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Efficacy of Cytokine Hemoadsorption with Efferon CT in Severe Acute Pancreatitis

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Summary

The aim of the study was to evaluate the effect of cytokine hemoadsorption on clinical manifestations and laboratory parameters in patients with severe acute pancreatitis (SAP).

Materials and methods. The single-center, observational, controlled pilot study included 34 patients, 25 men (73.4%) and 9 women (26.4%), treated for severe acute pancreatitis (SAP) at the N. V. Sklifosovsky Emergency Care Research Institute from May 2022 to August 2023 (ClinicalTrials.gov ID NCT05695001). The mean age of the patients was 42.7±12.6 years. Participants were divided into two groups. In the main group (8 men and 1 woman], mean age 37.2±9.4 years), standard care was supplemented by selective cytokine hemoadsorption (SCH) and renal replacement therapy (RRT) using continuous veno-venous hemofiltration (CVVH) in the first 72 hours after the onset of abdominal pain syndrome (APS). In the control group (N=25, 18 men and 7 women], mean age 44.7±13.2 years), patients were managed similarly except for SCH.

Results. After 24 hours in the ICU, the study group had significantly lower levels of lactate (P=0.045) and IL-6 (P<0.001) than the control group. Lactate and IL-6 concentrations remained significantly different between groups at 72 hours (P<0.001 and P<0.05, respectively). ICU stay was significantly shorter in the study group, with a median of 6 days [95% CI, 4–25] before transfer to the general ward, whereas patients in the control group spent 37 days [95% CI, 22–73] in the ICU (P<0.001).

Conclusion. CVVH is an effective method of extracorporeal detoxification in the management of SAP, but it is less specific than cytokine adsorption in terms of elimination of proinflammatory markers. The data obtained provide sufficient evidence to consider the combination of these two modalities as the most effective approach for the management of SAP.

Keywords: acute pancreatitis, cytokine hemoadsorption, Efferon CT, organ failure, proinflammatory cytokines

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

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Introduction

Acute pancreatitis (AP) is a demarcation-type aseptic inflammation characterized by underlying pancreatic acinar cell necrosis and enzyme release, followed by extensive pancreatic necrosis and degeneration, damage to adjacent tissues, distant organs and systems, and secondary bacterial infection [1]. Approximately 10% of AP patients develop severe disease with local and systemic complications, including multi-organ failure, which is associated with a mortality rate of up to 42%. [2, 3]. Early acute pancreatitis is characterized by both local and systemic inflammation. Acinar cell damage can lead to overstimulation of the inflammatory cascade, including increased synthesis of pro-inflammatory cytokines such as interleukin-1β, 6, 8, 18 (IL-1β, IL-6, IL-8, IL-18), which can cause a «cytokine storm». The early release of IL-6 is critical for the propagation of pro-inflammatory signals that can promote disease progression. At the same time, IL-6 and C-reactive protein (CRP), which is produced in the liver in response to IL-6 stimulation, are prognostic markers of poor disease outcome [4–7]. Interruption of the rapid and uncontrolled inflammatory cascade seems to be a logical pathogenetic approach to eliminate the manifestations of multiorgan failure and to stabilize hemodynamics [8]. However, the use of pharmacological schemes to modulate the inflammatory response in AP has not yet yielded results, which can be explained by the delayed onset of action of immunomodulatory drugs [9, 10]. Over the last decades, the effect of non-selective removal of a wide range of inflammatory mediators during continuous venovenous hemofiltration (CVVH) without significant changes in their serum concentrations and clinical outcomes in patients in late AP with septic shock and acute renal failure has been studied [11–17].

Thus, immediate elimination of proinflammatory markers in early AP via cytokine adsorption may be the most promising alternative pathogenetic strategy. Several recent studies have shown that cytokine adsorption effectively eliminates inflammatory mediators such as IL-1β, IL-6, IL-8, IL-10, and

TNF-α [18–22]. Furthermore, the results of numerous studies show that cytokine adsorption improves systemic hemodynamics and reduces mortality in patients with systemic inflammatory response syndrome (SIRS) and sepsis [23–32].

The aim of this study was to determine the effect of cytokine hemoadsorption on clinical manifestations and laboratory parameters in patients with severe acute pancreatitis (SAP).

Materials and Methods

A single-center, observational, controlled study included 34 patients, 25 men (73.5%) and 9 women (26.5%), who were treated at the N.V. Sklifosovsky Research Institute of Emergency Medicine of Moscow Health Department between May 2022 and August 2023 with a diagnosis of SAP (ClinicalTrials.gov ID NCT05695001).

Patients ranged in age from 25 to 80 years. The mean age was 42.7±12.6 years.

Inclusion criteria for the study were age 18–70 years, documented episode of SAP without signs of infection, diagnosed according to the criteria approved in the Russian Clinical Guidelines 2020, time no more than 72 hours from the onset of the pain attack before the start of extracorporeal detoxification.

Exclusion criteria were a history of chronic pancreatitis (exacerbated chronic pancreatitis), active surgical infection, terminal renal failure requiring chronic dialysis, the use of other methods of extracorporeal elimination of inflammatory mediators, including hemofilters with highly permeable and surface-modified membranes, inability to achieve or maintain a minimum mean arterial pressure ⩾65 mmHg despite vasopressor and infusion therapy within 24 hours, acute pulmonary embolism, blood transfusion reaction, severe congestive heart failure, myocardial infarction in the previous 4 weeks, oncologic disease not in remission, severe granulocytopenia (less than 500 cells/mm^3) or severe thrombocytopenia.

To assess the efficacy of therapy, patients were divided into two groups: prospective main group and retrospective control group. Disease severity in both groups was assessed using the SOFA (Sequential Organ Failure Assessment), BISAP (Bedside index for severity in acute pancreatitis), Ranson (scale for objective assessment of severity and mortality in patients with acute pancreatitis), SAPSII (Original Simplified Acute Physiology Score), APACHE II (Acute Physiology and Chronic Health Evaluation II) scales (Table 1).

The main group included 9 patients (8 men (88.9%) and 1 woman (11.1%), mean age 37.2±9.4 years) who were treated with standard conservative therapy according to the national clinical guidelines for acute pancreatitis (2020) and local protocols of the Moscow Health Department «Management of intestinal failure with underlying infected pancreatic necrosis» with additional administration of cytokine hemoadsorption (HA) on the Efferon CT device during 72 hours after the onset of abdominal pain (Fig. 1).

Efferon CT (AO Efferon, Moscow, Russia) is a device for extracorporeal blood purification by direct hemoperfusion. Detoxification is performed by adsorption of cytokines and other endogenous toxins on a super cross-linked highly porous sorbent. The range of absorbed molecules is from 0 to 55 kDa.

Cytokine hemoadsorption was performed in combination with renal replacement therapy in a single extracorporeal circuit with a blood flow rate of 140 mL/min (120; 150) and a duration of 10 hours (8; 15). The exchange rate was 2500–3300 mL/hour. Mortality in the main group was 11.1% (*N*=1).

To establish a comparison group, we retrospectively reviewed the case histories of 90 patients with SAP (Fig. 1). The detailed analysis revealed that in 30% (*N*=27) of the patients, the time of continuous CVVH initiation exceeded 72 hours from the onset of abdominal pain, 2.2% (*N*=2) refused inpatient treatment, 8.9% (*N*=8) were diagnosed with severe comorbidity that later influenced the outcome of the hospitalization, and 31.1% (*N*=28) did not have results of the required laboratory parameters at the specified time points.

Thus, the control group included 25 patients (18 males (72%) and 7 females (28%)) with a mean age of 44.7±13.2 years. They received standard therapy supplemented with CVVH during the first 72

Table 1. Demographic characteristics and baseline severity assessment of patients with SAP.

Parameter	Values in groups		*P*-value
	Main, *N*=9	Control, *N*=25	
Mean age, years	37.2±9.4	44.7±13.2	0.468
Sex			0.403
Female	1 (11.1%)	7 (28%)	
Male	8 (88.9%)	18 (72%)	
SOFA	4.1±2.8	4.3±2.6	0.684
BISAP	2.2±1.2	2.5±1.0	0.631
Ranson	3.5±1.2	3.8±1.4	0.599
SAPSII	18.0±5.3	17.5±4.7	0.742
APACHE II	12.9±2.5	13.6±2.0	0.708

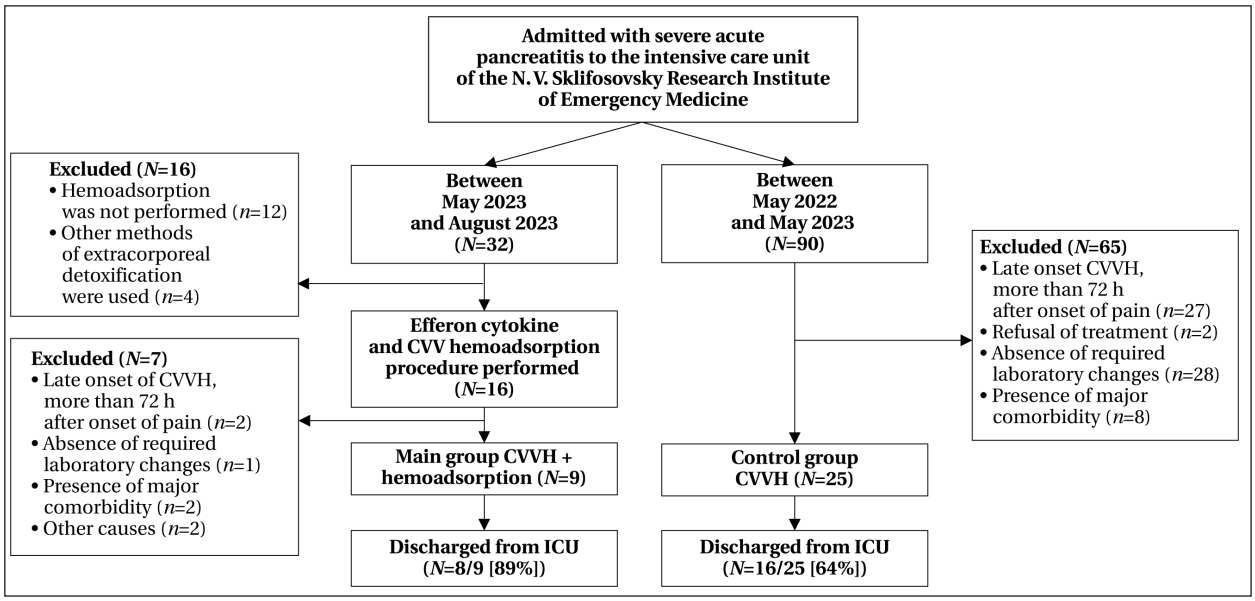

Fig. 1. Study flowchart.

hours after the onset of abdominal pain. The blood flow rate was 140 mL/min (120,150) and the duration was 18 hours (14,24). The exchange rate ranged from 2500 to 3300 mL per hour. The mortality rate in the control group was 36% (*N*=9).

Table 1 shows a comparison of the groups based on demographics and disease severity.

To evaluate the efficacy of non-selective cytokine adsorption, blood was collected on admission to the ICU and 24 and 72 hours later.

Complete blood counts were analyzed using Advia 2120i hematology analyzer (Siemens, Germany). Biochemical blood analysis was performed on an OLYMPUS AU 2700 analyzer (Japan) using reagents from Beckman Coulter, USA. The coagulation study was performed on an automatic coagulometer «ACL TOP-700», Instrumentation laboratory (USA), using reagents from Instrumentation laboratory (USA).

In order to prevent thrombotic complications due to baseline elevated levels of procoagulants and decreased levels of natural anticoagulants in patients with SAP [33], cytokines were adsorbed using the «Efferon CT» column with citrate-calcium anticoagulation and control of ionized calcium levels on the analyzer «ABL 800» (Radiometer, Denmark) in arterial or mixed venous blood.

The obtained data were processed using RStudio 2023 software. For all characteristics, we calculated the mean *(M)* and standard deviation *(±SD)* for normally distributed variables, and the median *(Me)* with 1st and 3rd quartiles *(Q1; Q3)* for variables with nonparametric distribution. The Shapiro–Wilk test was used to determine the type of distribution. Student's *t*-test was used to compare groups according to age and severity scales, and Fisher's exact test was used to compare gender characteristics. The Mann–Whitney *U* test between groups was used to analyze laboratory data, and the Wilcoxon signed-rank test was used to compare values at 24 and 72 hours versus 0 time point. ICU length of stay was analyzed using Kaplan–Meier curves and the log-rank test. The *P* value <0.05 was set as the threshold for assessing the significance of differences and changes. This was a pilot study and no adjustment for multiplicity was made.

Results and Discussion

On admission to the ICU, patients in both groups had elevated white blood cell counts and serum levels of lipase, triglycerides, lactate, CRP, D-dimer (Table 2), procalcitonin, and IL-6 (Fig. 1).

After a full course of treatment including CVVH, patients in the control group showed a decrease in APTT (*P*=0.047) 24 hours after admission to the ICU, and a decrease in neutrophils (*P*=0.005), lipase (*P*<0.001), creatinine (*P*=0.007), and APTT (*P*=0.004) 72 hours later. Meanwhile, in patients of the main group in which non-selective cytokine adsorption was used for extracorporeal detoxification, a decrease in leukocyte count (*P*=0.039), neutrophil count (*P*=0.031) and IL-6 level (*P*=0.032) was observed 24 hours after the start of the study (Fig. 2). After 72 hours, patients in this group showed a further decrease in WBC count (*P*=0.027), neutrophils (*P*=0.039), increase in lymphocytes (*P*=0.024), decrease in total bilirubin (*P*=0.007), CRP (*P*=0.034) (Table 2), IL-6 (*P*=0.035) and procalcitonin (*P*=0.015) (Fig. 2).

Significant differences between the groups were observed 24 hours after admission to the ICU, including

Table 2. Laboratory parameters of patients in the study groups. ***Me (Q1; Q3).***

Parameter	Hour in the ICU	Main group	P_1-value	Control group	P_1-value	P_c-value
Leucocyte count, 10^9/L	0	14.7 (13.0; 18.5)		12.6 (10.2; 16.6)		0.335
	24	10.4 (7.6; 11.8)	0.039	11.8 (9.8; 15.0)	0.470	0.441
	72	8.3 (6.8; 8.5)	0.027	10.2 (6.7; 15.7)	0.131	0.187
Neutrophils, %	0	89.8 (84.9; 90.8)		86.7 (82.9; 88.1)		0.162
	24	80.9 (79.7; 84.9)	0.031	81.6 (74.9; 87.5)	0.152	0.969
	72	75.6 (73.6; 85.3)	0.039	80.3 (74.0; 84.7)	0.005	0.938
Lymphocytes, %	0	6 (5.4; 7.3)		8.1 (6.2; 9.5)		0.175
	24	13 (6.5; 14.0)	0.308	8.0 (5.2; 11.7)	0.617	0.441
	72	11 (8.6; 14.7)	0.024	9 (5.9; 12.6)	0.429	0.419
Lactate, mmol/L	0	1.9 (1.0; 2.6)		2.2 (1.6; 3.4)		0.117
	24	1.3 (0.9; 2.3)	0.863	2.3 (1.7; 2.6)	0.787	0.045
	72	0.9 (0.8; 1.3)	0.135	1.9 (1.3; 2.1)	0.080	<0.001
Glucose, mmol/L	0	8.1 (6.9; 9.7)		7.9 (6.7; 8.7)		0.513
	24	6.6 (5.0; 7.7)	0.093	8.1 (7.1; 9.0)	0.429	0.093
	72	7.6 (6.1; 10.7)	0.796	7.4 (6.2; 9.9)	0.938	0.908
Lipase, U/L	0	731 (320; 1337)		592 (407; 966)		0.877
	24	256 (113; 410)	0.257	438 (304; 885)	0.246	0.218
	72	79 (34; 121)	0.064	202 (110; 400)	<0.001	0.053
Triglycerides, mmol/L	0	2.2 (1.3; 5.4)		2.4 (1.3; 4.0)		1.000
	24	1.5 (1.4; 1.9)	0.755	2.6 (1.9; 4.2)	0.441	0.222
	72	1.8 (1.7; 2.6)	0.833	3.2 (1.8; 4.5)	0.599	0.291
Creatinine, μmol/L	0	80 (70; 102)		98 (78; 123)		0.369
	24	82 (60; 93)	0.604	79 (67; 122)	0.246	0.369
	72	90 (62; 104)	0.730	74 (61; 87)	0.007	0.796
Urea, mmol/L	0	5.8 (4.7; 6.3)		5.3 (4.6; 6.9)		0.889
	24	4.1 (2.7; 9.8)	0.340	5.4 (3.9; 10.6)	0.926	0.289
	72	5.7 (4.7; 8.3)	0.730	5.3 (4.3; 8.3)	0.616	0.920
Total bilirubin, μmol/L	0	22.1 (18.2; 38.7)		17.9 (9.7; 29.8)		0.369
	24	18.6 (10.7; 31.1)	0.666	20.9 (13.6; 25.1)	0.991	1.000
	72	12.3 (9.3; 15.5)	0.007	19.4 (11.6; 23.8)	0.924	0.064
APTT, s	0	27.2 (26.6; 34)		23.4 (21.1; 30.8)		0.052
	24	28.6 (27.1; 34.4)	0.888	30.1 (26.2; 31.8)	0.047	0.740
	72	26.1 (25.5; 26.9)	0.002	29.8 (27.5; 35.0)	0.004	0.052
TT, s	0	15.5 (14.9; 20.2)		17.0 (16.4; 18.3)		0.519
	24	14.3 (14.1; 16.9)	0.276	17.6 (16.1; 18.9)	0.957	0.159
	72	20.1 (17.1; 60.8)	0.235	16.7 (15.7; 19.6)	0.789	0.090
INR	0	1.3 (1.1; 1.3)		1.3 (1.1; 1.4)		0.591
	24	1.2 (1.1; 1.2)	0.297	1.3 (1.2; 1.6)	0.441	0.054
	72	1.3 (1.1; 1.4)	0.814	1.3 (1.3; 1.5)	0.056	0.135
D-dimer, mg/L	0	3.9 (2.6; 5.5)		3.8 (3.0; 5.1)		0.955
	24	2.8 (2.3; 8.9)	1.000	4.8 (3.2; 6.6)	0.301	0.437
	72	3.3 (3.0; 4.9)	1.000	5.1 (4.0; 6.5)	0.161	0.210
CRP, mg/L	0	185 (144; 256)		209 (159; 282)		0.455
	24	168 (135; 249)	0.910	259 (147; 314)	0.499	0.174
	72	150 (138; 167)	0.034	168 (54; 252)	0.087	0.888

Note. P_1 — significance level of differences compared to day 1 of stay in ICU; P_c — compared to the control group; APTT — activated partial thrombin time; TT — thrombin time; INR — international normalized ratio; CRP — C-reactive protein.

a decrease in lactate (P=0.045) and IL-6 (P<0.001) levels. Similar changes were observed 72 hours after the start of the study, as evidenced by further decreases in several parameters (Table 2). There was also a trend towards a difference between groups in lipase (P=0.053) and total bilirubin (P=0.064) concentrations after 72 hours of treatment (Table 2).

In addition, changes in the levels of IL-6, IL-1β, IL-8, IL-10, IL-18 were evaluated in patients in the main group (Fig. 2).

The greatest specificity of cytokine adsorption using Efferon CT adsorbent appears to be with respect to IL-6, as no significant results were found when comparing changes in levels of other pro-inflammatory markers. Concentration of the anti-inflammatory IL-10 also remained relatively constant.

When analyzing the length of stay in the ICU, we found a trend toward shorter time for patients in the main group. The median time to ICU transfer for patients in the main group was 6 [95% CI, 4–25] days, while in the control group it was 37 days [95% CI, 22–73] (P=0.078) (Fig. 3). Mortality was 3.2 times lower in the main group (Fig. 3), suggesting that the addition of cytokine adsorption improves treatment outcomes.

Conclusion

Our results showed that CVVH is an effective method of extracorporeal detoxification in SAP patients, although it is less specific than cytokine ad-

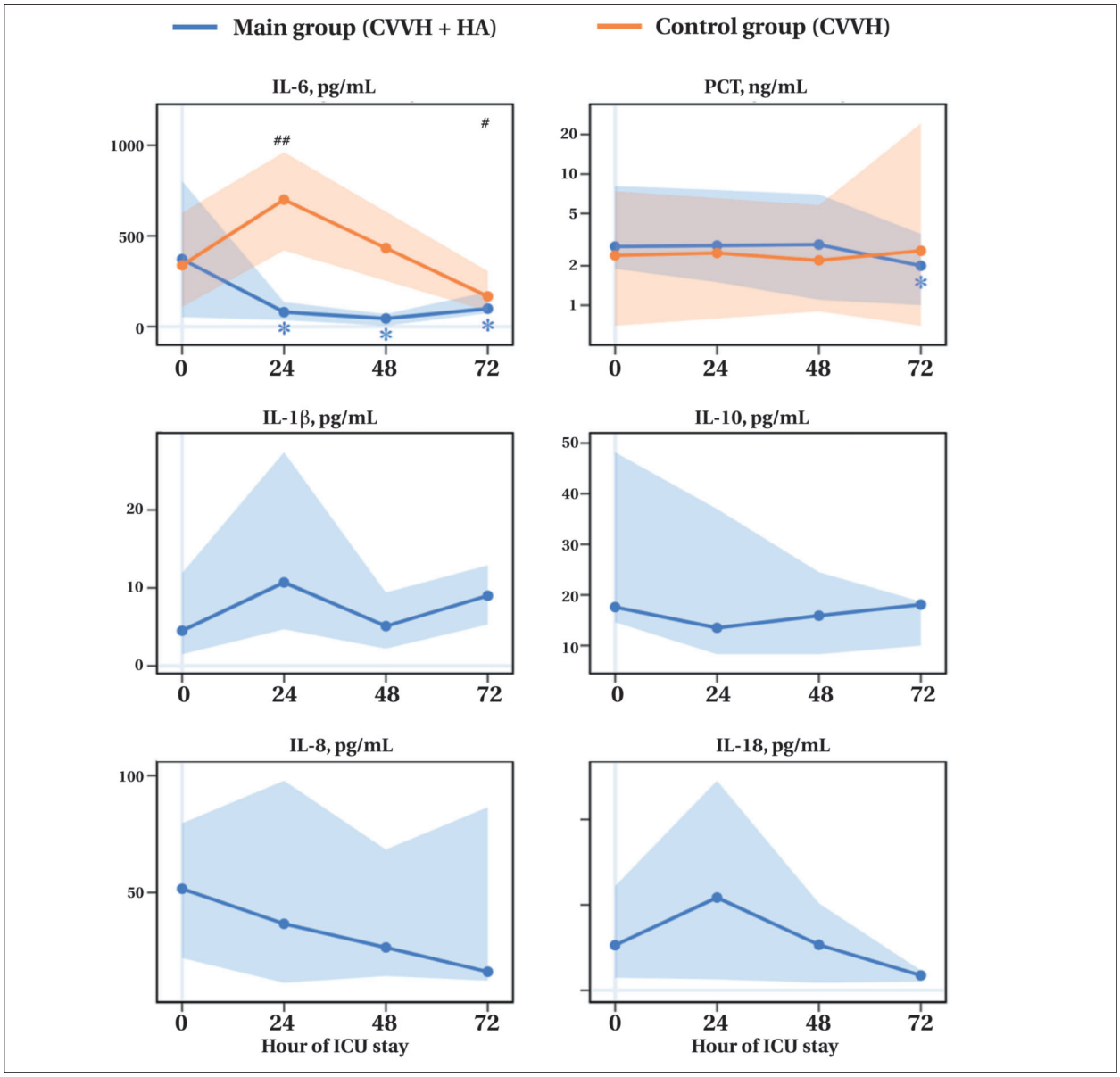

Fig. 2. Changes in interleukin and procalcitonin levels.
Notes. * — $P<0.05$ — within-group Wilcoxon test for differences from day 1 of ICU stay; # — $P<0.05$; ## — $P<0.001$ — between-group Mann–Whitney test. Shaded area (corridor) corresponds to interquartile range *(Q1; Q3)*. For Fig. 2, 3: CVVH — continuous veno-venous hemofiltration; HA — hemoadsorption.

sorption in terms of elimination of proinflammatory markers.

The use of cytokine hemoadsorption is associated with rapid elimination of IL-6, as evidenced by a significant decrease in its level after 24 hours of treatment, as well as a trend toward shorter ICU stays and lower mortality.

Based on the results of the study, we believe that the combination of the two indicated therapeutic approaches will provide the best efficacy in SAP patients.

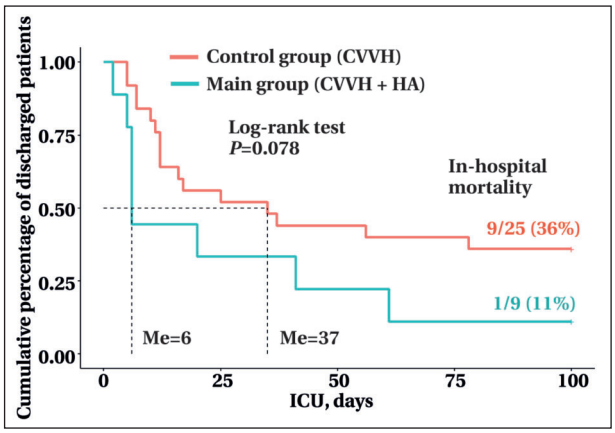

Fig. 3. Cumulative curves of ICU length of stay and mortality.

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