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# Therapeutic plasma exchange in patients with COVID-19 pneumonia in intensive care unit: a retrospective study

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In patients with COVID-19 pneumonia, high risk of thrombosis became a current issue, and D-dimer levels indicating fibrin degradation products (FDPs) in the plasma were found as a predictor for mortality [1, 2]. Although unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) decrease the production of FDPs by inhibiting factors Xa and II, they cannot contribute metabolization of existing FDPs. Furthermore, FDPs cannot be filtered by known cytokine filters because of their molecular weight (minimum 240 kDa) [3, 4]. Yet, FDPs can be removed by therapeutic plasma exchange (TPE) [5]. Therefore, recently, three consecutive TPE sessions were performed in selected patients with COVID-19 pneumonia in intensive care units (ICUs) after the assessment of their clinical and coagulation status. In the study, the effect of TPE on outcomes was retrospectively investigated in patients with COVID-19 pneumonia.

All COVID-19 patients admitted to 5 different tertiary ICUs between 10 March and 10 May 2020 were evaluated, and 73 of 91 patients were included in the study. The patients who died within the first 4 days and who were still in the ICUs on 10 May were excluded. According to the Turkish Health Minister Algorithm for COVID-19, all included patients received the same antiviral (favipiravir, hydroxychloroquine, azithromycin) therapy and anticoagulant prophylaxis (UFH infusion 100 mcg/kg or LMWH 0.01 mL/kg). Since two different protocols were used in 5 ICUs, patients with D-dimer ≥ 2 in 3 ICUs had only received therapeutic anticoagulation whereas patients with D-dimer ≥ 2 in the other 2 ICUs had received TPE plus therapeutic anticoagulation. In all ICUs, for all patients in GII, echocardiography, lower extremity venous Doppler, and, if pulmonary thrombosis suspected, thorax computerized tomography angiography were performed. After collecting data, 73 patients were divided into 2 groups as group I (GI) (D-dimer < 2 mg/L) and group II (GII) (D-dimer ≥ 2 mg/L), and then GII was also divided into 2 groups as GIIa (TPE+) and GIIb (TPE−). Patients' characteristics, respiratory and laboratory parameters, and outcomes were recorded. Propensity score matching (PSM) analysis was conducted on R v4.0.1 (0.2 caliper without replacement and nearest neighbor model, 1:1 ratio) by using 14 covariates (age, gender, CCI, APACHE II, SOFA score, lactate, leucocyte, lymphocyte, D-dimer and creatinine at the ICU admission, maximum respiratory support, the usage of steroid, IL-6 blocker, and cytokine filter).

The total mortality rate was 27.4%. Mortality rates of GI and GII were 5% and 35.9%, respectively. In GII, major thromboembolic events were not detected in any patients. The median (min-max) day for the starting TPE was 3 (2–4). In GIIa, APACHE II, SOFA scores, D-dimer and interleukin-6 (IL-6) levels at the ICU admission, and length of ICU stay were significantly higher than those of GI whereas mortality rates were similar in those groups (Table 1). The median values of the LOS-ICU in survivors and non-survivors in GII were 14 (6.5–21.5) and 15.5 (8–23), respectively ($p = 0.630$). In GIIa, lactate dehydrogenase (LDH), D-dimer, ferritin, IL-6, C-reactive protein (CRP), and procalcitonin levels were

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**Table 1** Comparisons of patients groups

| | GI (D-dimer < 2) (*n* = 20) | GII (D-dimer ≥ 2) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Before PSM | | | | After PSM | | |
| | | GIIa (TPE+) (*n* = 18) | GIIb (TPE–) (*n* = 35) | $p_1$ (GI and GIIa) | $p_2$ (GIIa and GIIb) | GIIa (TPE+) (*n* = 12) | GIIb (TPE–) (*n* = 12) | $p_2$ (GIIa and GIIb) |
| Age (years) | 60 ± 14 | 62 ± 12 | 62 ± 15 | 0.615 | 0.951 | 61 ± 14 | 64 ± 17 | 0.605 |
| Male, *n* (%) | 13 (65.0) | 14 (77.8) | 26 (74.3) | 0.386 | 0.780 | 8 (66.7) | 8 (66.7) | 1.000 |
| BMI (kg/m$^2$) | 27.3 (5.8) | 27.9 (5.5) | 27.3 (6.6) | 0.290 | 0.237 | 28.5 (6.1) | 25.0 (6.6) | 0.078 |
| CCI | 2.5 (4) | 3 (3) | 4 (3) | 0.919 | 0.422 | 3.0 ± 2.2 | 3.8 ± 1.7 | 0.270 |
| At the ICU admission | | | | | | | | |
| APACHE II | 12 ± 4 | 17 ± 4 | 17 ± 5 | ***0.002*** | 0.886 | 17 ± 3.3 | 17.5 ± 5.6 | 0.794 |
| SOFA Score | 5 (3) | 6 (1) | 7 (3) | ***0.002*** | 0.223 | 6 (2) | 6 (2) | 0.713 |
| $PaO_2/FiO_2$ ratio | 128 (68) | 97 (51) | 113 (79) | 0.251 | 0.229 | 108 (106) | 125 (103) | 0.551 |
| $SpO_2$ (%) | 89 (5) | 91 (7) | 89 (5) | 0.377 | 0.597 | 92 (10) | 91 (5) | 0.590 |
| Lactate (mmol/L) | 1.4 (0.6) | 1.4 (0.7) | 1.4 (0.9) | 0.988 | 0.631 | 1.5 (0.8) | 1.3 (0.5) | 0.291 |
| WBC (×10$^3$/μL) | 9.6 (3.9) | 6.9 (6.4) | 8.2 (6.5) | 0.573 | 0.353 | 8.7 ± 4.9 | 7.4 ± 2.7 | 0.430 |
| Lymc (×10$^3$/μL) | 0.82 ± 0.40 | 0.80 ± 0.34 | 0.89 ± 0.42 | 0.553 | 0.271 | 0.83 ± 0.3 | 0.82 ± 0.5 | 0.963 |
| D-dimer (mg/L)[&] | 1.2 (0.3–1.9) | 5.0 (2.1–35.2) | 7.2 (2.1–35.5) | ***< 0.001*** | 0.151 | 4.5 (2.1–35.2) | 6.0 (2.2–32.2) | 0.514 |
| Ferritin (ng/mL) | 1015 (1735) | 1735 (1853) | 900 (1454) | 0.158 | ***0.018*** | 1742 (2117) | 605 (1346) | ***0.012*** |
| IL-6 (pg/mL)[&] | 28.3 (5.3–1418)[(8)] | 134 (36.2–2958)[(13)] | 254 (33–5233)[(13)] | ***0.036*** | 0.101 | 155 (39.6–2958)[(8)] | 237 (33–4885)[(4)] | 0.933 |
| CRP (mg/dL) | 18.6 ± 10.9 | 22.2 ± 12.1 | 27.8 ± 10.4 | 0.340 | 0.086 | 19.2 ± 10.3 | 24.0 ± 11.0 | 0.275 |
| Creatinine (mg/dL) | 0.88 (0.29) | 0.87 (0.37) | 0.99 (0.82) | 0.874 | 0.051 | 0.91 ± 0.3 | 0.90 ± 0.3 | 0.944 |
| Urea (mg/dL) | 28 (29) | 32 (19) | 36 (26) | 0.942 | 0.288 | 28 (32) | 35 (14) | 0.291 |
| Number of damaged lobes, *n* (%)[&] | 3 (2–4) | 3 (2–5) | 3 (2–5) | 0.149 | 0.118 | 3 (2–5) | 3 (3–5) | 0.671 |
| In the first 48 h | | | | | | | | |
| Breath rate/min (max) | 34 (6) | 33 (9) | 33 (5) | 0.988 | 0.713 | 33 (11) | 33 (5) | 0.590 |
| $PaO_2/FiO_2$ ratio (min) | 117 ± 42 | 98 ± 30 | 105 ± 34 | 0.087 | 0.376 | 104 ± 32.4 | 120 ± 32.5 | 0.235 |
| $FiO_2$ (%) (max) | 75 (48) | 80 (30) | 80 (35) | 0.082 | 0.969 | 80 (25) | 80 (30) | 0.799 |
| PEEP ($cmH_2O$) (max) | 12 (6) | 12 (4) | 14 (4) | 0.502 | 0.056 | 12.0 ± 2.3 | 13.0 ± 1.9 | 0.215 |
| $C_{dyn}$ (ml/$cmH_2O$) (min) | 44 (6) | 37 (12) | 41 (8) | ***0.003*** | 0.058 | 36.3 ± 6.6 | 39.5 ± 7.0 | 0.265 |
| In the first week | | | | | | | | |
| WBC (×10$^3$/μL) (max) | 13.2 (5.8) | 11.0 (8.9) | 12.6 (6.6) | 0.077 | 0.086 | 10.4 (10.3) | 11.0 (6.7) | 0.590 |
| WBC (×10$^3$/μL) (min) | 5.9 (2) | 6.3 (4) | 4.9 (4) | 0.718 | 0.612 | 6.7 (4.4) | 4.6 (1.5) | 0.219 |
| Lymc (×10$^3$/μL) (min) | 0.48 (0.40) | 0.5 (0.28) | 0.49 (0.46) | 0.919 | 0.573 | 0.52 (0.29) | 0.45 (0.28) | 0.551 |
| NLCR (max) | 16.4 (16.2) | 15 (8) | 11 (11) | 0.460 | 0.517 | 13.6 (10.1) | 11.6 (11.5) | 0.843 |
| Lactate (mmol/L) (max) | 2.1 (0.7) | 2.4 (1.1) | 2.4 (0.8) | 0.087 | 0.955 | 2.3 (1.0) | 2.4 (1.6) | 0.347 |
| Fluid balance (mL) | 3670 (3198) | 4552 (2973) | 3849 (2196) | 0.874 | 0.441 | 4174 ± 2907 | 5331 ± 3170 | 0.361 |
| Total fluid (mL/kg/day) | 40.7 (9.3) | 44.3 (15.5) | 44.8 (11) | 0.696 | 0.910 | 44.8 ± 13.5 | 48.7 ± 12.0 | 0.460 |
| Respiratory support (max), *n* (%) | | | | | | | | |
| IMV | 13 (65.0) | 16 (88.8) | 30 (85.7) | 0.084 | 0.746 | 11 (91.7) | 12 (100) | 0.307 |
| NIMV | 3 (15.0) | 1 (5.6) | 3 (8.6) | 0.344 | 0.694 | 1 (8.3) | 0 | 0.307 |
| HFOT | 4 (20.0) | 1 (5.6) | 2 (5.7) | 0.188 | 0.981 | 0 | 0 | NA |

**Table 1** Comparisons of patients groups *(Continued)*

| | GI (D-dimer < 2) (*n* = 20) | GII (D-dimer ≥ 2) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Before PSM | | | | After PSM | | |
| | | GIIa (TPE+) (*n* = 18) | GIIb (TPE−) (*n* = 35) | $p_1$ (GI and GIIa) | $p_2$ (GIIa and GIIb) | GIIa (TPE+) (*n* = 12) | GIIb (TPE−) (*n* = 12) | $p_2$ (GIIa and GIIb) |
| Additional therapies, *n* (%) | | | | | | | | |
| Cytokine filters | 1 (5.0) | 3 (16.7) | 3 (8.1) | 0.427 | 0.434 | 2 (16.7) | 1 (8.3) | 0.592 |
| IL-6 blocker | 12 (60.0) | 9 (50.0) | 20 (57.1) | 0.536 | 0.621 | 7 (58.3) | 6 (50) | 0.682 |
| Steroids | 11 (55.0) | 10 (55.6) | 20 (57.1) | 0.357 | 0.912 | 7 (58.3) | 7 (58.3) | 1.000 |
| Duration of IMV (h)[&] | 168 (0–816) | 286 (0–1008) | 192 (0–720) | 0.1 12 | 0.067 | 316 ± 271 | 278 ± 139 | 0.671 |
| AKI, *n* (%) | 7 (35.0) | 6 (33.3) | 19 (54.3) | 0.914 | 0.148 | 3 (25) | 6 (50) | 0.206 |
| Tracheotomized patients, *n* (%) | 2 (10.0) | 2 (11.1) | 1 (2.9) | 0.911 | 0.218 | 1 (8.3) | 0 (0) | 0.307 |
| LOS-ICU, (days)[&] | 12 (6–34) | 20 (5–42) | 11 (7–35) | ***0.017*** | ***0.003*** | 20 ± 10 | 14 ± 5 | 0.067 |
| Mortality, *n* (%) | 1 (5.0) | 3 (16.7) | 16 (45.7) | 0.242 | ***0.037*** | 1 (8.3) | 7 (58.3) | ***0.009*** |

*AKI* acute kidney injury, *APACHE II* Acute Physiology and Chronic Health Evaluation, *BMI* body mass index, *CCI* Charlson comorbidity index, $C_{dyn}$ dynamic compliance, *CRP* C-reactive protein, *HFOT* high-flow oxygen therapy, I*CU* intensive care unit, *IL-6* interleukin-6, *IMV* invasive mechanical ventilation, *LOS* length of stay, *Lymc* lymphocyte count, *NIMV* non-invasive mechanical ventilation, *NLCR* neutrophil-lymphocyte count ratio, *PSM* propensity score matching, *SOFA*, sequential organ failure assessment, *TPE* therapeutic plasma exchange, *WBC* white blood cell. Results were given as percentage, mean ± sd, and median (IQR or min-max). [&]Minimum and maximum values. Student *t* and Mann-Whitney *U* tests were used for statistical analysis

significantly decreased after three consecutive TPEs (Table 2). Furthermore, although ferritin level at the ICU admission was higher in GIIa, the mortality rate in both before and after PSM was higher in GIIb (45.7% and 58.3%) than in GIIa (16.7% and 8.3%) ($p = 0.037$, $p = 0.009$, respectively) (Table 1).

Some patients with COVID-19 pneumonia have a high risk of thrombosis leading to worse outcomes. Therefore, monitoring D-dimer levels is crucial. In these groups of patients, TPE seems to be a treatment which may improve outcomes by effectively removing FDPs and restoring coagulation status. We are aware that TPE may not be routinely required in these patients [6]. However, we think that it should be featured as a part of the treatment especially in COVID-19 pneumonia patients with a high risk of thrombosis.

**Table 2** Comparisons of laboratory parameters in pre and post-TPE procedure

| | Pre-TPE | Post-TPE | *p* |
|---|---|---|---|
| WBC ($\times 10^3$/μL) | 9.08 ± 4.1 | 9.14 ± 3.5 | 0.951 |
| Neuc ($\times 10^3$/μL) | 7.38 ± 3.1 | 7.33 ± 3.3 | 0.953 |
| Lymc ($\times 10^3$/μL) | 0.9 (0.5–1.3) | 1.02 (0.77–1.27) | 0.053 |
| NLCR | 6.8 (1.8–11.7) | 6.7 (4.2–9.2) | 0.184 |
| LDH (IU/L) | 436 (322–550) | 239 (181–297) | ***0.001*** |
| D-dimer (mg/L)[&] | 7.8 (2.1–35.2) | 1.3 (0.6–3.9) | ***< 0.001*** |
| Ferritin (ng/mL)[&] | 1268 (399–6110) | 405 (157–1650) | ***0.001*** |
| IL-6 (pq/mL)[(13)&] | 161 (36.2–2958) | 24.5 (1.5–130) | ***0.001*** |
| CRP (mg/dL)[&] | 11.8 (0.4–29.7) | 0.9 (0.3–7.2) | ***< 0.001*** |
| Procalcitonin (ng/mL)[&] | 0.27 (0.02–87) | 0.1 (0.01–39) | ***0.002*** |

*CRP* C-reactive protein, *IL-6* interleukin-6, *LDH* lactate dehydrogenase, *Lymc* lymphocyte count, *Neuc* neutrophil count, *NLCR* neutrophil-lymphocyte count ratio, *TPE* therapeutic plasma exchange, *WBC* white blood cell. Results were given as percentage, mean ± sd, and median (quartiles or min-max). [&]Minimum and maximum values. Paired sample and Wilcoxon tests were used for the statistical analysis

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**Authors' contributions**
BG: design of the work, analysis and interpretation of data, and writing. EO: acquisition of the data. HKA: acquisition and interpretation of the data and substantial contribution to the conception. UC and LT drafted the work. COVID-19 Study Group: acquisition of the data. The authors read and approved the final manuscript.

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**Availability of data and materials**
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### Consent for publication
No applicable

### Competing interests
The authors declare that they have no competing interests.

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## Publisher's Note