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The Effect of Hemoadsorption with CytoSorb on Severe COVID-19 Complications

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Summary

The aim of the study was to assess the effect of hemoadsorption with CytoSorb on the inflammatory response, respiratory failure, and mortality in patients with severe novel coronavirus infection.

Materials and methods. A retrospective single-center cohort comparative study of hemoadsorbtion using the CytoSorb therapy included data from 124 COVID-19 ICU patients. Patients were divided into two groups: the study arm with hemoadsorption (group 1, *N*=93) and the control arm without hemoadsorption (group 2, *N*=31). Patients in group 1 had more severe respiratory failure at baseline, but were otherwise comparable to patients in group 2 in terms of clinical and demographic parameters.

Results. After hemoadsorption, group 1 patients showed significant improvement in 9 of 13 monitored clinical, instrumental, and laboratory parameters: fever (P=0.005), lactate dehydrogenase (LDH) ($P<0.001$), C-reactive protein (CRP) ($P<0.001$), and IL-6 ($P<0.001$) levels, as well as an increase in SpO_2/FiO_2 ratio ($P=0.041$), leukocyte count ($P<0.001$) and lymphocyte count ($P=0.003$), as well as no significant changes in SOFA score ($P=0.068$). The only improvement seen in group 2 patients was a reduction in fever ($P=0.003$). Other significant changes in group 2 were unfavorable, such as a decrease in SpO_2/FiO_2 ratio ($P=0.002$), an increase in inspiratory oxygen fraction FiO_2 ($P=0.001$), leukocyte count ($P<0.05$), LDH ($P=0.038$), procalcitonin ($P<0.001$), and IL-6 ($P=0.005$), as well as an increase in SOFA score from 3.0 to 7.0 (95%CI, 3.0–9.0) ($P=0.001$). The all-cause hospital mortality rate was 37.63% in group 1 and 74.20% in group 2.

Conclusion. The use of hemoadsorption with CytoSorb as a pathogenetic therapy targeting the hyperinflammatory response in the management algorithm of ICU patients with severe COVID-19 complications resulted in resolution of the inflammatory response and respiratory failure, as well as a significant reduction in mortality.

Keywords: hemoadsorption; hemoperfusion; CytoSorb; COVID-19; cytokines; hyperimmune response; inflammatory response; cytokine storm; multiorgan failure; respiratory failure

Conflict of interest. The authors declare no conflict of interest.

Introduction

Because of the high mortality rate among intensive care unit (ICU) patients with severe COVID-19, developing adjuvant techniques to improve the efficacy of routine ICU care for acute respiratory distress syndrome (ARDS) is still relevant today. COVID-19 is known to cause hyperactivation of the immune system and uncontrolled cytokine production [1]. In recent years, there has been increasing evidence for the role of pro-inflammatory cytokines in the pathogenesis of COVID-19 and its complications [2–4].

Studies have convincingly demonstrated that acute respiratory distress syndrome (ARDS) in COVID-19 is caused by an exaggerated immune response rather than viral load [5–7].

Taking into account the responses involving IL-6, which have traditionally been used to characterize the severity of the inflammatory response [8–10], it is possible to assess its role in pathophysiological gas exchange disturbances and increased pulmonary dysfunction. After production and binding to the receptor, the IL-6/sIL-6R complex binds to the membrane protein gp130, causing dimerization and activation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. Given the expression of gp130 in various cells, high levels of IL-6/sIL-6R and the consequences of JAK/STAT3 activation result in hyperproduction and release of various cytokines into the circulation, including IL-8, IL-6, vascular endothelial growth factor (VEGF), MCP-1, and E-cadherin. VEGF and E-cadherin increase vascular permeability and promote capillary leakage syndrome, leading to pathophysiological gas exchange disturbances and pulmonary dysfunction [11].

Tumor necrosis factor (TNF)-α, a cytokine that causes bronchial hyperreactivity, contributes to the progression of lung failure. TNF-α reduces airway diameter and promotes neutrophil migration into

the epithelium. In addition, this cytokine has the ability to directly degrade the airway epithelium, resulting in increased production of pro-inflammatory cytokines such as GM-CSF, IL-8 and intercellular adhesion molecules (ICAM). TNF-α stimulates neutrophils to release MMP-9. All of these events cause irreversible changes in lung tissue, leading to the development of pulmonary fibrosis [12]. IL-17A and TNF-α have been associated with lung injury in obese patients with COVID-19 [13]. Given the importance of elevated cytokine levels in the development, pathogenesis and outcome of lung injury in COVID-19 with severe complications, control and reduction of inflammatory mediator levels appears to be a clinically and pathophysiologically relevant intervention.

Steroid hormones are the primary inpatient anti-inflammatory therapy. When primary anti-inflammatory therapy fails, anti-cytokine therapy is prescribed to block the isolated receptors of a target cytokine. However, because many cytokines have duplicated mechanisms of action as well as pleiotropic and overlapping functions, monoclonal antibodies targeting only one of the pathways are insufficient to affect the mechanisms of hyperinflammatory response development [14].

Hemoadsorption is an adjuvant method for controlling cytokine hyperproduction and can be used as escalating anti-inflammatory therapy in COVID-19 patients. Hemoadsorption removes a wide range of substances from the patient's whole blood that contribute to the exacerbation of the hyperinflammatory response and the development of organ and tissue damage without the need for plasma separation. A number of large studies [15–17] have demonstrated the safety of hemoadsorption with the CytoSorb adsorber, and its use in the treatment of COVID-19 patients is associated with improved clinical outcomes [18–26] according to several international and Russian studies [27]. Given the proven safety of CytoSorb hemoadsorption, the high biocompatibility of the column, and the potential benefits of its use, this therapy deserves a place in the ICU armamentarium. However, because hemoadsorption is not currently included in ICU guidelines (except in a few European communities [28, 29]), it is not commonly used in severe COVID-19 complications. However, hemoadsorption allows pathogenetic treatment of the hyperinflammatory response that causes organ dysfunction in these patients.

Adsorption techniques have been extensively discussed in the scientific literature, but definitive conclusions about their applications have not been reached, and debates continue to this day. The authors of «Adsorption: The New Frontier in Extracorporeal Blood Purification», edited by Ronco and Bellomo, have concluded that as much research as possible is needed to enhance data accumulation on hemoadsorption and its role in critical care [30].

The aim of our work was to determine the effect of hemoadsorption on inflammatory response, respiratory failure and hospital mortality in patients with severe complications of COVID-19.

Materials and Methods

A single-center retrospective cohort comparative study was conducted at the V. P. Demikhov State Clinical Hospital of the Voronovskoye Moscow Clinical Center for Infectious Diseases.

The study included 124 ICU patients with severe COVID-19 and clinical and laboratory evidence of hyperimmune response admitted between January 1 and December 31, 2021.

Inclusion criteria were laboratory-confirmed COVID-19, ICU stay, age over 18 years, specific lung damage according to computed tomography; SpO_2/FiO_2 ratio < 200 mmHg and hemoadsorption in hemoperfusion mode using CytoSorb adsorber.

Patient exclusion criteria: hemoadsorption in combination with prolonged renal replacement therapy (RRT) or in combination with ECMO, or the use of other adsorption systems.

During 2021, 5293 patients diagnosed with COVID-19 were admitted to the ICU. Of these, 136 patients received extracorporeal therapy with the CytoSorb adsorber in the ICU (N=136). 43 patients were excluded based on the exclusion criteria (use of hemoadsorption in the RRT circuit and lateral flow ECMO). Thus, the main group was reduced to 93 patients (group 1). The control group (group 2) included 31 patients consecutively admitted to the ICU with progressive respiratory failure with underlying hyperinflammatory response.

The primary endpoint was to evaluate the effect of hemoadsorption on the inflammatory response and respiratory failure in patients with COVID-19, and the secondary endpoint was to compare in-hospital mortality between the study groups.

Patient examination, diagnosis of underlying disease, complications, comorbidities, and assessment of severity were performed according to the Interim Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus Infections (COVID-19), versions 8 and 9, in effect at the time of the study.

In the hospital, patients in both groups received primary anti-inflammatory therapy according to interim treatment guidelines. Methylprednisolone or dexamethasone was used as the primary anti-inflammatory therapy. If the primary anti-inflammatory therapy failed, anticytokine drugs (tocilizumab, levilizumab, or olokizumab) were administered.

After admission to the ICU, patients in group 1 were started on the next stage of hyperinflamma-

Table 1. Severity of lung injury based on CT.

Group	Frequency of degree				*P*-value
	1 (<25%)	2 (25–50%)	3 (50–75%)	4 (>75%)	
1 (main)	1	19	45	28	<0.001
2 (control)	8	9	4	10	

tory response therapy, hemoadsorption, within 48 hours.

For hemoadsorption in group 1, we used the Cytosorb adsorber of substances from whole blood, which is considered the most widely studied and used adsorption detoxification system in the world, according to the manual published by the world authorities in extracorporeal methods, Ronco and Bellomo, in 2023 [29]. Hemoadsorption was performed in the hemoperfusion mode, using the long-term renal replacement therapy device MultiFiltrate (Fresenius Medical Care AG, Germany) as a blood pump, and the CytoSorb adsorber was added to the circuit. The duration of a hemoadsorption session was 24 hours. Group 1 patients had an average of 2.67±1.3 hemoadsorption sessions each.

Group 2 patients did not receive hemoadsorption.

The groups were similar in terms of demographics (sex, age, BMI) and Charlson comorbidity index (Fig. 1).

The number of patients with different degrees of lung injury according to CT was found to differ significantly between groups (Table 1), which is typical in comparative studies with retrospective comparator groups and does not preclude comparison.

Data were collected at two time points: on admission to the ICU prior to hemoadsorption in group 1 (time point T_0) and on day 7 of hospitalization in the ICU after completion of hemoadsorption in group 1 (time point T_1).

When comparing the parameters at T_0, patients in group 1 had more severe respiratory failure, as evidenced by a lower SpO_2/FiO_2 ratio (Table 2). At the same time, body temperature was higher in group 2. There were no other significant differences between the groups.

Thus, patients in groups 1 and 2 were similar in 9 out of 13 clinical parameters, with patients in group 1 having more severe respiratory failure than patients in group 2 (Fig. 2).

All patients underwent the same series of laboratory, clinical and biochemical analyses, as well as analysis of blood acid-base balance and gases.

Traditionally, the IL-6 level has been used to assess the severity of the hyperinflammatory response, as it reflects the current immune status and is associated with the severity of inflammation [8–10]. IL-6 levels were measured using an enzyme-linked immunosorbent assay (Vector Best technology, Russia). Throughout the study, instrumental parameters were collected and recorded using Mindray N15 bedside monitors (Mindray, China).

Data collection and primary analysis were performed in Microsoft Excel spreadsheet editor, and comparative statistical analysis was performed using IBM SPSS Statistics 27.0 software package. Data samples were characterized using descriptive statistics (minimum, maximum, mean, 25th percentile, 50th percentile (median), 75th percentile, and standard deviation). Data visualization included the construction of box plots and bar graphs to illustrate the differences between the samples.To clarify the applicability of parametric methods, we assessed the normality of the data distribution using the Kolmogorov–Smirnov test with Liliefors correction. We found that due to the small number of outcomes, parametric criteria were not applicable for all parameters, so we used the nonparametric Wilcoxon test for comparative within-group analysis of related samples. The nonparametric Kruskal–Wallis *H* test (for quantitative parameters) and Pearson's χ^2 test (for categorical and binary parameters) were used for between-group comparisons. The log-rank test was used to assess statistically significant differeces in time to a specific outcome/event (death). The significance level used to reject the noll hypothesis of no differences between the groups studied for different treatments was set at 0.05.

When significant differences were found, the nonparametric Mann–Whitney *U* test with Bonferroni–Holm correction for multiple comparisons (for quantitative parameters) and Pearson's χ^2 test with Bonferroni–Holm correction (for categorical and binary parameters) were used. The significance level was set at 0.05 and 0.017 using the Bonferroni–Holm correction.

Results

Positive evolution of several parameters in Group 1 was observed both over time and in comparison with Group 2, including mortality. Thus, significant changes of 9 parameters out of 13 monitored ones were noted: decrease in body temperature (P=0.005), levels of lactate dehydrogenase (LDH) (P<0.001), C-reactive protein (CRP) (P<0.001) and IL-6 (P<0.001), as well as an increase in SpO_2/FiO_2 ratio (P=0.041), increase in the lymphocyte count (P=0.003) and leukocyte count (P<0.001), no changes in the SOFA score (P=0.068) compared to the values before hemoadsorption (Table 2). The mortality rate in group 1 was 37,63%.

Group 2 patients without hemoadsorption experienced positive changes in body temperature (P=0.003). Other parameters, however, showed unfavorable changes, including decreased SpO_2/FiO_2

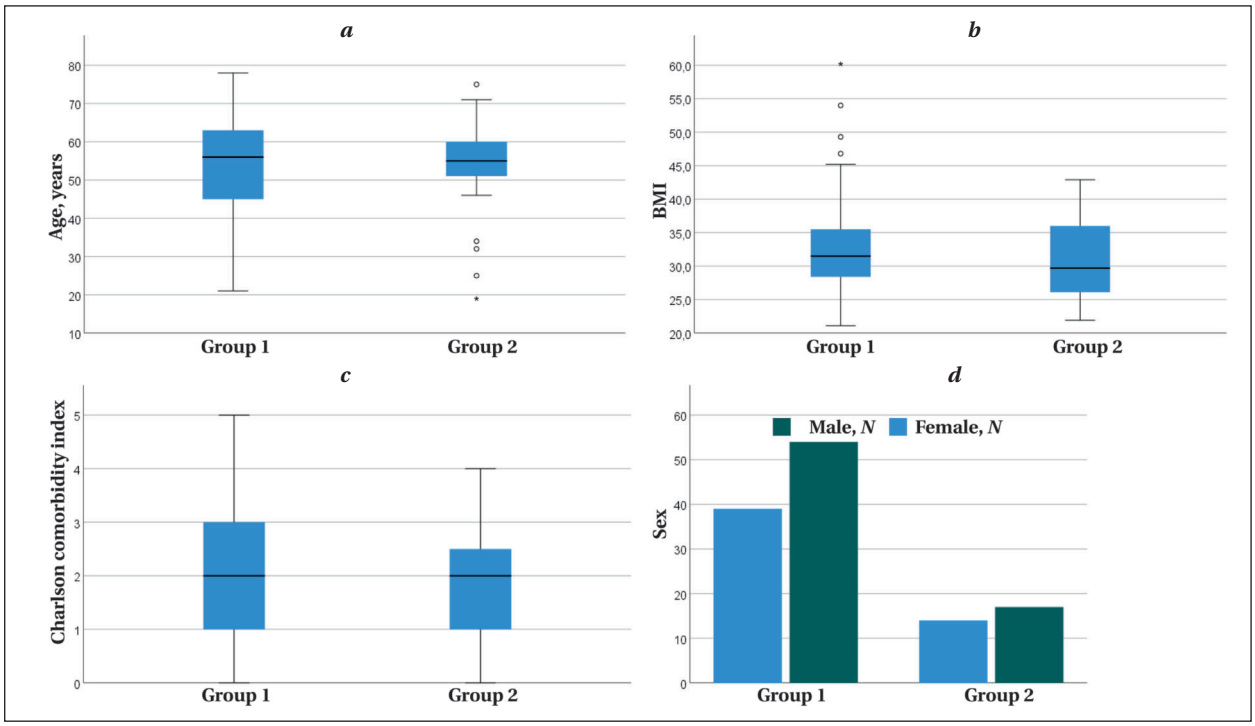

Fig. 1. Demographics and comorbidity index of groups 1 (main) and 2 (control).

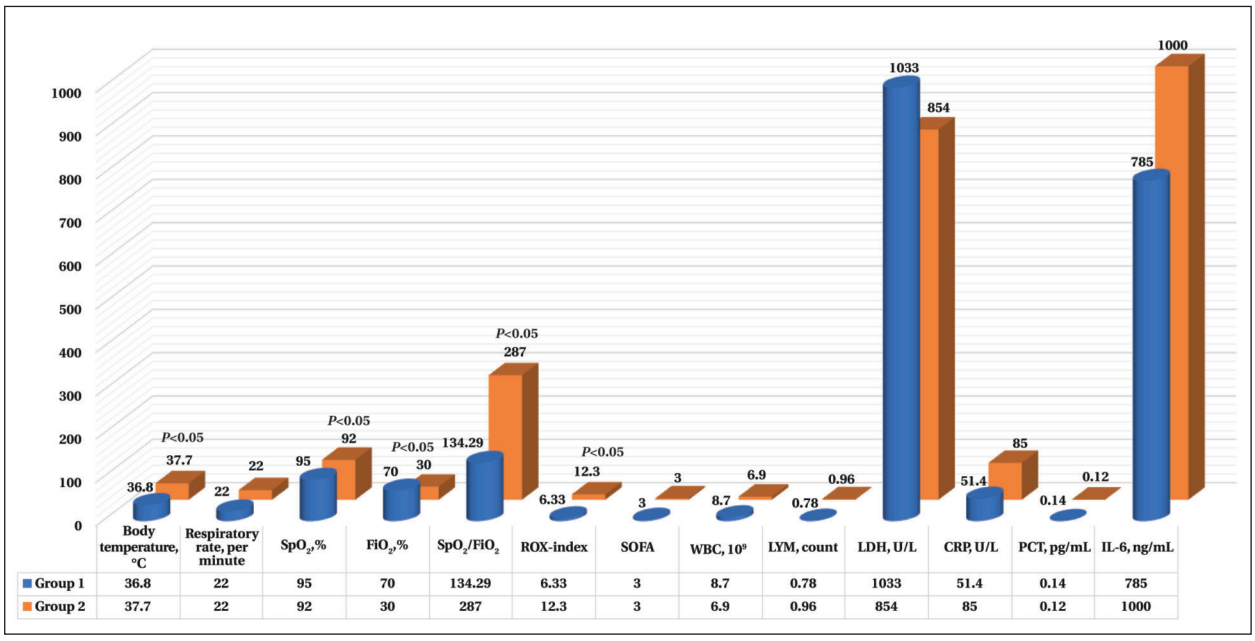

Fig. 2. Clinical characteristics of groups 1 and 2 at T_0.

ratio (P=0.002) and ROX index (P=0.001), as well as increases in leukocyte count (P<0.001), LDH (P=0.038), PCT (P=0.001), and IL-6 (P=0.005).

The SOFA score increased significantly from 3.0 to 7.0 (3.0; 9.0) (P=0.001), indicating that organ dysfunction had progressed in this group (Table 3). The mortality rate in Group 2 was 74.20%.

Comparing to group 2 on day 7, group 1 had significantly higher values of SpO_2 (P=0.003), SpO_2/FiO_2 ratio (P<0.001), ROX index (P<0.001), lower body temperature (P<0.001), and FiO_2 level (P<0.001) (Tables 2, 3).

Significantly lower levels of CRP (P<0.001) and IL-6 (P<0.001) were revealed in group 1 vs group 2. Pattern of secondary bacterial complications was more common in group 2 vs group 1, as evidenced by higher leukocyte counts (11.5×10^9 [9.1; 22.98], P<0.001), PCT levels (2.9 pg/mL [0.3; 9.1], P=0.001),

Table 2. Changes of studied parameters in patients of group 1 during 7 days of treatment in ICU.

Parameter	Values at different time points		*P*-value
	T_0	T_1	
Body temperature, °C	36.80 (36.65; 37.45)	36.7 (36.55; 36.95)	0.005
Respiratory rate, per minute	22.00 (20.00; 22.5)	22.0 (20; 23.5)	0.272
SpO_2, %	95 (93.0; 96.0)	96.0 (94.0; 97.0)	0.082
FiO_2, %	70 (60.0; 80.0)	70 (55.0; 80.0)	0.056
SpO_2/FiO_2	134 (117.5; 161.67)	137.14 (120.00; 175.45)	0.041
ROX index	6.33 (5.23; 7.64)	6.45 (5.19; 10.14)	0.024
SOFA	3.0 (2.0; 3.0)	3.0 (3.0; 4.0)	0.068
WBC, 10^9	8.7 (5.95; 11.30)	10.30 (8; 15.0)	<0.001
LYM, count	0.78 (0.56; 1.09)	0.91 (0.67; 1.28)	0.003
LDH, U/L	1033 (812.5; 1288.5)	898.0 (694; 1225.75)	<0.001
CRP, U/L	51.4 (12.75; 103.9)	10.40 (3.5; 36.08)	<0.001
PCT, pg/mL	0.14 (0.12; 0.23)	0.17 (0.12; 0.44)	0.051
IL-6, ng/mL	785 (54.55; 1000)	186.0 (31.0; 1000)	<0.001

Table 3. Changes of studied parameters in patients of group 2 during 7 days of treatment in ICU.

Parameter	Values at different time points		*P*-value
	T_0	T_1	
Body temperature, °C	37.7 (37.1; 38.6)	37.0 (36.6; 37.5)	0.003
Respiratory rate, per minute	22.0 (20.0; 24.0)	20.0 (18.0; 24.0)	0.168
SpO_2, %	92.0 (88.0; 96.0)	93.0 (88.0; 96.0)	0.927
FiO_2, %	30 (30.0; 70.0)	80.0 (30.0; 90.0)	0.001
SpO_2/FiO_2	287 (138.0; 316.70)	116.3 (103.5; 287.0)	0.002
ROX index	12.03 (5.83; 15.1)	5.88 (4.31; 15.71)	0.090
SOFA	3.0 (2.0; 4.0)	7.0 (3.0; 9.0)	0.001
WBC, 10^9	6.90 (5.5; 10.0)	11.5 (9.1; 22.98)	<0.001
LYM, count	0.96 (0.53; 1.18)	1.16 (0.54; 1.8)	0.115
LDH, U/L	854 (596.0; 1368.0)	1131 (703.0; 1612.0)	0.038
CRP, U/L	85 (34.9; 150.8)	53.0 (23.0; 166.6)	0.468
PCT, pg/mL	0.12 (0.12; 0.3)	2.9 (0.3; 9.1)	0.001
IL-6, ng/mL	1000 (500.6; 1000)	1000 (1000; 1000)	0.005

CRP levels (53.0 U/L [23.0; 166.6], *P*=0.468), and IL-6 concentrations (1000 ng/mL [1000; 1000], *P*=0.005).

Mortality in group 1 was 36.57% (1.97 times) lower than in group 2, *P*=0,017 (Fig. 3).

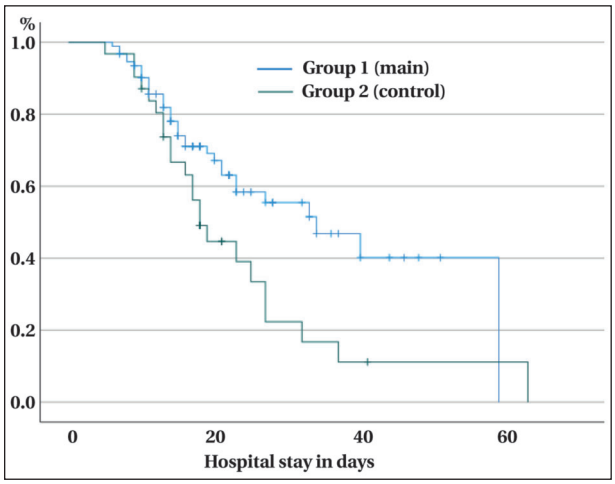

Fig. 3. Mortality rate and hospital stay.

Discussion

Our results show that hemoadsorption has a significant beneficial effect on hyperinflammatory response, severity of acute respiratory failure, and hospital mortality in patients with severe COVID-19 complications, both after within-group analysis and after between-group comparison.

The use of hemoadsorption allowed more effective control of proinflammatory cytokine concentrations, whereas the absence of hemoadsorption in the intensive care algorithm was associated with increased proinflammatory cytokine levels and organ dysfunction. Due to the duplicative mechanisms of cytokine action [31], monoclonal antibodies are not always capable to completely stop the development of the inflammatory response, resulting in the progression of COVID-19-induced ARDS and a number of other complications causing irreversible changes in the body.

Therefore, if primary anti-inflammatory treatment is not fully effective and hemoadsorption is not performed in the ICU, the patient will not receive true causal therapy for COVID-19 [6, 7].

High levels of proinflammatory cytokines are known to contribute to the development of secondary immunosuppression and the pattern of secondary infectious complications in patients with COVID-19.

E. A. Coomes et al. found that 86.8% of hospitalized patients with COVID-19 complications had significantly higher IL-6 concentrations than patients

with uncomplicated COVID-19, and 22.9% had more than a tenfold increase in plasma concentrations of this cytokine [9]. A. Alharthy et al. studied COVID-19 complications and showed that IL-6 concentration in ICU patients was a prognostic marker for mortality [31, 33].

The timely implementation of hemoadsorption in the management of patients with severe COVID-19 complications has been shown to effectively control IL-6 levels, which correlate with the severity of the inflammatory response. Several studies [16, 34, 35] and an experimental study by A. Jansen et al. (2023), using a standardized, highly reproducible technique, demonstrate a significant decrease in TNF (–58%, $P<0.0001$), IL-6 (–71%, $P=0.003$), IL-8 (–48%, $P=0.02$), and IL-10 (–26%, $P=0.03$) *in vivo* using the same sorption system as in our study [17].

A significant decrease in CRP in the hemoadsorption group indicated adequate control of the inflammatory response. Similar effects were described in a study by F. Hawchar et al. that evaluated the outcomes of over 1400 patients receiving hemoadsorption [15], with the concomitant decrease in CRP serving as additional evidence of the reduction in acute inflammation.

We attribute the observed strong positive effect of hemoadsorption on respiratory failure to a reduction in the severity of the hyperinflammatory response and cytokine concentration, as well as a limitation of their secondary damaging effects on lung tissue and gas exchange.

Similar findings were reported by S. David et al., in a large review by A. Akil et al., in a study by A. Alharty et al., and in our previous research [32, 36–39].

A. Supady et al. found that hemoadsorption had no beneficial effect on gas exchange [40]. However, in this study, hemoadsorption was performed during extracorporeal membrane oxygenation (ECMO), which was initiated significantly later than recommended by EuroELSO (after 11 days of ventilation versus the recommended 3 days), so these findings cannot be used as conclusive evidence for the absence of effects of adjuvant therapy in general.

In a pseudorandomized study of 19 pairs of patients, C. Sharf et al. found no differences in clinical parameters between those who received hemoadsorption and those who did not [41]. However, the indications for including hemoadsorption in the management of the patients described in this paper were extremely heterogeneous: some patients were undergoing organ transplantation, others were admitted with polytrauma, some patients developed ARDS as a result of other diseases, some patients were diagnosed with sepsis and septic shock, and the duration of the hemoadsorption session (90 minutes) did not seem sufficient to achieve positive changes [42].

The significantly lower mortality we observed in group 1 is consistent with the findings of Hayanga et al. in a registry of ECMO in patients with COVID-associated ARDS, as well as the results of D. Jarszak et al. who reported a higher survival rate in patients with severe COVID-19 complications when hemoadsorption was used (11 of 12 patients survived in the hemoadsorption group, 6 of 12 patients survived in the standard therapy group) [18, 43]. In a review of publications on the use of hemoadsorption as adjuvant therapy for COVID-19, J. C. Ruiz-Rodriguez et al. observed a trend toward decreased mortality in several of the studies reviewed by the authors [23]. J. He et al. found that the use of hemoadsorption in the pre-ECMO phase of COVID-19 treatment resulted in a significant increase in survival [44]. After reviewing data from over 500 patients on the timing of initiation of hemoadsorption, K. Kogelmann et al. concluded that early initiation of such therapy has a strong positive effect on survival, with each hour of delay increasing mortality by 1.5% ($P=0.034$) [16].

Thus, the initiation of hemoadsorption within the first two days from the patient's admission to the ICU was guided by the above considerations, as well as by the conclusions of the most important contemporary studies on this topic published in 2023 and 2024, such as the study by B. Einollahi et al. [45], which included 578 patients with COVID-19, a large review by Tomescu et al [46], the work by Calamani et al, where the researchers reported higher survival rates with a shorter delay in the initiation of hemosorption [47], and several other studies [48–52].

The findings of this study add to the growing body of knowledge regarding the role of hemoadsorption in treatment of severe COVID-19 complications.

Conclusion

As a result of the study, we found that timely introduction of hemoadsorption into the management of patients with hyperinflammatory response due to COVID-19 allows effective control of cytokine levels, has a strong and significant positive effect on respiratory failure, leading to its regression, as well as helps to reduce mortality in patients with severe complications of COVID-19.

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