BLOOD RESEARCH
VOLUME 58 · NUMBER 2
June 2023
ORIGINAL ARTICLE

Efficacy of plasmapheresis in neutropenic patients suffering from cytokine storm because of severe COVID-19 infection

Alireza Sadeghi[1], Somayeh Sadeghi[2], Mohammad Saleh Peikar[1], Maryam Yazdi[3], Mehran Sharifi[1,4], Safie Ghafel[5], Farzin Khorvash[6], Behrooz Ataei[2], Mohammad Reza Safavi[7], Elahe Nasri[2]

[1]Department of Internal Medicine, School of Medicine, [2]Infectious Diseases and Tropical Medicine Research Center, [3]Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, [4]Cancer Prevention Research Center Seyed Al-Shohada Hospital, [5]Mycology Reference Laboratory, Research Core Facilities Laboratory, [6]Acquired Immunodeficiency Research Center, [7]Department of Anesthesiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

p-ISSN 2287-979X / e-ISSN 2288-0011
https://doi.org/10.5045/br.2023.2022201
Blood Res 2023;58:91-98.

Received on October 9, 2022
Revised on April 11, 2023
Accepted on April 19, 2023

Correspondence to
Elahe Nasri, M.D.
Infectious Diseases and Tropical Medicine Research Center, Isfahan University of Medical Sciences, Hezar Jerib Avenue, Isfahan 81746-73461, Iran
E-mail: elahe.nasri@yahoo.com

Background
With the emergence of the coronavirus disease 2019 (COVID-19) and inability of health-care systems to control the disease, various therapeutic theories with controversial responses have been proposed. Plasmapheresis was administered as a medication. However, the knowledge of its efficacy and indications is inadequate. This study evaluated the use of plasmapheresis in critically ill patients with cancer.

Methods
This randomized clinical trial was conducted on 86 patients with malignancies, including a control group (N=41) and an intervention group (N=45) with severe COVID-19 during 2020-21. Both groups were treated with routine medications for COVID-19 management according to national guidelines, and plasmapheresis was applied to the intervention group. C-reactive protein (CRP), D-dimer, ferritin, lactate dehydrogenase, hemoglobin, and white blood cell, polymorphonuclear, lymphocyte, and platelet levels were measured at admission and at the end of plasmapheresis. Other variables included neutrophil recovery, intensive care unit admission, intubation requirements, length of hospital stay, and hospitalization outcomes.

Results
CRP ($P<0.001$), D-dimer ($P<0.001$), ferritin ($P=0.039$), and hemoglobin ($P=0.006$) levels were significantly different between the groups after the intervention. Neutrophil recovery was remarkably higher in the case than in the control group ($P<0.001$). However, plasmapheresis did not affect the length of hospital stay ($P=0.076$), which could have significantly increased survival rates ($P<0.001$).

Conclusion
Based on the study findings, plasmapheresis led to a significant improvement in laboratory markers and survival rate in patients with severe COVID-19. These findings reinforce the value of plasmapheresis in cancer patients as a critical population suffering from neutropenia and insufficient immune responses.

Key Words COVID-19, Plasmapheresis, Survival, Neutropenia

INTRODUCTION

In late 2019, a novel human-infecting beta coronavirus, known as coronavirus 2019 (COVID-19), emerged and has become a prominent issue affecting all aspects of human life, from health to social and economic relationships [1, 2]. Structural assessments of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus imply that spike glycoproteins are the most immunogenic part of the virus, which has been hypothesized to act as a receptor for angiotensin-converting enzyme 2 (ACE-2) to penetrate into host

cells [3]. ACE-2 receptors are widely distributed on the surface of diverse cells, including alveolar type 2 epithelial, endothelial, renal, cardiac, and intestinal cells. SARS-CoV-2 can affect various organs in the body, leading to the numerous clinical symptoms of COVID-19 [4].

The incubation period for COVID-19 ranges from 3–5 days after exposure. Patients may experience a wide course of the disease, ranging from mild to severe. The symptoms include flu-like syndrome, shortness of breath, fever, cough, fatigue, myalgia, and pneumonia [5]. However, the disease can have a severe course presented as severe pneumonia and acute respiratory distress syndrome (ARDS) [2].

SARS-CoV-2 infection may induce an excessive and prolonged inflammatory response in some patients, particularly those with underlying chronic medical conditions such as diabetes mellitus and cardiovascular, pulmonary, and kidney diseases [6]. Age is another risk factor with the highest chance for severe COVID-19 [7]. This phenomenon known as cytokine storm is the leading cause of ARDS and multiple organ dysfunction (MOD), the conditions accompanied by deteriorated status and death. Timely management of cytokine storm is pivotal for patient survival. Immunomodulation, cytokine antagonization, and a reduction in the burden of cytokines are crucial for the success of therapeutic approaches [8].

Plasmapheresis is administered therapeutically to remove abnormally accumulated substances, such as autoantibodies or cytokines, from the circulating plasma [1]. The American Society of Apheresis 2019 guidelines categorized the application of plasmapheresis, in which sepsis due to MOD is category three and grade 2B. Thus, plasmapheresis as an adjunctive therapy may control the cytokine storm caused by COVID-19 [9]. The current study investigated this hypothesis concerning the utility of plasmapheresis in COVID-19 patients experiencing a cytokine storm.

MATERIALS AND METHODS

Study population

This randomized clinical trial (RCT) was conducted on 86 patients with severe COVID-19 admitted to the Alzahra and Seyed-o-Shohada Hospitals affiliated with the Isfahan University of Medical Sciences from March 2020 to May 2021.

The study proposal that met the tenets of the Declaration of Helsinki was primarily proposed by the Ethics Committee of the Isfahan University of Medical Sciences and approved by the code number IR.MUI.MED.REC.1400.195. The study protocol has been signed into the Iranian Registry of Clinical Trials and obtained the code number IRCT20200414047076N2. The study process was explained to patients or their legal guardians. They were reassured of the confidentiality of their information and were requested to sign a written consent.

Patients over 18 years of age who met the criteria for cytokine storm condition, regardless of receiving antiviral and anti-inflammatory drugs for 2–3 days, suffered from life-threatening disorders (respiratory failure, septic shock, MOD/failure), or had early onset acute respiratory distress syndrome (ARDS)/ early onset acute lung injury (ALI) were included.

A cytokine storm was defined as decreased oxygen saturation (<90%) and bilateral lung involvement detected by high-resolution computed tomography (HRCT) concurrent with either IL-6 ≥40 or at least two of the following: 1) C-reactive protein (CRP) level ≥100 mg/L, D-dimer level >1,000 mg/mL, ferritin level >500 g/L, and lactate dehydrogenase (LDH) ≥300 IU/L [10].

Pregnancy, acute coronary syndrome based on electrocardiography and cardiac biomarkers, severe drug reactions requiring alteration in the therapeutic approach, hypersensitivity to fresh frozen plasma (FFP), uncontrolled heart failure, pulmonary thromboembolism, and hypoxemia-induced decrease in the level of consciousness were considered exclusion criteria.

Patients who met the inclusion criteria were randomly assigned to either the intervention or control group. Randomization was performed using Random Allocation Software, providing a particular number for each patient and allocating them to one group.

The study was performed in a double-blind manner, in which the patients and physician who completed the checklists were unaware of the regimen administered for the treatment.

Interventions

According to the Iranian national guidelines, the control group was treated with routine medications for COVID-19 management [11]. Plasmapheresis was administered to the intervention group in addition to the routine management of the controls.

Plasmapheresis was performed by centrifugation. A significant advantage of this method is that there is no limit to the size of the molecules removed [12]. The amount of replaced FFP was measured using the Caplan formula as follows:

"Body weight* 0.065* (1-hematocrit)" [13]

Two-thirds of the replaced fluid was FFP and the remaining one-third was sodium chloride (0.9%). Plasmapheresis was performed thrice for each patient every other day. The duration of plasmapheresis ranged from one to five times, considering the patients' clinical condition, including improvement in the patients' respiratory distress and reduction in inflammatory biomarkers.

The intervention group was recommended not to administer angiotensin convertase enzyme inhibitor (ACEI) agents within 24 h before plasmapheresis to prevent potential hypotension and cardiac monitoring during plasmapheresis treatment.

Electrolytes, including calcium, magnesium, and potassium, were checked daily and corrected if needed. Potassium and magnesium were preserved equal to or above 4 meq/L and 3 mg/dL, respectively [14].

Calcium (Ca) management was done as follows [14]:

Ca＜7.5 mg/dL: electrocardiography and postponement of plasmapheresis until Ca＞7.5 mg/dL was achieved,

7.5 mg/dL≤Ca＜8.5 mg/dL: a vial of calcium carbonate was infused before and during plasmapheresis, continued by two calcium carbonate pills every 8 h,

8.5 mg/dL≤Ca＜10.5 mg/dL: a vial of calcium carbonate was infused before and during plasmapheresis,

Ca≥10.5 mg/dL: plasmapheresis was performed without the requirement for calcium supplementation.

Due to the increased risk of coagulopathy in COVID-19, albumin was not administered during plasmapheresis, as it could lead to reduced levels of precoagulation factors and an increased risk of bleeding [15].

The National Institute of Health recommends similar therapeutic COVID-19 approaches for cancer patients and healthy subjects [16]. According to the Eastern Virginia Medical School guidelines, cancer patients who did not respond to routine anti-COVID-19 medications benefited from plasmapheresis [17]. These rules were applied at the Seyed-o-Shohada Hospital, which is the clinical center for the admission of patients with cancer.

Measurements

Patient characteristics, including age, sex, and medical history, were recorded. Gathered medical history included chronic conditions [hypertension (HTN), diabetes mellitus (DM), dyslipidemia, ischemic heart disease, thyroid gland dysfunctions (hyper-/hypothyroidism), and rheumatoid diseases] and type of malignancies (hematological disorders or solid organ malignancies). On-admission oxygen saturation and severity of lung involvement on HRCT [18] were also assessed. Laboratory markers, including complete blood count and differentiation (CBC diff), CRP, D-dimer, ferritin, and LDH, were assessed on admission and at the end of plasmapheresis treatment. Other assessments included orotracheal intubation and intensive care unit (ICU) admission requirements and neutrophil recovery [absolute neutrophil count (ANC)＞1,000 per mL]. The ultimate outcome of the treatment, including the period of medication use and vitality of patients, was also evaluated.

Statistical analysis

Quantitative variables are described as mean (median) and standard deviation [interquartile range (IQR)], and categorical variables are described using frequency and percentage. The Kolmogorov-Smirnov test was used to assess the normality of continuous variables.

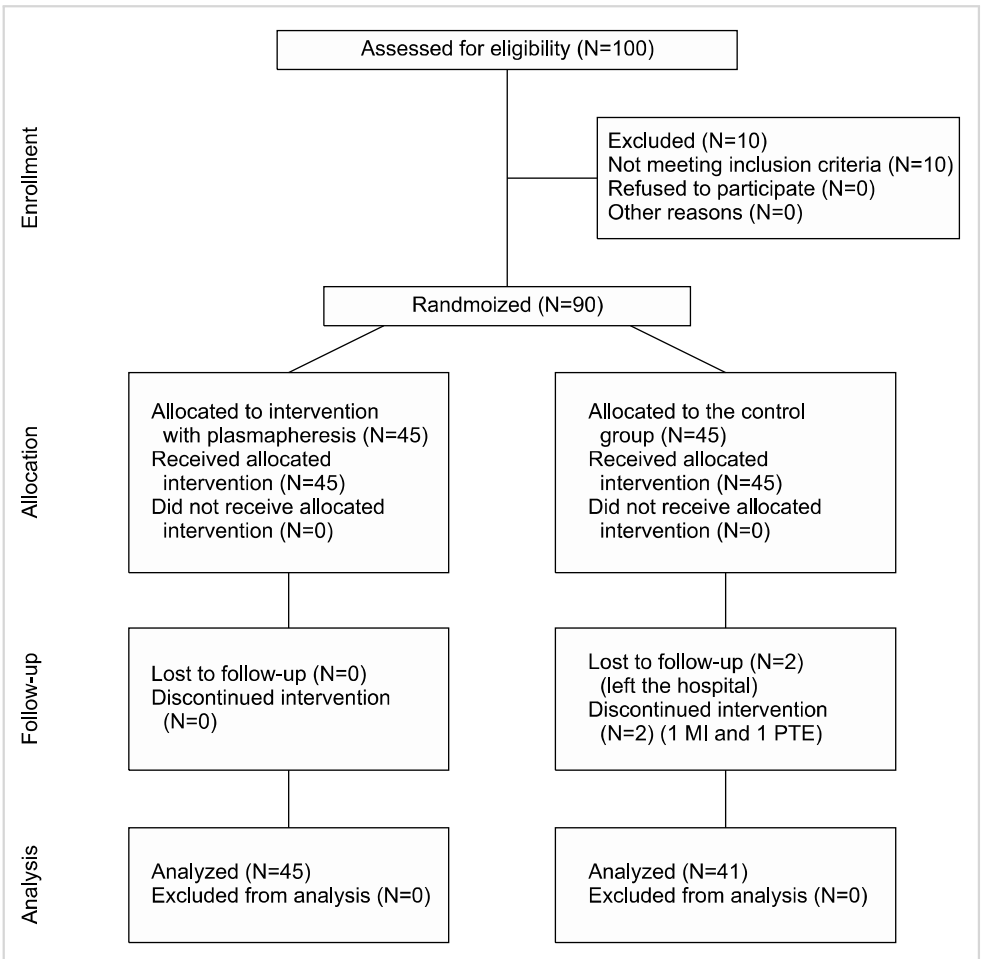

Fig. 1. Consort diagram of the studied population.

Univariate endpoints between the arms were compared using the Pearson chi-square test or Fisher's exact test for categorical variables and the t-test or Mann–Whitney test for continuous data. Clinical outcomes before and after plasma exchange were compared using Wilcoxon's test. Beslow's test was used to compare hospital length of stay (LOS) between groups, accounting for the competing risk of death. Statistical analyses were conducted using Statistical Package for Social Sciences version 23 (SPSS 23, IBM Corp., Armonk, NY, USA).

RESULTS

In the current study, data from 100 patients were collected, of which did not meet the study criteria. The remaining 90 patients were randomly assigned to the case or control group, each containing 45 patients. Four patients in the control group withdrew from the study (one had acute coronary syndrome, one had pulmonary thromboembolism during treatment, and two left the hospital). Accordingly, 45 and 41 patients from the case and control groups, respectively, were included in the analyses. Fig. 1 shows a diagram of the study population. Table 1 shows the demographic, medical, and clinical characteristics of the study participants.

The measured CRP ($P<0.001$), D-dimer ($P<0.001$), ferritin ($P=0.039$), and hemoglobin ($P=0.006$) levels after the intervention were significantly different between the two groups. Moreover, the comparison of CRP ($P<0.001$), ferritin ($P=0.042$), and LDH ($P=0.004$) levels measured before and after plasmapheresis in the intervention group showed statistically significant changes. Detailed information is provided in Table 2.

As shown in Table 3, neutrophil recovery was remarkably higher in the intervention group ($P<0.001$), while the two groups did not differ in terms of ICU admission ($P=0.057$) or orotracheal intubation ($P=0.118$) requirements.

Table 4 compares the effect of plasmapheresis on the length

Table 1. Demographic, medical, and on-admission clinical characteristics of the studied groups.

		Intervention group (N=45)	Control group (N=41)	P[a]
Demographic characteristics				
Age (yr), mean±standard deviation		51.55±8.07	52.60±8.45	0.486[b]
Gender, N (%)	Female	23 (51.1)	17 (41.5)	0.370
	Male	22 (48.9)	24 (58.5)	
Medical characteristics				
Chronic medical conditions	DM	6 (13.3)	4 (9.8)	
	HTN	5 (11.1)	3 (7.3)	
	RA	1 (2.2)	0 (0)	
	DLP	1 (2.2)	0 (0)	
	Hypothyroid	1 (2.2)	0 (0)	
	IHD	0 (0)	2 (4.9)	
Health status, N (%)	Diseased	37 (82.2)	36 (87.8)	0.470
	Healthy	8 (17.8)	5 (12.2)	
Type of malignancy	ALL	1 (2.2)	2 (4.9)	
	AML	6 (13.3)	9 (22.0)	
	Aplastic anemia	2 (4.4)	1 (2.4)	
	Breast cancer	4 (8.9)	2 (4.9)	
	CLL	5 (11.1)	5 (12.2)	
	Lymphoma	5 (11.1)	4 (9.8)	
	MDS	1 (2.2)	1 (2.4)	
	MM	4 (8.9)	4 (9.8)	
	Unknown new case	2 (4.4)	2 (4.9)	
	Ovarian cancer	1 (2.2)	0 (0)	
	Pancreatic cancer	1 (2.2)	0 (0)	
	Refractory All	1 (2.2)	0 (0)	
	TTP	1 (2.2)	0 (0)	
	Colon cancer	1 (2.2)	2 (4.9)	
	Gastric cancer	1 (2.2)	4 (9.8)	
Clinical characteristics				
On-admission oxygen saturation (%), mean±standard deviation		78.16±10.29	79.68±10.75	0.323
The severity of lung involvement (%), mean±standard deviation		18.01±4.02	17.40±4.34	0.353

[a]Chi-square test or Fisher's exact test for qualitative variables and Mann–Whitney's test for quantitative variables. [b]Independent t-test.
Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; DLP, dyslipidemia; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; ITP, idiopathic thrombocytic purpura; MDS, myelodysplastic syndrome; MM, multiple myeloma; RA, rheumatoid arthritis; TTP, thrombocytopenic thrombotic purpura.

Table 2. Clinical indexes, laboratory findings, and ventilator parameters before and after plasma exchange.

		Plasma exchange group (N=45)		Control group (N=41)		P2
		Mean±SD	Median (Q1, Q3)	Mean±SD	Median (Q1, Q3)	
CRP (mg/L)	Before	108.21±33.61	121.2 (80.1, 137)	-	-	
	After	15.65±26.19	6 (2, 14)	72.42±22.07	71 (58, 86)	<0.001
	P1		<0.001			
D-dimer (mg/L)	Before	984.19±783.31	850 (200, 1,700)	-	-	
	After	957.67±714.07	700 (350, 1,600)	2,641.86±2,723.33	1,600 (1,150, 3,152)	<0.001
	P1		0.472			
Ferritin (ng/mL)	Before	6,780.70±12,019.87	1,656.5 (637.5, 6,637)	-	-	
	After	5,275.60±9,139.49	1,346 (630, 4,655)	6,470.25±17,332.62	2,747.5 (1,329, 5,400)	0.039
	P1		0.042			
LDH (U/L)	Before	1,269.53±1,242.82	869 (648.5, 1,395)	-	-	
	After	1,098.34±1,173.67	715.5 (532.5, 1,132.5)	1,350.02±1,645.29	780 (670, 1,422.5)	0.228
	P1		0.004			
WBC (per microliter)	Before	13.70±29.07	7.4 (3.65, 11.05)	-	-	
	After	15.24±28.31	8.2 (3.6, 16.1)	10.51±16.47	5.5 (2.48, 11.4)	0.129
	P1		0.319			
Hemoglobin (g/dL)	Before	11.35±3.49	11.3 (8.9, 13.25)	-	-	
	After	10.88±2.26	11 (8.9, 12.8)	9.50±2.01	9.4 (7.85, 10.95)	0.006
	P1		0.735			
PMN (%)	Before	74.64±21.61	83.6 (69, 87.425)	-	-	
	After	71.71±21.29	78.85 (66.75, 83.875)	61.99±27.51	68.1 (47.4, 85.95)	0.126
	P1		0.153			
Lymph (%)	Before	15.79±16.03	10.4 (5.1, 18.45)	-	-	
	After	17.41±17.00	12.7 (8.675, 21.875)	23.37±18.33	23.6 (7.8, 32.8)	0.081
	P1		0.592			
PLT (per microliter)	Before	122.11±86.74	129 (29.5, 189)	-	-	
	After	126.03±88.54	115 (47, 212)	126.24±166.89	85 (27, 168.5)	0.271
	P1		0.44			

Abbreviations: CRP, C-reactive protein; IQR, interquartile range; LDH, lactate dehydrogenase; P1, Wilcoxon's test for within-group comparisons; P2, Mann–Whitney's test for between-group comparisons; PLT, platelet; PMN, polymorphonuclear cells; Q1, the first quartile; Q3, the third quartile; SD, standard deviation; WBC, white blood cells.

Table 3. Complications related to the interventions.

		Plasma exchange group (N=45)	Control group (N=41)	$P^{a)}$
Neutrophil recovery, N (%)	Yes	0 (0)	11 (26.8)	<0.001
	No	45 (100.0)	30 (73.2)	
ICU admission, N (%)	Yes	33 (73.3)	22 (53.7)	0.057
	No	12 (26.7)	19 (46.3)	
Intubation, N (%)	Yes	4 (8.8)	0 (0)	0.118
	No	0 (0)	0 (0)	

[a)]Chi-square test or Fisher's exact test for qualitative variables and Mann–Whitney's test for quantitative variables.

Table 4. The logistic regression assessment of plasmapheresis impact.

	Plasma exchange group (N=45)	Control group (N=41)	P
Length of hospital stay (day), median (IQR)	10 (6, 18.5)	8 (6.5, 15.5)	0.076[a)]
Vitality, N (%)			
Dead	13 (28.9)	30 (73.2)	<0.001[b)]
Alive	32 (71.1)	11 (26.8)	

[a)]Breslow test, [b)]logistic regression adjusted for disease history.
Abbreviation: IQR, interquartile range.

of hospital stay and patient vitality using logistic regression assessments. Accordingly, plasmapheresis did not affect the length of stay (P=0.076); however, it significantly improved the vitality of patients (P<0.001).

Three patients with AML who had profound (ANC< 100/microliter) prolonged neutropenia (neutropenia for more than 10 days) were randomly assigned to the plasmapheresis-treated group and did not respond to treatment.

DISCUSSION

The current study was designed to evaluate the efficacy of plasmapheresis for severe life-threatening MOD or ARDS

in COVID-19 inducing cytokine storm through clinical outcomes. Our investigation revealed outcomes in favor of plasmapheresis administration, as most of the markers representative of acute-phase reaction and inflammation were reduced after therapeutic plasmapheresis in the intervention group; however, these biomarkers were remarkably less in the intervention group than in the control group. In addition, plasmapheresis efficiently affected the survival of patients compared to the control group.

SARS-CoV-2-induced pneumonia can cause progressive hypoxia and severe inflammatory responses, potentially leading to devastating conditions such as acute lung injury and MOD [19]. COVID-19 induced ARDS has been accompanied with higher mortality than other diseases [20]. Despite all the improvements achieved in the manifestations of COVID-19 since its emergence, incubation, infection, and management, ARDS treatment in COVID-19 remains a matter of debate and is limited to supportive actions. However, no specific treatments are currently available [11]. The use of antimicrobial, antiviral, antimalarial, and corticosteroid agents has shown controversial and variable effectiveness [21-23].

This study aimed to clinically assess the efficacy of plasmapheresis for the management of critically ill COVID-19 patients. In agreement with our study, Hassaniazad *et al.* [24] performed a study in which they represented the dramatic response of their patients to blood replacement therapy as the patients experienced significant improvement in their symptoms and a reduction in CRP, interleukin-1 (IL-1), IL-6, interferon gamma (IFN-γ), and I-17. Another study by Adeli *et al.* [25] demonstrated similar outcomes in a small population of eight patients with severe COVID-19 receiving concurrent antiviral and corticosteroid therapy. Consistent with our study findings, a significant reduction in ferritin levels was noted after plasmapheresis in six COVID-19 patients with meningoencephalitis [26]. Another study by Morath *et al.* [27] in vasopressor-dependent patients with acute respiratory failure revealed a considerable reduction in IL-6, CRP, ferritin, LDH, and D-dimer levels following plasmapheresis. All the studies mentioned above are in line with the findings of the current study; however, the most superior aspect of our study is primarily the use of plasmapheresis in patients with cancer, who are a critical group due to their underlying disease. This study's considerably larger sample population than the others in the literature is the secondary notifying characteristic of this investigation.

Mortality was another parameter assessed in this study. A systematic review reported a significant effect of plasmapheresis in reducing mortality among critically ill patients with sepsis [28]. Clinical studies have shown that blood purification techniques play a crucial role in reducing mortality in patients with severe COVID-19 [29]. However, insufficient evidence is available for the routine use of plasmapheresis to manage hypoxia, which can cause MOD because of the advanced modes of treatment [30].

Blood replacement therapy has shown promising efficacy in removing inflammatory mediators and immune complexes and in managing cytokine storms in various disorders [31, 32]. There is evidence favoring successful plasmapheresis in critically ill COVID-19 patients [33]. Plasma exchange leads to the depletion of IL-6 and the TNF family, which are cytokines responsible for the intensity of the inflammatory response. Studies assessing IL-6 levels in the bronchoalveolar lavage fluid of patients with ARDS revealed a significant direct correlation with mortality [34]. Moreover, patients with severe COVID-19 had higher levels of IL-6 and TNF-alpha, particularly those who required ICU admission [35]; however, we found no difference between the cases and controls regarding their intensive care requirements. Another potential benefit of plasmapheresis is the removal of IL-1, which plays a crucial role in the early stages of ARDS and the subsequent chemokine production responsible for edema [36].

The most noteworthy point in our study is that not only does plasmapheresis effectively affect the immune response to COVID-19 infection in the general population, but it can also be efficiently administered to neutropenic patients with malignancies. We assume that as neutropenic patients suffer from inappropriate immune function, plasmapheresis depletes the excessive cytokines released due to the cytokine storm. Therefore, the immune system can rehabilitate itself to better react to the pathological processes caused by SARS-CoV-2 viremia. However, studies have not well documented the application of plasmapheresis in patients with malignancies.

In summary, however, the gathered data regarding the routine use of plasmapheresis for COVID-19 infection is insufficient, as the studies have been conducted on small populations and the territories for blood exchange are not well-explained; in agreement with the current study, all previous investigations have presented promising outcomes.

Limitations

The small sample size of this study is a significant limitation; however, performing a multicenter study is a strong point of our investigation, potentially leading to more generalizable outcomes. Another factor that may have affected the study outcomes is the variety of cancer types assessed. Although we do not have sufficient information regarding the effect of cancer type and its grading on the response to plasmapheresis in COVID-19, the diversity of assessed hematological and solid organ malignancies in the studied groups might have negligible effects on the outcomes, which should be considered in further studies.

One finding that might be a matter for further investigation in the current study is the level of ANC in response to the applied medications and plasmapheresis. Despite the random allocation of patients to the groups, we noted that all patients with profound prolonged neutropenia, who were allocated to treatment with plasmapheresis, died. However, this was not considered in our study and further investigation is strongly recommended. In addition, neutropenia intensity, a factor that can potentially affect disease severity and response to treatment, can be a matter of potential bias that

should be considered in further evaluations.

CONCLUSION

Based on the findings of this study, plasmapheresis led to significant improvement in laboratory markers and survival rate in patients with a severe course of COVID-19 infection. These findings reinforce the value of plasmapheresis in cancer patients as a critical population suffering from neutropenia and insufficient immune responses.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Harapan H, Itoh N, Yufika A, et al. Coronavirus disease 2019 (COVID-19): a literature review. J Infect Public Health 2020;13:667-73.
2. Sadeghi S, Nasri P, Nasirian M, et al. On admission hemoglobin and albumin, as the two novel factors associated with thrombosis in COVID-19 pneumonia. J Renal Inj Prev 2022;11:9.
3. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol 2020;94:e00127-20.
4. Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol 2020;39:2085-94.
5. Sadeghi S, Nasirian M, Keivany E, Nasri P, Mirenayat MS. The demographic, clinical, and medical manifestations of pulmonary thromboembolism development in COVID-19. Blood Res 2021;56:293-300.
6. Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. BMJ 2020;368:m1198.
7. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13.
8. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. J Infect 2020;80:607-13.
9. Turgutkaya A, Yavaşoğlu İ, Bolaman Z. Application of plasmapheresis for Covid-19 patients. Ther Apher Dial 2021;25:248-9.
10. Hu B, Huang S, Yin L. The cytokine storm and COVID-19. J Med Virol 2021;93:250-6.
11. Sadeghi S, Keivany E, Nasirian M, Nasri P. On-admission versus in-hospital thromboembolism due to COVID-19 infection. What is the particular characteristic of those with early thrombotic events? Adv Respir Med 2021;89:484-92.
12. Balagholi S, Dabbaghi R, Eshghi P, Mousavi SA, Heshmati F, Mohammadi S. Potential of therapeutic plasmapheresis in treatment of COVID-19 patients: immunopathogenesis and coagulopathy. Transfus Apher Sci 2020;59:102993.
13. Schwartz J, Padmanabhan A, Aqui N, et al. Guidelines on the use of therapeutic apheresis in clinical practice–evidence-based approach from the writing committee of the American Society for Apheresis: the seventh special issue. J Clin Apher 2016;31:149-62.
14. Szczeklik W, Wawrzycka K, Włudarczyk A, et al. Complications in patients treated with plasmapheresis in the intensive care unit. Anaesthesiol Intensive Ther 2013;45:7-13.
15. Tabibi S, Tabibi T, Conic RRZ, Banisaeed N, Streiff MB. Therapeutic plasma exchange: a potential management strategy for critically Ill COVID-19 patients. J Intensive Care Med 2020;35:827-35.
16. Kuriakose S, Singh K, Pau AK, et al. Developing treatment guidelines during a pandemic health crisis: lessons learned from COVID-19. Ann Intern Med 2021;174:1151-8.
17. Marik P. EVMS critical care Covid-19 management protocol. Norfolk, VA: Eastern Virginia Medical School, 2020.
18. Saeed GA, Gaba W, Shah A, et al. Correlation between chest CT severity scores and the clinical parameters of adult patients with COVID-19 pneumonia. Radiol Res Pract 2020;2021:6697677.
19. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475-81.
20. Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. Lancet Infect Dis 2020;20:773.
21. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395:1569-78.
22. Molina JM, Delaugerre C, Le Goff J, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Mal Infect 2020;50:384.
23. Rosca A, Balcaen T, Lanoix JP, et al. Mortality risk and antibiotic use for COVID-19 in hospitalized patients over 80. Biomed Pharmacother 2022;146:112481.
24. Hassaniazad M, Vahedi MS, Samimagham HR, et al. Improvement of clinical outcome, laboratory findings and inflammatory cytokines levels using plasmapheresis therapy in severe COVID-19 cases. Respir Med 2021;189:106669.
25. Adeli SH, Asghari A, Tabarraii R, et al. Therapeutic plasma exchange as a rescue therapy in patients with coronavirus disease 2019: a case series. Pol Arch Intern Med 2020;130:455-8.
26. Dogan L, Kaya D, Sarikaya T, et al. Plasmapheresis treatment in COVID-19–related autoimmune meningoencephalitis: case series. Brain Behav Immun 2020;87:155-8.
27. Morath C, Weigand MA, Zeier M, Speer C, Tiwari-Heckler S, Merle U. Plasma exchange in critically ill COVID-19 patients. Crit Care 2020;24:481.
28. Rimmer E, Houston BL, Kumar A, et al. The efficacy and safety of plasma exchange in patients with sepsis and septic shock: a systematic review and meta-analysis. Crit Care 2014;18:699.
29. Yang XH, Sun RH, Zhao MY, et al. Expert recommendations on blood purification treatment protocol for patients with severe COVID-19. Chronic Dis Transl Med 2020;6:106-14.
30. Fonseka CL, Lekamwasam S. Role of plasmapheresis and extracorporeal membrane oxygenation in the treatment of

leptospirosis complicated with pulmonary hemorrhages. J Trop Med 2018;2018:4520185.
31. Schwindenhammer V, Girardot T, Chaulier K, et al. oXiris® use in septic shock: experience of two French centres. Blood Purif 2019;47(Suppl 3):1-7.
32. Bucciarelli S, Espinosa G, Cervera R, et al. Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients. Arthritis Rheum 2006; 54:2568-76.
33. Novacescu AN, Duma G, Buzzi B, et al. Therapeutic plasma exchange followed by convalescent plasma transfusion in severe and critically ill COVID-19 patients: a single centre non-randomized controlled trial. Exp Ther Med 2022;23:76.
34. Donnelly SC, Strieter RM, Kunkel SL, et al. Interleukin-8 and development of adult respiratory distress syndrome in at-risk patient groups. Lancet 1993;341:643-7.
35. Wang R, Pan W, Jin L, et al. Human papillomavirus vaccine against cervical cancer: opportunity and challenge. Cancer Lett 2020;471: 88-102.
36. Hashemian SM, Mortaz E, Tabarsi P, et al. Elevated CXCL-8 expression in bronchoalveolar lavage correlates with disease severity in patients with acute respiratory distress syndrome resulting from tuberculosis. J Inflamm (Lond) 2014;11:21.