (intercellular adhesion molecule [ICAM-1] and vascular cell adhesion molecule [VCAM-1]).[4,7] These adhesions molecules promotes interactions of neutrophils and monocytes with ECs leading to further damage through the release of reactive oxygen species[8] and production of neutrophil extracellular traps.[4,7]

The degradation of the glycocalyx layer[4] disrupts the normal mechanisms that regulate the coagulation cascade and inhibit platelets adhesion. This results in tissue factor mediated thrombin generation, increased thrombomodulin activity and impaired anti-thrombin production.[7,8] Additionally, Endothelial dysfunction results in the release of Von-Willebrand factor (VWF) from Weibel-Palade bodies,[9,10] which has been reported in COVID-19,

leading to platelets aggregation and thrombus formation.[6-8] Evidence of endothelial activation, dysfunction, injury and formation of capillary microthrombi are supported by findings of postmortem studies.[11-13] Furthermore, some studies show morphological evidence of complement mediated injury.[14]

COVID-19 has been associated with high-serum levels of other cytokines and chemokines including: interleukin-2 (IL-2), interleukin-7 (IL-7), interleukin-10 (IL-10), granulocyte-colony stimulating factor (G-CSF), macrophage inflammatory protein (MIP)1A/CCL3, monocyte chemoattractant protein-1 and C-X-C motif chemokine 10 (CXCL10)/interferon gamma-induced protein 10 (IP-10).[15] A recent study reported that ICU patients with COVID-19 infection have high levels of TNF-α, granzyme B, heat shock protein 70, interleukin-18 (IL-18), interferon-gamma-inducible protein 10, and elastase 3. Additionally, heat shock protein 70 is also strongly associated with increased mortality.[16]

Therapeutic plasma exchange (TPE) has been used to treat critically ill patients with sepsis,[17] as well as patients with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome,[18,19] and may potentially improve outcomes by removing harmful cytokines and free oxygen in patients with severe SARS-CoV-2 infection.[20] The aim of this study was to evaluate the impact of TPE on inflammatory biomarkers and clinical outcomes in patients with severe COVID-19 infection in Oman.

2 | METHODS

2.1 | Study protocol

The study protocol was approved by the Royal Hospital Research Committee (SRC#74/2020). TPE was performed on patients with severe SARS-CoV-2 infection who were admitted to the ICU at the Royal Hospital, Muscat, Oman, during the period April 17, 2020 to July 2, 2020. Consent was obtained from the health proxy of the intubated patients on admission. All patients received standard of care as per the "National Treatment Protocol by Ministry of Health, Oman."

The decision to start TPE was multidisciplinary, including hematology, infectious disease and ICU teams and according to the following criteria: age ≥ 18 years old, confirmed SARS-CoV-2 with PCR and any of the following: severe ARDS, defined as, partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2/FIO_2) of ≤100 mmHg with positive end-expiratory pressure (PEEP) of ≥5, worsening lung infiltrates of >50% within 24 to 48 h; worsening levels of ferritin and IL-6

levels (≥2-fold increase from baseline) despite tocilizumab and convalescent plasma (CP) transfusion, septic shock, and/or multiple organ dysfunction or failure. Patients were excluded if clinical parameters (PaO_2/FIO_2, PEEP, lung infiltrate, ferritin, and IL-6) were improving on standard of care, no consent given, pregnant, had significant or uncontrolled bleeding, history of allergy to fresh frozen plasma (FFP) or albumin, arrhythmias and if "do not attempt to resuscitate order" was in place.

Patients who received TPE (intervention group) in addition to the standard of care modalities were compared to patients who were only receiving standard of care without TPE (control group).

2.2 | Intervention

TPE was performed using Spectra OptiaApheresis System (TermuBact, Japan) and standard plasma exchange kit (502058310220). One plasma volume was replaced with FFP in all patients. The total volume to be replaced is calculated as per the following equation, replacement fluid (L) = body weight (kg) × (1/13) × (100-hematocrit). TPE was performed through a standard femoral line (10-12 Fr). The anticoagulant citrate dextrose solution, solution A (ACD-A) was used to prevent clotting of the circuit. The available data from published case reports have shown that 2 to 3 sessions are sufficient for clinical improvement.[21-33] Additionally, findings from our pilot study[34] supported the use of a total of five sessions in our patients. Therefore, a maximum of five TPE sessions was

adopted and based on patient's daily clinical assessment, the median number of TPE administered was five sessions. The number of sessions were 5, 4, 3 and 2 in thirty-two, three, five and five patients, respectively. TPE was initiated after 5 days from transfusion of CP and 3 days after the last dose of tocilizumab.

2.3 | Data collection

The following parameters were recorded at admission for both the intervention and the control groups: demographic data, sequential organ function assessment (SOFA), acute physiology and chronic health evaluation (APACHE) II scores, radiological findings and laboratory parameters (absolute lymphocyte count and absolute neutrophil count, platelet count, hemoglobin level, red distribution width, albumin, lactate dehydrogenase [LDH], alanine aminotransferase [ALT], aspartate aminotransferase [AST], troponin, ferritin, prothrombin time [PT], activated partial thromboplastin time [APTT], fibrinogen and D-dimer levels, C-reactive protein [CRP] and IL-6 levels).

The clinical outcomes for both groups were: length of hospital stay (LOS), length of stay in ICU, vasopressor changes, mortality at days 14 and 28 as well as overall cumulative mortality. Furthermore, the following outcomes were collected for the TPE group: changes in SOFA scores (baseline to last treatment with the TPE), changes on chest x-rays at day 0 pre-TPE and day 7 post TPE, changes in the laboratory parameters (CRP, LDH,

TABLE 1 Sample size, number of treated and comparison subjects, standardized mean differences (SMD) as well as variance ratios (VR) of the various matching methods

Matching method	N	TPE	No TPE	SMD	VR	SMD >0.1	SMD >0.25
1. Augmented inverse probability weighting	80	38	42	0.05	0.91	11	4[a]
2. Inverse probability weighting	80	38	42	0.05	0.91	11	4[a]
3. Inverse probability weighting RA	80	38	42	0.05	0.91	11	4[a]
4. Nearest-neighbor matching	80	38	42	0.05	0.91	11	4[a]
5. Mahalanobis-distance matching	80	38	42	0.05	0.89	9	5[b]
6. Propensity-score matching	80	38	42	0.02	1.00	17	10[c]
7. Entropy balancing	80	38	42	0.03	0.89	8	1[d]

Note: The covariates in the logistic regression model (in which TPE was the dependent variable) included age, sex, obesity, diabetes mellitus, hypertension, chronic kidney disease, ferritin levels on admission, SOFA scores on admission, APACHI II scores on admission, Horowitz scores for lung function, C-reactive protein on admission, lactate dehydrogenase on admission, D-dimer levels on admission, anakinra, tocilizumab, hydroxycholorquine, steroid, convalescent plasma, days of illness prior to admission.
Abbreviations: TPE, therapeutic plasma exchange; RA, regression adjustment.
[a]The four variables included age, sex, diabetes mellitus, and days of illness prior to admission.
[b]The five variables included SOFA scores, Horowitz scores, days of illness prior to admission, tocilizumab, and steroid.
[c]The 10 variables included age, hypertension, SOFA scores, APACHI II scores, Horowitz scores, days of illness prior to admission, hydroxychloroquine, tocilizumab, steroid, and convalescent plasma.
[d]The one variable was tocilizumab.

TABLE 2 Covariate balance across therapeutic plasma exchange (TPE) and comparison groups before and after entropy balancing matching method

Characteristic, mean	Original sample TPE			Matched sample TPE		
	Yes	No	SMD	Yes	No	SMD
Age, years	49.11	50.83	−0.12[a]	50.05	50.42	−0.03
Male gender	0.89	0.83	0.18[a]	0.88	0.84	0.10[a]
Obesity	0.11	0.14	−0.11[a]	0.10	0.15	−0.15[a]
Diabetes mellitus	0.45	0.48	−0.06	0.46	0.46	0.01
Hypertension	0.37	0.40	−0.07	0.37	0.39	−0.04
Chronic kidney disease	0.08	0.05	0.13[a]	0.06	0.06	0.00
Ferritin levels on admission, μg/L	1800.13	1689.74	0.05	1677.36	1687.31	0.00
SOFA scores on admission	5.68	7.95	−0.62[b]	6.41	7.34	−0.25[a]
APACHI II scores on admission	17.18	19.67	−0.31[b]	17.99	19.07	−0.13[a]
Horowitz scores for lung function	105.95	124.60	−0.27[b]	110.44	121.39	−0.16[a]
C-reactive protein on admission, mg/dL	136.53	145.14	−0.10[a]	141.33	143.67	−0.03
Lactate dehydrogenase on admission, U/L	593.79	634.74	−0.13[a]	599.10	620.12	−0.07
D-dimer levels on admission, μg/L	5.96	7.87	−0.14[a]	6.46	6.93	−0.03
Days of illness prior to admission	5.87	8.14	−0.56[b]	6.62	7.58	−0.24[a]
Anakinra	0.11	0.14	−0.11[a]	0.11	0.13	−0.06
Tocilizumab	0.76	0.45	0.66[b]	0.66	0.53	0.26[b]
Hydroxycholorquine	0.76	0.71	0.11[a]	0.77	0.71	0.12[a]
Steroid	0.79	0.60	0.43[b]	0.73	0.66	0.16[a]
Convalescent plasma	0.68	0.76	−0.17[a]	0.69	0.74	−0.11[a]

Note: The covariates in the logistic regression model (in which TPE was the dependent variable) included age, sex, obesity, diabetes mellitus, hypertension, chronic kidney disease, ferritin levels on admission, SOFA scores on admission, APACHI II scores on admission, Horowitz scores for lung function, C-reactive protein on admission, lactate dehydrogenase on admission, D-dimer levels on admission, anakinra, tocilizumab, hydroxycholorquine, steroid, convalescent plasma, days of illness prior to admission.

[a]SMD value above 0.1.

[b]SMD value above 0.25.

ferritin, urea, creatinine, IL-6, absolute lymphocyte, absolute neutrophil, albumin, PT, APTT, fibrinogen and D-dimer at day 0 [pre-TPE], day 3 and day 7 post-TPE). Day 7 was chosen to ensure that the changes in the laboratory parameters reflects a sustained response of TPE rather than a transient effect. Finally, serious adverse events (SAEs) secondary to TPE were also reported.

2.4 | Statistical analysis

Descriptive statistics were used to describe data. For categorical variables, frequencies and percentages were reported. Differences between groups were analyzed using Pearson's $\chi 2$ tests (or Fisher's exact tests for expected cells of <5). For continuous but abnormal distributed variables (LOS, days on ventilatory support) were presented as median and interquartile range and analyzed using Wilcoxon-Mann-Whitney test. Changes in X-ray and SOFA scores before and after the plasma exchange were analyzed using McNemar's $\chi 2$ and Wilcoxon signed-rank test, respectively. Laboratory investigations and ventilatory parameters of the intervention group over the course of the hospital admission (day 0 to day 7), as presented in Table 3 were analysed using the repeated measures analysis of variance (ANOVA) and the P values for the differences over time were corrected using the Greenhouse-Geiser correction factor. Statistical analyses were conducted using STATA version 16.1 (STATA Corporation, College Station, Texas).

Different matching methods (a) augmented inverse probability weighting, (b) inverse probability weighting, (c) inverse probability weighting with regression adjustment, (d) nearest-neighbor matching, (e) mahalanobis-distance matching, (f) propensity-score matching (PSM), and (g) entropy-balancing (Table 1) were compared with

regards to the standardized mean differences (SMD) and their respective variance ratios (VR) as well as exploring the numbers of absolute SMDs above 0.1 and 0.25, the cut-offs which are indicative of covariate imbalance, as suggested by *Normand and colleagues*[35] as well as *Ruben*,[36] respectively. In the PSM method, the nearest-neighbor matching with replacement and a caliper width of 0.11 (20% of the square root of the SD of the probability scores) was used. The covariates in the logistic regression model, in which TPE was the dependent variable, included age, sex, obesity, diabetes mellitus, hypertension, chronic kidney disease, ferritin levels on admission, SOFA scores on admission, APACHI II scores on admission, Horowitz index for lung function, CRP on admission, LDH on admission, D-dimer levels on admission, anakinra, tocilizumab, hydroxychloroquine, steroid, CP, and days of illness prior to admission.

3 | RESULTS

The study enrolled a total of 95 COVID-19 patients that were treated among other standard therapies with TPE, with an overall mean age of 51 ± 14 years. About 87% (n = 83) were males and 32% (n = 30) were Omani. A total of 47% (n = 45) of the patients had TPE, in addition to the standard of care modalities. Shortness of breath (71%; 65/91), fever (69%; 65/94), and cough (56%; n = 53), were the three most prominent symptoms on admission. All patients had bilateral diffuse lung infiltration on the chest x-ray (≥50% of lung fields). Only five patients in the TPE group were on continuous positive airway pressure ventilation (CPAP) and five required renal replacement therapy in comparison to none in the control group.

The three most prevalent comorbidities were diabetes mellitus (44%; 41/94), hypertension (40%; n = 38), and chronic kidney disease (6.3%; n = 6). The overall median admission SOFA, APACHE scores and Horowitz index scores were 7.5 ± 3.9, 19 ± 8.0, and 111 ± 69, respectively. All the patients, in both the TPE and the standard of care groups, received antibiotics and/or antifungals (100%; n = 95), while lopinavir/ritonavir, hydroxychloroquine, steroids and convalescent plasma (73%; n = 69) were prescribed in 92% (n = 87), 73% (n = 69), 73% (n = 69), and 74% (n = 70), respectively.

TABLE 3 Laboratory parameters of the entropy-balancing matched therapeutic plasma exchange (TPE) cohort during hospital admission

Investigation, normal range, units	Day 0, mean ± SD (nonmissing numbers)	Day 3, mean ± SD (nonmissing numbers)	Day 7, mean ± SD (nonmissing numbers)	Trend P value over time
ALC, normal: 1.2-4 × 10⁹/L	1.5 ± 1.6 (38/38)	2.2 ± 2.6 (38/38)	2.6 ± 4.7 (32/38)	.082
ANC, normal: 1-5 × 10⁹/L	10.2 ± 5.1 (38/38)	9.7 ± 4.9 (38/38)	10.0 ± 5.6 (32/38)	.641
LDH, normal: 120-246 U/L	652 ± 412 (38/38)	514 ± 816 (26/38)	578 ± 885 (22/38)	.348
CRP, normal: 0-5 mg/dl	96 ± 106 (31/38)	37 ± 41 (29/38)	44 ± 65 (22/38)	.002
Total protein, normal: 57-82 g/L	55.9 ± 6.9 (32/38)	51.8 ± 4.1 (25/38)	63.4 ± 29.1 (20/38)	.211
Total bilirubin, normal: 5-21 μmol/L	18 ± 16 (32/38)	22 ± 22 (25/38)	16 ± 10 (20/38)	.164
Albumin, normal: 32-48 g/L	33 ± 4.2 (28/38)	32 ± 4.8 (19/38)	34 ± 4.1 (16/38)	.339
ALT, normal: 10-49 IU/L	113 ± 93 (33/38)	61 ± 34 (26/38)	63 ± 46 (20/38)	.584
AST, normal: 0–34 IU/L	93 ± 73 (22/38)	64 ± 35 (18/38)	47 ± 22 (11/38)	.494
Urea, normal: 2.5-7 mmol/L	10.7 ± 7.3 (38/38)	12.3 ± 11.5 (38/38)	13.1 ± 11.1 (33/38)	.082
Creatinine, normal: 48-84 μg/L	106 ± 102 (38/38)	111 ± 122 (38/38)	118 ± 111 (33/38)	.616
Ferritin, normal: 13-150 μg/L	1411 ± 1142 (36/38)	516 ± 342 (25/38)	724 ± 659 (19/38)	<.001
IL-6, normal: 0–7 pg/mL	1400 ± 1874 (31/38)	537 ± 751 (18/38)	271 ± 394 (15/38)	.013
PTT, normal: 9.8-11.9 s	11.1 ± 1.0 (37/38)	11.0 ± 0.7 (33/38)	10.7 ± 0.9 (23/38)	.087
aPTT, normal: 26.4-38.9 s	43 ± 35 (37/38)	33 ± 5.4 (33/38)	33 ± 7.5 (23/38)	.051
Fibrinogen, normal: 1.6-4 g/L	4.3 ± 4.3 (37/38)	3.1 ± 1.5 (33/38)	4.4 ± 212 (23/38)	.032
D-dimer, normal: 0.1-0.5 μg/L	6.3 ± 7.9 (33/38)	3.4 ± 2.5 (22/38)	4.3 ± 4.4 (15/38)	.094

Abbreviations: ALC, absolute lymphocyte count; ALT, alanine transminase; ANC, absolute neutrophil count; aPTT, activate partial thromboplastin time; AST, aspartate aminotransferase; CRP, C-reactive protein; IL-6, interleukin 6; LDH, lactate dehydrogenase; PTT, partial thromboplastin time.
Note: The analyses were performed using the repeated measures analysis of variance (ANOVA) and the *P* values for the differences over time were corrected using the Greenhouse-Geiser correction factor.

TABLE 4 Clinical outcome characteristics of the study cohort stratified by therapeutic plasma exchange (TPE)

Outcome, median (IQR) unless specified otherwise	Before entropy-balancing matching				After entropy-balancing matching			
	All (N = 95)	TPE		P value	All (N = 80)	TPE		P value
		No (n = 50)	Yes (n = 45)			No (n = 42)	Yes (n = 38)	
Total LOS, days	17 (11-29)	13 (9–20)	22 (15-36)	<.001	18 (12-30)	14 (10-25)	23 (15-36)	.002
Stay in ICU, days	12 (8-24)	9 (6-12)	16 (11-28)	<.001	12 (8-25)	9 (5-12)	16 (11-30)	<.001
Inotropes stopped[a], n (%)	27 (36%)	10 (20%)	17 (71%)	<.001	22 (37%)	9 (21%)	13 (72%)	<.001
Days on ventilatory support	10 (6-19)	8 (4-11)	14 (9-25)	<.001	10 (6-21)	8 (4-11)	14 (9-28)	<.001
Mortality, n (%)								
14-day	20 (21%)	14 (28%)	6 (13%)	.080	13 (16%)	10 (24%)	3 (7.9%)	.071
28-day cumulative	26 (27%)	17 (34%)	9 (20%)	.126	18 (23%)	13 (31%)	5 (13%)	.066
Total all-cause	29 (31%)	17 (34%)	12 (27%)	.438	21 (26%)	13 (31%)	8 (21%)	.315

Abbreviations: ICU, intensive care unit; IQR, interquartile range; LOS, hospital length of stay.
[a]Inotrope changes were applicable to only 74 and 70 patients before and after entropy-balancing matching.

After the evaluation of the various matching methods in terms of SMDs and their respective VRs as well as exploring the numbers of absolute SMDs above 0.1 and 0.25 (Table 1), the entropy balancing matching method fared the best with not only the lowest mean SMDs and VRs but also the fact that only one of the SMDs was greater than 0.25. In fact, the SMD for tocilizumab was 0.26, just above the threshold of 0.25. Table 2 outlines the covariate balance across the TPE and comparison groups before and after entropy-balancing matching method. There were largely no significant differences among the groups with regards to demographic and clinical characteristics (most of the SMDs well below 0.25). Matching has largely balanced the groups in all the covariates except for the three variables (SOFA scores at admission, days of illness prior to admission, and tocilizumab use) for which the SMDs were just below or above the cut-off threshold of 0.25.

Table 3 outlines laboratory parameters of the entropy-balancing matched TPE group over the course of hospital admission from day 1 to day 7. Patients that received TPE had reductions in the inflammatory markers; CRP (96 to 44 mg/dl; $P = .002$), serum ferritin (1411 to 721 μg/L; $P < .001$), and IL-6 (1400 to 271 pg/mL; $P = .013$). There were, however, largely no statistically significant changes during the hospital course in the other inflammatory markers.

Table 4 shows clinical outcome characteristics of the study cohort stratified by TPE before and after matched analysis. After employing entropy-balancing matching method, those on TPE were more likely to be associated with inotropes discontinuation (72% vs 21%; $P < .001$). However, they were more likely to be associated with longer LOS (23 vs 14 days; $P = .002$) and longer days on ventilatory support (14 vs 8 days; $P < .001$). Those on TPE had a tendency towards lower mortality at day 14-day (7.9% vs 24%; $P = .071$; power = 36%) and at 28-day (13% vs 31%; $P = .066$; power = 37%) but no statistically significant differences in the overall mortality (21% vs 31%; $P = .315$; power = 11%). Furthermore, SOFA scores had decreased from the time of admission and after administration of TPE (5 vs 4; $P = .01$). Additionally, abnormalities (worse) on chest X-ray pre-TPE had also improved significantly from 74% (28/38) to only 7.9% (3/38) post-TPE ($P < .001$). However, the results should be interpreted with caution due to low study power.

4 | DISCUSSION

SAR-CoV-2 virus induced cytokine storm is complex and appears to be similar to that occurring in sepsis.[37,38] Whether this cytokine storm is initiated by a state of immune-paresis allowing replication of the virus followed by an exaggerated immune response is uncertain. The cytokine profile is similar to that described in conditions like autoimmune diseases, CAR-T cell therapy and hemophagocytic lympho-histiocytosis (HLH), but it appears that the key cytokines differ in different diseases.[37-39] This potentially limits the clinical benefit of specific cytokines inhibitors (eg, tocilizumab, anakinra) in controlling the cytokine storm in COVID-19 disease, and can prolong virus clearance if not combined with an effective anti-viral therapy.[39]

We have conducted a retrospective analysis on use of TPE in 38 critically ill patients admitted with COVID-19

infection. This group was compared to an entropy-balancing matched control group. Our study confirms the effect of TPE on reducing the inflammatory markers (ferritin, IL-6, CRP, and fibrinogen) and lesser extent on D-dimer. These findings are consistent with several published case reports and series.[28,29,40-43] The reduction was pronounced after the third session of TPE and as described in other studies.[29,41,42,44] TPE protocol of one volume plasma replacement with FFP performed daily is comparable to one volume plasma replacement with 5% albumin with or without normal saline, in absence of coagulopathy performed every 48 h as reported in other studies.[28,42,43] In this cohort, FFP was used to ensure daily sessions and avoid interruption because of hypofibrinogenemia.

Our study included patients on invasive MV (IMV) except for only five patients in the TPE group who were on CPAP. All patients in both TPE and control groups fulfilled the World Health Organization (WHO) criteria for severe disease (based on more than 50% chest infiltration and hypoxemia) and had moderately severe lung injury as per Horowitz index (119 ± 67) and (106 ± 75), respectively. Patients in TPE group had significantly longer LOS (23 vs 14 days), longer ICU stay (16 vs 9 days) and longer ventilatory support (14 vs 8 days), when compared to entropy-balancing matched control group. Similar findings were also reported by Gucyetmez et al on 18 ICU-patients who had longer LOS in the ICU with median values of 14 and 15.5 days ($P = .63$) in survivors and nonsurvivors, respectively.[29] In terms of reduction in the oxygenation requirements, published case reports and case series have shown that nonventilated patients are more likely to benefit from TPE while patients on IMV show variable response.[22,30-33,45-47] Gluck et al described 10 patients; all nonventilated patients stopped supplemental oxygen by 5.25 days. However, all ventilated patients, although showed improvement in oxygenation by day 3, only two patients out of six were extubated within 14 days.[41]

In contrast, Kamran et al reported in a retrospective propensity score-matched analysis on 280 patients with cytokine storm, a statistically significant reduced LOS in TPE treated group compared to the control group (10 days vs 15 days; $P < .01$).[43] Despite that majority of the patient's disease severity was graded as severe and critical in 40 (44.4%) and 44 (49%) respectively, only 6 (6.6%) patients required IMV while 38 (42.2%) received CPAP. The same study reported a median time to start TPE of 3.5 (2–5) days (and a mean of 3.96 days) and median duration of illness of 7 days. The different finding in our study could be due to the fact that we have more patients on IMV and TPE was used as a rescue therapy where mean time to first TPE was 6.6 ± 4.3 days. In the current study, the TPE group mean days of illness was 5.2 ± 3.4 days. Nevertheless, our TPE group was more likely to discontinue inotropes (72% vs 21%; $P < .001$), showed reduction in SOFA score (5 vs 4; $P = .01$) as well as improvements in chest x-ray abnormalities (74% vs 7.9%; $P < .001$).

Our study showed a tendency towards lower day 14 mortality in the TPE group compared with the standard care group (7.9% vs 24%) but did not reach statistical significance due to low-study power (36% instead of the usual of at least 80% and above). In a study by Hashemian et al, which included 15 patients, nine patients on CPAP survived whilst all patients on IMV died.[42] Similar mortality rates in the TPE subgroup of 16.7% with a total mortality rate of 27.4% have been reported previously.[29] Kamran et al[43] reported a significantly superior overall, 28-day survival in TPE group compared to PS-matched controls (91.1% vs 61.5%), even after adjusting to age, comorbidities, disease severity and duration of symptoms.

The use of CP and tocilizumab are important potential confounding factors, however, data on the efficacy of CP in COVID-19 infection is variable. This is probably due to the inconsistent definitions used by investigators regarding the severity, days of illness and outcomes. Nonetheless, data still supports the use of high titer (anti-spike protein receptor binding domain titer of ≥1:1350) CP therapy, within 72 h of admission for early mild to moderate illness.[48-50] However, CP did not significantly improve clinical outcomes in patients with severe or life-threatening COVID-19.[51-54]

Furthermore, recently Stone et al reported the results of a randomized, double-blind, placebo-controlled trial that enrolled 243 patients with cytokine storm, where 18.0% of the patients in the tocilizumab group and 14.9% of the patients in the placebo group had had worsening of disease by day 14. Tocilizumab was found ineffective in preventing intubation or death in moderately ill hospitalized patients with COVID-19.[55] Additionally, clinical deterioration of COVID-19 patients, after receiving tocilizumab or anakinra, and who improved after TPE has been reported.[33,44]

In terms of TPE safety in our cohort, decreased arterial blood pressure was reported in 4.1% (n = 5) of procedures, of which 3.0% (n = 4) required vasopressors support. Potential line related infections were detected in 13% (n = 6) of the patients. However, transfusion related adverse events, arrhythmias and venous thromboembolic events were not observed. A study conducted on ICU patients who received TPE for various indications, had reported a decrease in arterial blood pressure and severe events including shock, decrease in blood pressure requiring vasopressors in 8.4% and 2.16% of procedures, respectively.[56]

In our study, the TPE group included patients with severe COVID-19 infection on MV and worsening clinical condition despite medical therapy that included steroids, CP and tocilizumab. Whether earlier initiation of TPE would have resulted in better outcomes is unclear at this stage.[43] The use of CP and tocilizumab are unlikely to have affected the clinical outcomes in our cohort based on currently available data. TPE remains as an acceptable option of therapy as it removes nonselectively proinflammatory cytokines, immune-complexes, antifibrinolytic mediators and antibodies (IgM, IgG, and IgA) without theoretically suppressing viral clearance and has been used in sepsis. It is unclear if TPE may have a role in reducing antibody-dependent enhancement (ADE) effect in this infection, specially that high-antibodies titer has been linked to poorer outcome.[57]

Our study has several limitations that include the small size, short follow up of patients and lack of data on changes in the SOFA score, inflammatory parameters and chest x-rays findings during the admission for the control group to compare it with TPE group. Nonetheless, it reflects the possible beneficial role of TPE in the management of patient of COVID-19 infection and that early initiation could be considered, especially in the patients who have high-oxygen requirements and impending intubation. Tendency towards improved mortality was observed in our study coupled with low-study power. The apparent covariate balance occurred at the expense diminished sample size (from 95 to 80 subjects) resulting from matching. Due to the small sample, matching could not eliminate all the imbalances. Hence further studies with larger sample sizes are warranted to corroborate the findings.

5 | CONCLUSIONS

In this study, TPE was performed on patients with severe COVID-19 infection on MV and worsening clinical condition despite medical therapy that included steroids, CP and tocilizumab. TPE was effective in reducing inflammatory markers in patients with severe COVID-19 infection and had a tendency towards lower day 14 and day 28 mortality. Further randomized controlled clinical trials are warranted to draw final, conclusive findings.

AUTHOR CONTRIBUTIONS

Faryal Khamis, Huda Al-Khalili and Juhi Chandwani were responsible for enrolling the patients for TPE and follow up. Sabria Al-Hashami, Faryal Khamis were responsible for the study design, write-up and revision of manuscript. Ibrahim Al-Zakwani was responsible for statistical analysis and write up of the Results section as well as revision of the whole article. Maha Al-Yahyay, Samata Al-Dowaiki and Louza Al-Mashaykhi were responsible for data collection. Issa Al-Salmi contributed to manuscript revision.

CONFLICT OF INTEREST
All authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT
Data available on request due to privacy/ethical restrictions

ORCID
Sabria Al-Hashami https://orcid.org/0000-0002-0698-5272

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