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Effects of cytokine hemadsorption as salvage therapy on common laboratory parameters in patients with life-threatening COVID-19

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ABSTRACT

Background: The COVID-19 pandemic has led to emergency approval of treatment modalities unusual for viruses, such as therapeutic cytokine Hemadsorption(HA). This study aims to investigate the experience of salvage HA therapy and the effect of HA on routine laboratory tests.

Methods: Life-threatening COVID-19 patients followed up between April 2020 and October 2022 who underwent HA salvage therapy were retrospectively enrolled. Data derived from the medical records were evaluated to meet the assumptions of statistical tests, and those that met the relevant statistical rules were selected for further analysis. Tests of Wilcoxon, Paired-T, and repeated measures-ANOVA were used to analyse the laboratory tests performed before and after HA among the surviving and nonsurviving patients. $P < 0.05$ was selected for the statistical significance of the alpha.

Results: A total of 55 patients were enrolled in the study. Fibrinogen ($p = 0.007$), lactate dehydrogenase (LDH) ($p = 0.021$), C-reactive protein (CRP) ($p < 0.0001$), and platelet (PLT) ($p = 0.046$) levels showed a significant decrease with the HA effect. WBC ($p = 0.209$), lymphocyte ($p = 0.135$), procalcitonin (PCT) ($p = 0.424$), ferritin ($p = 0.298$), and D-dimer ($p = 0.391$) levels were not affected by HA. Ferritin level was significantly affected by survival status ($p = 0.010$). All patients tolerated HA well, and 16.4 % ($n = 9$) of the patients with life-threatening COVID-19 survived.

Conclusion: HA is well tolerated even when used as a last option. However, HA may not affect WBC, lymphocyte, and D-dimer levels. In contrast, the effect of HA could limit the benefits of LDH, CRP, and fibrinogen in various clinical assessments. This study suggests that HA treatment could be beneficial even if selected as a salvage therapy

1. Background

The highly contagious viral illness of Coronavirus disease 2019 (COVID-19) has caused the pandemic leading to a worldwide health crisis, and has prompted emergency approval of treatment modalities unusual for viruses [1,2]. The elevated cytokines, such as IL-2 and IL-6 in non-surviving patients, indicate that cytokines play an essential role in severe COVID-19 [3,4]. Additionally, cytokine release syndrome (CRS) is a crucial milestone in the pathogenesis of acute respiratory distress syndrome (ARDS) in COVID-19 cases [3–6]. It has been established that the homeostasis of various cytokine groups is disrupted. The increased production of proinflammatory cytokines results in multiple organ failure and death in individuals with severe COVID-19 [7]. The balance between cytokine groups was thought to be restored by removing these proinflammatory cytokines from the plasma [8,9]. Hemadsorption (HA) decreases the levels of proinflammatory cytokines via the pores placed in the cartridge column that capture cytokines [10–12]. Considering the critical role of proinflammatory cytokines in pathogenesis, HA is a promising technique for treating COVID-19 [9].

In the literature, there is controversial information about the effect of

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HA on laboratory tests frequently used in the practice of COVID-19 [13,14]. Furthermore, the role of HA used as salvage therapy in cases with severe COVID-19 has yet to be fully established [13]. Despite having emergency use authorization, no guideline recommendation on HA therapy exists for COVID-19 [13,15]. Therefore, further studies analyzing the changes in biochemical and hematological parameters in addition to the experience of HA as salvage therapy are needed to provide additional data on HA therapy [13,14].

The aim of this study is to represent the experience of HA used as salvage therapy in patients with severe COVID-19 who did not respond to standard treatments, as well as to evaluate the effect of HA on the results of common laboratory tests.

2. Materials and methods

2.1. Ethical approval and study population

This study was approved by the Fırat University Committee of Ethics (approval date and number: 18.03.2021 and 2021/04–29A). Patients over 18 years who received HA treatment via the hematology apheresis unit between April 2020 and October 2022 were enrolled retrospectively.

In addition to the HA, patients with a positive result on COVID-19 PCR, pulmonary involvement detected by computerized tomography (CT), administration of standard treatments, admission to the ICU for the management of severe respiratory failure, and diagnosis of CRS secondary to COVID-19 were included in the study.

2.2. Management of COVID-19

All patients received Low-molecular-weight heparin 4000 units/day and methylprednisolone 80 mg/day. All patients received anti-cytokine therapy or antimicrobials due to active sepsis(who couldn't take it as anti-cytokine therapy was contraindicated) [16–18]. All patients were treated with either tocilizumab (800 mg) or anakinra (at least three days with 3x200mg/day) or given appropriate antimicrobial therapy for sepsis for 72 h. Cases with worsened clinical signs and symptoms, (or) cases involving the development of ARDS, (or) cases with an increased need for oxygenation/intubation, (or) cases with multiple organ dysfunction, (or) cases with increased vasopressor support were planned to include in the study [16–18]. Additionally, infectious diseases and hematology specialists evaluated all of these patients with no further treatment choice and were selected as "***patients with life-threatening COVID-19***".

2.3. Administration of hemadsorption

As salvage therapy, life-threatening COVID-19 patients received HA in addition to their current(standard) treatment. All patients were scheduled to undergo HA in three sessions [19]. HA was administered to the patients through femoral or jugular venous catheters at a blood flow rate of 250–300 mL/min using disposable resin-directed Jafron©-HA330 hemadsorption cartridges [11,12].

2.4. Data collection

The patient's age, gender, comorbidities (chronic obstructive pulmonary disease (COPD), congestive heart failure, etc.), pulmonary involvement rates in computerized tomography (CT), bacterial pneumonia, intubation, or oxygen requirements, tocilizumab, anakinra and/or steroid treatment, and need of vasopressor were recorded. Comorbidities were assessed via the Charlson index [20]. Pre-HA: Parameter measurement was calculated based on the last parameter checked prior to the first HA procedure. Post-HA: Parameter measurement was calculated based on the first parameter checked after HA. In addition to the pre-HA and post-HA levels of Fibrinogen (mg/dL), Lactate dehydrogenase (LDH) (u/L), D-dimer (mg/L), Ferritin (ng/mL), C-reactive protein (CRP) (mg/L), and procalcitonin (PCT) (ng/mL), White Blood Cell (WBC), the absolute count of Lymphocytes (Lym) (x/mm^3), Neutrophils (Neu) $x10^3/mm^3$, and Platelets (PLT) $x10^3/mm^3$ were measured at the time of pre-HA and post-HA. HA-related adverse events (such as nausea, vomiting, bleeding, hypotension, shock, acute coronary syndrome, cerebrovascular accident, mesenteric ischemia, or pulmonary embolism) were recorded [21]. Additionally, the survival status of the patients was registered with the time data. Patients who underwent cytokine adsorption together with plasmapheresis and patients with missing data > 30 % were excluded (Fig. 1).

2.5. Statistical analysis

Numbers and percentages were used for categorical data in descriptive analysis. Categorical data were compared using the Chi-square test. Mean±standard deviation (Mean±SD) was used for the parametric, and median (25–75 percentile) was used for the non-parametric continuous variables. Comparisons of means of increment in parameters between groups were made using Student's t-test for independent samples and repeated-measures factorial analysis of variance (RM-ANOVA), split-plot for repeated measures (pre-HA and post-HA) to verify HA as a within-factor, the status of survival as a between-factor, and interaction (HA and survival) effects. Data of the parameters were analyzed separately after log10-transformation of the skewed continuous variables to achieve homoscedasticity and normal distribution for the assumption of the RM-ANOVA. Because some data still differed significantly from normal distribution even after log10-transformation, these data were analyzed using the tests of Wilcoxon and Mann-Whitney-U. $P < 0.05$ was defined as the statistical significance of the alpha. Power > 80 % was described as a probability of avoiding a type-II error. Statistical analyses were conducted with IBM-SPSS-V21 and G*power (Version-3.1).

3. Results

3.1. Descriptive data and clinical characteristics

A total of 55 patients, 21 (38.2 %) of whom were women, were enrolled in the study. The mean age of the patients was 58.5 ± 12.5 years. There were 47 (85.5 %) patients with a rate of 25 % or more pulmonary infiltration on CT images (Table 1). Seven (14.5 %) patients with advanced sepsis secondary to nosocomial pneumonia accompanying CRS had pulmonary infiltration below 25 %.

Before the salvage therapy, there were 30 (54.5 %) patients receiving tocilizumab treatment and three (5.5 %) patients receiving anakinra (3×200mg/day) (Table 1). Twenty-two (40 %) patients received vasopressors for septic shock secondary to nosocomial bacterial pneumonia whom anti-cytokine therapy (anakinra/tocilizumab) was contraindicated.

Nosocomial pneumonia developed in all patients. At the HA initiation, 24 (43.6 %) patients used antibiotics (AB). AB simultaneously with HA therapy was started on 22 (40 %) patients. Antibiotics while receiving HA were given to nine (16.4 %) patients. At the HA-initiation, there were 27 (49.1 %) intubated patients, 18 (32.7 %) patients who received continuous positive airway pressure, and 10 (18.2 %) patients who inhaled oxygen with a high-flow cannula.

Forty-six (83.6 %) patients did not survive. After the initiation of HA, nine (16.4 %) patients survived (Fig. 1). No HA-related adverse events occurred during the HA application in any patient, and all patients tolerated all HA sessions well.

3.2. Analysis of pre and post-HA laboratory parameters

Both pre-HA and post-HA levels of laboratory tests were summarized in Table 2. The changes in the levels of laboratory tests between survived

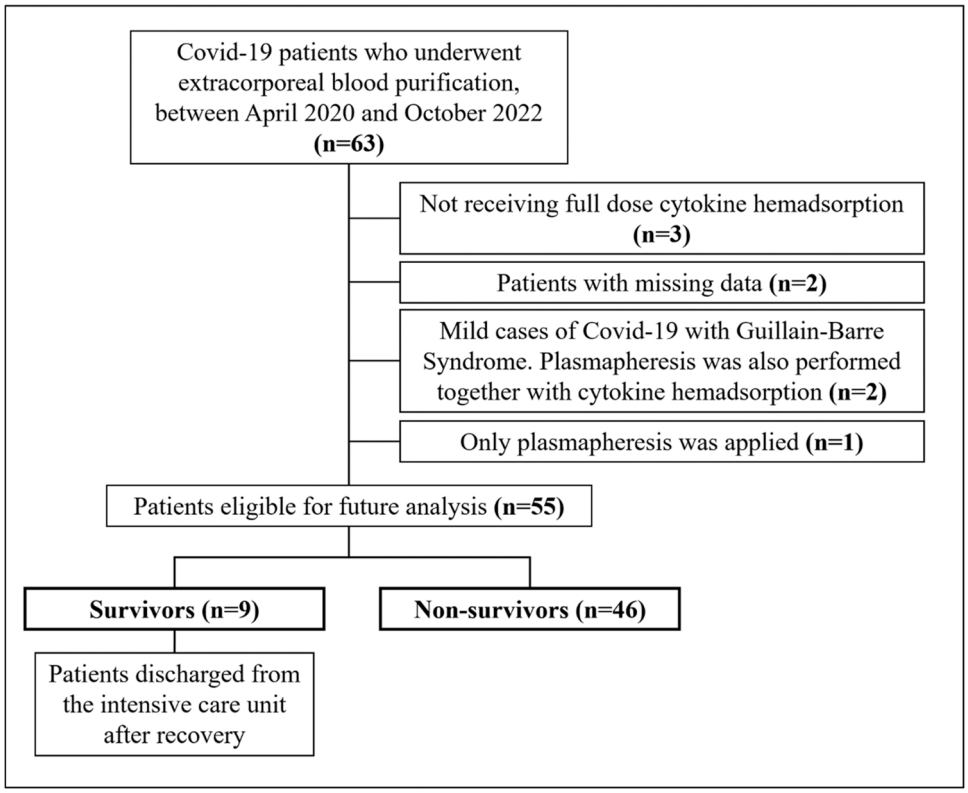

Fig. 1. The selection of the study population is given with a flow diagram.

and non-survived cases were illustrated in the box-plot graphs in Fig. 2.

A significant main effect of HA ($F = 7.970$, $\eta2 = 0.133$, $p = 0.007$) was observed regarding fibrinogen levels. There is no significant main effect of the survival ($F = 0.009$, $\eta2 < 0.0001$, $p = 0.927$) or no significant HA and survival interaction ($F = 0.017$, $\eta2 < 0.0001$, $p = 0.896$) was observed for fibrinogen levels. These results indicate that pre-HA levels of fibrinogen were higher than post-HA levels in all cases (Figure-2A).

The pre-HA level of LDH was 730 (516−945) u/L, and the post-HA level of LDH was 600 (464−768) u/L (Wilcoxon; $p = 0.021$). The difference between pre- and post-HA levels of LDH was (−137) ((−343)-(131)) u/L in survivors and (−81) ((−114)-(−37))u/L in non-survivors ($p = 0.563$). All pre-HA levels of LDH were significantly higher than post-HA levels. This result indicates that, HA has a signigicant main effect on LDH levels (Fig. 2B). Regarding D-dimer levels, no significant main effect of HA ($p = 0.391$) or no significant main effect of survival ($p = 0.804$) or no significant HA and survival interaction ($p = 0.536$) was observed (Fig. 2C).

In respect of ferritin levels, no significant effect of HA ($p = 0.298$) was observed. In contrast, a significant main effect of survival ($F = 7.101$, $\eta2 = 0.127$, $p = 0.010$) was observed. Additionally, the interaction between HA and survival was significant with $F = 9.669$; $\eta2 = 0.165$ ($p = 0.003$), indicating that the change in ferritin levels among surviving/non-surviving groups significantly differed (Fig. 2D). Pre-HA and post-HA levels of ferritin were 1019 (520–1459) and 1369 (641–1935) ng/mL in non-survivors, respectively ($p = 0.007$). Pre-HA and post-HA levels of ferritin were 637 (544–1090) and 318 (270−456) ng/mL in the surviving cases, respectively ($p = 0.025$) (Fig. 2D).

As for CRP levels, a significant main effect of HA ($F = 19.686$, $\eta2 = 0.278$, $p = 0.000049$) was observed. However, no significant effect for survival ($p = 0.588$) or no significant HA and survival interaction ($p = 0.066$) were observed (Fig. 2E). These results indicate that the pre-HA levels of CRP were higher than the post-HA levels in all cases. Concerning PCT levels, no significant effect of HA ($p = 0.424$) and no significant effect of survival ($p = 0.928$) were observed. The interaction between HA and survival was significant with $F = 6.691$; $\eta2 = 0.114$ ($p = 0.013$), indicating that the change in PCT levels was found to decrease gradually in survivors ($p = 0.038$), while it showed a statistically insignificant and partial increase in non-survivors ($p = 0.068$) (Fig. 2F).

As to lymphocyte count, no significant effect of HA ($p = 0.135$) or no significant effect of survival ($p = 0.184$) or no significant HA and survival interaction ($p = 0.604$) were observed (Figure-2 G). The pre-HA and post-HA neutrophil counts were not significantly different ($p = 0.209$). The difference between pre- and post-HA neutrophil counts was not significantly different between survivors and non-survivors ($p = 0.152$) (Fig. 2H). A significant main effect for HA ($F = 4.184$, $\eta2 = 0.073$, $p = 0.046$) was observed regarding PLT count. In contrast, no significant effect for survival ($p = 0.211$) and no significant HA and survival interaction ($p = 0.097$) were observed. These results indicate that PLT counts were decreased with HA (Fig. 2I).

4. Discussion

4.1. Evidence on the efficacy of hemadsorption therapy in the management of COVID-19

In the studies aiming to evaluate the efficacy of the HA application, there are heterogeneous groups of patients collected with varied classification methods. While some studies do not include groups that may have a severe course among the patients who underwent HA, others include groups with various levels of clinical severity of COVID-19. In studies involving patients with moderate-like clinical conditions, mortality rates after HA were between 20 % and 50 % [22–25]. In addition to HA treatment, this rate was between 33.3 % and 58 % in patients with renal failure [26–30].

The early application of HA is predicted to be more beneficial in

Table 1
Demographics and comorbidities of the patients.

		Status of survival			
		Non-survivors (n = 46)	Survivors (n = 9)	Total (n = 55)	P value
Gender (female)		18 (39.1 %)	3 (33.3 %)	21 (38.2 %)	0.743
Age (years)		59 (51–68)	51 (50–64)	59 (51–67)	0.212
Comorbid diseases*		26 (56.5 %)	7 (77.8 %)	33 (60 %)	0.413
Diabetes mellitus		10 (21.7 %)	3 (33.3 %)	13 (23.6 %)	
Connective tissue disease **		3 (6.5 %)	0	3 (5.5 %)	
Malignancy ***		8 (17.4 %)	1 (11.1 %)	9 (16.4 %)	
Chronic kidney disease		4 (8.7 %)	1 (11.1 %)	5 (9.1 %)	
Chronic obstructive pulmonary disease		2 (4.3 %)	1 (11.1 %)	3 (5.5 %)	
Charlson comorbidity index		2 (0–6)	2 (0–4)	2 (0–6)	0,674
Charlson comorbidity score % (10 years mortality)		90 (2–98)	90 (53–98)	90 (2–98)	
The rate of pulmonary involvements related to COVID-19 in computerized tomography	> 75 %	16 (34.8 %)	5 (55.6 %)	21 (38.2 %)	0.636
	50–74 %	19 (41.3 %)	2 (22.2 %)	21 (38.2 %)	
	25–49 %	4 (8.7 %)	1 (11.1 %)	5 (9.1 %)	
	0–24 %	7 (15.2 %)	1 (11.1 %)	8 (14.5 %)	
Tocilizumab treatment pre-HA		26 (56.5 %)	4 (44.4 %)	30 (54.5 %)	0.506
Anakinra treatment pre-HA		3 (6.5 %)	0	3 (5.5 %)	-
Vasopressor treatment at HA-initiation		21 (45.7 %)	1 (11.1 %)	22 (40 %)	0.118
Intubation at HA-initiation		25 (54.3 %)	2 (22.2 %)	28 (50.9 %)	0.162

* One patient with diabetes mellitus and chronic obstructive pulmonary disease (n = 1).
* One patient with diabetes mellitus and rheumatoid arthritis (n = 1).
* One patient with diabetes mellitus and chronic lymphocytic leukemia (n = 1).
* One patient with congestive heart failure and chronic obstructive pulmonary disease (n = 1).
* One patient with systemic lupus erythematosus and chronic kidney disease (n = 1).
** Two patient with rheumatoid arthritis (n = 2), one patient with systemic lupus erythematosus (n = 1).
*** Three patient with chronic lymphocytic leukemia (n = 3), two patient with multiple myeloma (n = 2), one patient with acute myeloid leukemia (n = 1), one patient with chronic myeloid leukemia (n = 1), one patient with diffuse large b-cell lymphoma (n = 1), and one patient with prostate carcinoma (n = 1).

clinically deteriorating patients [31–33]. As a result, HA-initiation criteria, such as $PaO_2/FiO_2 < 200$ or started before mechanical ventilation (MV) and intubation, had been established [31,32], and mortality rates were between 13.3 % and 37.1 %, lower than in patients who received late HA [31,32,34].

Mortality was even higher in patients with severe ARDS, those on MV, or those receiving vasopressor [14,35]. Although some publications report that HA is applied as a salvage therapy, these studies are mostly case series, including a limited number of patients [14,36]. In addition, it is thought that the patients in these studies may have relatively milder than those in the current study [14,36]. In another study, patients undergoing HA had more favorable clinical findings than those in the current study, and the mortality rate was 67.3 % [11]. In contrast, the mortality rate (37.5 %) after HA was found to be relatively lower in a group of patients with severe ARDS who received MV and norepinephrine and had high lactate and IL-6 levels [37].

Table 2
The descriptive of data according to the hemadsorption as a within-factor and survival status as a between-factor.

		Status of the survival	
	Total (n = 55)	Survivors (n = 9)	Non-survivors (n = 46)
Pre-HA Fibrinogen (mg/dL)	447 (225–664)	431 (276–735)	454 (225–657)
Post-HA Fibrinogen (mg/dL)	298 (194–488)	350 (207–443)	295 (194–488)
	Paired T; p = 0.000506	Paired T; p = 0.002	Wilcoxon; Z:− 3.15; p = 0.002
Pre-HA LDH (u/L)	730 (516–945)	497 (417–616)	789 (557–1012)
Post-HA LDH (u/L)	600 (464–768)	464 (371–535)	623 (497–793)
	Wilcoxon; Z:− 2.306; p = 0.021	Wilcoxon; Z:− 1.84; p = 0.066	Wilcoxon; Z:− 2.02; p = 0.043
Pre-HA D-dimer (mg/L)	4.41 (1.83–7.50)	6.54 (2.10–8.20)	3.55 (1.83–6.97)
Post-HA D-dimer (mg/L)	3.59 (1.53–7.50)	3.48 (1.47–7.50)	4.06 (1.9–7.44)
	Paired T/Log10; p = 0.090	Paired T/Log10; p = 0.870	Paired T/Log10; p = 0.085
Pre-HA Ferritin (ng/mL)	898.1 (519.6–1420.4)	637 (544–1090)	1019 (520–1459)
Post-HA Ferritin (ng/mL)	1321.6 (505.5–1650)	318 (270–456)	1369 (641–1935)
	Paired T/Log10; p = 0.251	Paired T/Log10; p = 0.025	Paired T/Log10; p = 0.007
Pre-HA CRP (mg/L)	82 (24–150)	74.8 (24–138)	183 (82–188)
Post-HA CRP (mg/L)	39 (10.8–90)	38.1 (11.4–90.1)	40.3 (10.6–70.4)
	Paired T-test p = 0.000218	Paired T-test p = 0.006	Paired T-test p = 0.011
Pre-HA PCT (ng/mL)	0.75 (0.14–2.30)	0.51 (0.14–4.60)	0.8 (0.14–2.10)
Post-HA PCT (ng/mL)	1.0 (0.22–2.90)	0.25 (0.12–0.56)	1.30 (0.38–2.90)
	Paired T/Log10; p = 0.247	Paired T/Log10; p = 0.038	Paired T/Log10; p = 0.068
Pre-HA lymphocyte (/mm^3)	450 (310–790)	415 (310–790)	600 (370–630)
Post-HA lymphocyte (/mm^3)	620 (320–890)	550 (290–860)	700 (630–910)
	Paired T/Log10; p = 0.544	Paired T/Log10; p = 0.175	Paired T/Log10; p = 0.465
Pre-HA neutrophil (x10^3/mm^3)	11.54 (6.09–16.95)	11.02 (5.95–16.95)	12.16 (9.17–16.53)
Post-HA neutrophil (x10^3/mm^3)	13.21 (7.35–16.95)	13.22 (7.72–18.83)	9.53 (6.42–14.44)
	Paired T-test; p = 0.144	Paired T-test; p = 0.106	Paired T-test; p = 0.376
Pre-HA PLT (x10^3/mm^3)	171 (115–253)	171 (125–241)	196 (112–253)
Post-HA PLT (x10^3/mm^3)	124 (83–210)	121 (70–132)	161 (140–227)
	Paired T-test p = 0.000091	Paired T-test; p = 0.000062	Wilcoxon; Z:− 4.11; p = 0.000039

Pre-HA: Parameter measurement was calculated based on the parameter checked before HA.
Post-HA: Parameter measurement was calculated based on the parameter checked after HA.

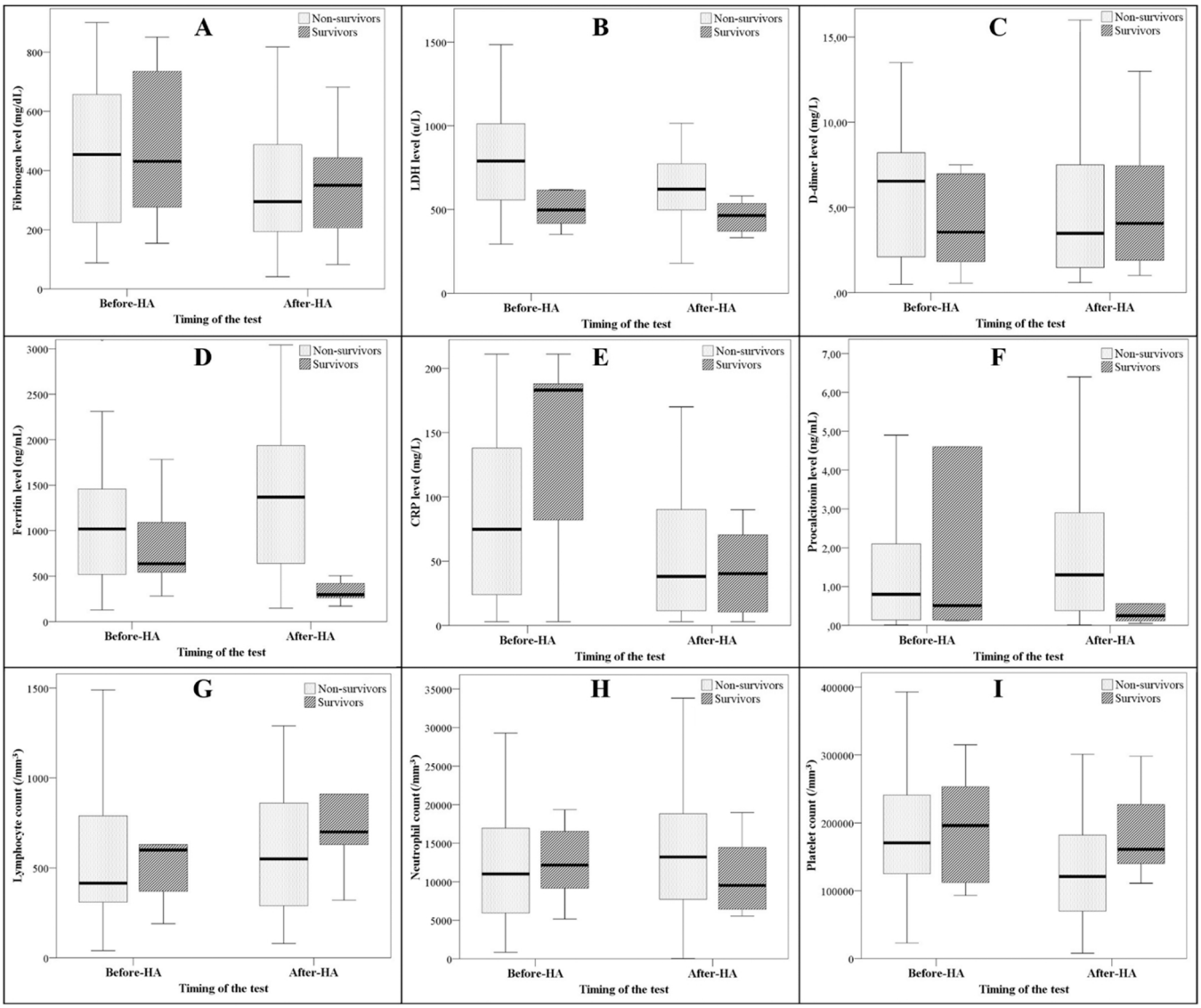

Fig. 2. Box plots of the data according to the hemadsorption as a within-factor and survival status as a between-factor.

4.2. Interpretation of hemadsorption as salvage therapy

The rate of 83.6 % mortality found in the current study is the highest rate among the given studies. However, no further treatment option which prevents progression to death can be seen as the condition causing the usage of HA as a salvage therapy. Additionally, these patients were selected as non-responders in the severe cases of COVID-19. Therefore, despite having no control group, it is a fact that all patients would have progressed to death in this study. Thus, the mortality rate would have been 100 % if the HA was not initiated. That's why HA was selected as salvage therapy in the current study, and nine (16.4 %) patients might have survived due to HA treatment. Furthermore, HA treatment is generally well tolerated, even when used as a last option in patients, as in the present study with poor general conditions [21].

4.3. Effect of hemadsorption on laboratory parameters

Neutrophil count increases with bacterial infections, sepsis, and corticosteroids. For instance, Neutrophils may gradually decrease in a healing bacterial infection. However, receiving corticosteroids in the same patient may neutralize the effect of healing [38]. In the current study, all patients received steroids. Additionally, many patients (83.6 %) whose general condition worsened due to uncontrolled sepsis, superimposed bacterial infections, and progressed to death. Therefore, no significant difference was found in Neutrophil counts of pre- and post-HA and between survivors and non-survivors. Despite some studies with different results, a greater number of studies, including the current study, indicate that neither HA treatment nor survival status has an effect on Neutrophil count [14,22,39,40]. That's why many confounders have already consisted in the recent study. Some patients received corticosteroids, and others recently started to take antibiotics for sepsis. Therefore, while neutrophils may increase in some patients, they may decrease in others.

Several studies indicate an increase in lymphocyte counts with HA effect [23,26,39,41]. While some studies have shown no significant difference in lymphocyte count between pre- and post-HA, report an increase in lymphocytes among survivors, but not in non-surviving patients [28,32]. It is well-known that a decrease in lymphocyte count in COVID-19 patients without HA treatment is a predictor of a poor prognosis [42]. In the current study, however, no significant change was found regarding HA or survival in lymphocyte count. Therefore, a change in lymphocyte may not be helpful as a prognostic factor in COVID-19 patients treated with HA.

Lactate dehydrogenase (LDH) is a prognostic indicator in patients

with COVID-19 [43]. Studies are reporting a decreasing effect of HA on LDH independent of death [39,44]. However, there are also studies indicating that compared to the pre-HA measurement of non-surviving patients, LDH tended to increase, whereas, in surviving patients, the opposite was the case [28]. In this context, it was found in this study that LDH decreased after HA, but there was no significant difference between the surviving and non-surviving patients. It should be kept in mind that LDH may decrease independently in patients undergoing HA treatment, and the LDH levels in the follow-up may be partially misleading.

Although statistical significance is not achieved in some studies, many studies report that PLT decreased with the effect of HA in both groups [14,26,28,33,35,40,44]. In this study, PLT decreased in all surviving and non-surviving patients after HA therapy. Due to the possibility of high thrombocytopenia, clinicians should be careful about thrombocytopenia and thrombocytopenia-related bleeding events in patients treated with HA.

In the literature, there are also studies showing that D-dimer decreased after HA compared to before HA therapy in survivors [24,28,36,45], but in non-survivors, it remained the same [24,28]. Only one study indicates that D-dimer did not change significantly with the effect of HA [26], and the findings of our study are similar to this one.

While some studies state that PCT does not significantly change with the effect of HA [26,33,35,40] some studies report that PCT gradually decreases in survivors and does not change in non-survivors [24].

In this study, the single effects of HA and survival status could not statistically affect PCT. However, a decrease in PCT levels in surviving patients and relative PCT stability in non-surviving patients were observed because of the interaction between HA and survival. This study suggests that the main determinant of PCT may be another factor, such as bacterial sepsis [46,47].

Although there are publications suggesting that CRP levels are elevated with HA [28,35], studies demonstrating decreased CRP levels are far more common in the literature [23,24,26,32,36,40,41,44–46,48]. In this study, it was clearly observed that HA decreased the levels of CRP. However, no correlation between survival and CRP levels was found, similar to the dominant result in the literature. Therefore, a decreased CRP may not reflect the clinical improvement and be misinterpreted in COVID-19 patients undergoing HA.

Studies report that ferritin levels decrease [25,33,42,45,49] or remain unchanged [26,46] with the effect of HA. In this study, HA has no effect on ferritin. On the other hand, survival status significantly affects ferritin levels. In COVID-19 cases treated with HA, ferritin levels decreased gradually in survivors but increased in non-survivors (Table 2). Since ferritin is an acute phase reactant, it may be expected to elevate with the severity of COVID-19 [49]. Likewise, ferritin levels can be predicted to decrease in surviving patients [24,28,36]. This was also the case in our patients undergoing HA. For this reason, monitoring changes in ferritin levels would be advantageous as a prognostic marker in COVID-19 cases treated with HA.

Fibrinogen is an acute-phase reactant up-regulated in response to injury, inflammation, and tissue damage [50]. Fibrinogen levels have been previously shown to be lowered following HA [26,41], and this effect was also seen in the current study. However, survival status was found to have no relation with fibrinogen levels (Fig. 2A). Therefore, the change in fibrinogen levels could mislead the clinical decisions of the patients treated with HA.

5. Conclusion

This study points out that HA is a well-tolerated treatment and could benefit (up to 16.4 %) the mortality rates even if selected as salvage therapy. On the other hand, the PLT, LDH, CRP, and Fibrinogen levels can decrease with the effect of HA. In this context, applying HA to patients with thrombocytopenia may bring new risks in bleeding and coagulation. Furthermore, LDH is a prognostic biomarker used in COVID-19, but the effect of HA reduced its clinical benefit. The same is true for CRP and Fibrinogen as well. For this reason, it may be wrong to conclude that the patient has recovered by monitoring CRP, Fibrinogen, or LDH in patients treated with HA. Finally, HA was not found to directly affect Neutrophil, Lymphocyte, D-dimer, PCT, and Ferritin levels.

Ethical approval

This study was conducted under the Declaration of Helsinki and approved by the Fırat University Committee of Ethics (approval date and number: 18.03.2021 and 2021/04–29A).

Financial disclosure

The authors have nothing to disclose.

CRediT authorship contribution statement

Serhat Uysal: Conceptualization, Project administration, Software, Supervision, Validation, Visualization, Formal analysis, Methodology, Writing - original draft, Writing - review & editing. **Mustafa Merter:** Conceptualization, Data curation, Investigation, Resources, Software, Validation, Visualization, Writing - review & editing. **Ayşe Uysal:** Conceptualization, Project administration, Software, Formal analysis, Investigation, Supervision, Writing - original draft. **Ayhan Akbulut:** Data curation, Investigation, Resources, Supervision, Validation, Visualization, Writing – review & editing.

Declarations of interest

There are no conflicts of interest to report.

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