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Research Article
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Extracorporeal Methods of Hemocorrection in Patients with Abdominal Sepsis

O.V. Nikitina ✉, S.I. Rey, Y.V. Zabrodskaya, V.I. Avfukov, A.G. Lebedev, P.A. Yartsev, G.A. Berdnikov, A.M. Kaziyeva, E.A. Ostrogina

Department of Emergency Surgery, Endoscopy and Intensive Care
N.V. Sklifosovsky Research Institute for Emergency Medicine
3, Bolshaya Sukharevskaya Sq., Moscow 129090, Russian Federation

✉ **Contacts:** Olga V. Nikitina, Candidate of Medical Sciences, Senior Researcher, N.V. Sklifosovsky Research Institute for Emergency Medicine. Email: o.v.nikitina@mail.ru

BACKGROUND Theoretical data convincingly support the use of extracorporeal hemocorrection (ECHC) methods in the treatment of sepsis. However, a large number of researchers have still not been able to convincingly prove the advantage of ECHC methods; there is no unanimity of opinion.
We tried to analyze our own experience in using ECHC methods in the treatment of abdominal sepsis over the past 3 years.

AIM OF STUDY To analyze the use of ECHC methods in the early stages of treatment of abdominal sepsis, to determine whether their use had an advantage for survival.

STUDY DESIGN Prospective cohort

DESCRIPTION OF THE METHOD In 50 cases (group 1), ECHC was performed early after surgery. The median time from admission to the intensive care unit after surgery to the start of ECHC was 25.3 (17.7; 36.5) hours. When determining the ECHC modality, we were guided by the individual approach and clinical experience of the ECHC specialist. Apheresis methods alone were performed in 8% of patients (4/50), a combination of apheresis methods and renal replacement therapy was performed in 40% (20/50), renal replacement therapy (RRT) methods were performed in 98% (46/50), plasmapheresis/plasma exchange/selective plasma filtration were performed in 30% (15/50), selective hemosorption of cytokines was performed in 4% (2/50), selective hemosorption lipopolysaccharides was performed in 24% (12/50).
We analyzed outcomes, assessments of the severity of functional disorders and sepsis-associated organ dysfunction according to the APACHE scales II and SOFA and their dynamics, probabilities of outcomes depending on the scores on the indices (logistic regression); life times, cumulative survival rate (Kaplan-Meier method).

SAMPLE CHARACTERISTICS There were 113 patients after emergency laparotomy due to widespread peritonitis, abdominal sepsis, aged from 23 to 90 years. 67 men, 46 women. In 50 cases of observation (group 1), ECHC was performed in the early stages; in 63 cases, methods of active hemocorrection were not used (group 2). In group 1 there were 35 patients with septic shock and 15 patients with stable hemodynamics (subgroup 1/shock and subgroup 1/sepsis). In group 2 there were 20 patients with shock and 43 with stable hemodynamics (subgroup 2/shock and subgroup 2/sepsis).

RESEARCH RESULTS ECHC methods allowed survival of patients with more severe APACHE scores II and SOFA: in survivors in subgroup 1/shock Me 29 (24; 31) versus 23 (14; 26) in the subgroup 2/shock and 8 (4; 10) versus 4 (2; 6) points, p=0.048 and p=0.010; with stable hemodynamics in survivors in subgroup 1/sepsis Me 20 (17; 22) versus 15 (11; 19) in subgroup 2/sepsis, p=0.016. ECHC changed the survival threshold in favor of more severe patients from 29 to 33 points; reduced the likelihood of an unfavorable outcome 1.2-fold for each point on the APACHE scale II and 1,276 times over the entire range of estimates; prolonged survival time in hemodynamically unstable patients at a significance level of p=0.083, shifting the first quartile of survival from 1 to 12 days, the median from 12 to 20, the third quartile from 27 to 45 days. When performing ECHC, the cumulative survival rate was higher throughout the entire hospital observation period: 0.886 (95% CI 0.780–0.939) in 2 days versus 0.700 (95% CI 0.499–0.802); 0.800 (95% CI 0.667–0.868) in 10 days versus 0.545 (95% CI 0.325–0.658); 0.653 (95% CI 0.494–0.734) in 14 days versus 0.416 (95% CI 1.185–0.533).
Overall mortality from all causes was 35.4% (40/113), 67.3 (37/55) with shock, 5.2% (3/58) with stable hemodynamics. The maximum risk of an unfavorable outcome occurred in the early stages: 30% (12/40) of all deaths occurred in the first 4 days after surgery, 20% (8/40) in the first 24 hours. In shock patients, 10-day mortality was lower when performing ECHC: 20.0% (7/35) versus 45.0% (9/20), p=0.050, 1st stage. Fisher's test, P=0.38 insufficient. Hospital mortality in the shock subgroups was equal, all the advantages of ECHC achieved in the early stages were lost; although in most late outcomes the peritonitis was relieved; which was confirmed during the section.

CONCLUSIONS The power of the study was sufficient to identify statistically significant advantages of extracorporeal hemocorrection in the treatment of abdominal sepsis based on APACHE index estimates II and SOFA. For the Kaplan–Meier method, differences were obtained for shock patients at a significance level of 0.083; the number of observations must be doubled to detect statistically significant differences. The final results of hospital mortality require additional in-depth analysis, since in the later stages many deaths were not associated with abdominal sepsis and occurred with already resolved peritonitis. It is necessary to understand to what extent they were associated with experienced sepsis, and to what extent with comorbid pathology; whether there was an association with methods of extracorporeal hemocorrection.

Keywords: sepsis, septic shock, mortality, long-term renal replacement therapy, selective hemosorption lipopolysaccharides, extracorporeal hemocorrection

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Affiliations

Olga V. Nikitina	Candidate of Medical Sciences, Senior Researcher, Department of Emergency Surgery, Endoscopy and Intensive Care, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0002-3516-5492, ovnikitina@mail.ru; 55%, concept and design, data collection, statistical analysis, analysis and interpretation, article writing, participation in literature review
Sergey I. Rey	Candidate of Medical Sciences, Senior Researcher, Department of Emergency Surgery, Endoscopy and Intensive Care, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0001-7802-2283, reysi@sklif.mos.ru; 12%, concept and design, analysis and interpretation, participation in writing the article, literature analysis, ECHC procedures
Yana V. Zabrodskaya	Head of the Department of Resuscitation and Intensive Care, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0003-2012-9461, yzabrodskaya@yandex.ru; 6%, monitoring of intensive care in the intensive care unit, data collection, analysis and interpretation, participation in writing the article
Vladimir I. Avfukov	Candidate of Medical Sciences, Scientific Consultant of the Department of Emergency Surgery, Endoscopy and Intensive Care, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0001-6736-9265, avfukov@list.ru; 5%, data collection, analysis and interpretation
Aleksandr G. Lebedev	Doctor of Medical Sciences, Chief Researcher of the Department of Emergency Surgery, Endoscopy and Intensive Care, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0003-4008-6462, lebedev_ag@mail.ru 5%, analysis and interpretation
Pyotr A. Yartsev	Doctor of Medical Sciences, Professor, Head of the Department of Emergency Surgery, Endoscopy and Intensive Care, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0003-1270-5414, 79262265893@yandex.ru; 5%, concept and design, general responsibility
Gennady A. Berdnikov	Candidate of Medical Sciences, Senior Researcher at the Department of Emergency Surgery, Endoscopy and Intensive Care of the N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0002-3726-3256, polina1905@yandex.ru; 4%, carrying out ECHC procedures
Albina M. Kaziyeva	Anesthesiologist and Resuscitator of the Department of Resuscitation and Intensive Care of the N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0003-0016-784X, albatrosik2012@yandex.ru; 4%, intensive care monitoring in the intensive care unit, data collection
Elena A. Ostrogina	Anesthesiologist and Resuscitator of the Department of Resuscitation and Intensive Care of the N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0002-4552-9595, o.elena80@gmail.com; 4%, intensive care monitoring in the intensive care unit, data collection

AKI – acute kidney injury
APACHE II – Acute Physiology And Chronic Health Evaluation
BMI – body mass index
CI – confidence interval
ECHC – extracorporeal hemocorrection
ICC – comorbidity index Charlson (Charlson M.E., 1987)
MPI – Mannheim Peritonitis Index (Linder M.M., 1987)
OR – odds ratio
RRT – renal replacement therapy
SOFA – Sepsis-related Organ Failure Assessments Score

INTRODUCTION

Over the past decades, a significant number of experimental and clinical studies have accumulated on the use of extracorporeal hemocorrection (ECHC) methods in the treatment of abdominal sepsis and septic shock. This applies not only to the methods of renal replacement therapy (RRT), which are used both in patients with acute kidney injury (AKI) and for “extrarenal indications,” but also for the selective sorption of endotoxin in gram-negative sepsis, and the selective sorption of cytokines. There are encouraging results using plasma exchange and a combination of ECHC methods [1–3].

However, convincingly demonstrating the superiority of ECHC methods has proven difficult. When summarizing a large number of studies, there is no unanimity of opinion. Two recently published meta-analyses showed improved outcomes in patients with sepsis using hemofiltration / hemodiafiltration, but the authors noted that differences in mortality were not found in studies conducted in Europe and the United States, and were expressed in studies conducted in Asian countries [2]. Another 2021 meta-analysis revealed improved survival with the use of hemofiltration in patients with sepsis [4]. In a 2018 review, the authors concluded that the expected benefit of RRT for sepsis-associated AKI has not yet been convincingly demonstrated; RRT does not appear to improve renal survival or recovery. At the same time, the authors note that RRT was often used in the late stages of AKI in the presence of absolute indications: acidosis, hyperkalemia, oliguria /anuria, volume overload [5].

Estimates of the effectiveness of selective sorption of endotoxin vary. The results of the ABDOMIX study published in 2015 did not show a decrease in mortality in patients with abdominal sepsis; but during the study, completely complete 2 lipopolysaccharide procedures hemosorption was successful only in 69.8% of patients [6]. In 2018, the results of the "EUPHRATES" study were published in patients with septic shock and endotoxin activity levels above 0.6 conventional units; in the primary analysis, 28-day mortality did not differ in the study and control groups; subsequently, with the exclusion of patients with endotoxin activity more than 0.89 conventional units the authors found a statistically significant reduction in 28-day mortality [7, 8]. A 2019 meta-analysis revealed reduction in mortality [2].

In the early 2000s, encouraging results were obtained using plasma exchange in patients with sepsis; a meta-analysis noted a statistically significant reduction in mortality [4].

There are no specific strategies in the application of ECHC methods. The Chinese authors of a 2021 review said it was too early to say whether RRT should be part of standard treatment for sepsis. Conflicting results on survival warrant further research; it is necessary to determine the indications, choice of method, start time, duration of RRT, dose; since there is not enough information to favor one strategy over others [9]. German authors note that methods should be selected individually, and they should not be considered as competing [10]. D. Jarczak et al. in an article devoted to the pathophysiology of sepsis and basic therapeutic concepts, noted that evidence-based therapy still consists of basic causal and supportive measures, while adjuvant interventions, such as ECHC methods, still remain without evidence of effectiveness [11]. Experts from the Surviving Sepsis Campaign Sepsis Campaign, having considered a number of pressing issues in 2021, recommend continued clinical trials to determine ideal patient selection and ideal ECHC technology [12].

We tried to analyze our own experience in using ECHC methods in the treatment of abdominal sepsis over the past 3 years.

Study type: prospective cohort

Tested hypothesis: the use of ECHC methods in the early stages of treatment of abdominal sepsis has a survival benefit.

Inclusion criteria: age 18 - 90, diffuse secondary and tertiary peritonitis, abdominal sepsis.

Exclusion criteria: atonic coma, pregnancy, oncohematological diseases, terminal phase of peritonitis, terminal stage of chronic diseases.

Time period: from July 2019 to April 2022 (34 months).

MATERIAL AND RESEARCH METHODS

General characteristics of patients: 113 patients were treated in the intensive care unit in the - postoperative period after emergency laparotomy due to diffuse peritonitis (diagnosed during abdominal surgery) aged from 23 to 90 years, mean age 64±17 years, median 65 (57; 77). 67 men, 46 women.

In 50 cases (group 1), ECHC was performed in the early stages. The median time from admission to the intensive care unit after surgery to the start of ECHC was 25.3 (17.7; 36.5) hours.

In 63 cases, standard therapy for sepsis was performed (group 2).

Blood samples were taken in the observed patients on the first day after surgery and in 5 days of intensive care to determine the main metabolites, markers of systemic inflammation, gas and cellular composition; Based on a combination of clinical and laboratory parameters, an assessment was made using the APACHE II and SOFA scales.

General characteristics of the comparison groups are presented in Table 1. Group 1 consisted of 50 patients who, in the early stages after surgery, median time 25.3 (17.7; 36.5) hours, after compensation of hypovolemia, ECHC was started. The decision to perform ECHC was made with the participation of a specialized specialist based on a cumulative assessment of the clinical condition, the risk of death according to the APACHE II scale, the severity of organ dysfunction, the presence and stage of AKI, and markers of systemic inflammation. The patient's metabolic and volemic status, the need for volumetric infusion therapy, and parenteral nutrition were taken into account. When determining the ECHC modality, we were guided by the individual approach and clinical experience of the ECHC specialist.

In group 2 (63 people) standard therapy for sepsis was carried out.

The groups did not differ in age, gender, body mass index (BMI); severity of peritonitis, assessed by the Mannheim Index (MPI) [13]; severity of comorbid pathology, assessed by the comorbidity index Charlson (ICC) [14] (see Table 1).

Group 1 included 35 patients with septic shock according to Sepsis-3 [15] and 15 people with stable hemodynamics (subgroup 1/shock and subgroup 1/sepsis). Group 2 included 20 people with shock and 43 with stable hemodynamics (subgroup 2/shock and subgroup 2/sepsis). Patients in the shock and stable hemodynamic subgroups also did not have statistically significant intergroup differences in these parameters (see Table 1).

In group 1 there were statistically significantly more patients with unstable hemodynamics (correction with catecholamines): 70.0% (35 of 50) versus 31.7% (20 of 63), p <0.0001; and in general, group 1 was more “severe” compared to group 2. Baseline assessments of functional changes and organ dysfunction associated with sepsis, according to the APACHE-II and SOFA scales, were statistically significantly higher in group 1 compared to group 2: 26 (20; 30) vs. 18 (13; 24) and 8 (4; 10) vs. 4 (2; 6), p <0.0001 (Table 2).

Groups 1 and 2 differed greatly in the presence and severity of AKI (stages according to the 2012 KDIGO version) [16]. In group 1, all 50 patients had signs of AKI, and in group 2, in 19 cases there were no signs of AKI. In group 1, severe kidney damage (stages 2–3) prevailed (92%); in group 2, severe disorders accounted for only 25.4% (see Table 1).

Table 1

Characteristics of comparison groups and subgroups

	Share in %, Me (Q1; Q3)		p two-tailed Mann–Whitney test two-tailed Fisher test
	Group 1 (n =50)	Group 2 (n =63)	
Age, years	66 (60; 79)	64 (54; 77)	0.270
Body mass index	24 (23; 31)	27 (22; 30)	0.732
MPI, score	32 (27; 36)	28 (24; 37)	0.150
ICC, score	6 (3; 9)	5 (2; 10)	0.432
Male/female	60%/40% (31/20)	59%/41% (37/26)	0.850
Septic shock	70% (35 out of 50)	32% (20 out of 63)	<0.001
AKI (KDIGO 2012)	100% (50/50)	69.8% (44/63)	<0.001
– 1st stage	8% (4/50)	44.4% (28/63)	<0.001
– 2nd stage	26.0% (13/50)	9.5% (6.63) 0.024	
– 3rd stage	66.0% (33/50)	15.9% (10/63)	<0.001
	Subgroup 1/shock (n =35)	Subgroup 2/shock (n =20)	
Age, years	69 (58; 81)	73 (63; 83)	0.295
Body mass index	25 (23; 28)	27 (23; 30)	0.228
MPI, score	32 (28; 36)	33 (29; 40)	0.166
ICC, score	7 (3; 10)	8 (5; 13)	0.122
Male/female	63%/37% (22/13)	40%/60% (8/12)	0.159
	Subgroup 1/sepsis (n =15)	Subgroup 2/sepsis (n =43)	
Age, years	63 (60; 71)	60 (45; 74)	0.266
Body mass index	27 (22; 35)	27 (23; 30)	0.515
MPI, score	32 (24;37)	25 (20; 34)	0.173
ICC, score	4 (3; 6)	4 (2; 7)	0.712
Male/female	53%/47% (8/7)	67%/33% (29/14)	0.363

Notes: ICC – Charlson comorbidity index; BMI – body mass index; MPI – Mannheim peritonitis index; AKI (KDIGO-2012) – acute kidney injury; Kidney Disease: Improving Global Outcomes

MODALITY OF EXTRACORPOREAL HEMOCORRECTION METHODS

In table Table 3 provides information on ECHC methods used in intensive care for patients in group 1.

Table 2

The influence of age, severity of peritonitis (MPI), severity of comorbid pathology (ICP) on the development of hemodynamic disorders in abdominal sepsis (key parameters of logistic regression models)

	n	χ^2	p	β^1	p for β^1	Attitude of disagreement	% concordance	Shock Confirmation %	% Shock Elimination	Cut off
Age, years	113	6.4	0.014	-0.033	0.009	3.6	65.5	60.0	70.7	65 years old
	OR per unit change 1.034 (95% CI 1.008–1.060); OR for range 9.285 (95% CI 1.758–49.026)									
MPI, score	113	13.4	0.0003	-0.102	0.0004	2.7	61.9	63.6	60.3	32 score
	OR per unit change 1.071 (95% CI 1.047–1.171); OR for range 35.039 (95% CI 4.956–247.668)									
ICC, score	113	11.5	0.0007	-0.159	0.002	3.9	65.5	58.2	72.4	6 score
	OR per unit change 1.172 (95% CI 1.063–1.293); OR for range 14.874 (2.803–78.924)									

Notes: ICC – Charlson comorbidity index; MPI – Mannheim peritonitis index; OR – odds ratio

Table 3

Characteristics of the methods and modes of ECHC used in group 1 (n=50)

Modality of ECHC methods	Number of patients and the percent who received various ECHC methods			
	n=50	Survivors (n=24)	Deceased (n=26)	p Fisher test, Mann–Whitney test
Apheresis methods in isolation	4 (8%)	2 (8.3%)	2 (7.7%)	1.000
Combination of apheresis and renal replacement therapy	20 (40%)	9 (37.5%)	11 (42.3%)	0.779
Methods of renal replacement therapy	46 (92%)	22 (91.7%)	24 (92.3%)	1.000
Plasmapheresis, plasma exchange, selective plasma filtration	15 (30%)	8 (33.3%)	7 (26.9%)	1,000
Selective hemosorption lipopolysaccharides	12 (24%)	5 (20.8%)	7 (26.9%)	0.745
Selective hemosorption of cytokines	2 (4%)	1 (4.2%)	1 (3.8%)	1.000
Selected characteristics of ECHC methods				
Use of highly permeable membranes for RRT	21 (42%)	13 (54.2%)	8 (30.8%)	0.046
Volume of removed plasma during plasmapheresis and selective plasma filtration, ml	1800 (1500; 3000)	1800 (1500; 3000)	1800 (1500; 4500)	1.000
Number of selective hemosorption procedures lipopolysaccharides: — Alteco LPS Adsorber; - Toraymyxin; — Efferon LPS	14 6 4 4	5 4 1 0	9 2 3 4	0.352
Average duration of selective hemosorption procedures lipopolysaccharides, hours	8 (8; 10)	8 (8; 8)	8 (8; 16)	0.330
Methods and regimens of renal replacement therapy (total 125 procedures)				
Total RRT procedures	125	45	80	
Lengthy procedures	58	24 of 45	34 out of 80	0.267
Extended Methods	67	21 of 45	46 out of 80	0.267
Hemodiafiltration	81	26 of 45	55 out of 80	0.171
Hemofiltration	44	19 of 45	25 out of 80	0.171
Number of RRT procedures per patient	2.0 (1; 3)	1.0 (1.0; 2.0)	3.0 (1.0; 4.5)	0.035
Average duration of procedure, hours	23 (12; 40)	13.5 (12.0; 33.0)	30.5 (17; 28)	0.109
Achieved daily dose, ml/kg/h	25.6 (20.1; 30.5)	24.2 (20.1; 30.3)	27.1 (20.9; 31.6)	0.248
Ultrafiltration deficit, ml	1550 (800; 3200)	1100 (500; 2050)	2500 (1500; 4000)	0.008

Notes: RRT – renal replacement therapy; ECHC – extracorporeal hemocorrection; n — number of observations; p — level of significance of differences; Alteco LPS Adsorber, Toraymyxin, Efferon LPS — various types of sorbents produced by different manufacturers

As can be seen from the description of ECHC methods, surviving and deceased patients did not differ in the frequency of using apheresis methods alone and in combination with RRT (p = 0.779). In both cases, RRT methods were predominantly used, both for renal and "extrarenal" indications (91.7 and 92.3%).

Survivors were more likely to use high-flux hemofilters and dialyzers (Filtryzer BK-F, TORAY, Japan and Ultraflux EMiC 2, Fresenius Medical Care, Germany), in 54.2 and 30.8%, p = 0.046.

On average, the deceased had a greater number of RRT procedures (3 (1; 5) vs. 1 (1; 2), p = 0.035); their duration was longer (30.5 hours versus 13.5, p = 0.109); the larger volume on average was an ultrafiltration deficit (2500 (1500; 4000) ml versus 1100 (500; 2050), p = 0.008). At the same time, the achieved daily dose of RRT did not differ and was 27.1 and 24.2 ml/kg/h (p = 0.248), which corresponded to the international KDIGO recommendations (20–25 ml/kg/h) [14].

Selective hemosorption lipopolysaccharides was carried out in 20.8% of surviving patients and in 26.9% of deceased patients (p = 0.745) with a median time of 8 hours (p = 0.330); Alteco LPS Adsorber and Alteco sorbents were used Medical AB, Sweden; Toraymyxin, TORAY, Japan; Efferon LPS, JSC Efferon, Russian Federation).

Statistical data analysis. Statistical processing of the obtained data was carried out using application packages STATISTICA 10, StatSoft Inc. (USA), MS Excel.

About 80% of the distributions, when assessed by the Shapiro– Wilk test, did not have a normal distribution; central tendencies and their variations are represented by medians with quartile range Me (1 quart, 3 quart).

In some cases (with normal distributions), the power of comparison (P) and the standardized effect (Es) were calculated; in such cases, the tables additionally provide mean values and standard deviations M±SD.

Comparisons of quantitative data of independent groups were carried out using the nonparametric Manny -Whitney test, and comparisons of dependent groups were carried out using the Wilcoxon test. Threshold value p < 0.05, exact p value indicated in text and tables.

Fractional comparisons were performed using a two-tailed Fisher test, and in some cases, a one-tailed test. For proportional estimates, 95% confidence intervals (95% CI) were calculated.

The relationship between a binary and a quantitative trait was studied using logistic regression.

The Kaplan–Meier method was used to estimate survival as a function of time. A Cox proportional intensity regression model was used to analyze the association of several variables with observed lifetimes.

In the analysis, hospital bed days were taken into account from the moment of surgical intervention that verified the diagnosis of generalized peritonitis.

RESEARCH RESULTS

The influence of age, assessment of the severity of peritonitis according to the MPI and assessment of comorbid pathology according to the ICC on the development of hemodynamic disorders. In the presented sample, hemodynamically unstable (septic shock) patients accounted for 49% (55/113), hemodynamically stable (sepsis) patients accounted for 51% (58/113).

According to selective estimates, patients with shock were statistically significantly older than hemodynamically stable patients, 69 (60; 83) years versus 61 (53; 73), p = 0.007; they had a higher MPI score: 33 (28; 38) versus 26 (22; 34), p = 0.0004; and ICC 8 (5; 10) versus 4 (2; 7), p = 0.0006.

To clarify the relationship of the listed parameters with hemodynamic disorders and to clarify the approximate cut-off points, logistic regression analysis was carried out; the results are presented in table 2. Models are correct at a high level of significance; the predictive value of the models is low (low values of the ratio of disagreement and percentage of concordance); however, the cut-off points obtained can be used as guidelines. Each year of age increased the chance of developing shock 1.03-fold, and across the entire age range from 23 to 90 years, the chance of hypotension increased 9.3-fold. Each additional MPI point was accompanied by a 1.07-fold increase in the chance of hemodynamic disorders; over the entire range from 12 to 47 points, the chance increased by 35.0 times. Each ICC point increased the chance of developing shock 1.17-fold; 14.9-fold over the entire range from 0 to 17 points. The 95% CIs for all odds ratio values did not cross one. Of the three variables, the comorbidity index had the strongest effect.

Assessment of the severity of functional disorders using the APACHE II scale and the severity of organ dysfunction using the SOFA scale. The severity of functional disorders and organ dysfunction associated with sepsis was statistically significant and significantly greater in group 1 due to the high proportion of shock patients (70% of the total group): the APACHE II score was 26 (20; 30) versus 18 (13; 24), p =0.00003, Es =0.75, P =0.98; SOFA score 8 (4; 10) versus 4 (2; 6), p = 0.00007 (Table 4).

Table 4

The comparison of baseline severity scores of functional changes using the APACHE scale II and severity of organ dysfunction according to the SOFA scale

Scales	Group 1, n=50 Me (1 sq.; 3 sq.) M±SD	Group 2, n=63 Me (1 sq.; 3 sq.) M±SD	p Mann–Whitney test	P	Es
APACHE II	26 (20; 30) 26±7	18 (13; 24) 20±9	<0.001	0.98	0.75
SOFA	8 (4; 10)	4 (2; 6)	<0.001		
	Shock, n=35	Shock, n=20			
APACHE II	28 (25; 32)	29 (21; 36)	0.658		
SOFA	9.0 (7.0; 11.0)	8.0 (5.0; 10.0)	0.136		
	Sepsis, n=15	Sepsis, n=43			
APACHE II	20 (17; 25) 20±5	15 (11; 19) 15±5	0.004	0.91	0.92
SOFA	4.0 (2.0; 5.0)	2.0 (2.0; 4.0)	0.191		

Notes: APACHE II — scale for assessing acute and chronic functional changes (Acute Physiology And Chronic Health Evaluation); Es — standardized effect; M — average value; Me — median; 1 quart.; 3 quart. — first quartile; third quartile; n—number of observations; p—level of significance of differences; P — research power; SD — standard deviation, square error; SOFA — Sepsis-related Organ Failure Assessments Score)

Obviously, for a correct comparison it was necessary to identify subgroups with unstable and stable hemodynamics and compare their intergroup differences.

Shock patients in the comparison subgroups did not differ statistically significantly either on the APACHE II scale or on the SOFA: p = 0.658 and p = 0.136.

But hemodynamically stable patients in subgroup 1/sepsis were statistically significantly and much "severe" than subgroup 2/sepsis, which led to the appointment of ECHC: APACHE score 20 (17; 25) versus 15 (11; 19), p =0.004, P =0.91; Es =0.92, high. And although index scores in subgroup 1/sepsis were statistically significantly lower than both shock subgroups (20 (17; 25) points versus 28 (25; 32) and 29 (21; 36), p <0.0001 and p = 0.003)), it was in these hemodynamically stable patients with fairly high index scores that the effect of ECHC was most positive.

To compare the strength of the detoxification stabilizing effect of ECHC and infusion therapy in both groups, longitudinal comparisons were made according to the APACHE II and SOFA indices between the first point (day 1) and point 2 (after 5 days of intensive therapy). Comparisons were made in patients who survived this period and continued treatment in the intensive care unit (Table 5). By the 5th day of the postoperative period, 6 people each dropped out of subgroup 1/shock and subgroup 2/shock (6 out of 35 and 6 out of 20). All dropouts had deaths with very high APACHE II scores of 35 (33; 37) and 38 (36; 40) points and SOFA scores of 12.5 (10.3; 14.8) and 10.5 (8.5; 12.5) points. In the subgroup of hemodynamically stable, but at the same time "severe" organ dysfunction patients who underwent ECHC (subgroup 1/sepsis), no changes occurred; all 15 continued intensive therapy. In the mildest subgroup 2/sepsis, 10 people were transferred to the surgical department (10 out of 43).

When using ECHC in unstable patients (group 1/shock), the APACHE II score decreased statistically significantly and strongly: from 27 (24; 30) points to 19 (15; 26), p = 0.0004, P = 1.00, Es =1.09. The decrease on the SOFA scale from 9 (6; 10) to 6 (3; 8) points did not reach the level of statistical significance: p = 0.052, P = 0.51, although the standardized effect was noticeable, of medium strength Es = 0.52.

With conventional treatment methods (subgroup 2/shock), the APACHE II score also decreased statistically significantly and strongly: from 25 (20; 30) points to 15 (13; 18), p = 0.007, P = 0.95, Es = 1.08. There was no statistically significant decrease in the SOFA score in this subgroup, p = 0.374.

Table 5

The dynamics of assessments of the severity of functional changes according to the APACHE scale II and severity of organ dysfunction according to the SOFA scale

	Scales	Point 1 Me (1 sq.; 3 sq.) M±SD	Point 2 Me (1 sq.; 3 sq.) M±SD	p test Wilcoxon	P	Es
Subgroup 1/shock, n=29	APACHE II	27 (24; 30) 27±6	19 (15; 26) 20±6	0.0004	1.00	1.09
	SOFA	9 (6; 10) 8.1±3.2	6 (3; 8) 6.5±3.7	0.052	0.51	0.52
Subgroup 2/shock, n=14	APACHE II	25 (20; 30) 25±7	15 (13; 18) 17±7	0.007	0.95	1.08
	SOFA	6 (5; 8)	5 (1; 9)	0.347		
Subgroup 1/sepsis, n=15	APACHE II	20 (17; 25) 20±5	13 (10; 17) 13±4	<0.001	1.00	1.53
	SOFA	4 (2; 5)	2 (1; 4)	0.038	0.61	0.59
Subgroup 2/sepsis, n=33	APACHE II	15 (12; 19) 16±5	11 (8; 13) 11±4	<0.001	1.00	1.11
	SOFA	3 (2; 4)	1 (1; 2)	<0.001		

Notes: Point 1 – day 1; Point 2 – in 5 days of treatment; APACHE II – Acute Physiology And Chronic Health Evaluation; Es —standardized effect; M — average value; Me — median; 1 quart.; 3 quart. - first quartile; third quartile; n — number of observations; p — level of significance of differences; P – research power; SD — standard deviation, square error; SOFA – Sepsis-related Organ Failure Assessments Score

In “severe” patients with stable hemodynamics, during electromechanical dissection (subgroup 1/sepsis), a statistically significant and most powerful (Es) decrease in the APACHE II index was recorded: from 20 (17; 25) to 13 (10; 17), p <0.001, P =1.00, Es =1.53. The SOFA index also decreased: from 4 (2; 5) to 2 (1; 4), p = 0.038, P = 0.61, Es = 0.59.

In the “mildest” subgroup (group 2/stable hemodynamics), both indices decreased statistically significantly: APACHE II decreased from 15 (12; 19) points to 11 (8; 13), p <0.001, P = 1.00, Es = 1.11; SOFA decreased from 3 (2; 4) points to 1 (1; 2), p <0.001. All patients in this subgroup ultimately survived.

The Table 6 presents estimates among surviving patients. They illustrate that both with the development of shock and with stable hemodynamics, extracorporeal detoxification allowed survival of much sicker patients according to the values of the APACHE II and SOFA indices. Thus, among shock patients, when using ECHC, patients with an initial average APACHE II score of 29 (24; 31) points managed to survive, while without the use of ECHC only patients with a much lower score of 23 (14; 26) managed to survive; p=0.052, P =0.51, the power is low, but the standardized effect Es=0.97, that is, the power of the difference is large. The difference on the SOFA scale is even stronger: 10 (8; 11) and 5.5 (3; 8), p = 0.010, P = 0.73, Es = 1.48 which is very high.

APACHE II score was more sensitive for assessing changes in status, although it is a prognostic score for assessing the probability of death at the initial point of the disease. The dynamic SOFA index showed some rigidity in its dynamic assessments.

The category “hemodynamic stability” turned out to be very broad: group 1 included hemodynamically stable patients with high scores of functional disorders and organ dysfunction, in contrast to group 2, where similar indicators were statistically significantly different for the better (see Table 4). The format of this study did not allow us to judge whether patients with severe organ dysfunction and stable hemodynamics could survive without ECHC. An open question was also what criteria should be used when deciding whether to prescribe ECHC to hemodynamically stable patients. Is it possible to use index scores, and where are the cut-off points?

The survival threshold in group 2 was an APACHE II score of 29 points; all patients with an index above this value died. Whereas in group 1 this threshold was a score of 33 points. For the SOFA scale, the survival threshold was 8 and 12 points, respectively.

Fig. 1 illustrates that hemocorrection methods allowed patients who were more severe according to APACHE II to survive. In Fig. 1 survival proportions for high initial scores on the APACHE II scale are showed with cut-off points of 21 points (that is, all patients with an index of 21 points and above), 22 points, etc. Thus, when performing ECHC among patients with an index of more than 22 points, 25.5% of patients survived, and in group 2 only 12.9%, p <0.001. If we combine all patients in group 1 with scores of 23 points and above, then 26.0% of them survived, and in group 2 only 9.5% survived; p =0.024. All comparisons of proportions have a statistically significant difference (see legend to Fig. 1). The purpose of the chart is to illustrate the trend of survival of sicker patients with ECHC.

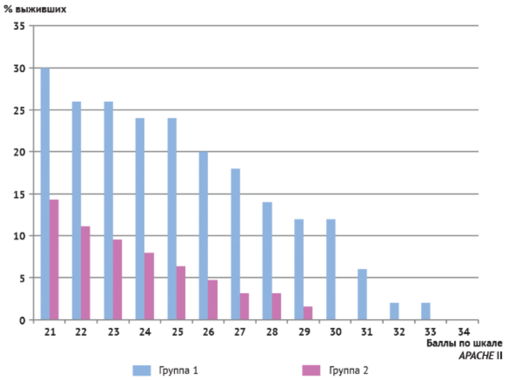
To determine the nature of the relationship with the outcome and the approximate ¬cutoff points for a high probability of death, logistic regression analysis was performed (Table 7).

Table 6

Comparison of initial APACHE score II and SOFA scale among surviving patients

Scales	Group 1, n=50 Me (1 sq.; 3 sq.) M±SD	Group 2, n=63 Me (1 sq.; 3 sq.) M±SD	p Mann–Whitney test	P	Es
	Shock, n=12	Shock, n=6			
APACHE II	29 (24; 31) 27±6	23 (14; 26) 21±6	0.053 0.048	0.51	0.97
SOFA	10 (8; 11) 8.9±2.6	5.5 (3; 8) 5.1±2.8	0.010	0.73	1.48
	Sepsis, n=12	Sepsis, n=43			
APACHE II	25 (17; 22) 19±5	15 (11; 19) 15±5	0.016	0.44	0.94
SOFA	4 (2; 5)	2 (2; 4)	0.237		

Notes: Point 1 – day 1; Point 2 – in 5 days of treatment; APACHE II – Acute Physiology And Chronic Health Evaluation; Es —standardized effect; M — average value; Me — median; 1 quart.; 3 quart. – first quartile; third quartile; n — number of observations; p — level of significance of differences; P – research power; SD — standard deviation, square error; SOFA – Sepsis-related Organ Failure Assessments Score



Баллы по шкале *APACHE* II	Доля выживших, %		*p* тест Фишера	
	Группа 1	Группа 2	Двусторонний	Односторонний
21 и более	**30,0**	**14,3**	**0,063**	0,036
22 и более	**26,0**	**11,1**	**0,049**	0,035
23 и более	**26,0**	**9,5**	**0,024**	0,019
24 и более	**24,0**	**7,9**	**0,032**	0,017
25 и более	**24,0**	**6,4**	**0,013**	0,008
26 и более	**20,0**	**4,8**	**0,016**	0,013
27 и более	**18,0**	**3,2**	**0,011**	0,010
28 и более	**14,0**	**3,2**	**0,075**	0,039
29 и более	**12,0**	**1,6**	**0,043**	0,029
30 и более	**12,0**	**0**	**0,006**	0,006
31 и более	**6,0**	0	–	–
32 и более	**2,0**	0	–	–
33 и более	**2,0**	0	–	–
34 и более	**0**	0	–	–

Fig. 1. Survival proportions in group 1 and group 2 with high initial APACHE scores II. Blue chart bars show in group 1 proportion of surviving patients with baseline APACHE index II 21 points and above, then — 22 points and above, etc. Purple bars indicate the proportion of surviving patients with similar index scores in group 2. At all cut-off points, the survival rate in the group with electromechanical dissociation was higher, for most positions it was statistically significantly higher. Thus, during extracorporeal hemocorrection among patients with an index of 22 points or more, 25.5% of patients survived, and in group 2 — only 12.9%, p<0.001, two-sided Fisher test

The Table 7 presents the key parameters of the group 1 and group 2 log models for index estimates according to APACHE II. The models are correct (p =0.0036, p <0.00001). The model for group 2 has the best characteristics: disagreement ratio 58.8; concordance rate 90.5%; the model correctly classifies favorable outcomes in 95.9%; cut-off point 23 points. The model for group 1 is of slightly worse quality, however, it correctly predicts 76.9% of deaths. The cut-off point of 26 points can be considered as indicative. Thus, the cut-off point for group 1 is 26 points, and 23 points for group 2. It follows that with standard therapy, the probability of an unfavorable outcome increased sharply with an APACHE II score above 23 points, and with ECHC with a score above 26.

Odds ratios (OR) 0.873 (95% CI 0.787–0.970): each unit of APACHE II index reduced the chance of survival in group 1 0.873-fold and increased the chance of death 1.145-fold; in group 2, it reduced the chance of survival 0.729-fold, and increased the likelihood of death 1.373-fold. Thus, the influence of one point on any outcome in group 2 was 1.2-fold stronger than in group 1. And over the entire range, from the minimum to the maximum score (in group 1 from 11 to 40, in group 2 from 6 to 41 APACHE II), the chance of outcome in group 1 changed 51-fold, and in group 2 65,000-fold. That is, the chance of outcome in group 2 changed 1,276-fold more on the range; therefore, ECHC was a very powerful survival factor.

Correct logistic models regarding the sample SOFA index values were not obtained: p >0.005.

Mortality analysis. Point estimates of 5-10-14-day and hospital mortality are presented in Table. 8.

Table 7

The influence of the severity of initial functional changes (assessed on the APACHE scale II) on the outcome (key parameters of logistic regression models)

	n	χ^2	p	β^1	p for β^1	Attitude of disagreement	Concordance percentage	Confirmation of survivors	Confirmation of the dead	Cut-off point
Group 1	50	8.5	0.0036	-0.136	0.012	3.9	66.0%	54.2%	76.9%	26 points
	Survival: OR per unit change 0.873 (95% CI 0.787–0.970) OR for range 0.020 (0.001–0.408) Fatal outcome: OR per unit change 1.145 (1.031–1.272) OR for range 50.9 (2.5–1058.7)									
Group 2	63	38.1	<0.000001	-0.317	0.0004	58.8	90.5%	95.9%	71.4%	23 points
	Survival: OR per unit change 0.729 (0.615–0.863) OR for range 0.00001 (0.00000004–0.006) Fatal outcome: OR per unit change 1.372 (1.159–1.625) OR for the range 65000.7 (175.7–24048750)									

Notes: OR — odds ratio; n — the number of observations; χ^2 – xi-square; β 1 — coefficient β^1; p — level of significance of differences; p for β^1 — significance level of p for coefficient β 1

Table 8
The 5-day, 10-day, 14-day and hospital mortality in comparison subgroups

Group 1								
Subgroups	Shock, n=35				Sepsis, n=15			
Time	5 days	10 days	14 days	Hospital mortality	5 days	10 days	14 days	Hospital mortality
Dead	6	7	12	23	0	0	1	3
Survivors	29	28	23	12	15	15	14	12
Mortality, %	17.1	20.0	34.3	65.7	0	0	6.7	20.0
Group 2								
Subgroups	Shock, n=20				Sepsis, n=43			
Dead	6	9	10	14	0	0	0	0
Survivors	14	11	10	6	43	43	43	43
Mortality, %	30.0	45.0	50.0	70.0	0	0	0	0
p, two-tailed Fisher test	0.319	0.067	0.270	1	1	1	0.259	0.015
p, one-tailed Fisher test	0.219	0.050	0.195				0.259	0.015
P, study power	0.21	0.38	0.21				0.20	0.60

Deaths occurred almost exclusively among patients with hemodynamic disorders. Almost all of the hemodynamically stable patients survived in both groups; there were only three adverse outcomes (on the 14th, 15th and 38th days); all were associated with concurrent disease and late complications of already resolved peritonitis.

Among shock patients, after 5 days of treatment, mortality during electromechanical dissociation was 17.1% (6/35), and 30.0% with standard therapy (6/20); The differences did not reach statistical significance, p = 0.319, P = 0.21. In 10 days it was 20.0% versus 45.0%, p = 0.050 for one-tailed Fisher test; this was the closest result to statistical significance. In 14 days it was 34.3% versus 50.0%, p = 0.270, P = 0.21. The estimated number of observations based on sample data for which a statistically significant result can be identified must exceed $n_1 = n_2$ 80/80 cases. The final mortality rate for shock patients was equivalent: 65.7% (23/35) and 70.0% (14/20), p = 1.0.

All hemodynamically stable patients survived the 5- and 10-day period. The final mortality rate for stable patients (subgroup 1/sepsis, subgroup 2/sepsis) was 20.0% (3/15) and 0% (0/43), p = 0.015, P = 0.60.

Thus, although the 10-day assessment showed a trend toward a survival advantage for ECHC, overall linear mortality estimates did not reveal a statistically significant benefit.

Next, a comparative assessment of survival was carried out taking into account the function of time using the Kaplan–Meier method.

We preliminarily present a comparison of survival curves in patients with impaired and stable hemodynamics for this sample, which obviously once again demonstrated that depression of systemic hemodynamics in abdominal sepsis indicated severe systemic disorders, global disintegration of compensatory mechanisms, in fact, the fatality of the condition (Fig. 2). The red curve for shock patients is significantly lower than the blue curve, representing hemodynamically stable patients; the probability of differences in survival curves at a very high level of significance p < 0.00001 for all five comparison criteria from the STATISTICA package (Wilcoxon-Gehan, Cox- Mantel, Wilcoxon-Peto, log-rank, F-test).

The probability of surviving the first 6 days after surgery for hemodynamically unstable patients was 75% (25th percentile); and the probability of surviving 16 days is 50% (50th percentile, median). Whereas with stable hemodynamics, the probability of staying alive for the same time periods was 100 and 92%. The 75th percentile for septic shock was 37 days, meaning only a quarter of patients could survive 37 days. Whereas without hemodynamic disorders, the probability of survival over this time period was 69%. With the same probability of 69%, stable patients could survive until day 57.

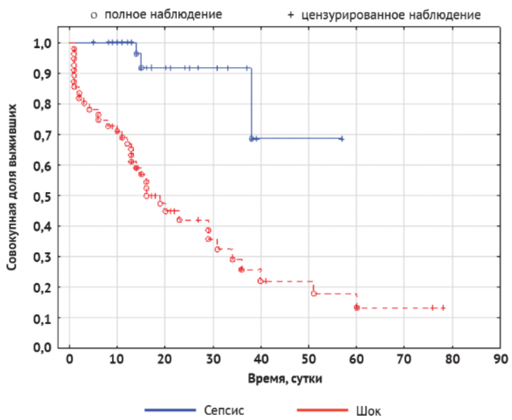


Fig. 2. Kaplan–Meier survival curves. SHOCK group, red curve: 25th percentile — 6 days, 50th percentile, median - 16 days; 75th percentile — 37 days. Sepsis group (stable hemodynamics) - blue curve: 8th percentile — 15 days, 31st percentile — 38 days; There was no further decrease in survival throughout the follow-up period. The significance level of differences between two curves p<0.00001 Wilcoxon– Gehan, Wilcoxon– Peto, Cox–Mantel test, Cox F-test, log-rank test

The maximum duration of hospital treatment among patients with unstable hemodynamics was 78 days, and among stable ones it was 57. The average values also differed statistically significantly: in shock patients, the duration of intensive care in the intensive care unit was longer, 9 (3; 16) days versus 4 (3; 6), p = 0.001; the duration of the hospital period did not differ: 14 (6; 27) and 13 (10; 17), p = 0.73.

The Kaplan-Meier plot also showed that, firstly, deaths occurred predominantly in septic shock, 37 of all 40 negative outcomes. Secondly, the most intensive fatal attrition occurred in the early stages: 30% (12 out of 40) of all deaths were recorded in the first 4 days after surgery, and 20% (8 out of 40), during the first 24 hours.

The Figure 3 shows the survival functions of shock patients: blue line is subgroup 1/shock, in which ECHC was performed, red line is subgroup 2/shock, standard therapy. The blue curve of subgroup 1/shock is located above the red one. Comparison of survival percentages is in favor of ECHC: 25th percentile: 12 days versus 1, median: 20 days versus 11, 75th percentile: 45 versus 27 days. The survival CIs (cumulative proportion of survivors ± standard error) over the entire observation period from days 1 to 40 either did not overlap at all or partially overlapped, maintaining a statistically significant difference (Fig. 4). However, the power of comparison for each of the time periods, presented in the last column of the table to the figure, did not reach a critical value; the best value P =0.65 is for 10-day survival. Significance level of differences throughout the observation period: p = 0.083 for the Wilcoxon-Gehan and Wilcoxon-Peto tests. To achieve a statistically significant result, it is necessary to increase the power of the study.

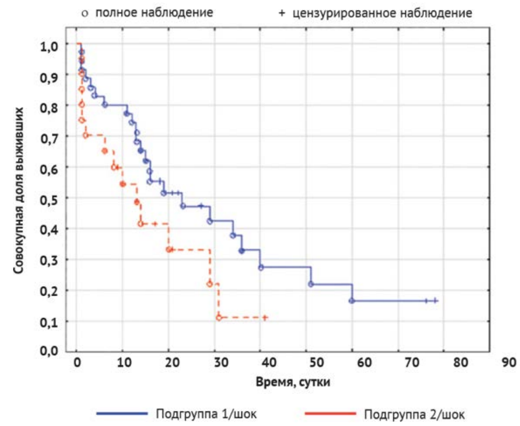
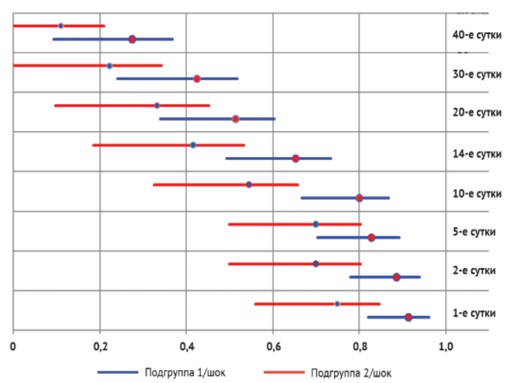


Fig. 3. The comparison of survival curves shock patients who underwent extracorporeal hemocorrection methods in the early stages after surgery (group 1/shock, blue color) with those who did not undergo extracorporeal hemocorrection (group 2/shock - red color). Survival in group 1/shock: 25th percentile — 12 days, 50th percentile, median — 20 days; 75th percentile — 45 days. Survival in group 2/shock: 25th percentile — 1 day, 50th percentile, median — 12 days; the 75th percentile is 27 days. Significance level of differences between two curves p=0.083 — Wilcoxon– Gehan test, p=0.083 — Wilcoxon– Peto test, p=0.083 — Cox–Mantel test



Время, сут	Подгруппа 1/шок			Подгруппа 2/шок			P
	S(t)	95% ДИ-	95% ДИ+	S(t)	95% ДИ-	95% ДИ+	
1	0,914	0,822	0,962	0,750	0,560	0,847	0,55
2	0,886	0,780	0,939	0,700	0,499	0,802	0,57
5	0,829	0,704	0,892	0,700	0,499	0,802	0,29
10	0,800	0,667	0,868	0,545	0,325	0,658	0,65
14	0,653	0,494	0,734	0,416	0,185	0,533	0,48
20	0,514	0,340	0,603	0,332	0,097	0,452	0,28
30	0,424	0,241	0,518	0,222	0	0,342	0,35
40	0,275	0,093	0,368	0,111	0	0,210	0,32

Fig. 4. Survival probability values (S(t), survival function, cumulative survival fraction) expressed as fractions of unity with 95% confidence interval (95% CI±) at different periods after surgery. Blue lines indicate values for subgroup 1/shock, red lines for subgroup 2/shock. Numerical values are shown below. P — power of comparisons

So it is possible to state only trend, the application of ECHC increased survival shock patients.

The final result is difficult to interpret. It is probably wrong to unequivocally conclude that there are no advantages of using ECHC in the treatment of sepsis, since in the later stages the clear advantage in the effectiveness of relieving severe manifestations of abdominal sepsis was offset by the development of surgical and non-surgical complications, and exacerbation of combined competing diseases. Among fatal complications, conditions not directly related to peritonitis and abdominal sepsis prevailed.

Of the 12 deaths in subgroup 1/shock that occurred in the period from 15 to 60 days after surgery, in 6 cases the outcomes were due to surgical complications, including failure of intestinal sutures. However, in another 6 cases, the causes of death were not directly related to the underlying surgical disease, sepsis and peritonitis.

Further collection of observations and optimization of the study design are required.

To clarify the relationship of ECHC with the observed survival times in abdominal sepsis with - hemodynamic disorders, another analysis method was used. A Cox proportional-intensity regression model was constructed for three variables, two quantitative and one dichotomous: for APACHE II scores, maximum venous blood lactate level recorded on the first postoperative day, and for the use of extracorporeal hemocorrection methods in the treatment of septic shock. Options models presented are presented in Table 9.

On charts constructed to compare the probabilities of survival at fixed values of APACHE II score (28 points) and lactate level (5 mmol /l), one can probabilistically estimate the significance of using hemocorrection methods for the survival times of the observed patients (Fig. 5). Thus, for a patient with unstable hemodynamics, an APACHE II score of 28 points and a venous blood lactate level of 5.0 mmol /l, the prognostic probability of surviving 10 days in the case of ECHC methods would be 83.2%, and in the case of only standard therapy — 67.8%; the probability of surviving 20 days is 48.3% and 21.5%, respectively; 30 days — 34.5% and 10.6%; 40 days — 15.6% and 1.9%.

Table 9

Key parameters of the Cox proportional intensity model for three variables (χ^2 =30.9, p<0.000001) for septic shock (n =55)

Variables	β	SE for β	t	p	OR (95% CI)
APACHE II Index	0.105	0.032	3.24334	0.001	1.111 (1.043–1.184)
Lactate	0.124	0.043	2.89697	0.004	1.131 (1.041–1230)
ECHC	-0.747	0.373	-2.00190	0.045	0.473 (0.228–0.984)

Notes: RR (95% CI) — relative risk and its 95% confidence interval; ECHC — extracorporeal hemocorrection; APACHE II — scale for assessing acute and chronic functional changes; β — coefficient β ; SE for β — the standard error for the coefficient β ; t — t-criterion is equal to the ratio of β to its standard error t = β /SE; p — significance level

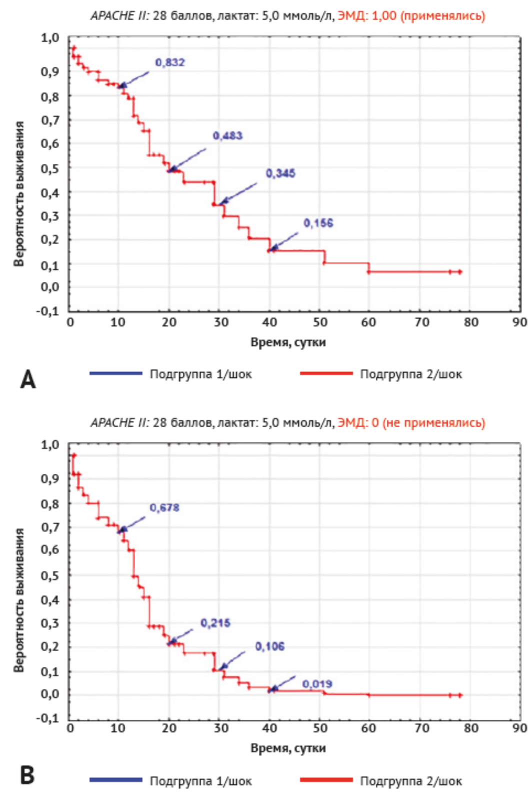


Fig. 5. Based on the obtained sample model of Cox proportional intensities, hypothetical diagrams of the probability of life times were constructed provided that methods of extracorporeal hemocorrection were carried out (upper diagram) and provided that they were absent (lower diagram). In both diagrams the values of the APACHE index II and blood lactate levels are fixed at the average sample values of 28 points and 5.0 mmol/l. With equal severity of functional disorders (28 points) and metabolic acidosis (lactate 5.0 mmol/l), the probability of surviving longer with extracorporeal hemocorrection is higher: the probability of surviving 10 days is 83.2% versus 67.8%, and the probability of surviving 40 days is 15.6% versus 1.9%

DISCUSSION

In each specific observation, the effectiveness of the applied ECHC method in the treatment of a septic patient was obvious to the clinician. In each case, with rare exceptions, a positive result was observed over a certain period of time in the form of regression of the manifestations of organ dysfunction, stabilization of the condition when other treatment methods were ineffective. Theoretical data clearly support the use of ECHC [17–21]. However, for a long time, many researchers have been unable to obtain unambiguous, statistically impeccable evidence of the advantages of ECHC methods in the treatment of sepsis. In publications, the relative risk of death is sometimes reduced, sometimes not, sometimes decreased with great reservations; even in rigorous randomized trials [1, 2, 4, 6].

We were not able to show a decrease in mortality in a simple proportion (survivors/deads).

The present study showed that the maximum risk of an unfavorable outcome occurred in the early stages: 30% of deaths occurred in the first 4 days after surgery, with 20% in the first 24 hours. This is an argument in favor of early use of ECHC methods.

Adverse outcomes occurred predominantly among patients with unstable hemodynamics: 13.5 times more often compared with stable ones (OR 13.006; 95% CI 4.480–51.108); mortality 67.3% (95% CI 52.8–81.8) versus 5.2% (95% CI -2.4–17.7), $p < 0.00001$, $P = 1.00$. And hemodynamic instability, among other things, was associated with older age, a more “severe” MPI assessment of peritonitis, and the presence of an unfavorable comorbid background. Older age and serious comorbidity could greatly limit infusion detoxification therapy. This is also an argument in favor of ECHC methods.

It was possible to statistically significantly prove the advantage of ECHC when comparing estimates based on the APACHE II and SOFA indices. The use of ECHC greatly increased the survival threshold, from 29 to 33 points according to the APACHE II index, from 8 to 12, according to the SOFA index. In group 2, all patients with an APACHE II score above 29 points died, and in group 1 all patients above 33 score died. In group 2, all patients with a SOFA score above 8 points died, and in group 1 patients with a score above 12 died.

The probability of an unfavorable outcome increased 1.15-fold with an increase in APACHE II score by one unit using ECHC methods, and 1.37-fold without methods; that is, the probability of death without the use of ECHC was 1.2-fold higher compared with patients in whom ECHC methods were used.

For the full range of APACHE II scores, the differences are as follows: when using ECHC, the odds of an unfavorable outcome at an index score of 40 points were 50.9-fold higher (95% CI 2.45–1058.7) compared to a score of 11 points; with standard therapy, the probability of an unfavorable outcome with an index of 41 points was 65,000.7-fold higher (95% CI 175.7–24048750) compared to a score of 6 points. The difference in probabilities across the range was 1277 times.

The risk of outcome with ECHC changed to a lesser extent, more smoothly: for each point on the APACHE II scale it was 1.2-fold weaker, for the entire range of estimates it was 1,276-fold weaker.

That is, when assessing the probabilities of outcome based on the APACHE II and SOFA indices, a very powerful advantage of ECHC methods over standard detoxification methods was shown.

In addition, according to the results of a repeated index assessment after 5 days of intensive therapy, the maximum strength of the effect from the use of ECHC methods was noted in patients with stable hemodynamics: Es 1.53 versus Es 1.09 in unstable patients. Severe, but still hemodynamically stable patients responded better and more strongly to hemocorrection methods ; and as a result, the vast majority of them survived; 3 deaths occurred in the late stages with already resolved peritonitis (section data). This is an argument in favor of using ECHC methods not only in shock, but also in hemodynamically stable patients with a high score on the APACHE II and SOFA indices. Moreover, early use, not after, without waiting for decompensation and absolute indications for RRT.

A higher probability of survival (cumulative survival rate) when performing ECHC in hemodynamically unstable patients during almost the entire period of hospital treatment was shown when analyzing life times using the Kaplan-Meier method. These comparisons lacked power to achieve statistical significance (did not exceed 0.65); however, the trend was stable throughout the observation period.

Finally, in the Cox proportional intensity model for the three variables, ECHC was statistically significant and the strongest predictor of survival at a given time point, reducing the odds of an unfavorable outcome 0.473-fold (95% CI 0.228–0.984).

Fractional estimates of simple proportions did not reveal statistically significant differences.

Overall all-cause mortality was 35.4% (40/113); for septic shock it was 67.3% (37/55), 5.2% (3/58) with stable hemodynamics, p = 0.00002.

The mortality in group 1 was 52.0% (26/50); in group 2 it was 22.0% (14/63), p = 0.001. The groups were not comparable in severity of the condition, in the proportion of patients with unstable hemodynamics and acute kidney injury. Therefore, quantitative comparisons were made between comparable subgroups, and probabilities of outcomes and life times were estimated between groups using more sophisticated and powerful methods.

Ten-day mortality among patients with shock differed at a statistically significant level of 20.0% versus 45.0%, p = 0.05; however, the power of comparison for the 35 and 20 subgroups was only 0.38. The required comparison power for 5–10–20–30-day mortality can be achieved by increasing the number of observations by 30–40%.

The final result was paradoxical: hospital mortality in the shock subgroups was equal, that is, all the advantages of ECHC achieved in the early stages were eventually lost; Moreover, in the majority of late outcomes, peritonitis was managed, which was confirmed during section. An in-depth analysis of late complications is required, an understanding to what extent they were associated with experienced sepsis, and to what extent - with comorbid pathology; whether there was an association with ECHC methods.

CONCLUSION

Thus, in certain areas, the advantage of using extracorporeal hemocorrection methods in the early postoperative period for abdominal sepsis was proven. The use of extracorporeal hemocorrection methods improved and stabilized the patients' condition, statistically significantly and greatly reduced the assessment of the severity of functional disorders on the APACHE II scale (Es = 1.07; Es = 1.56 at P = 1.00), and allowed patients with more severe multiorgan disorders to survive, changed the threshold towards survival of more severe patients from 29 to 33 points, reduced the probability of an unfavorable outcome 1.2-fold for each score point on the APACHE II scale and 1,276-fold for the entire range of scores; prolonged survival time in hemodynamically unstable patients at a significance level of p = 0.083, shifting the median survival from 12 to 20 days. Finally, in the Cox proportional intensity model, the use of extracorporeal hemocorrection methods for septic shock was a stronger predictor of survival over a given period of time than the APACHE II score and venous blood lactate level.

The size of the studied sample was sufficient to identify statistically significant advantages of extracorporeal hemocorrection based on the APACHE II and SOFA index scores and the probability of survival times (Cox proportional intensity model). For the Kaplan–Meier method, the number of observations must be doubled to detect statistically significant differences. To compare mortality, the statistical significance level of differences in the 20-day period after surgery can be achieved by increasing the number of observations by 30–40%. And the final survival results require additional in-depth analysis, since in the later stages many deaths were not associated with abdominal sepsis and occurred with already resolved peritonitis.

1. Adverse outcomes from abdominal sepsis occurred 13.5 times more often among patients with unstable hemodynamics compared with stable ones: (hazard ratio 13.5; confidence interval 95% ± 4.7–52.9).

2. The early postoperative period was the most dangerous for an unfavorable outcome: 30% (12 out of 40) of all deaths occurred in the first 4 days after surgery; 20% (8 out of 40) occurred during the first day.

3. The development of hemodynamic disorders was associated with older age, a more “severe” assessment of peritonitis according to the Mannheim Peritonitis Index, and an unfavorable comorbid background. Each year of age increased the odds of an unfavorable outcome 1.033-fold (95% confidence interval 1.008–1.060); each Mannheim index score — 1.033-fold (95% confidence interval 1.008–1.060); each point of the comorbidity index — 1.172-fold (1.062–1.293)). Approximate cut-off points can be considered age of 65 years, a score on the Mannheim Peritonitis Index of 31 points, a score on the comorbidity index Charleson 6.

4. Hemocorrection methods allowed survival of patients with more severe APACHE II and SOFA scores: for shock Me 29 (24; 31) versus 23 (14; 26) and 8 (4; 10) versus 4 (2; 6), p =0.048 and p =0.010; with stable hemodynamics, Me 20 (17; 22) versus 15 (11; 19), p = 0.016.

5. The use of extracorporeal hemocorrection in hemodynamically stable patients with a high score

on the APACHE II and SOFA scales prevented the escalation of organ dysfunction and hemodynamic decompensation in all observations, and allowed them to survive the period of intensive therapy; Abdominal sepsis and peritonitis were relieved in all patients.

6. The use of extracorporeal hemocorrection increased the survival threshold from 29 to 33 points on the APACHE II scale; reduced the probability of an unfavorable outcome per scale unit 1.2-fold, per range — 1,277-fold.

7. The use of extracorporeal hemocorrection for hemodynamic disorders increased survival time (Kaplan-Meier method): 1st quartile: one day versus 12, median: 12 days versus 20, 3rd quartile: 27 days versus 45; at the significance level p = 0.083.

8. The use of extracorporeal hemocorrection showed an advantage in the probability of survival (cumulative survival rate) of patients with septic shock over time periods of 5, 10, 14, 20 and 30 days:

0.829 (95% confidence interval 0.703–0.892) vs. 0.700 (95% confidence interval 0.499–0.802);

0.800 (95% confidence interval 0.667–0.868) vs. 0.545 (95% confidence interval 0.325–0.658);

0.653 (95% confidence interval 0.494–0.734) vs. 0.416 (95% confidence interval 0.185–0.533);

0.515 (95% confidence interval 0.340–0.603) vs. 0.332 (95% confidence interval 0.097–0.452);

0.424 (95% confidence interval 0.241–0.518) vs. 0.222 (95% confidence interval 0.000–0.342).

However, the power of all these comparisons did not exceed 0.65.

9. In the three-factor Cox proportional intensity model (extracorporeal hemocorrection, APACHE II score, venous blood lactate), extracorporeal hemocorrection was a statistically significant and the strongest factor in the intensity function (instantaneous risk); hazard ratio 0.473-fold (95% confidence interval 0.228–0.984).

10. The use of electromechanical dissociation had no effect on hospital mortality from all causes in septic shock: 65.7% versus 70.0%; late deaths were due to either surgical complications, such as intestinal suture failure, or comorbid pathology.

REFERENCES

1. Monard _ C, Rimmelé T, Ronco C. Extracorporeal Blood Purification Therapies for Sepsis. Blood Purif. 2019;47 Suppl 3:1–14. PMID: 30974444 https://doi.org/10.1159/000499520
2. Putzu A, Schorer R, Lopez-Delgado JC, Cassina T, Landoni G. Blood Purification and Mortality in Sepsis and Septic Shock a Systematic Review and Metaanalysis of Randomized Trials. Anesthesiology. 2019;131(3):580–593. PMID: 31246600 https://doi.org/10.1097/ALN.0000000000002820
3. Girardot T, Schneider A, Rimmelé T. Blood Purification Techniques for Sepsis and Septic AKI. Semin Nephrol. 2019;39(5):505–514. PMID: 31514914 https://doi.org/10.1016/j.semnephrol.2019.06.010
4. Snow TAC, Littlewood S, Corredor C, Singer M, Arulkumaran N. Effect of Extracorporeal Blood Purification on Mortality in Sepsis: A Meta-Analysis and Trial Sequential Analysis. Blood Purif. 2021;50(4–5):462-472. PMID: 33113533 https://doi.org/10.1159/000510982
5. Romagnoli S, Ricci Z, Ronco C. CRRT for sepsis-induced acute kidney injury. Curr Opin Crit Care. 2018;24(6):483–492. PMID: 30239411 https://doi.org/10.1097/MCC.0000000000000544
6. Payen DM, Guilhot J, Launey Y, Lukaszewicz AC, Kaaki M, Veber B, et al. Early Use of Polymyxin B Hemoperfusion in Patients with Septic Shock Due to Peritonitis: a Multicenter Randomized Control Trial/. Intensive Care Med. 2015;41(6):975–984. PMID: 25862039 https://doi.org/10.1007/s00134-015-3751-z
7. Dellinger RP, Bagshaw SM, Antonelli M, Foster DM, Klein DJ, Marshall JC, et al. Effect of Targeted Polymyxin B Hemoperfusion on 28-Day Mortality in Patients with Septic Shock and Elevated Endotoxin Level: The EUPHRATES Randomized Clinical Trial. JAMA.2018;320(14):1455–1463. PMID: 30304428 https://doi.org/10.1001/jama.2018.14618
8. Klein DJ, Foster D, Walker PM, Bagshaw SM, Mekonnen H, Antonelli M. Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial. Intensive Care Med. 2018;44(12):2205–2212. PMID: 30470853 https://doi.org/10.1007/s00134-018-5463-7
9. Zhang L, Feng Y, Fu P. Blood purification for sepsis: an overview. Precis Clin Med. 2021;4(1):45–55. PMID: 35693122 https://doi.org/10.1093/pcmedi/pbab005
10. Seeliger B, Stahl K, David S. Extracorporeal techniques for blood purification in sepsis: an update. Internist (Berl). 2020;61(10):1010–1016. (In German) PMID: 32897403 https://doi.org/10.1007/s00108-020-00862-5
11. Jarczak D, Kluge S, Nierhaus A. Sepsis-Pathophysiology and Therapeutic Concepts. Front Med (Lausanne). 2021;8:628302. PMID:34055825 https://doi.org/10.3389/fmed.2021.628302
12. Martin- Loeches I, Nunnally ME, Hellman J, Lat I, Martin GS, Jog S, et al. Surviving Sepsis Campaign: Research Opportunities for Infection and Blood Purification Therapies. Crit Care Explorer. 2021;3(9):e0511. PMID: 34514420 https://doi.org/10.1097/CCE.0000000000000511
13. Linder MM, Wacha H, Feldmann U, Wesch G, Streifensand RA, Gundlach E. [The Mannheim peritonitis index. An instrument for the intraoperative prognosis of peritonitis]. Chirurg. 1987;58(2):84–92. PMID: 3568820
14. Charlson ME, Pompei P, Ales KL, McKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis. 1987;40(5):373–383. PMID: 3558716 https://doi.org/10.1016/0021-9681(87)90171-8
15. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–810. PMID: 26903338 https://doi.org/10.1001/jama.2016.0287
16. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Available at: https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf [Accessed Jul 06, 2023]

17. Triantafilou M, Triantafilou K. Sepsis: molecular mechanisms underlying lipopolysaccharide recognition. Expert Rev Mol Med. 2004;6(4):1–18. PMID: 14987416 https://doi.org/10.1017/S1462399404007409
18. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med. 2013;369(9):840–851. PMID: 23984731 https://doi.org/10.1056/NEJMra1208623
19. Moriyama K, Nishida O. Targeting Cytokines, Pathogen-Associated Molecular Patterns, and Damage-Associated Molecular Patterns in Sepsis via Blood Purification. Int J Mol Sci. 2021;22(16):8882. PMID: 34445610 https://doi.org/10.3390/ijms22168882
20. Ronco C, Piccinni P, Rosner MH (eds.). Endotoxemia and Endotoxin Shock: Disease, Diagnosis and Therapy. Karger; 2010. https://doi.org/10.1159/isbn.978-3-8055-9485-1. [Russ. ed.: Ronko K, Pichchinni P, Rozner MG (ed.). Endotoxemia i endotoxic shok. Pathogenez, diagnosis i lechenie. Moscow: Izdatel 'IB Balabanov ; 2012]
21. Bulava GV, Rey SI, Berdnikov GA, Nikitina OV, Shabanov AK, Borovkova NV, et al. The Use of Selective Hemosorption of Lipopolysaccharides in the Complex Treatment of Sepsis. Russian Sklifosovsky Journal Emergency Medical Care. 2020;9(2):201–209. https://doi.org/10.23934/2223-9022-2020-9-2-201-209

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