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Outcomes of COVID-19 Patients Undergoing Therapeutic Plasma Exchange in Intensive Care Units

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ABSTRACT

Aim: The place of therapeutic plasma exchange in severe COVID-19 patients is a controversial issue. Data on the relationship between the clinical variables and dynamics of inflammatory markers and outcomes are limited. In this study, we aimed to investigate the effects of clinical variables and laboratory dynamics on patient outcomes in severe COVID-19 patients undergoing therapeutic plasma exchange in intensive care units.

Study design: Single-center retrospective study

Material and Methods: Adult intensive care unit (ICU) patients with severe COVID-19 infection who underwent at least one therapeutic plasma exchange procedure in a single tertiary center were analyzed. The primary outcome of the study was hospital mortality. Secondary outcomes were ICU and 14th day mortality, hospital and ICU length of stay.

Results: Sixty-four patients with a mean age of 56 were included to the study. A total of 51 patients (79%) died. In the multivariate analysis; there were no demographic, clinical or laboratory parameters affecting hospital mortality, ICU mortality or 14th day mortality. Platelet count before first therapeutic plasma exchange has positive moderate correlation with both hospital (r=0.454) and ICU (r=0.449) length of stay.

Conclusion: This study shows that there is no single laboratory test or clinical parameter to define the patients likely to benefit from TPE. Further studies are essential to determine the role of TPE for severe COVID-19 patients to reduce mortality.

Keywords: COVID-19, Sepsis, Multiple organ failure, Therapeutic plasma exchange

Introduction

At the end of 2019, a novel coronavirus named SARS-CoV-2 spread rapidly across the globe and the information available in the published literature is rapidly increasing (1). COVID-19 symptoms vary from mild to severe and may include extreme pneumonia (2,3). Beyond the extreme inflammation, coagulopathy (thromboinflammatory storm) is a major problem in COVID-19 (4,5). While using current available drugs, scientists are trying hard to develop new potential therapeutic strategies (6). Antiviral and vaccine resistance, which may occur as a result of mutations in SARS-CoV-2, may lead to treatment failure; this makes researchers think of developing non-drug treatments as an option (7).

Blood purification therapies are various and therapeutic plasma exchange (TPE) is one of them (8). Therapeutic plasma exchange is used in sepsis and multiple organ failure (MOF) with category III and grade 2B recommendation according to American Society for Apheresis guidelines (9). The guideline allows use on a case-to-case basis in sepsis and the clinician's challenge remains to identify those patients most likely to benefit from this adjunct therapy without specific laboratory markers (5). Data on the relationship between the dynamics of inflammatory markers and clinical outcomes are very scarce. In this study, we aimed to investigate the effects of clinical variables and laboratory dynamics on patient outcomes in severe COVID-19 patients undergoing TPE in intensive care units (ICUs).

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Materials and Methods

Patient Characteristics

Adult patients (age ≥18 years) with severe COVID-19 infection who underwent at least one TPE procedure between 19.04.2020-01.09.2021 followed in the ICUs at a single tertiary center (serving as a pandemic hospital), were retrospectively analyzed. COVID-19 severity is determined according to World Health Organization COVID-19 guidelines and patients with clinical signs of pneumonia plus respiratory rate >30 breaths per minute and/or severe respiratory distress and/or or oxygen saturation of <90% on room air were accepted as severe (10). Patients whose data were accessible as printed or electronic records are included in the study. COVID-19 infection diagnosis was accepted if the nasopharyngeal quantitative reverse transcriptase polymerase chain reaction assay was positive for COVID-19. COVID-19 cases without ICU admission were excluded.

Therapeutic Plasma Exchange

Therapeutic plasma exchange procedures were performed by the Fresenius Com.Tec® (version 4.3-8) machine, as a continuous centrifugation method. Acid citrate dextrose formula-A was used as anticoagulant. Therapeutic plasma exchange was performed by the hematology department, and the decision to perform TPE involved a multidisciplinary approach. The hematology was consulted by the attending intensivist and each case was reviewed by hematologists. If the consulting hematologist agreed that TPE would potentially benefit the patient, then TPE would be performed. Vascular access was obtained by venous insertion of a 12-French double-lumen temporary hemodialysis catheter or a large peripheral venous catheter. Therapeutic plasma exchange was performed using 1.5 times the calculated total plasma volume, adjusting for obesity. Treatments were performed daily or every other day, according to the comorbidities and patients' clinical status until the intensivist felt that further treatment was not clinically warranted. Fresh frozen plasma (FFP) or normal saline and albumin (concentration 20%) or both were the preferred replacement fluids. Which replacement fluids would be used and their percentages (ie, normal saline and FFP) differed according to the clinical condition and coagulation profile of the patients. If any complication develops during and after the TPE session, prospective records are kept by the apheresis team.

Definition of Variables

Demographic variables, comorbidities, Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II scores, presence of acute respiratory distress syndrome (ARDS), presence of intubation, presence of acute kidney injury (AKI) and, administration of hemodialysis were recorded. Acute respiratory distress syndrome is defined as profound hypoxia with bilateral opacities, not fully explained by cardiac failure or fluid overload (10). Acute kidney injury was defined according to KDIGO criteria (11). Cytokine release syndrome (CRS) is determined according to national protocols (www.covid19.saglik.gov.tr) and MOF is defined as two or more organs failing. Acute phase reactants and the hematological and coagulation related laboratory parameters (absolute lymphocyte count, C-reactive protein, D-dimer, ferritin, fibrinogen, platelet count and, interleukin-6) were recorded. The differences between the baseline value before the first TPE, the value after the last TPE and the final values at the discharge or death were calculated.

Patients were followed until death/discharge or the date of the last hospital visit after discharge. The primary study outcome was hospital mortality. Secondary outcomes included ICU mortality, 14th day mortality, ICU length-of-stay (LOS) from first TPE procedure, hospital LOS from first TPE procedure. In order to determine the post-TPE period more accurately, LOS times were determined starting from the first TPE. The time from diagnosis to TPE was also investigated.

Statistics

Statistical analyses were performed by using version 20 of the Statistical Packages for the Social Sciences software. Mann Whitney U was used for the quantitative data that was not normally distributed. Univariate analyses were performed via Chi-square test for qualitative data (or Fisher exact test when Chi-square assumptions do not hold due to low expected cell counts). The Wilcoxon's test was used to compare related variables. Multivariate analyses were done by Logistic regression analysis. While investigating the associations between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using the Spearman's test. A p-value of less than 0.05 was considered to show a statistically significant result.

Ethics

This study was approved by the Ministry of Health of Turkish Republic and the Local Institutional Ethics Committee (Ankara City Hospital, E1-22-2465, 09.Mar.2022). Informed consent was not required as the study reports observational, retrospective data obtained from hospital records.

Results

Sixty-four ICU patients with severe COVID-19 infection were included in the study. Mean age was 56.2 ±15.2. There were more males (n=45) than females (n=19). Forty-seven (73%) patients had one or more comorbidities. Most common comorbidities were hypertension (26.5%), type 2 diabetes mellitus (20.3%), chronic renal problems (9.3%) and, chronic pulmonary pathologies (9.3%). Immunosuppression was seen in 17% of patients. Median APACHE II score was 18 (2-58).

Table 1. Treatments applied for COVID-19 until therapeutic plasma exchange

Drugs	n=64 (%)
Favipravir	56 (87.5)
Steroids	54(84.3)
Anti-cytokine treatment Anakinra Tocilizumab	24(37.5) 22(34.3) 2(3.1)
Hydroxychloroquine	20(31.2)
Intravenous immunoglubulin	12(18.7)
Cytokine hemoadsorbtion	9(14)
Convalescent plasma	6(9.3)
Remdesivir	2(3.1)
Azithromycin	1(1.5)

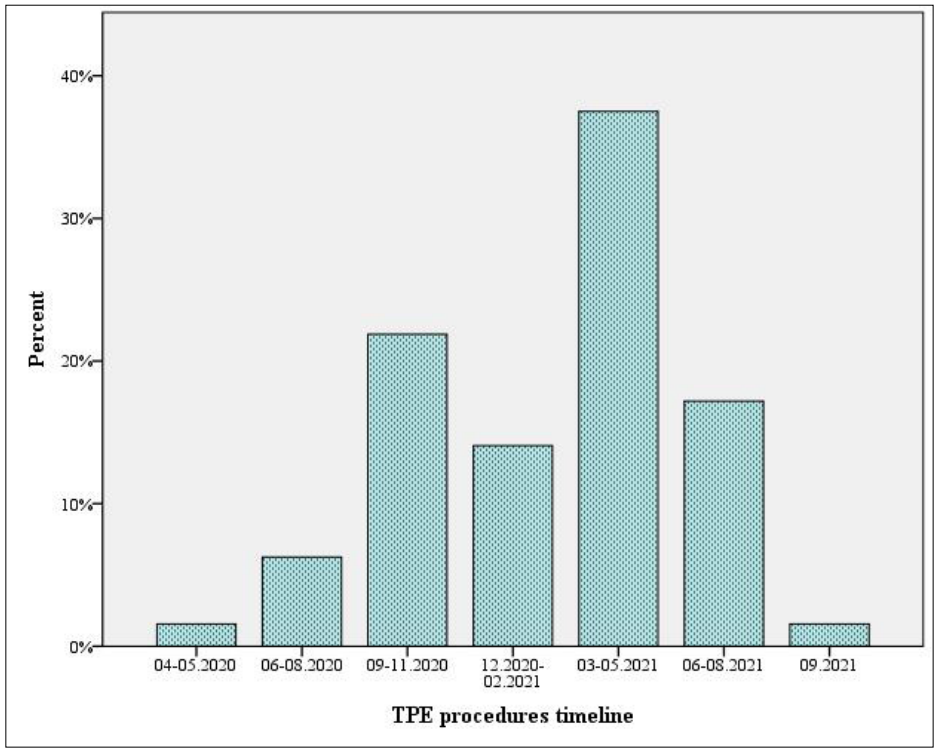

Figure 1. Percentage of therapeutic plasma exchange procedures according to years and seasons

Medications and procedures used specifically for COVID-19 are listed in Table 1. Steroids were given as 250 mg methylprednisolone for 3 days. Cytokine release syndrome, ARDS and MOF were seen in our patients at a rate of 93%, 78% and 46% respectively. Eighty-nine percent of our patients were intubated. Hemodialysis was performed in 20% of the patients. Therapeutic plasma exchange was utilized for severe COVID-19 and neurological complications (Guillain-Barre Syndrome/Acute Motor Sensory Axonal Neuropathy) in 10 cases and, myocarditis in two cases. Most of the procedures were applied during spring of 2021 as shown in Figure 1.

Median time from diagnosis of COVID-19 to first TPE procedure was 12 days (0-52). Median number of TPE procedure was two (1-10). Albumin was used in 22 cases, FFP was used in 17 cases; albumin and FFP were used together in 25 cases as the replacement fluids. Convalescent plasma (CP) was not used as a replacement fluid. Only one adverse event was stated (hypotension) in one patient.

The absolute lymphocyte count (ALC) before first TPE was found to be significantly lower in patients who were administered corticosteroids before first TPE compared to those who were not administered (p=0.036). Corticosteroid administration did not affect other laboratory parameters and anti-cytokine treatment administration did not affect any laboratory parameter investigated in this study.

Ferritin, C-reactive protein (CRP), D-dimer (DD), platelet count and, fibrinogen levels were found to significantly decrease while ALC levels were found to significantly increase after completion of TPE procedures (before first TPE procedure- after last TPE procedure) (Table 2).

Platelet count and DD levels were found to significantly decrease while ferritin, Interleukin (IL)-6 and, ALC levels were found to significantly increase from the time before the first TPE procedure-to the time of discharge or death (Table 3).

Table 2. Laboratory parameters before first exchange and after last exchange

	Median (IQR) value before the first TPE	Median (IQR) value after the last TPE	p
Ferritin, mg/dL	782 (935)	490 (506)	<0.001
D-dimer, µg/mL	16 (33)	4.3 (8)	<0.001
Fibrinogen, mg/dL	460 (303)	235 (239)	<0.001
C-reactive protein, mg/dL	90 (110)	46 (63)	<0.001
ALC/µL	520 (520)	570 (760)	<0.001
Platelets, 10^9/L	218 (151)	158 (137)	<0.001

ALC: Absolute lymphocyte count, **IQR:** Interquartile range, **TPE:** therapeutic plasma exchange

Table 3. Laboratory parameters before first exchange and at the discharge or death

	Median (IQR) value before the first TPE	Median (IQR) value at the end-of-the study	p
Ferritin, mg/dL	782 (935)	1551(7569)	<0.001
D-dimer, µg/mL	16 (33)	4.6 (12)	<0.001
Interleukin-6, pg/mL	60 (207)	220(953)	<0.001
ALC/µL	520 (520)	1000 (1013)	<0.001
Platelets, 10^9/L	218 (151)	166(194)	0.029

ALC: Absolute lymphocyte count, **IQR:** Interquartile range, **TPE:** therapeutic plasma exchange

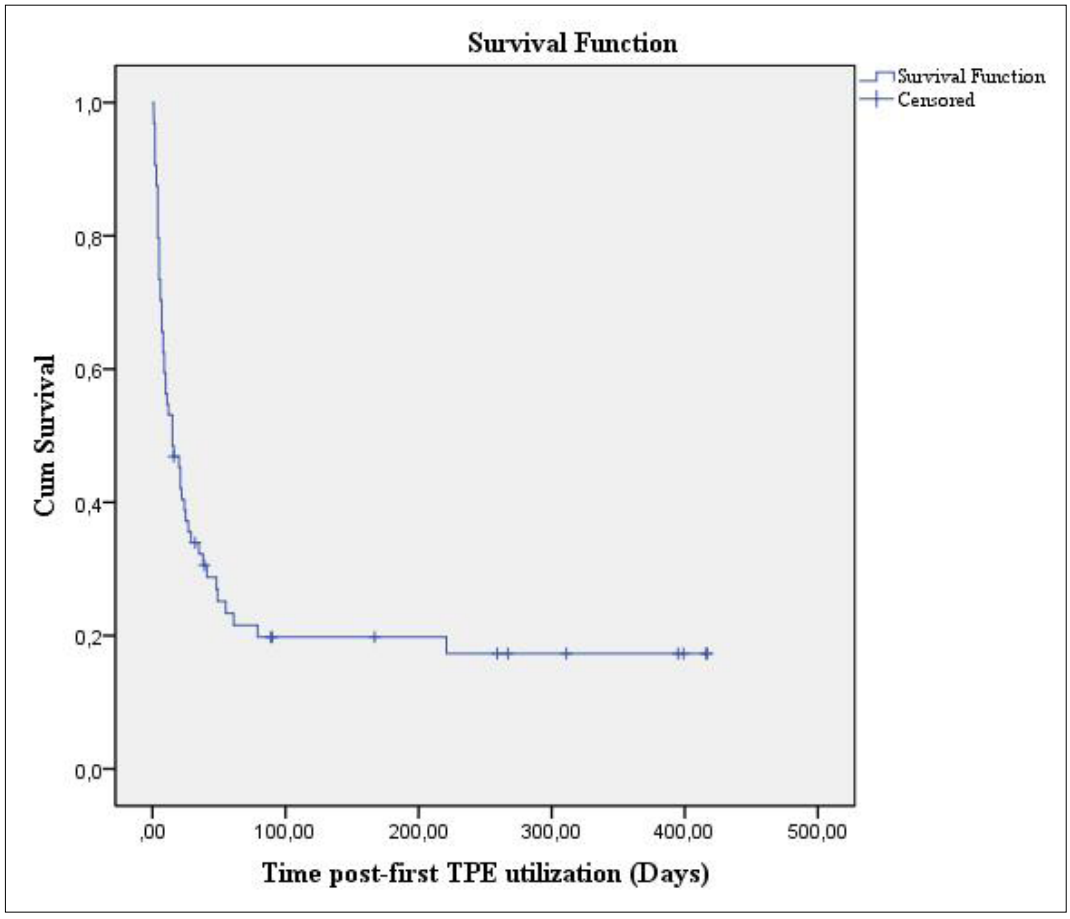

Figure 2. Kaplan-Meier survival curve in the therapeutic plasma exchange treated patients

In total 51 patients (79%) died in hospital. There were no demographic, clinical or laboratory parameters affecting hospital mortality in the multivariate analysis. Forty-eight (75%) patients died in the ICU. There were no demographic, clinical or laboratory parameters affecting ICU mortality in the multivariate analysis.

The mortality at 14th day was 46%. There were no demographic, clinical or laboratory parameters affecting 14th day mortality in the multivariate analysis. Kaplan-Meier survival curve is given in Figure 2 and shows that the majority of deaths occur within 100 days.

Median hospital LOS after the first TPE procedure was 15 days (1–221). Median LOS in the ICU after the first TPE procedure was 11.5 days (1–164). Hospital LOS was related with ARDS (p=0.045), AKI (p=0.007), hemodialysis (p=0.042), CRS (p=0.016) and, MOF (p=0.005). Intensive care unit length-of-stay was related with ARDS (p=0.046), AKI (p=0.004), CRS (p=0.035) and, MOF (p=0.006). There was moderate positive correlation between hospital LOS and, platelet count before first TPE procedure (p=0.000, r=0.454). There was moderate positive correlation between ICU LOS and platelet count before first TPE procedure (p=0.000, r=0.449).

Discussion

Experiences in the previous epidemics of H1N1 (12), severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) (3) and sepsis (13) aroused curiosity in the potential effect of TPE on COVID-19 (14, 15). According to the authors; TPE may alleviate the need for multiple medications against various cytokines by clearing of the inflammatory and anti-fibrinolytic mediators and viral particle clearance is a notable mechanism (15, 16).

Small case series related to the use of TPE in COVID-19 took their place in the literature with good results in the early stages of the pandemic (2, 17). In a case report, Keith et al. reported successful use of TPE for severe COVID-19 with cardiomyopathy (5). One of the indications for TPE in our study was COVID-19-associated cardiomyopathy. Unfortunately, one of the two cases was died.

Those case reports gave rise to succeeding retrospective studies investigating survival outcomes. Gucyetmez et al. showed decreased mortality but similar ICU stays in TPE treated patients compared with TPE untreated COVID-19 patients with DD levels ≥2 mg/L (18). Khamis et al. demonstrated higher extubation rates, lower 14 day post-TPE mortality and a marginally lower all-cause mortality in the TPE group (n= 11) compared to the non-TPE cohort (n=20) (19). Cegolon et al., carried out a single-centered retrospective observational non-placebo-controlled trial enrolling 73 COVID-19 patients with pneumonia and showed lower mortality in TPE treated group. But the effect of TPE on lower mortality was attributed to patient selection bias (20). The

79% mortality in our study is higher than the meta-analysis of Qin and colleagues (mortality varying between 17.9-44.7%) and the mean mortality of studies reviewed by Carlson et al (20.2%, ranging 9.1-50%) (7, 21). We think that the reason for the high mortality rate in our cohort is that TPE is generally preferred as a rescue strategy in severe, complicated COVID-19 patients who have been unresponsive to anti-cytokine medications. In a very recent prospective, open-label study the 35 day mortality rate was 20.9% in the TPE treated group; which seems less when compared to our cohort (35 day mortality 67%). But in this prospective trial, TPE was utilized at a median of two days after the ICU admission and the 35-day mortality was calculated from the first day of admission to the ICU. This study is the only randomized controlled trial to date (22). In the following period, we come across meta-analyses (7, 23, 24). These meta-analyses similarly included one randomized controlled trial (22) but included different case-controlled studies or case series. The common result of these meta-analyses and recent reviews is that TPE has a positive effect on mortality (7, 21, 23-26).

In our cohort, there was no single basal laboratory finding that helped to identify the patients who would likely benefit in terms of mortality from TPE in the multivariate analysis. Lowering of any circulating parameters (CRP, ferritin) can be a result of the procedure per se and not a biological effect. The increase in IL-6 and ferritin observed after the cessation of TPE may be related to the loss of TPE effect or secondary infections that developed during the ICU follow-up period. Although it is a common result of many studies that inflammatory markers decrease with TPE (26) ; we have not yet come across an evidence that specifically defines the relationship between marker dynamics and clinical outcomes.

In our study, median time to the first TPE procedure was mainly in the early phases of COVID-19. The timing of TPE can be important. Cytokine storm with severe disease was mainly seen around 7–14 days; thus, authors conclude that early initiation of plasmapheresis within this period could be related to better outcomes (3, 19, 27, 28). An expert report recommends that blood purification treatment should be initiated as soon as possible when the serum inflammatory mediator levels of patients with severe COVID-19 reach more than five times the upper limit of normal or increase>1 time within 24 hours (29).

Determining the replacement fluid is another challenging point. Although some authors encourage its use (26, 28, 30-32), CP or intravenous immunoglobulin was never used in our study population as replacement fluids. Antibody-dependent enhancement of infection would be a potential issue affecting the outcomes of the patients to discuss if it was used. Fresh frozen plasma usage is potentially two times riskier than albumin use (3). In order to minimize those risks, we prefer FFP if the patient has coagulopathy with high bleeding risk.

In our study, the treatments before plasma exchange in COVID-19 patients were not determinative of end-points and there was heterogeneity in the preferences according to the patients' status. The possibility that these agents contributed to the recovery of patients could not be ruled out.

Limitations

There are a number of limitations of this study. Unfortunately, TPE consultations in COVID-19 patients are performed in a non-standardized manner. This is due to the fact that a standardized approach has not yet been formed for TPE in COVID-19. The retrospective nature of our study and the absence of a control group also reduce the level of evidence. There were no recorded complications attributed to catheter placement, or immediate or noticeable adverse effects with the TPE procedure. It should be kept in mind that the retrospective design of the study was not optimal to detect adverse events associated with TPE.

Conclusion

This study shows that there is no single laboratory test or clinical parameter to define the patients likely to benefit from TPE. Platelet count before first TPE can be a marker to detect length of hospital stay.

We think that further studies are essential to determine the optimum timing, the optimum volume and safety of TPE to stabilize critically ill or rapidly deteriorating patients to reduce mortality. There is an unmet need of randomized controlled trials to decide the benefits and to specify the place of TPE.

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AUTHOR CONTRIBUTIONS:

Concept: MSA, GO, IOT, SI; **Design:** MSA; **Supervision:** IOT, SD, GO; **Resources:** MSA, AGA, SGB; **Materials:** MSA; **Data Collection and/or Processing:** MSA, DE, DG, FC; **Analysis and/or Interpretation**: MSA; **Literature Search:** MSA; **Writing Manuscript**: MSA, MSP; **Critical Review:** SI, GO.

Ethics Committee Approval: This study was approved by the Ministry of Health of Turkish Republic and the Local Institutional Ethics Committee (Ankara City Hospital, E1-22-2465, 09.Mar.2022).

Informed Consent: Retrospective data

Peer-review: Externally peer-reviewed.

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