www.reanimatology.com
ISSN 2411-7110 (online)

GENERAL REANIMATOLOGY

SCIENTIFIC-AND-PRACTICAL JOURNAL

ОБЩАЯ РЕАНИМАТОЛОГИЯ

научно-практический журнал

Volume 21 Том 21

№ 2

Юбилей заслуженного деятеля науки Российской Федерации, доктора медицинских наук, профессора Аркадия Михайловича Голубева

20 апреля 2025 г. исполняется 85 лет заведующему лабораторией патологии клетки при критических состояниях НИИ общей реаниматологии им. В. А. Неговского ФНКЦ РР, заместителю главного редактора научно-практического рецензируемого журнала «Общая реаниматология» профессору Аркадию Михайловичу Голубеву.

Уже более 60 лет жизнь Аркадия Михайловича неразрывно связана с научной деятельностью. В 1963 г. он окончил лечебный факультет Астраханского государственного медицинского института. В 1967 г. — защитил кандидатскую диссертацию на тему «Материалы по вопросу о морфологических и гистохимических изменениях в миокарде при мертворождаемости и смерти новорожденных детей», а в 1974 г. — докторскую диссертацию на тему «Гистохимия коронарогенных некрозов и токсических повреждений миокарда».

Аркадий Михайлович участвовал в реализации проекта Государственного комитета по науке и технике по созданию кровезаменителя с функцией транспорта кислорода на основе перфторуглеродов, а также в разработке и внедрении новейших медицинских технологий, способствовавших повышению эффективности диагностики и лечения острого респираторного дистресс-синдрома.

Под руководством А. М. Голубева успешно реализованы 3 темы научно-исследовательской работы по государственному заданию, выполнено 7 докторских и 18 кандидатских диссертаций.

В настоящее время Аркадий Михайлович — автор более 300 научных работ, 14 монографий и 11 изобретений, инициатор и организатор многих научных конференций и симпозиумов, проводимых в России и за рубежом.

Аркадий Михайлович является не только авторитетным патологом, но и высокопрофессиональным организатором науки и здравоохранения. В 1974 г. он был назначен на должность проректора по учебной работе Астраханского государственного медицинского института, а с 1977 по 1984 гг. совмещал эту должность с заведованием кафедрой патологической анатомии.

С 1984 по 1998 гг. А. М. Голубев, работая в должности ректора Дагестанского государственного медицинского института, внес неоценимый вклад в развитие данного вуза, обеспечив международное сотрудничество, интенсивную научную деятельность, качественное обучение, а также улучшение бытовых условий сотрудников и студентов.

С 1998 по 2000 гг. А. М. Голубев работал в должности начальника отдела по работе с регионами Министерства здравоохранения Российской Федерации, а затем заместителя руководителя департамента организации медицинской помощи населению.

С 2000 г. по настоящее время А. М. Голубев является заведующим лабораторией патологии клетки при критических состояниях НИИ общей реаниматологии им. В. А. Неговского ФНКЦ РР. Научная деятельность лаборатории осуществляется с использованием современных методов, открывающих новые возможности для морфологических исследований, учетом последних достижений медицинской науки и опорой на фундаментальные принципы общей патологии, что позволяет вносить весомый вклад в результаты исследований общей патологии при критических состояниях.

Научная и организаторская деятельность Аркадия Михайловича отмечена рядом наград и званий: Отличник здравоохранения СССР (1978), Заслуженный деятель науки ДАССР (1995); Лауреат премии Правительства Российской Федерации в области науки и техники (2010), Заслуженный деятель науки Российской Федерации (2014), Почетная медаль «300 лет РАН» (2024), Почетное звание «Почетный работник науки и высоких технологий Российской Федерации» Минобрнауки России (2025).

Высокий профессионализм, преданность науке, оптимизм, тонкое чувство юмора, умение вдохновлять молодое поколение исследователей, внимательное и чуткое отношение к людям, тактичность, доброжелательность и мудрость Аркадия Михайловича восхищают! Сердечно поздравляем Аркадия Михайловича с юбилеем и желаем крепкого здоровья, бодрости духа, новых научных достижений, прекрасного настроения, душевного тепла, и достойных учеников. Мы гордимся, что имеем честь работать с Вами!

Сотрудники редакции журнала «Общая реаниматология» присоединяются к поздравлению юбиляра. А. М. Голубев выступил одним из основателей и учредителей данного журнала. Способствовал его подготовке и вступлению в авторитетные отечественные и международные базы данных, в том числе РИНЦ, RSCI, Scopus, DOAJ, а также список ВАК. Как заместитель главного редактора, Аркадий Михайлович продолжает совершенствовать контент журнала, стремится сделать его интересным и полезным для профессионального круга. Редакция журнала «Общая реаниматология» выражает благодарность Аркадию Михайловичу за работу по развитию журнала, желает и дальше плодотворно совмещать роли автора, рецензента и редактора научных статей!

С глубоким уважением,
Коллективы сотрудников Федерального научно-клинического центра реаниматологии и реабилитологии, редакции журнала «Общая реаниматология»

ISSN 1813-9779 (print) ISSN 2411-7110 (online)

GENERAL REANIMATOLOGY

OBSHCHAYA REANIMATOLOGIYA

Scientific-and-Practical Peer-Reviewed Journal
Since 2005

• Covers issues of critical care medicine
• Manuscripts in Russian and English are published free-of-charge
• Included in SCOPUS (since 2015), RINTs, RSCI, DOAJ, and other databases, as well as in the Official list of editions recommended for publication of dissertations (PhD, DSci) by the Russian Higher Attestation Commission

Registration certificate of the Journal «Obshchaya reanimatologiya» (General Reanimatology): ПИ № ФС77-18690, November 2, 2004, Federal Service for Supervision of Compliance with Legislation in the Sphere of Mass Communications and Protection of Cultural Heritage
Publication Frequency: 6 numbers per year.
Founder:

ОБЩАЯ РЕАНИМАТОЛОГИЯ

OBŜAÂ REANIMATOLOGIÂ

научно-практический рецензируемый журнал
Выходит с 2005 г.

• охватывает вопросы медицины критических состояний
• публикует рукописи на русском и английском языках бесплатно
• включен в базы данных SCOPUS (с 2015 г.), РИНЦ, RSCI, DOAJ и др. базы данных; Перечень изданий, рекомендованных ВАК для публикации результатов диссертационных работ

Свидетельство о регистрации: ПИ № ФС77-18690 от 02 ноября 2004 г. Печатное издание журнал «Общая реаниматология» зарегистрирован Федеральной службой по надзору за соблюдением законодательства в сфере массовых коммуникаций и охране культурного наследия.
Периодичность: 6 раз в год
Учредитель: © Фонд «Медицина критических состояний», Москва, Россия

Publisher:
Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology, Moscow, Russia
Издатель:
Федеральный научно-клинический центр реаниматологии и реабилитологии (ФНКЦ РР), Москва, Россия

Supported by Russian Federation of Anesthesiologists and Reanimatologists
При поддержке Общероссийской общественной организации «Федерация анестезиологов и реаниматологов»

Artwork: Natalia V. Golubeva
Page-proof: Sergey V. Shishkov
Printing House:
Printed at LLC «Advanced Solutions». 19, Leninsky prospekt, build. 1, Moscow, 119071. www.aov.ru
Contacts:
25 Petrovka Str., Bldg. 2, 107031 Moscow, Russia.
Tel. +7-495-694-17-73.
E-mail: **journal_or@mail.ru;**
Web: **www.reanimatology.com**

Subscription:
Index 46338, refer to catalog of «Книга-Сервис»
Signed for printing: 21.05.2025

Оригинал-макет: Н. В. Голубева
Верстка: С. В. Шишков
Типография: отпечатано в ООО «Адвансед солюшнз». 119071, г. Москва, Ленинский пр-т, д. 19, стр. 1. www.aov.ru
Контакты с редакцией:
Россия, 107031, г. Москва, ул. Петровка, д. 25, стр. 2.
Тел.: +7-495-694-17-73.
E-mail: **journal_or@mail.ru;**
сайт: **www.reanimatology.com**

Подписка и распространение: индекс издания по каталогу «Книга-Сервис» — 46338.
Цена свободная
Подписано в печать: 21.05.2025

CONTENTS **СОДЕРЖАНИЕ**

https://doi.org/10.15360/1813-9779-2025-2-2472

Prediction of Mortality in ICU Patients with SARS-CoV-2-Associated Pneumonia

Pavel N. Savilov[1]*, Sofya S. Kurdyumova[2], Svetlana V. Shutova[2], Svetlana V. Buchneva[1], Alexander V. Baranov[2]

[1] Tambov Central District Hospital,
4 Polevaya Str., 392524 Pokrovo-Prigorodnoe, Tambov District, Tambov Region, Russia
[2] Medical Institute, G.R. Derzhavin Tambov State University,
93 Sovietskaya Str., 392000 Tambov, Russia

For citation: *Pavel N. Savilov, Sofya S. Kurdyumova, Svetlana V. Shutova, Svetlana V. Buchneva, Alexander V. Baranov.* Prediction of Mortality in ICU Patients with SARS-CoV-2-Associated Pneumonia. *Obshchaya Reanimatologiya = General Reanimatology.* 2025; 21 (2): 4–15. https://doi.org/10.15360/1813-9779-2025-2-2472 [In Russ. and Engl.]

***Correspondence to:** Pavel N. Savilov, p_savilov@mail.ru

Summary

Aim: to determine the predictive value of selected routine clinical and laboratory parameters and to assess their prognostic significance for modeling mortality risk in intensive care unit (ICU) patients with SARS-CoV-2-associated pneumonia.

Materials and Methods. A retrospective case-control analysis of 73 medical records was performed. The control group included 20 records of surviving patients, while the primary group comprised 53 records of non-survivors treated between January and February 2022. The study parameters included leukocyte differential count, C-reactive protein (CRP), ferritin, blood oxygen saturation (SpO_2) via pulse oximetry, and the neutrophil ratio (NR) defined as the percentage of band neutrophils divided by the percentage of segmented neutrophils. The prognostic value of identified predictors was assessed using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC), 95% confidence interval (CI), sensitivity (Se), specificity (Sp), and cutoff point (CP) were determined, with CP defined as the predictor value yielding the highest sum of sensitivity and specificity.

Results. The most informative predictors of mortality in SARS-CoV-2-associated pneumonia were:

On the day of hospital admission: Ferritin levels (AUC=0.826; 95% CI: 0.717–0.905; $P<0.001$, CP⩽0.473 mg/L; Se=78%; Sp=75%). On ICU day 1: Granulocyte count (GRA, AUC=0.711; 95% CI: 0.589–0.814; $P<0.002$, CP>6×10^9/L; Se=94%; Sp=75%), NR (AUC=0.713; 95% CI: 0.541–0.850; $P<0.016$, CP>18; Se=91%; Sp=62%). On the final day in ICU: CRP (AUC=0.825; 95% CI: 0.522–0.973; $P<0.013$, CP>14 mg/L; Se=75%; Sp=100%); NR (AUC=0.862; 95% CI: 0.724–0.947; $P<0.0001$, CP>16; Se=94%; Sp=82%); SpO_2 (AUC=0.909; 95% CI: 0.819–0.963; $P<0.0001$, CP⩽91%; Se=77%; Sp=100%); White blood cell count (WBC, AUC=0.833; 95% CI: 0.725–0.912; $P<0.001$, CP>12.2×10^9/L; Se=80%; Sp=81%). Using a stepwise elimination approach, a mathematical model was proposed for predicting mortality probability *(P)* in SARS-CoV-2-associated pneumonia.

Conclusion. The most valuable prognostic model for predicting mortality risk is represented by the equation: $P=1/(1+e^{-Z})\times100\%$ using routine laboratory parameters such as ferritin, neutrophil ratio and blood oxygen saturation. The model showed a sensitivity of 84.0% and a specificity of 94.1%.

Keywords: SARS-CoV-2-associated pneumonia, mortality predictors, prognostic model

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

Funding. The study was conducted as part of the development program of G.R. Derzhavin Tambov State University under the «Priority-2030» initiative.

Information about the authors:
Pavel N. Savilov: http://orcid.org/0000-0003-0506-8939
Sofya S. Kurdyumova: http://orcid.org/0009-0003-4632-2080
Svetlana V. Shutova: http://orcid.org/0000-0002-4929-7787
Svetlana V. Buchneva: http://orcid.org/0009-0007-9375-3165
Alexander V. Baranov: http://orcid.org/0000-0002-9978-0048

Introduction

The emergence of COVID-19, caused by the SARS-CoV-2 virus, has highlighted the unpreparedness of modern medicine to effectively combat such infections, despite advances in therapeutic strategies [1]. This has necessitated the search not only for novel pharmacological agents [2] and medical technologies [3, 4], but also for reliable prognostic criteria to predict disease outcome. Researchers have investigated the impact of comorbid conditions on COVID-19 survival [5, 6] and evaluated the diagnostic value of both routine [7, 8] and specialized medical examinations [9, 10]. Attempts have been made to predict in-hospital mortality in COVID-19 patients based on disease severity [10]. However, these predictive models were primarily constructed using sociodemographic and anamnestic parameters.

In critically ill COVID-19 patients requiring high-flow oxygen therapy, proposed predictors of mortality risk included age, serum albumin levels,

interleukin-6 (IL-6), and D-dimer concentrations [11]. However, each of these predictors was analyzed independently and showed only moderate prognostic accuracy, and no comprehensive predictive algorithm for estimating the probability of mortality was formulated in this study.

Some investigators have used the severity of lung involvement on computed tomography (CT) as a prognostic marker for COVID-19 mortality [12]. However, the degree of lung damage was assessed visually rather than quantitatively using dedicated software. In addition, evidence suggests that partial pressure of oxygen (PO_2), blood pH, and the number of antibiotics administered during treatment may serve as significant risk factors for mortality, varying by type of health care facility (community, federal, or private clinics) [13]. However, the prognostic value of these parameters was not explicitly defined, and only odds ratios were reported. In severe SARS-CoV-2-associated pneumonia, serum and urinary cystatin C concentrations have demonstrated high prognostic utility [14]. However, this biomarker is not included in the standard panel of routine clinical and laboratory tests used in clinical practice.

Currently, a nomogram has been developed based on a multifactorial analysis of predictors of 30-day mortality in hospitalized COVID-19 patients. By assessing patient age, comorbidities, serum C-reactive protein (CRP), and lactate dehydrogenase (LDH) levels at the time of ICU admission, the authors obtained a model with relatively high prognostic accuracy (AUC=0.811 [0.733–0.874], $P<0.001$) [15]. However, the model did not include changes in leukocyte differentials and ferritin levels during hospitalization, which could have further improved its predictive performance.

Other studies have demonstrated the potential utility of certain leukocyte differential parameters as outcome predictors in COVID-19 patients [16]. However, these studies did not take into account the duration of ICU stay, the level and type of oxygen support, including at the time of death, or the relationship between leukocyte differentials and acute-phase blood proteins [16].

Given these limitations, further investigation of the prognostic value of routine blood parameters for predicting COVID-19 outcomes is warranted.

The aim of this study was to evaluate the predictive value of selected routine clinical and laboratory parameters and their prognostic utility in modeling mortality risk in ICU patients with SARS-CoV-2-associated pneumonia.

Materials and Methods

A total of 262 medical records of patients diagnosed with COVID-19 and treated in the intensive care unit (ICU) of the Tambov Central District Hospital, which had been temporarily converted to a COVID-19 facility, were analyzed for the study (Fig. 1). From this cohort, 100 medical records were randomly selected, including both male and female patients with confirmed disease.

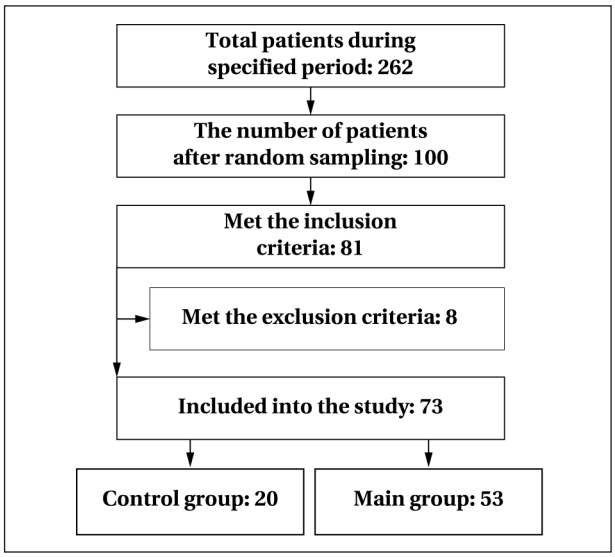

Fig. 1. Diagram of patient selection for the study.

The COVID-19 severity classification and treatment protocols followed the official interim clinical guidelines of the Russian Ministry of Health in effect at the time of the study (January–February 2022).

Inclusion criteria:

— SARS-CoV-2-associated pneumonia confirmed by computed tomography (CT) scan

— Age ⩾ 18 years

Exclusion criteria:

— Comorbidities, including

- Cancer (including cases after recent chemotherapy or radiotherapy prior to hospitalization), *N*=4
- Systemic lupus erythematosus, *N*=1
- Rheumatoid arthritis, *N*=1
- History of recent intestinal surgery, *N*=2.

The duration of ICU stay was not included in the analysis.

The study was conducted as a retrospective case-control analysis with a random selection of medical records. The selected cases were divided into two groups:

— Control group: 20 medical records of survivors (10 males and 10 females).

— Main group: 53 medical records of non-survivors (26 men and 27 women) who were in the ICU at the time of death.

The extent of lung involvement was assessed based on computed tomography (CT) findings at hospital admission. Serial chest radiographs were performed to monitor disease progression. At the time of death, all ICU patients in the main group had radiographic evidence of multilobar pneumonia.

Patients were admitted to the ICU if they met at least two of the following criteria:

Table 1. Distribution of Patients by Disease Duration at Hospital Admission, Age, and Lung CT Findings [*Me (Q25, Q75)*].

Parameter	Values in groups	
	Control group, *N*=20	Main group, *N*=53
Disease duration at admission (days)	7.0 [5.0; 12.0]	7.5 [5.0; 9.0]
Mean age (years)	66 [57; 72]	70 [65; 82]*
Lung CT Severity		
CT 1–2	12 (60%)	30 (57%)
CT 3	7 (35%)	12 (22%)
CT 4	1 (5%)	11 (21%)

Note. * — statistically significant difference compared to the control group ($P<0.05$).

— Impaired consciousness

— Respiratory rate >35 breaths/min

— Oxygen saturation (SpO_2) ⩽ 92% as measured by pulse oximetry, despite oxygen therapy via nasal cannula or oxygen mask.

On admission to the ICU, patients in both groups were started on non-invasive ventilation (NIV) using MEKICS MV 2000 (South Korea, Belarus) or ZISLINE MV300 K1.22 (Triton-Electronics, Russia) ventilators. NIV was delivered in the following modes:

— Continuous positive airway pressure (CPAP) at 7–10 cmH_2O.

— Pressure support (PS) at 14–24 cmH_2O.

— Inspiratory oxygen fraction (FiO_2) typically set between 0.6 and 1.0.

Patients were intubated and placed on MV if they exhibited:

— Persistent hypoxemia (SpO_2<92%) with accessory respiratory muscle involvement.

— Rapid deep breathing.

— Respiratory fatigue.

— Respiratory arrest.

— Hemodynamic instability.

Patients were discharged from the ICU when they no longer required NIV, as evidenced by:

— Clear consciousness and stable hemodynamics.

— Sustained SpO_2⩾93% with FiO_2⩽40%.

— Positive end-expiratory pressure (PEEP) ⩽ 5 cm H_2O.

— Respiratory rate (RR) < 30 breaths/min.

The study aimed to identify potential predictors of mortality risk based on routine hematologic parameters. These included complete blood count (CBC) indices, specifically leukocyte differentials, measured using the Drew 3 Hematology Analyzer (USA). In addition, leukocyte subpopulations in peripheral blood smears were assessed manually under a microscope. C-reactive protein (CRP) and ferritin levels were quantified using the ACCENT-200 analyzer (Poland). Oxygen saturation (SpO_2) was measured by pulse oximetry.

Data for analysis were collected at four time points:

— On hospital admission.

— On ICU day 1.

— On the last ICU day.

— At hospital discharge (for survivors).

For each parameter, sensitivity, specificity, and predictive accuracy were determined as predictors of mortality risk. The prognostic value was assessed by receiver operating characteristic (ROC) curve analysis. Binary logistic regression modeling was used to estimate the probability of mortality, including predictors with an area under the ROC curve (AUC) greater than 80%.

Model validation was performed by constructing ROC curves to assess overall model significance, sensitivity, and specificity, with statistical significance confirmed for AUC values significantly greater than 0.5.

Data were processed using Statistica 10.0 (Dell Inc., USA) and MedCalc 12.4 (MedCalc Software, Belgium). As most variables had non-normal distribution (Shapiro–Wilk test), results were expressed as medians with interquartile ranges *(Me [Q25; Q75])*.

Statistical comparisons were performed using

— Wilcoxon test (for paired data)

— Mann–Whitney *U* test (for independent groups)

— Spearman correlation coefficient (to assess relationships between variables).

Statistical significance was set at $P<0.05$, with Bonferroni correction for multiple comparisons.

Results

At the time of hospital admission, both groups had similar disease duration. However, the mean age of the main group (non-survivors) was significantly higher than that of the control group (survivors) (Z=2.31, P=0.021).

A statistically significant positive Spearman correlation was found between patient age and mortality in COVID-19 cases complicated by SARS-CoV-2-associated pneumonia (R=0.270, P=0.020).

In the group of non-survivors who were on mechanical ventilation (CMV/VCV; CMV/PCV, FiO_2>60%, PEEP 6–10 cm H_2O) at the time of death, SpO_2 values on the day of death were significantly higher compared to the values on admission. However, they remained below the generally accepted lower normal limit of 95% (Table 2).

The highest prognostic value (AUC: 0.909; 95% CI: 0.819– 0.963, P<0.001) as a predictor of imminent mortality risk in patients with SARS-CoV-2-associated

Table 2. Levels of C-reactive protein, serum ferritin, and saturation in patients with SARS-CoV-2-associated pneumonia *(Me (Q25, Q75))*.

Parameter	Values at study stages				*P value*		
	Day of admission (1)	Day 1 in the ICU (2)	Last day in the ICU (3)	Day of discharge from the hospital (4)	1–2	1–3	1–4
Control group (survivors), *N*=20							
SpO_2	86.0	78.0	95.0	95.0	0.084	<0.001	<0.001
	(80.0; 87.0)	(74.0; 88.0)	(92.0; 97.0)#	(92.0; 98.0)#			
CRP, mg/L	82.00	112.00	5.00	5.00	0.374	0.012	0.068
	(57.00; 112.00)	(62.00; 140.00)	(5.00; 14.00)	(5.00; 28.00)			
Ferritin, μg/L	0.529	0.509	0.394	0.228	0.176	0.068	0.109
	(0.403; 0.573)	(0.426; 0.601)	(0.352; 0.444)	(0.228; 0.405)			
Main group (non-survivors), *N*=53							
SpO_2	85.0	80.0	88.0	—	0.148	0.007	—
	(80.0; 87.0)	(74.0; 88.0)	(82.0; 91.0)#				
CRP, mg/L	89.00	89.50	49.00	—	0.351	0.225	—
	(50.00; 132.00)	(39.00; 150.50)	(11.00; 103.00)				
Ferritin, μg/L	0.401	0.420	0.448	—	0.136	0.715	—
	(0.340; 0.465)*	(0.354; 0.480)*	(0.410; 0.612)				
***P* values for the intergroup differences**							
SpO_2	0.769	0.636	<0.001				
CRP, mg/L	0.875	0.719	0.057				
Ferritin, μg/L	0.004	0.015	0.186				

Note. SpO_2 — blood oxygen saturation by pulse oximetry; CRP – C-reactive protein; * — $P<0.05$, statistically significant difference between survivors and non-survivors groups; # — $P<0.05$, statistically significant difference from values on the day of admission; *N* — number of patients in the group.

pneumonia was the SpO_2 level measured on the day of death (Fig. 2, *a*). In addition, the presence of patients with SARS-CoV-2-associated pneumonia on mechanical ventilation at the time of death in CMV/VCV or CMV/PCV modes with FiO_2>60% and PEEP 6–10 cm H_2O influenced the cut-off point, which in this case was 91%. Below this threshold, the prognostic accuracy for imminent mortality in patients with SARS-CoV-2-associated pneumonia on mechanical ventilation was 83.8%.

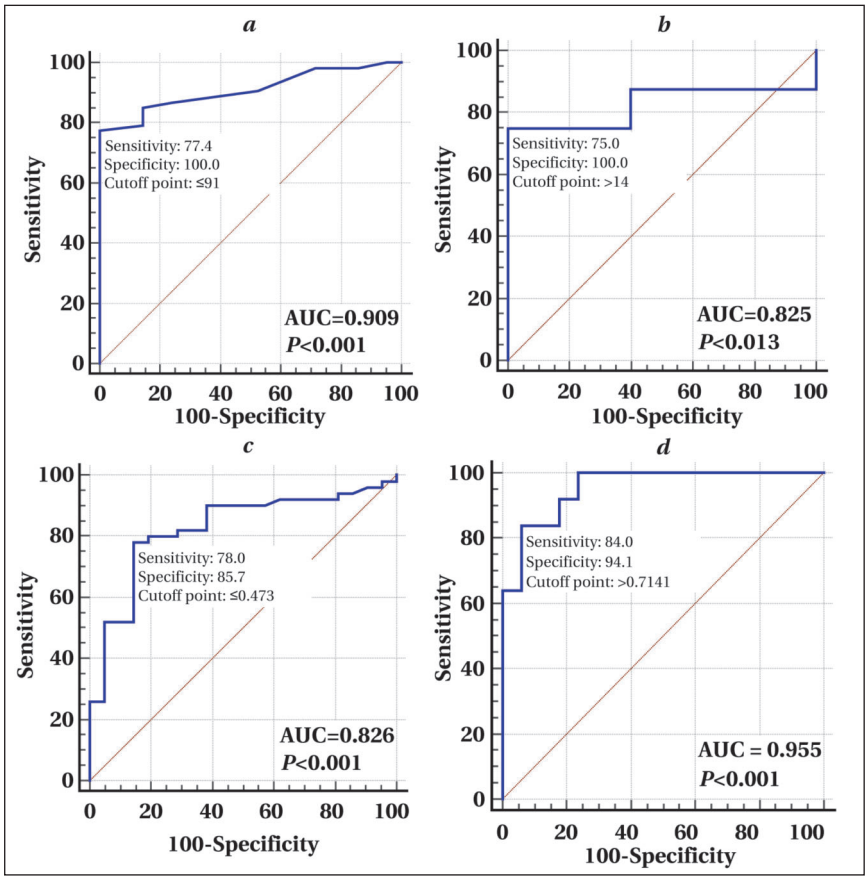

Fig. 2. Informative value of routine parameters in predicting the probability of mortality in patients with SARS-CoV-2-associated pneumonia admitted to the ICU.
Note. *a* — Blood oxygen saturation on the last day in the ICU; *b* — C-reactive protein level in blood on the last day in ICU; *c* — Blood ferritin level on the day of admission; *d* — Result of the quality assessment of the logit model for prognosis.

As shown in Table 2, the serum CRP levels of patients in both groups were significantly above the established normal range (0–3 mg/L) at hospital admission. However, only in the survivors did CRP levels decrease significantly on the last day in the ICU. During this period, a significant positive correlation (R=0.553, P=0.049) was observed between mortality and CRP levels. Furthermore, the probability of mortality was 82.1% when the CRP level exceeded 14 mg/L on the last day in the ICU (Fig. 2, *b*).

On the day of admission and the first day in the ICU, ferritin levels were significantly lower in non-survivors than in survivors, by 24% and 17%, respectively (Table 2). Negative

Table 3. Parameters of WBC differential in patients with SARS-CoV-2 associated pneumonia *(Me (Q25, Q75))*.

Parameter	Values at study stages				*P value*		
	Day of admission (1)	Day 1 in the ICU (2)	Last day in the ICU (3)	Day of discharge from the hospital (4)	1–2	1–3	1–4
Control group (survivors), *N*=20							
WBCs, ×10⁹/L	6.2 (4.0; 11.7)	7.7 (5.3; 12.8)	9.7 (7.40; 12.2)	9.4 (7.30; 10.7)	0.109	0.095	0.191
Lymphocytes							
Absolute count, ×10⁹/L	1.3 (0.8; 1.9)	0.9 (0.7; 1.5)	0.8 (0.7; 1.3)	1.6 (1.0; 2.1)	0.090	0.191	0.552
Percentage, %	16.6 (10.4; 43.9)	9.5 (7.5; 16.4)#	10.0 (6.7; 11.5)#	17.6 (8.8; 21.5)	0.004	0.006	0.079
MLC							
Absolute count, ×10⁹/L	0.5 (0.4; 0.9)	1.1 (0.5; 1.3)#	1.2 (0.7; 1.4)#	1.1 (0.7; 1.3)	0.006	0.008	0.014
Percentage, %	8.5 (7.3; 9.4)	9.1 (8.3; 11.0)	10.9 (8.5; 14.5)#	10.5 (9.4; 13.1)#	0.158	0.006	0.002
Granulocytes							
Absolute count, ×10⁹/L	3.5 (2.2; 9.7)	8.8 (5.4; 10.7)#	7.9 (5.8; 9.4)	6.0 (5.1; 8.5)	0.005	0.092	0.266
Percentage, %	70.8 (47.3; 81.6)	79.4 (70.9; 83.7)	78.2 (70.3; 83.9)	70.3 (66.8; 79.4)	0.026	0.073	0.274
Eosinophils, %	1.0 (1.0; 2.0)	1.0 (1.0; 2.0)	1.0 (1.0; 1.0)	1.0 (1.0; 2.0)	0.686	0.735	0.990
Band neutrophils, %	4.0 (2.0; 9.0)	6.0 (6.0; 10.0)	7.0 (6.0; 9.0)	6.0 (6.0; 8.0)	0.043	0.107	0.128
Segmented neutrophils, %	63.0 (41.0; 66.0)	65.0 (61.0; 66.0)	64.0 (63.0; 67.0)	62.5 (58.5; 65.0)	0.176	0.093	0.753
BSNR	0.07 (0.05; 0.16)	0.10 (0.08; 0.16)	0.11 (0.09; 0.14)	0.11 (0.09; 0.12)	0.176	0.374	0.128
Main group (non-survivors), *N*=53							
WBCs, ×10⁹/L	9.1 (5.2; 14.4)	11.7 (7.2; 15.7)#*	16.2 (13.0; 24.7)#*		0.001	<0.001	
Lymphocytes							
Absolute count, ×10⁹/L	1.1 (0.8; 1.5)	1.0 (0.8; 1.5)	1.1 (0.8; 1.5)		0.808	0.591	
Percentage, %	10.7 (7.1; 20.2)*	7.6 (6.8; 11.7)#	6.4 (4.3; 9.1)#*		0.004	<0.001	
MLC							
Absolute count, ×10⁹/L	0.7 (0.4; 1.0)	0.9 (0.6; 1.4)#	1.4 (0.9; 2.2)#*		0.001	<0.001	
Percentage, %	7.0 (4.4; 9.3)*	7.7 (5.5; 9.9)#	7.5 (5.8; 10.9)*		0.005	0.123	
Granulocytes							
Absolute count, ×10⁹/L	7.4 (4.6; 12.6)*	10.4 (6.3; 14.7)#*	13.6 (10.4; 21.6)#*		0.001	<0.001	
Percentage, %	81.3 (70.2; 86.7)*	82.8 (78.6; 86.7)*	85.6 (81.1; 88.5)#*		0.055	0.011	
Eosinophils, %	2.00 (1.00; 2.00)	2.00 (1.00; 2.00)	1.00 (1.00; 2.00)		0.950	0.068	
Band neutrophils, %	7.0 (4.0; 9.5)	9.5 (6.0; 17.0)	12.0 (8.0; 20.0)#*		0.030	0.014	
Segmented neutrophils, %	63.5 (59.0; 65.0)	63.0 (57.0; 65.0)	59.0 (53.0; 63.0)*		0.726	0.890	
BSNR	0.11 (0.07; 0.16)	0.18 (0.09; 0.30)#*	0.21 (0.16; 0.39)#*		0.016	0.012	
***P* values for the intergroup differences**							
WBCs, ×10⁹/L	0.057	0.046	<0.001				
Lymphocytes							
Absolute count, ×10⁹/L	0.476	0.794	0.228				
Percentage, %	0.015	0.172	0.002				
MLC							
Absolute count, ×10⁹/L	0.376	0.886	0.215				
Percentage, %	0.027	0.099	0.004				
Granulocytes							
Absolute count, ×10⁹/L	0.016	0.032	<0.001				
Percentage, %	0.007	0.038	<0.001				
Eosinophils, %	0.683	0.175	0.736				
Band neutrophils, %	0.131	0.060	0.001				
Segmented neutrophils, %	0.709	0.076	0.011				
BSNR	0.356	0.043	<0.001				

Note. Statistically significant difference ($P<0.05$): * — intergroup; # — compared to the values on the day of admission. BSNR — band-to-segmented neutrophil ratio; MLC — myeloid lineage cells.

correlations between ferritin levels and mortality risk were found on these days (R=–0.343, P = 0.003; R=–0.331, P = 0.014, respectively). As shown in Fig. 2, *c*, ferritin concentration at admission was the most potent prognostic predictor of mortality risk (AUC=0.826; 95% CI: 0.717–0.905; $P<0.001$), with a cutoff of ⩽0.473 μg/L. Ferritin levels below this threshold indicated an 80.2% probability of death (prognostic accuracy).

Table 3 shows that in the comparison group, there were no significant changes in the absolute WBC count during hospitalization. In contrast, in the main group, the WBC count increased by 29% on the first day and by 86% on the last day in the ICU compared with the day of admission. Notably, on both the first and last days in the ICU, non-survivors had significantly higher WBC counts than survivors, by 52% and 67%, respectively (Table 3).

A significant positive correlation was found between mortality and blood leukocyte count in patients with SARS-CoV-2-associated pneumonia on both the first and last day of ICU stay (P=0.045 and $P<0.0001$, respectively). At the time of admission, the percentage of lymphocytes was lower than the normal range (25–50%) in both groups, with a significantly greater reduction (by 36%) in

the main group compared with the control group (Table 3). On the first and last day of ICU stay, a significant decrease in relative lymphocyte count (%) was observed in both groups compared to the day of hospitalization (Table 2). However, in non-survivors, this parameter was 36% lower on the last day of ICU stay than in survivors during the same period (Table 3).

As shown in Table 3, the absolute number of monocytes, eosinophils, basophils, and immature cells (myeloid lineage cells, MLC) in non-survivors at the time of hospitalization was almost identical to that in survivors (Table 3). On the first ICU day, there was a significant increase in the MLC count in both groups compared with the day of admission, and it remained elevated until the last day of ICU stay (Table 3). However, on the last ICU day, the absolute MLC count was significantly (17%) higher in non-survivors (Table 3).

However, the relative percentage of MLC (%) showed a totally different trend. In survivors, it increased on the last day of ICU stay and on the day of discharge compared to the day of admission, whereas in non-survivors, no significant changes were observed during the same period (Table 3).

As shown in Table 2, the absolute granulocyte count in the blood of non-survivors with SARS-CoV-2-associated pneumonia was significantly higher (by 105%) on the day of hospitalization compared with survivors during the same observation period. On the first day of ICU stay, granulocyte counts increased in both survivors and non-survivors by 151% and 40%, respectively, compared with the day of admission. In non-survivors, the granulocyte count remained significantly elevated on the last ICU day compared to the day of admission (Table 3). Compared to the survivors, the granulocyte count in the main group was increased by 17% and 52% on the first and last day of ICU stay, respectively (Table 3).

A positive correlation was found between mortality and granulocyte count on admission, on the first ICU day, and on the last ICU day, with correlation coefficients of R=0.287 (P=0.015), R=0.259 (P=0.031), and R=0.552 (P<0.0001), respectively. Regarding the relative granulocyte percentage, its value in non-survivors significantly exceeded that of survivors on the day of hospitalization and on the first and last ICU days by 18%, 5%, and 10%, respectively (Table 3). In survivors, the relative granulocyte percentage remained almost unchanged compared to the day of admission, whereas in non-survivors it increased on the last day of ICU stay (Table 3).

On the last day of ICU stay, the percentage of band neutrophils in the blood of non-survivors was 71% higher than on the day of hospitalization (Table 2). Meanwhile, the percentage of segmented neutrophils in non-survivors was significantly reduced (by 8%) on the last ICU day (Table 3).

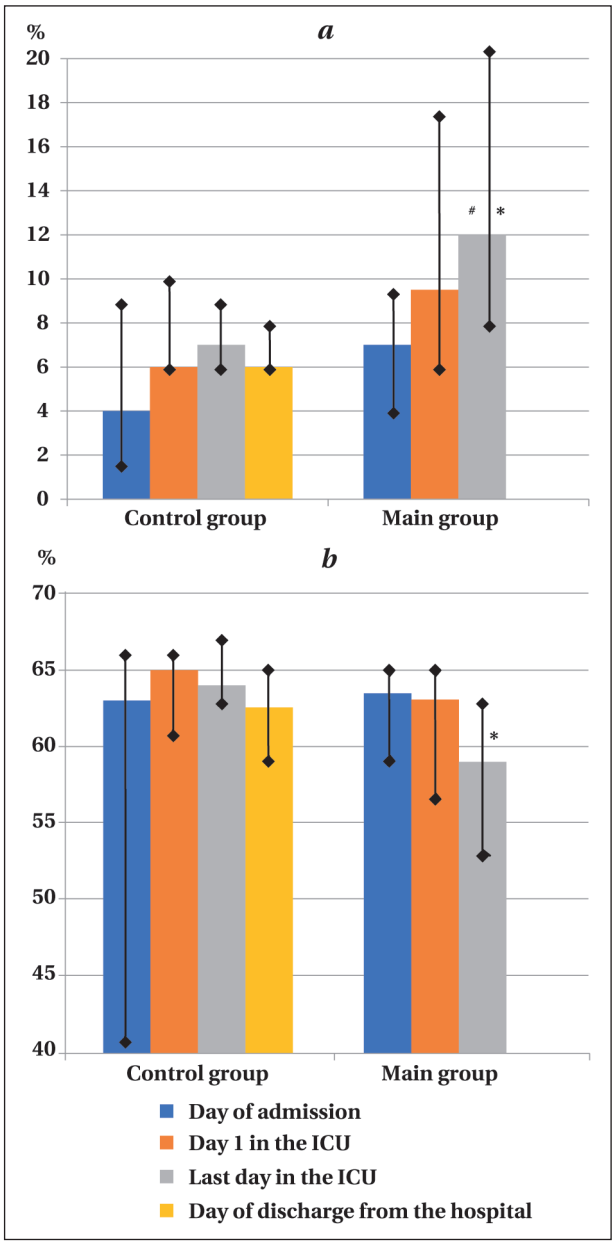

Fig. 3. Changes in the percentage of band neutrophils (*a*) and segmented neutrophils (*b*) in the blood of ICU patients.
Note: Statistically significant difference (P<0.05): * — between groups; # — compared with the values on the day of admission. Vertical lines represent the range Q25-Q75.

In the main group, an abnormal neutrophil shift with a significant decrease in percentage of segmented neutrophils along with an increase in band neutrophils was most pronounced on the last ICU day, i. e. the day of death (Fig. 3).

Among all leukocyte differential parameters, the band-to-segmented neutrophil ratio showed the highest prognostic value as a predictor of mortality risk in patients with SARS-CoV-2-associated pneumonia (Table 4). It was a significant predictor on both the first and last day of ICU stay. As death approached, its predictive value increased, as indicated by an increased prognostic accuracy from 61.6% to 82.4%.

Table 4. Results of prognostic value assessment of WBC differential parameters (based on ROC analysis) for predicting mortality risk in patients with SARS-CoV-2-associated pneumonia in the ICU.

Parameter	Area under the curve (AUC) ROC	95% CI	*P value* (AUC = 0.5)	Sensitivity, %	Specificity, %	Prognostic accuracy, %	Cutoff
Day 1 in the ICU							
Granulocytes, $\times10^9$/L	0.711	от 0.589 до 0.814	0.002	93.7	42.9	79.3	>6
BSNR	0.713	от 0.541 до 0.850	0.016	50	90.9	61.6	>0.18
Last day in the ICU (day of death in patients of the main group)							
WBC count, $\times10^9$/L	0.833	от 0.725 до 0.912	0.001	79.6	81	79.9	>12.2
Granulocytes, $\times10^9$/L	0.848	от 0.742 до 0.923	<0.0001	71.4	90.5	76.8	>11.3
PMNs, %	0.830	от 0.687 до 0.926	<0.0001	66.7	88.2	72.8	>10
BSNR	0.862	от 0.724 до 0.947	<0.0001	77.8	94.1	82.4	>0.16

Table 5. Parameters of prediction model for estimating the probability of death in patients with SARS-CoV-2-associated pneumonia admitted to the ICU.

Parameter	Regression coefficient	Mean squared error (MSE)	*P value*	Odds ratio (OR)
Ferritin (μg/mL) at the day of admission	–0.951	4.992	0.849	0.386
SpO_2 at the last day in the ICU	–0.493	0.192	0.010	287.3
BSNR at the last day in the ICU	24.081	10.979	0.028	0.611
Intercept	41.477	15.848	0.009	

According to the presented ROC analysis results (Fig. 2, *a–c* and Table 4), each parameter shows good or satisfactory prognostic value. Although many parameters showed statistically significant informativeness ($P \leqslant 0.05$), it is impractical to rely on a single criterion as a predictor of mortality risk because its prognostic accuracy is far from 100%. Therefore, a unified mathematical model incorporating the assessment of multiple parameters simultaneously was developed (Table 5).

Two of the three predictors characterized the patient's condition on the «last day in the ICU». Since this determination is possible only retrospectively, it is clinically advisable to calculate the probability of mortality on a daily basis, taking into account the clinical and laboratory parameters corresponding to the day of assessment.

Based on the calculations performed, the equation for estimating the probability *(P)* of mortality is as follows

$$\mathbf{P=1/(1+e^{-Z}) \times 100\%,}$$

where

$Z=41.477-0.951\times X_1+24.081\times X_2-0.493\times X_3$.

Here,

— X_1 is the serum ferritin concentration (mg/L) at hospital admission,

— X_2 is the band-to-segmented neutrophil ratio on the day of the ICU assessment, and

— X_3 is the oxygen saturation (%) on the day of ICU assessment.

The developed mathematical model accounts for 86.3% of the experimental values (R^2=0.863), with an overall prediction accuracy of 85.7%.

In logistic regression, predicted values for the dependent variable range from 0 to 100, independent of the values of the independent variables. When $y>0.5$, there is a high probability of death.

The model was validated by receiver operating characteristic (ROC) curve analysis of the predicted values (Fig. 2, *d*). The constructed model demonstrated substantial prognostic power in identifying mortality risk, with a sensitivity of 84.0% and a specificity of 94.1%. The area under the ROC curve (AUC) was 0.955 with Z=16.1 ($P<0.001$).

Discussion

There was no significant difference in SpO_2 levels between the two groups at hospital admission and on the first day in the ICU (Table 1), indicating similar impairment of lung oxygenation at these time points. However, in the main group, the treatment administered, including respiratory support by MV in CMV/VCV and CMV/PCV modes with FiO_2>60% and PEEP of 6–10 cm H_2O, did not prevent pulmonary disease progression, resulting in a fatal outcome.

Post-mortem examinations revealed that patients in the main group had diffuse alveolar damage, as evidenced by massive fibrin deposition in the alveolar spaces and interalveolar septal fibrosis. As previously reported in the literature [15], these histopathological changes indicate the progression of inflammation in the lung tissue associated with SARS-CoV-2 pneumonia. This may explain why the SpO_2 level at death was higher than at admission, but did not reach the low limit of normal range (Table 2).

The progression of lung inflammation in SARS-CoV-2-associated pneumonia, often complicated by secondary bacterial infections, may contribute to the development of refractory hypoxemia. This condition is seen in mechanically ventilated patients with ARDS, where changes in ventilatory settings do not correct hypoxemia [18]. Mechanical ventila-

tion could not restore SpO_2 to normal levels in the main group, indicating the presence of refractory hypoxemia (see Table 1).

One of the key markers of systemic inflammation is an elevated level of CRP in the blood. As a soluble pattern recognition receptor (PRR), CRP binds to danger-associated molecular patterns (DAMPs) and plays a crucial role in regulating both inflammatory and immune responses [19]. Its production is primarily driven by the pro-inflammatory cytokine interleukin-6 (IL-6) [19], which is known to contribute to lung injury in COVID-19 [20]. Therefore, persistently high CRP levels in critically ill patients at the time of death not only suggest ongoing inflammation in the lungs despite treatment but also indicate excessive production of pro-inflammatory cytokines, particularly IL-6.

CRP also functions as an opsonin, recognizing specific ligands on bacterial pathogen-associated molecular patterns (PAMPs) and endogenous DAMPs. This interaction triggers both the classical and, to a lesser extent, the alternative complement activation pathways [19]. The complement system, a key component of innate immunity, has evolved as a primary defense mechanism against infections [21]. Given this, persistently elevated CRP levels in COVID-19 patients strongly suggest the presence of a secondary bacterial infection.

Currently, there is no consensus on the role of hyperferritinemia in the pathogenesis of COVID-19 [22, 23]. Specifically, it remains unclear whether ferritin in COVID-19 serves merely as a byproduct of the inflammatory response or acts as a pathogenetic mediator [23]. Some researchers have identified an association between mortality and a rapid increase in ferritin levels ($\geqslant$1,000 μg/L) [23]. Others have reported that the restoration of pulmonary gas exchange function in SARS-CoV-2-associated pneumonia during hyperbaric oxygen therapy was accompanied by a reduction in hyperferritinemia, although ferritin levels did not fully normalize [24].

The conflicting data on the role of ferritin in COVID-19 may be attributed to the unique structure of its protein molecule, which consists of light (L) and heavy (H) chains. Notably, only the H subunit possesses redox activity. The quantitative ratio of L and H chains varies depending on tissue type and homeostatic conditions, influencing the functional properties of ferritin [25].

Our findings indicate a high probability of fatal outcomes in SARS-CoV-2-associated pneumonia when ferritin levels at the time of hospitalization are $\leqslant$0.473 μg/L. This suggests that, unlike the control group, patients in the main group had a delayed development of hyperferritinemia as a systemic response to SARS-CoV-2-induced lung injury. Consequently, this delay may have contributed to an increased risk of mortality as the disease progressed.

Since the degree of leukocytosis reflects the intensity of the inflammatory response [20], the observed increase in leukocytosis in the main group (Table 2) suggests the development of secondary bacterial infection driving the progression of pulmonary inflammation. This is further supported by the predominance of granulocytic lineage cells within the peripheral blood leukocyte pool, leading to the development of relative lymphocytopenia. The progressive decrease in lymphocyte percentage observed in critically ill patients from the main group in the ICU (Table 2) can be considered a prognostically unfavorable marker for mortality. This conclusion is supported by the negative correlation between lymphocyte percentage and mortality, both on the day of admission (R=–0.288, P=0.014) and on the last day in the ICU (R=–0.378, P=0.001).

Regarding granulocytes, a notable finding in the main group was the progression of neutrophilia due to an increased presence of immature neutrophil forms, which occurred alongside a reduction in segmented neutrophils (Table 2). This biological marker should be considered an adverse prognostic indicator of mortality risk in SARS-CoV-2-associated pneumonia. Notably, on the last day of ICU stay, a significant positive correlation was found between mortality and the percentage of band neutrophils (R=0.508, $P<0.001$), while a significant negative correlation was observed between mortality and the percentage of segmented neutrophils (R=–0.387, P=0.010).

An elevated blood neutrophil count was associated with poor outcome in patients with suppurative lung disease, regardless of whether they had a history of COVID-19. Meanwhile, separate analyses showed that this association was statistically significant only in those without a history of COVID-19 [26]. The available data suggest that the authors of this study examined the total number of circulating neutrophils without considering the proportion of band and segmented neutrophils.

However, our research demonstrated that shifts in the ratio of these neutrophil subtypes — expressed as the band-to-segmented neutrophil ratio — could serve as an early predictor of mortality in SARS-CoV-2-associated pneumonia, as early as the first day of ICU admission.

Furthermore, the prognostic value of the band-to-segmented neutrophil ratio increased as the fatal outcome approached (Table 3).

The mechanism behind the prognostic significance of the neutrophil ratio may be related to an impaired immune response to bacterial infection in the presence of SARS-CoV-2. This dysfunction leads to uncontrolled production of neutrophils by the bone marrow. In response to microbial agents,

these neutrophils produce excessive free radicals and cytokines — not only to eliminate pathogens within phagosomes, but also by releasing them into the extracellular environment. This uncontrolled response causes collateral tissue damage, particularly to the vascular endothelium [26].

As a result, disruption of the endothelial glycocalyx and increased permeability of the tissue-blood barrier [27] contribute to pulmonary edema and abnormal deposition of blood proteins, such as fibrinogen, in the lung interstitial tissue [15]. In addition, endothelial damage in pulmonary capillaries impairs endothelial antithrombotic function, leading to the formation of microthrombi [28], a process that has been well documented in SARS-CoV-2-associated pneumonia [15].

Study limitations. The results of this study should be interpreted with caution because of several limitations. First, the authors used random sampling with a small sample size, which reduces the strength of the evidence. In addition, inclusion and exclusion criteria were applied after the random selection of medical records, which further reduces the reliability of the study. Another limitation is the lack of internal cross-validation or external validation to confirm the accuracy of the model.

Conclusion

This study suggests that common blood inflammation markers — such as CRP, ferritin, absolute leukocyte and granulocyte counts, percentage of granulocytes and band neutrophils, as well as band-to-segmented neutrophil ratio and oxygen saturation measured by pulse oximetry — can help assess the risk of poor outcome in patients with SARS-CoV-2-associated pneumonia admitted to or already in the ICU.

In addition, an association was found between these parameters and specific hospitalization time points, including the day of admission, the first day in the ICU, and the last day in the ICU.

Among these factors, the most valuable prognostic tool was a mathematical model incorporating ferritin levels, band-to-segmented neutrophil ratio, and oxygen saturation. This model had a sensitivity of 84.0% and a specificity of 94.1% for predicting adverse outcomes in ICU patients with SARS-CoV-2-associated pneumonia.

To determine whether this prediction model is specific to SARS-CoV-2-associated pneumonia, further studies are needed to assess its applicability to lung inflammation caused by other pathogens.

References

1. *Глыбочко П. В., Фомин В. В., Моисеев С. В., Авдеев С. Н., Яворовский А. Г., Бровко М. Ю., Умбетова К. Т., с соавт.* Исходы у больных с тяжелым течением COVID-19, госпитализированных для респираторной поддержки в отделения реанимации и интенсивной терапии. *Клиническая фармакология и терапия.* 2020; 3: 25–36. *Glybochko P. V., Fomin V. V., Moiseev S. V., Avdeev S. N., Yavorovsky A. G., Brovko M.Yu., Umbetova K. T., et al.* Outcomes in patients with severe COVID-19 hospitalized for respiratory support in intensive care units. *Clinical Pharmacology and Therapy = Klinicheskaya Farmakologiya i Terapiya.* 2020; 3: 25–36. (In Russ.).
DOI: 10.32756/0869-5490-2020-3-25-36.
2. *Жукова О. В., Каграманян И. Н., Хохлов А. Л.* Сравнительный анализ эффективности лекарственных препаратов в терапии тяжелых форм COVID-19 на основании методик атрибутивной статистики и анализа межлекарственных взаимодействий. *Фармация и фармакология.* 2020; 8 (5): 316–324. *Zhukova O. V., Kagramanyan I. N., Khokhlov A. L.* Comparative analysis of drug efficacy in the treatment for COVID-19 severe forms, based on attribute-based statistic methods and analysis of drug interactions. *Pharmacy and Pharmacology = Farmaciya i Farmakologiya.* 2020; 8 (4): 316–324. (In Russ.).
DOI: 10.19163/2307- 9266-2020-8-5-316-324.
3. *Savilov P. N.* On the possibility of using hyperbaric oxygenation in the treatment of SARS-CoV-2-infected patients. *Danish Scientific Journal.* 2020; 1 (36): 43–49.
4. *Henry B. M., Lippi G.* Poor survival with extracorporeal membrane oxygenation in acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19): pooled analysis of early reports. *J Crit Care.* 2020; 58: 27–28.
DOI: 10.1016/j. jcrc.2020.03.011. PMID: 32279018.
5. *Шепетько М. М., Искров И. А., Лендина И. Ю., Стома И. О.* Предикторы неблагоприятного исхода инфекции COVID-19 у пациентов с онкогематологическими заболеваниями. *Проблемы здоровья и экологии.* 2021; 18 (1): 27–34. *Shepetkska M. M., Iskrov I. A., Lendina I. Yu., Stoma I. O.* Predictors of adverse COVID-19 outcomes in patients with oncohematological diseases. *Health and Environmental Issues = Problemy Zdorovya i Ekologii.* 2021; 18 (1): 27–34. (In Russ.).
DOI: 10.51523/2708-6011.2021-18-1-4.
6. *Kahathuduwa C. N., Dhanasekara C. S., Chin S. H.* Case fatality rate in COVID-19: a systematic review and meta-analysis. *MedRxiv.* 2020.
DOI: 10.1101/2020.04.01.20050476.
7. *Хаджиева М. Б., Грачева А. С., Ершов А. В., Чурсинова Ю. В., Степанов В. А, Авдейкина Л. С., Гребенчиков О. А, с соавт.* Биомаркеры повреждения структур аэрогематического барьера при COVID-19. *Общая реаниматология.*2021; 17 (3): 16–31. *Khadzhieva M. B., Gracheva A. S., Ershov A. V., Chursinova Yu. V., Stepanov V. A., Avdeikina L. S., Grebenchikov O. A., et al.* Biomarkers of air-blood barrier damage in COVID-19. *General Reanimatology = Obshchaya Reanimatologiya.* 2021; 17 (3): 16–31 (In Russ.&Eng.).
DOI: 10.15360/1813-9779-2021-3-2-0.
8. *Салухов В. В., Гуляев Н. И., Дорохина Е. В.* Оценка системных воспалительных реакций и коагулопатии на фоне гормональной терапии при ковид-ассоциированном поражении легких. *Медицинский совет.* 2020; (21): 230–237. *Salukhov V. V., Gulyaev N. I., Dorokhina E. V.* Assessment of systemic inflammatory reactions and coagulopathy against the background of hormone therapy in covid-associated lung damage. *Medical Council = Meditsinskiy Sovet.* 2020; (21): 230–237. (In Russ.).
DOI: 10.21518/2079-701X-2020-21-230-23.
9. *Ulu M., Kaya M., Tunc Y., Yildirim H., Halici A., Coskun A.* Mortality prediction in the emergency service intensive care patients with possible COVID-19: a retrospective cross-sectional study. *Ann Crit Care.* 2024; 4: 157–166.
DOI: 10.21320/1818-474X-2024-4-157-166.
10. *Талько А. В., Невзорова В. А., Ермолицкая М. З., Бондарева Ж. В.* Возможности методов интеллектуального анализа данных для оценки исходов COVID-19 у пациентов с заболеваниями системы крови. *Бюллетень физиологии и патологии дыхания.* 2023; 88: 50–58. *Talko A. V., Nevzorova V. A., Ermolitskaya M. Z., Bondareva Zh. V.* The possibilities of data mining methods for assessing the outcomes of COVID-19 in patients with diseases of the blood system. *Bulletin Physiology and Pathology of Respiration = Bulleten Fiziologii i Patologii Dykhaniya.* 2023; 88: 50–58. (In Russ.).
DOI: 10.36604/1998-5029-2023-88-50-5.
11. *Rubio-Rivas M., Mora-Luján J. M., Formiga F., Arévalo-Cañas C., Ramos J. M. L., Villalba García M. V., Fonseca Aizpuru E. M., et al.* WHO ordinal scale and inflammation risk categories in COVID-19. Comparative study of the severity scales. *J Gen Intern Med.* 2022; 37 (8): 1980–1987.
DOI: 10.1007/s11606-022-07511-7. PMID: 35396659.
12. *Popadic V., Klasnja S l., Milic N., Rajovic N., Aleksic A., Milenkovic M., Crnokrak B., et al.* Predictors of mortality in critically ill COVID-19 patients demanding high oxygen flow: a thin line between inflammation, cytokine storm, and

coagulopathy. *Oxid Med Cell Longev*. 2021; 2021: 6648199.
DOI: 10.1155/2021/6648199. PMID: 33968298.

13. *Мареев В. Ю., Беграмбекова Ю. Л., Мареев Ю. В.* Как оценивать результаты лечения больных с новой коронавирусной инфекцией (COVID-19)? Шкала Оценки Клинического Состояния (ШОКС–КОВИД). *Кардиология*. 2020; 60 (11): 35–41. *Mareev V. Yu., Begrambekova Yu. L., Mareev Yu. V.* How evaluate results of treatment in patients with COVID-19. Symptomatic Hospital and Outpatient Clinical Scale for COVID-119 (SHOCS–COVID). *Cardio-logy = Kardiologiia*. 2020; 60 (11): 35–41. (In Russ.).
14. *Аврамов А. А., Иванов Е. В., Мелехов А. В., Мензулин Р. С., Никифорчин А. И.* Факторы риска неблагоприятного исхода COVID-19 в ОРИТ перепрофилированных стационаров разного типа. *Общая реаниматология*. 2023; 19 (3): 20–27. *Avramov A. A., Ivanov E. V., Melekhov A. V., Menzulin R. S., Nikiforchin A. I.* Risk factors for COVID-19 adverse outcome in ICU settings of various types repurposed hospitals. *General Reanimatology = Obshchaya Reanimatologiya*. 2023; 19 (3): 20–27. (In Russ.&Eng.).
DOI: 10.15360/1813-9779-2023-3-20-27.
15. *Корабельников Д. И., Магомедалиев М. О., Хорошилов С. Е.* Прогностическое значение цистатина С как предиктора неблагоприятного исхода при пневмонии тяжелого течения, ассоциированной с COVID-19. *Общая реаниматология*. 2023; 19 (3): 4–11. *Korabelnikov D. I., Magomedaliev M. O., Khoroshilov S. E.* Prognostic value of cystatin C as a predictor of adverse outcome in severe pneumonia associated with COVID-19 *General Reanimatology = Obshchaya Reanimatologiya*. 2023; 19 (3): 4–11. (In Russ.&Eng.).
DOI: 10.15360/1813-9779-2023-3-4-11.
16. *Кузовлев А. Н., Ермохина Л. В., Мельникова Н. С., Берикашвили Л. Б., Ядгаров М. Я., Каданцева К. К., Чаус Н. И., с соавт.* Номограмма для прогнозирования госпитальной летальности у пациентов с COVID-19, находившихся в отделении реанимации и интенсивной терапии. *Вестник анестезиологии и реаниматологии*. 2022; 19 (1): 6–17. *Kuzovlev A. N., Ermokhina L. V., Melnikova N. S., Berikashvili L. B., Yadgarov M. Ya., Kadantseva K. K., Chaus N. I., et al.* A nomogram for predicting hospital mortality in patients with COVID-19 admitted to the intensive care unit. *Messenger of Anesthesiology and Resuscitation = Vestnik Anesthesiologii i Reanimatologii*. 2022; 19 (1): 6–17. (In Russ.).
DOI: 10.21292/2078-5658-2022-19-1-6-17.
17. *Кузник Б. И., Смоляков Ю. Н., Хавинсон В. Х., Шаповалов К. Г., Лукьянов С. А., Фефелова Е. В., Казанцева Л. С.* Нейтрофилы, лимфоциты и их соотношение как предикторы исходов у больных COVID-19. *Патологическая физиология и экспериментальная терапия*. 2021; 65 (4): 34–41. *Kuznik B. I., Smolyakov Yu. N., Khavinson V. H., Shapovalov K. G., Lukyanov S. A., Fefelova E. V., Kazantseva L. S.* Neutrophils, lymphocytes and their ratio as predictors of outcome in patients with COVID-19. *Pathological Physiology and Experimental Therapy = Patologicheskaya Fiziologiya i Eksperimental'naya Terapiya*. 2021; 65 (4): 34–41. (In Russ.).
DOI: 10.25557/0031-2991.2021.04.34-41.
18. *Рыбакова М. Г., Карев В. Е., Кузнецова И. А.* Патологическая анатомия новой коронавирусной инфекции COVID-19. Первые впечатления. *Архив патологии*. 2020; 82 (5): 5–15. *Rybakova M. G., Karev V. E., Kuznetsova I. A.* Anatomical pathology of novel coronavirus (COVID-19) infection. First impressions. *Russian Journal of Archive of Pathology = Arkhiv Patologii*. 2020; 82 (5): 5–15. (In Russ.).
DOI: 10.17116/patol2020820515.
19. *Vutha A. K., Patenaude R., Cole A., Kumar R., Kheir J. N., Polizzotti B. D.* A microfluidic device for real-time on-demand intravenous oxygen delivery. *Proc Natl Acad Sci USA*. 2022; 119 (13): e2115276119.
DOI: 10.1073/pnas.2115276119.
PMID: 35312360.
20. *Гусев Е. Ю.* С-реактивный белок: патогенетическое и диагностическое значение *Уральский медицинский журнал*. 2014; 1 (115): 113–121. *Gusev E. Y.* C-reactive protein: pathogenetic and diagnostic value. *Ural Medical Journal = Uralskiy Meditsinskiy Zhurnal*. (In Russ.).
21. *Giamarellos-Bourboulis E. J., Netea M. G., Rovina N., Akinosoglou K., Antoniadou A., Antonakos N., Damoraki G., et al.* Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host Microbe*. 2020; 27 (6): 992–1000.e3.
DOI: 0.1016/j.chom.2020.04.009.
PMID: 32320677.
22. *Гусев У. Ю., Черешнев В. А.* Системное воспаление: теоретические и методологические подходы к описанию модели общепатологического процесса. Часть 1. Общая характеристика процесса *Патологическая физиология и экспериментальная терапия*. 2012; 4: 3–14. *Gusev U. Yu., Chereshnev V. A.* Systemic inflammation: theoretical and methodological approaches to description of general pathological process model. Part 1. General characteristics of the process. *Pathological Physiology and Experimental Therapy = Patologicheskaya Fiziologiya i Eksperimental`naya Terapiya*. 2012; 4: 3–14. (In Russ.).

23. *Cheng L., Li H., Li L., Liu C., Yan S., Chen H., Li Y.* Ferritin in the coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *J Clin Lab Anal.* 2020; 34 (10): e3618. DOI: 10.1002/jcla. 23618. PMID: 33078400.
24. *Полушин Ю. С., Шлык И. В., Гаврилова Е. Г., Паршин Е. В., Гинзбург А. М.* Роль ферритина в оценке тяжести COVID-19. *Вестник анестезиологии и реаниматологии.* 2021; 18 (4): 20–28. *Polushin Yu. S., Shlyk I. V., Gavrilova E. G., Parshin E. V., Ginzburg A. M.* The role of ferritin in assessing COVID-19 severity. *Messenger of Anesthesiology and Resuscitation = Vestnik Anesthesiologii i Reanimatologii.* 2021; 18 (4): 20–28. (In Russ.). DOI: 10.21292/2078-5658-2021-18-4-20-28.
25. *Струк Ю. В., Савилов П. Н., Якушева О. А., Вахтина Е. Б., Ефремова О. Ю., Первеева И. М., Вериковская А. В.* Применение гипербарической оксигенации у больных новой коронавирусной инфекцией COVID-19. *Морская медицина.* 2023; 9 (2): 56–67. *Struk Yu. V., Savilov P. N., Yakusheva O. A., Vakhtina E. B., Efremova O. Yu., Perveeva I. M., Verikovskaja A. V.* Application of hyperbaric oxygenation in patients with a new coronavirus infection COVID-19: prospective study. *Marine Medicine = Morskaya Meditsina.* 2023; 9 (2): 56–67. (In Russ.). DOI: 10.22328/2413-5747-2023-9-2-56-67.
26. *Кузнецов И. А., Потиевская В. И., Качанов И. В., Куравлёва О. О.* Роль ферритина в биологических средах человека. *Современные проблемы науки и образования* (электронный журнал). 2017; 5. *Kuznetsov I. A., Potievskaya V. I., Kachanov I. V., Kuravleva O. O.* The role of ferritin in human biological environments. *Current Problems of Science and Education = Sovremenniye Problemy Nauki i Obrazovaniya.* (electronic journal). 2017; 5. (In Russ.). https://science-education. ru/ru/article/view?id = 27102.
27. *Фетлам Д. Л., Чумаченко А. Г., Вязьмина М. Д., Мороз В. В., Кузовлев А. Н., Писарев В. М.* Прогностические маркеры гнойно-деструктивных заболеваний легких. *Общая реаниматология.* 2024; 20 (2): 14–28. *Fetlam D. L., Chumachenko A. G., Vyazmina M. D., Moroz V. V., Kuzovlev A. N., Pisarev V. M.* Prognostic markers of acute suppurative lung disease. *General Reanimatology = Obshchaya Reanimatologiya.* 2024; 20 (2): 14–28. (In Russ.&Eng.). DOI: 10.15360/1813-9779-2024-2-14-28.
28. *Zhang H., Wang Y., Qu M., Li W., Wu D., Cata J. P., Miao C.* Neutrophil, neutrophil extracellular traps and endothelial cell dysfunction in sepsis. *Clin Transl Med.* 2023; 13 (1): e1170. DOI: 10.1002/ctm2.1170. PMID: 36629024.
29. *Кузник Б. И., Хавинсон В. Х., Линькова Н. С.* COVID-19: влияние на иммунитет, систему гемостаза и возможные пути коррекции. *Успехи физиологических наук.* 2020; 51 (4): 51–63. *Kuznik B. I., Havinson V. H., Linkova N. S.* COVID-19: impact on immunity, hemostasis and possible methods of correction. *Successes of Physiological Sciences = Uspekhi Physiologicheskikh Nauk.* 2020; 51 (4): 51–63. (In Russ.). DOI: 10.31857/S030-117982-0040037

Received 17.05.2024
Accepted 24.12.2024
Accepted in press 24.03.2025

https://doi.org/10.15360/1813-9779-2025-2-2541

Biochemical Predictors of Clinical Outcome in Liver Failure Associated with Obstructive Jaundice

Irina V. Mamoshina[1]*, Marina V. Petrova[2,3], Andrian V. Mamoshin[4]

[1] Oryol Regional Clinical Hospital
10 Pobedy Boulevard, Oryol, 302028 Oryol Region, Russia
[2] Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology,
25 Petrovka Str., Bldg. 2, 107031 Moscow, Russia
[3] Medical Institute, Patrice Lumumba Peoples Friendship University of Russia,
6 Miklukho-Maclaya Str., 117198 Moscow, Russia
[4] A.V. Vishnevsky National Medical Research Center for Surgery, Ministry of Health of Russia,
27 Bolshaya Serpukhovskaya Str., 115093 Moscow, Russia

For citation: *Irina V. Mamoshina, Marina V. Petrova, Andrian V. Mamoshin.* Biochemical Predictors of Clinical Outcome in Liver Failure Associated with Obstructive Jaundice. *Obshchaya Reanimatologiya = General Reanimatology.* 2025; 21 (2): 16–24. https://doi.org/10.15360/1813-9779-2025-2-2541 [In Russ. and Engl.]

***Correspondence to:** Irina V. Mamoshina, mamoshinai@mail.ru

Summary

The study of predictors of adverse outcomes in liver failure is driven by the rapid increase in patients with obstructive jaundice (OJ) and the lack of standardized diagnostic criteria for assessing liver functional status.

Aim. To investigate the changes of liver injury biomarkers in liver failure associated with OJ.

Materials and Methods. A prospective observational cohort study was conducted on serum biomarkers of liver injury — L-FABP protein, 5'-nucleotidase, liver arginase, and hyaluronic acid — in patients with liver failure due to benign OJ. The study included 53 patients who underwent biliary decompression. Based on the course of disease, patients were divided into two groups: those with favorable outcomes (group 1, N=27) and those with unfavorable outcomes (group 2, N=26). A control group consisted of 25 healthy donors. Serum biomarker levels were assessed on admission and on days 3, 7 and 11 post-decompression. The study used enzyme-linked immunosorbent assay (ELISA). Statistical analysis was performed using IBM SPSS Statistics 22, including Friedman two-way analysis, Kruskal–Wallis H test, Mann–Whitney U test, and two-sample Kolmogorov–Smirnov test, with significance set at $P<0.05$.

Results. At hospital admission, median biomarker levels were significantly higher in both patient groups than in the comparison group. Group 1 showed a statistically significant decrease in all biomarkers during treatment (P=0.01 for L-FABP, 5'-nucleotidase, liver arginase; P=0.03 for hyaluronic acid). In group 2, only L-FABP levels decreased significantly (P=0.04). Sensitivity and specificity for predicting disease outcome were 89.2–92.3% and 88.9–96.3% for L-FABP, 53.8–69.2% and 81.5–85.2% for 5'-nucleotidase, 57.7–76.9% and 77.8–88.9% for arginase, and 38.5–46.2% and 74.1–81.5% for hyaluronic acid, respectively.

Conclusion. Among the studied biomarkers, L-FABP showed the highest specificity and sensitivity values for prediction of outcome in liver failure associated with OJ, while other biomarkers demonstrated less significant results.

Keywords: obstructive jaundice; liver failure; biomarkers of liver injury; L-FABP; 5'-nucleotidase; liver arginase; hyaluronic acid

Conflict of interest. The authors declare no conflict of interest. Preliminary results have been published in the conference proceedings: I. V. Mamoshina, M. V. Petrova. Molecular markers as predictors of liver failure in obstructive jaundice syndrome. XXIV All-Russia Conference with International Participation «Life Support in Critical Conditions». Moscow, November 11–12, 2002. I. M. Sechenov First Moscow State Medical University, Ministry of Health of the Russian Federation, 2022; 152-153.

Information about the authors:
Irina V. Mamoshina: http://orcid.org/0000-0003-2150-3662
Marina V. Petrova: http://orcid.org/0000-0003-4272-0957
Andrian V. Mamoshin: http://orcid.org/0000-0003-1787-5156

Introduction

In recent years, there has been a marked increase in the number of patients diagnosed with obstructive jaundice (OJ) (ranging from 12% to 25.2%) and liver failure (LF) associated with diseases of the hepatobiliary and pancreatic region [1, 2]. The etiologic spectrum of OJ includes choledocholithiasis in 50% of cases, tumors of the bile ducts, greater duodenal papilla, pancreas, and gallbladder in 40%, and stenosis of the greater duodenal papilla, biliary strictures or atresia, cholangitis, pancreatitis, and hepatic neoplasms in the remaining 10% [1–3]. The initial severity of OJ and the subsequent development of LF are important determinants of mortality, which can reach 20–40% [2, 4]. Endogenous intoxication and liver failure are the leading causes of death in patients with this pathology [1, 4, 5].

Liver dysfunction in the setting of OJ almost invariably leads to the development and progression of LF, although early diagnosis remains challenging. However, the extent of liver dysfunction plays a critical role in determining the outcomes of patients with OJ [1, 2].

Current diagnostic criteria for LF in the context of OJ are based on clinical data assessing the intensity and duration of jaundice, as well as laboratory and instrumental studies. Numerous prognostic scoring systems and assessment tools for hepatocellular dysfunction in various pathologies focus primarily on changes in biochemical markers such as bilirubin fractions, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, and lactate dehydrogenase [6-8]. However, several studies have shown that these criteria do not always accurately reflect the severity of liver failure and often provide only indirect or approximate assessments. This highlights the need for additional objective diagnostic criteria to complement standard approaches in patients with OJ [9].

A number of researchers have emphasized the critical importance of identifying and applying biological markers of liver injury that can be used at different stages of the disease [10]. A prognostically relevant marker should have high anatomical specificity, diagnostic accuracy, sensitivity, predictive value for clinical outcome, and the ability for dynamic monitoring [11, 12].

In particular, biomarkers such as liver-type fatty acid binding protein (L-FABP), 5'-nucleotidase (5-NT), hepatic arginase, and hyaluronic acid (HA) are considered promising preclinical indicators that reflect the development of hepatic decompensation. These markers provide valuable insight into key pathomorphological changes within the liver parenchyma and demonstrate adequate topographic specificity, sensitivity, and diagnostic accuracy [11, 12].

However, despite the significant number of potential biological markers under investigation in liver failure, their application in the context of obstructive jaundice remains controversial. Their clinical utility requires further validation through accumulated clinical experience and large-scale studies.

The aim of the study was to investigate the changes in liver injury biomarkers in patients with different outcomes of liver failure associated with obstructive jaundice.

Materials and Methods

An observational prospective cohort study was conducted to quantitatively assess serum levels of liver injury biomarkers — liver-type fatty acid-binding protein (L-FABP), 5'-nucleotidase (5-NT), hepatic arginase, and hyaluronic acid (HA) — in patients with LF associated with benign OJ. Biomarker levels were measured by enzyme-linked immunosorbent assay (ELISA).

The study cohort included patients hospitalized at the Department of Anesthesiology and Intensive Care at the Oryol Regional Clinical Hospital (Oryol, Russia) between June 2019 and March 2021. The study was approved by the Ethics Committee of the People's Friendship University of Russia (Protocol No. 14, dated May 21, 2019).

A total of 53 patients aged 35–75 years were enrolled. The cohort consisted of 26 males (49%) and 27 females (51%).

Inclusion criteria:

- age over 18 years;
- moderate or severe liver failure (corresponding to classes B and C according to the classification of E. Galperin et al., 2012) secondary to benign OJ;
- previous biliary decompression.

Exclusion criteria:

- decompensated comorbidities;
- chronic inflammatory liver diseases;
- mild OJ (class A);
- patient refusal to participate;
- surgical complications related to the intervention (massive bleeding, hemorrhagic shock);
- inability to assess the study variables.

Depending on the clinical course and outcome of the disease, patients were divided into two groups:

- Group 1 — patients with favorable outcome (those who achieved clinical stabilization and were discharged from the hospital, *N*=27)
- Group 2 — patients with unfavorable outcome (those who did not achieve clinical stabilization and died during hospitalization, *N*=26) (Table 1).

The mortality structure in the second group was as follows: in 15% of cases (*N*=4) the adverse outcome occurred in the immediate postoperative period (the first 5 days after surgery), while in 85% of cases (*N*=22) it occurred in the early postoperative period (from the 5th to the 21st day after surgery).

Table 1. Characteristics of patients in the study groups, *N* (%) or *Me* [IQR].

Parameter	Values in groups		*P value*
	Group 1, *N*=27	Group 2, *N*=26	
Age, years (minimal-maximal)	63.5 (37–85)	61.9 (35–88)	0.2
Male/female, *N* (%)	14/13 (51.9/48.1)	12/14 (48.3/51.7)	>0.05
SOFA score, points	7.4 [4–9]	8.8 [6–10]	>0.05
APACHE II score, points	20.1 [9–32]	21.8 [12–32]	>0.05

Note. IQR — interquartile range.

Pathophysiological and morphological abnormalities in LF with the underlying cholestasis, despite biliary decompression, triggered local and systemic complications, including coagulopathy, renal dysfunction, and systemic hypotension. As these complications progressed, they led to multiple organ failure and an unfavorable outcome.

In the patients included in the study, cholestasis was caused by benign biliary strictures (5.5%) and cholelithiasis (94.5%).

The diagnosis of «mechanical jaundice syndrome» was made on the basis of clinical and history data in accordance with the clinical guidelines of the Russian Society of Surgeons, approved by the Ministry of Health of the Russian Federation in 2018.

The number of patients with the severity of OJ corresponding to class B (moderate) was 23 (43.4%), and class C (severe) was 30 (56.6%).

The severity of LF was assessed according to the classification of V. Fedorov and V. Vishnevsky (2004). In addition, the severity of the patient's condition on admission was assessed using the APACHE II scale. On the day of admission and on the 3rd, 7th, and 11th days after decompressive surgery, MELD, Child-Turcotte-Pugh scores were assessed; the probability of developing multiple organ failure was determined for all patients at the aforementioned time points using the SOFA scale.

Comorbidities were assessed using the Charlson Comorbidity Index (CCI), which revealed 12 (22.6%) patients with ischemic heart disease and chronic heart failure, 5 (9.4%) with peripheral vascular disease, 6 (11.3%) with a history of peptic ulcer disease, 4 (7.5%) with severe bronchopulmonary disease, and 11 (20.8%) with diabetes mellitus. The CCI averaged 7.5±2.4 points in the favorable outcome group and 8.7±1.9 points in the unfavorable outcome group, ranging from 6 to 16 points.

The study groups were comparable with respect to sex ($P>0.05$) and age ($P=0.2$) and showed no statistically significant differences in the main assessment scales at baseline: APACHE II ($P>0.05$), SOFA ($P>0.05$), and CCI.

Patients hospitalized for hyperbilirubinemia in the setting of obstructive cholestasis were treated according to the clinical guidelines of the Russian Society of Surgeons, approved by the Ministry of Health of the Russian Federation in 2018, which include both conservative and surgical strategies.

Conservative therapy addressed the following aspects: pain management, detoxification, resolution of cholestasis consequences, hepatorenal failure, gastrointestinal erosions and acute ulcers, and cholangitis. Treatment included intravenous detoxification therapy, hepatoprotective agents, antibiotics (administered empirically in cases of systemic inflammatory response until bacteriologic results were available, with subsequent adjustments), and adequate nutritional support.

Surgical management followed a staged approach. On the first day of hospitalization, all patients underwent a minimally invasive procedure aimed at retrograde or antegrade biliary decompression to relieve the OJ and restore bile flow to the duodenum or establish an external biliary drainage. In some cases (26.49%), this was the definitive treatment.

In the second stage, after gradual resolution of OJ (assessed by monitoring bilirubin levels) and normalization of organ function, definitive (including radical) surgical intervention was performed (27.51%).

For patients with bile duct stones, the definitive treatment (85% of cases) was endoscopic retrograde transpapillary intervention. When this approach was not feasible or effective (15% of cases), alternative methods were used such as choledocholithotomy via mini-laparotomy, laparoscopic choledocholithotomy, or open choledocholithotomy via laparotomy.

In cases of benign biliary strictures, definitive treatment consisted of endoscopic correction (70%) or reconstructive plastic biliary surgery (30%).

The following reagents were used to quantify biological markers: for L-FABP, HBT L-FABP ELISA (BioKhimMak, Russia); for 5-NT, HBT 5-NT-I ELISA (BioKhimMak, Russia); for arginase, HBT Arginase-I ELISA (BioKhimMak, Russia); and for HA, HBT GK-I ELISA (BioKhimMak, Russia). All assays were performed on an automated microplate immunoanalyzer (Immunomat™). Serum levels of liver injury biomarkers in OJ were measured at hospital admission and on days 3, 7, and 11 of hospitalization.

The control group consisted of 25 healthy volunteers. Their biomarker levels were established as reference values for individuals without liver diseases.

Statistical analysis. Sample size was calculated using PS Power and Sample Size Calculations software, version 3.0.11 for MS Windows. To reject the null hypothesis with 80% power at $\alpha=0.05$, the minimum sample size required was 26 participants per group.

Statistical analysis was performed with IBM SPSS Statistics 22. The significance of differences was tested using nonparametric methods: the Mann–Whitney U test for between-group comparisons, supplemented by the Kolmogorov–Smirnov two-sample test. Null hypotheses were rejected at $P<0.05$.

Multivariable logistic regression with stepwise variable selection was used for predictive modeling. Methods recommended for small sample sizes were also used, including two-factor nonparametric (rank) Friedman's analysis of variance and Kruskal–Wallis H test for nonparametric (rank) one-way analysis of variance. The significance of the regression coefficients was evaluated using the Wald statistic, and model fit was assessed using the Hosmer-Lemeshow test. Model performance was compared

using ROC–AUC analysis. Only sensitivity and specificity were reported as predictive characteristics.

Results

Upon hospital admission, the median serum levels of liver injury biomarkers (L-FABP, arginase, HA, 5-NT) were significantly higher in patients of both groups than in healthy volunteers of the control group. The levels were significantly higher in patients of the second group compared to the first group ($P<0.05$), except for HA ($P=0.05$) (Table 2).

The changes in biomarker levels during the different treatment phases are shown in Table 3.

At all time points after the initial measurement, the concentration of liver injury biomarkers remained significantly higher in group 2 compared to group 1 ($P<0.05$), with the exception of HA levels on days 3 ($P=0.15$) and 7 ($P=0.09$) (Table 3).

In group 1, a statistically significant sequential decrease in the concentration of most biomarkers was observed by day 11 of treatment: L-FABP and 5'-nucleotidase ($P=0.01$) and hyaluronic acid ($P=0.03$). An exception was the increase in hepatic arginase concentration on day 3 compared to baseline ($P=0.01$). However, by day 7, arginase levels had fallen below baseline levels and continued to decline through day 11 ($P=0.01$) (Table 3).

In group 2, only the concentration of L-FABP showed a statistically significant decrease ($P=0.04$). Changes in the levels of the other biomarkers during the study were not significant ($P=0.39$–0.68) (Table 3).

At the final time point (day 11), none of the biomarker levels in either group had decreased to the median reference values. The biomarker concentrations closest to the reference medians were those of L-FABP and arginase in Group 1 (control vs. group 1: 12.90 vs. 13.70 ng/mL; 15.40 vs. 18.50 ng/mL, respectively) (Tables 2 and 3).

Area under the ROC curve (AUC) data for each biomarker over the study period are shown in Table 4.

The predictive performance of the models, in terms of sensitivity and specificity, varied depending on the treatment time point and showed the following characteristics:

- L-FABP: sensitivity ranged from 89.2% to 92.3%, specificity from 88.9% to 96.3%. The cutoff ranged from 21.6 to 40.0 ng/mL.
- Arginase: sensitivity ranged from 57.7% to 76.9%, specificity from 77.8% to 88.9%, with a consistent cutoff of 34.0 ng/mL.
- HA: sensitivity ranged from 38.5% to 46.2%, specificity from 74.1% to 81.5%. The cutoff value varied over a wide range; however, due to the low predictive performance of models based on HA, a reliable cutoff value could not be determined.
- 5-NT: sensitivity ranged from 53.8% to 69.2%, specificity from 81.5% to 85.2%. The empirically estimated cutoff was 34.4 IU/L.

The model with the predictor «L-FABP concentration» demonstrated the best performance

Table 2. Levels of liver injury biomarkers upon hospital admission in the study groups, *Me (Q1–Q3).*

Biomarker	Values of parameters in groups			*P value**
	Control group, *N*=25	Group 1, *N*=27	Group 2, *N*=26	
L-FABP, ng/mL	12.90 (12.55; 13.50)	26.40 (23.30; 34.10)	56.79 (39.09; 71.12)	0.01
Arginase, ng/mL	15.40 (13.60; 16.65)	22.40 (21.40; 28.40)	39.05 (32.85; 50.43)	0.01
Hyaluronic acid, ng/mL	41.0 (22.0; 69.0)	175.0 (86.0; 423.0)	290.5 (148.5; 517.0)	0.05
5'-nucleotidase, IU/L	1.56 (1.56; 1.71)	25.56 (19.34; 32.21)	36.60 (26.44; 55.56)	0.02

Note. The reference group represents values considered normal. * — significant difference between Group 1 and Group 2.

Table 3. Changes in liver injury biomarker levels during the study period.

Biomarker	Group	Values during study stages				Significance of changes, *P value**
		At admission, >*Me (Q1–Q3)*	Day 3, *Me (Q1–Q3)*	Day 7, *Me (Q1–Q3)*	Day 11, *Me (Q1–Q3)*	
L-FABP, ng/mL	Group 1	26.40 (23.30; 34.10)	21.40 (17.60; 30.30)	17.30 (14.90; 20.90)	13.70 (12.40; 17.60)	0.01
	Group 2	56.79 (39.09; 71.12)	45.80 (35.68; 78.75)	46.65 (32.90; 82.38)	44.15 (27.15; 84.50)	0.04
Between-group *P value***		0.01	0.01	0.01	0.01	—
Arginase, ng/mL	Group 1	22.40 (21.40; 28.40)	22.80 (20.80; 24.90)	19.90 (17.10; 22.90)	18.50 (16.40; 20.70)	0.01
	Group 2	39.05 (32.85; 50.43)	40.60 (34.53; 49.03)	40.10 (34.43; 49.03)	41.80 (34.93; 50.70)	0.68
Between-group *P value***		0.01	0.01	0.01	0.01	—
Hyaluronic acid, ng/mL	Group 1	175.0 (86.0; 423.0)	147.0 (72.0; 286.0)	135.0 (54.0; 274.0)	110.0 (56.0; 242.0)	0.03
	Group 2	290.5 (148.5; 517.0)	256.0 (138.5; 499.5)	258.5 (130.5; 511.5)	255.5 (131.5; 462.0)	0.58
Between-group *P value***		0.05	0.15	0.09	0.03	—
5′-nucleotidase, IU/L	Group 1	25.56 (19.34; 32.21)	24.43 (18.85; 30.38)	22.67 (15.76; 30.08)	15.90 (13.21; 20.61)	0.01
	Group 2	36.60 (26.44; 55.56)	34.92 (16.35; 56.02)	40.55 (24.31; 63.18)	34.70 (20.31; 63.18)	0.39
Between-group *P value***		0.02	0.02	0.01	0.01	—

Note. **P*— Friedman ANOVA (within-group comparison). ***P*— two-sample Kolmogorov–Smirnov test (between-group comparison).

characteristics, with an AUC ranging from 0.926 to 0.979 (95% CI: 0.851–1.000) (Fig.).

Discussion

To date, the search continues for promising laboratory biomarkers that can objectively assess the condition of patients with LF in the context of OJ and help predict the likelihood of an unfavorable outcome. From this perspective, liver injury biomarkers such as L-FABP, 5-NT, arginase and hyaluronic acid, appear to be relevant indicators of LF severity and prognosis in the setting of OJ.

A number of studies have demonstrated the clinical significance of L-FABP in various liver conditions, including liver allograft rejection [13], hepatocellular carcinoma [14–16], alcohol-induced chronic LF [17], and cirrhosis [14]. According to the literature, L-FABP is a sensitive marker of hepatocyte injury both in vivo and in vitro [14–17]. It is predominantly localized in the cytoplasm of hepatocytes, with smaller amounts found in the nucleus and outer mitochondrial membrane [13, 14].

L-FABP belongs to a family of relatively small (15 kDa) cytosolic lipids that are constitutively expressed in the liver. A distinctive feature of L-FABP is the presence of a β-barrel binding cavity, which enables the capture and transport of bile acids, eicosanoids and heme [16,18] to the mitochondria for oxidation [11].

This biomarker has strong diagnostic properties: it is cytosolic, highly specific for liver tissue, present at high intracellular concentrations, and has a low molecular weight [19]. During treatment, patients with favorable outcomes showed a statistically significant decrease in serum L-FABP levels, while those with poor outcomes maintained persistently elevated levels.

Logistic regression modeling demonstrated the predictive value of L-FABP for patient outcomes in LF associated with OJ. Depending on the time point during hospitalization, sensitivity ranged from 89.2% to 92.3%, specificity from 88.9% to 96.3%, and the cutoff ranged from 21.6 to 40.0 ng/mL. These findings underscore the high sensitivity and specificity of L-FABP in detecting hepatocellular injury in LF secondary to OJ, likely due to its cytoplasmic localization and rapid release into the circulation upon hepatocyte injury.

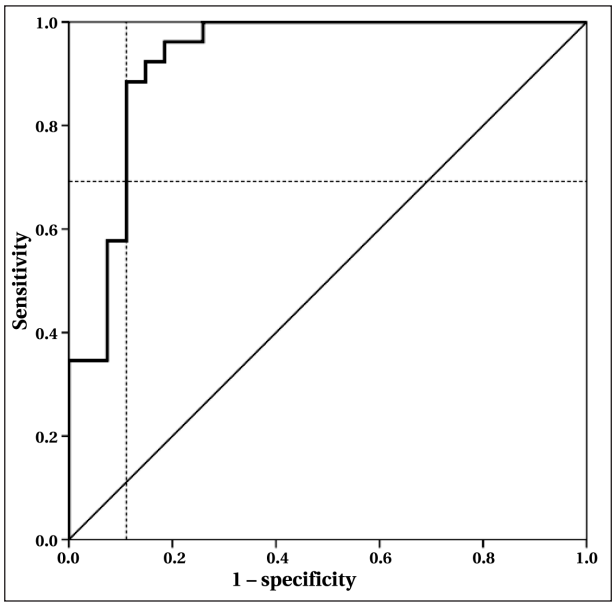

Fig. ROC curve for the logistic model with «L-FABP level» predictor.

5-NT is an integral membrane glycoprotein classified as a phosphatase that catalyzes the hydrolysis of nucleoside 5-phosphates [20]. In the liver, it is localized in the plasma membranes of biliary canalicular cells, sinusoids and Kupffer cells [21, 22]. In clinical practice, 5-NT serves as a highly specific marker for the diagnosis of hepatobiliary pathology in patients with and without obstructive jaundice.

Cholestasis of any etiology is typically associated with a parallel increase in ALP and 5-NT levels [21]. It is considered a reliable marker of both primary and secondary liver tumors, hepatobiliary disease with intrahepatic or extrahepatic bile duct obstruc-

Table 4. Predictive value of liver injury biomarkers according to ROC analysis.

Biomarker	Area under the curve [95% CI]	
	Group 1, *N*=27	Group 2, *N*=26
	L-FABP, ng/mL	
At admission	0.994 [0.982; 1.000]	1.000
Over treatment period	0.926–0.979 [0.851–1.000]	
	Arginase, ng/mL	
At admission	0.748 [0.612–0.884]	0.993 [0.978; 1.000]
Over treatment period	0.812–0.886 [0.048–0.063]	
	Hyaluronic acid, ng/mL	
At admission	0.868 [0.774; 0.963]	0.951 [0.899; 1.000]
Over treatment period	0.685–0.687 [0.542–0.829]	
	5′-nucleotidase, IU/L	
At admission	0.970 [0.913; 1.000]	0.985 [0.953; 1.000]
Over treatment period	0.671–0.781 [0.519–0.911]	

Note. CI — confidence interval. «Over treatment period» represents a range of AUC values observed at different treatment days (Day 3, 7, 11). Group 1: patients with favorable outcomes; Group 2: patients with unfavorable outcomes.

tion [13, 23], viral hepatitis [21, 24], early-stage biliary cirrhosis, third-trimester pregnancy, and graft-versus-host disease [15, 23].

Although 5-NT is a well-established and highly specific biomarker of liver disease, no clear correlation between 5-NT levels and disease severity or outcome in patients with OJ has been reported in the literature. In our study, significantly higher 5-NT levels were observed in patients with unfavorable outcomes, with only a nonsignificant decrease over the treatment period. In contrast, patients with favorable outcomes showed a statistically significant decrease in 5-NT levels, although levels remained above the reference range.

The prognostic value of 5-NT for predicting outcome in patients with LF secondary to OJ was modest. The area under the ROC curve (AUC) for 5-NT-based models ranged from 0.671 to 0.781 (95% CI, 0.519-0.911; *P*=0.02), with sensitivity ranging from 53.8% to 69.2% and specificity from 81.5% to 85.2%, depending on the time point during hospitalization. The cut-off value determined empirically was 34.4 IU/L.

Hepatic arginase catalyzes the hydrolysis of L-arginine to ornithine and urea [25]. Arginase serves two homeostatic purposes: the elimination of ammonia via urea synthesis and the production of ornithine, a precursor for polyamines and proline [25]. Because hepatic arginase activity is higher than in other tissues, an increase in serum arginase levels may be relatively specific to liver pathology. Arginase levels may serve not only as an early marker of liver injury, but also as an indicator of recovery or resolution (e. g., after surgery) [13]. According to the literature, a concurrent increase in serum arginase and gamma-glutamyl transpeptidase may be particularly informative in detecting hepatocellular injury and cholestasis [26].

Our results showed an initial increase followed by a sustained decrease in serum arginase levels from day 7 in patients with favorable outcomes, whereas persistently high concentrations were observed in patients with unfavorable outcomes. The predictive performance of the arginase-based models, as assessed by the area under the ROC curve (AUC), was «good» at baseline (AUC 0.748 [95% CI, 0.612–0.884]) and «very good» on days 3, 7 and 11 of intensive care (AUC 0.812–0.886 [95% CI, 0.048–0.063]), with sensitivity ranging from 57.7% to 76.9% and specificity from 77.8% to 88.9% at a cut-off of 34.0 ng/mL.

Hyaluronic acid (HA) is a glycosaminoglycan, a high molecular weight polysaccharide with a linear, unbranched structure [27]. Under physiological conditions, sinusoidal endothelial cells express specific receptors that facilitate rapid clearance of HA from the circulation (within 5–6 minutes) by the enzyme hyaluronidase. This clearance is impaired in cholestasis, resulting in elevated serum HA levels [28]. HA serves as a biomarker of liver fibrosis, which is clinically relevant in LF associated with OJ, where portal hypertension and cholangitis are common and often lead to fibrosis [13, 29].

There is a documented correlation between serum HA levels and liver disease severity as measured by the Child-Pugh score [28]. In addition, several studies have investigated the use of HA as a tumor marker, including in hepatocellular carcinoma, due to its interaction with CD44 and RHAMM receptors on the cell surface [27, 30].

In our study, patients with favorable outcomes showed a significant initial increase followed by a decrease in HA levels during treatment, while those with poor outcomes maintained consistently high levels. The predictive ability of HA-based models on admission and on day 3 of treatment was determined, with AUC values of 0.685–0.687 [95% CI, 0.542–0.829], sensitivity of 38.5–46.2% and specificity of 74.1–81.5%.

Conclusion

This study highlights the diagnostic and prognostic relevance of several biological markers for the assessment of liver function in the setting of obstructive jaundice.

Among them, dynamic monitoring of L-FABP levels during the overt phase of the disease showed the highest sensitivity and specificity for predicting outcome in patients with liver failure secondary to obstructive jaundice.

References

1. *Кабанов М. Ю., Семенцов К. В., Бояринов Д. Ю., Мянзелин М. Н., Беликова М. Я., Алексеев В. В.* Трудности оценки тяжести дисфункции печени при механической желтухе. *Анналы хирургической гепатологии*. 2021; 26 (2): 129–136. *Kabanov M. Yu., Sementsov K. V., Boyarinov D. Yu., Myanzelin M. N., Belikova M. Ya., Alekseev V. V.* Difficulties in assessing the severity of liver dysfunction for obstructive jaundice. *Annals of HPB Surgery = Annaly Khirurgicheskoy Gepatologii*. 2021; 26 (2): 129–136. (In Russ.).
DOI: 10.16931/10.16931/1995-5464.2021-2-129-136.
2. *Винник Ю. С., Пахомова Р. А., Кочетова Л. В., Воронова Е. А., Козлов В. В., Кириченко А. К.* Предикторы печеночной недостаточности при механической желтухе. *Хирургия. Журнал им. Н. И. Пирогова*. 2018; (3): 37–41. *Vinnik Yu. S., Pakhomova R. A., Kochetova L. V., Voronova E. A., Kozlov V. V., Kirichenko A. K.* Predictors of hepatic insufficiency in obstructive jaundice. *Pirogov Russian Journal of Surgery = Khirurgiya. Zurnal im. N. I. Pirogova*. 2018; (3): 37–41. (In Russ.).
DOI: 10.17116/hirurgia2018337-41.
3. *Fernández J., Bassegoda O., Toapanta D., Bernal W.* Acute liver failure: a practical update. *JHEP reports*. 2024; 6 (9): 101131.
DOI: 10.1016/j.jhepr.2024.101131. PMID: 39170946.
4. *Liu J.-J., Sun Y.-M., Xu Y., Mei H.-W., Guo W., Li Z.-L.* Pathophysiological consequences and treatment strategy of obstructive jaundice. *World J Gastrointest Surg*. 2023; 15 (7): 1262–1276.
DOI: 10.4240/wjgs.v15.i7.1262. PMID: 37555128.
5. *Sha J., Dong Y., Niu H.* A prospective study of risk factors for in-hospital mortality in patients with malignant obstructive jaundice undergoing percutaneous biliary drainage. *Medicine (Baltimore)*. 2019; 98 (15): e15131.
DOI: 10.1097/MD.0000000000015131. PMID: 30985679.
6. *Tamber S. S., Bansal P., Sharma S., Singh R. B., Sharma R.* Biomarkers of liver diseases. *Mol Biol Rep*. 2023; 50 (9): 7815–7823.
DOI: 10.1007/s11033-023-08666-0. PMID: 37482588.
7. *Mangia A.* Biomarkers use and development in hepatology: insights on the latest applications. *Cells*. 2022; 12 (1): 104.
DOI: 10.3390/cells12010104. PMID: 36611898.
8. *Петрова М. В., Мамошина И. В.* Прогнозирование неблагоприятного исхода у больных с печеночной недостаточностью на фоне синдрома механической желтухи: проспективное наблюдательное исследование. *Вестник интенсивной терапии им. А. И. Салтанова*. 2024; 2: 83–93. *Petrova M. V., Mamoshina I. V.* Predicting an unfavorable outcome in patients with liver failure associated with obstructive jaundice syndrome: a prospective observational study. *Ann Crit Care = Vestnik Intensivnoy Terapii im AI Saltanova*. 2024; 2: 83–93. (In Russ).
DOI: 10.21320/1818-474X-2024-2-83-93.
9. *Liang Y., Guo G. L., Zhang L.* Current and emerging molecular markers of liver diseases: a pathogenic perspective. *Gene expr*. 2022; 21 (1): 9–19.
DOI: 10.14218/GEJLR.2022.00010.
PMID: 38911667.
10. *Власов А. П., Шейранов Н. С., Маркин О. В., Власова Т. И., Муратова Т. А., Рязанцев В. Е., Тимошкин Д. Е., с соавт.* Способ оценки тяжести механической желтухи неопухолевого генеза. *Журнал им. Н. В. Склифосовского «Неотложная медицинская помощь»*. 2021; 10 (1): 174–180. *Vlasov A. P., Sheyranov N. S., Markin O. V., Vlasova T. I., Muratova T. A., Ryazantsev V. E., Timoshkin D. E., et al.* A method for assessing the severity of obstructive jaundice of non-neoplastic origin. *Russian Sklifosovsky Journal «Emergency Medical Care» = Zhurnal im. N. V. Sklifosovskogo «Neotlozhnaya Meditsinskaya Pomoshch»*. 2021; 10 (1): 174–180. (In Russ.)
DOI: 10.23934/2223-9022-2021-10-1-174-180.
11. *Рузибойзода К. Р., Гулов М. К., Сафарзода А. М., Сафаров Б. И., Халимов Дж.С., Гуломов Л. А., Нуров З. Х.* Оптимизация лечения печеночной недостаточности у больных механической желтухой. *Вестник НМХЦ им. Н. И. Пирогова*. 2023; 18 (3): 66–70. *Ruziboyzoda K. R., Gulov M. K., Safarzoda A. M., Safarov B. I., Khalimov J. S., Gulomov L. A., Nurov Z. Kh.* Optimization of the treatment of liver failure in patients with obstructive jaundice. *Bulletin of Pirogov National Medical & Surgical Center = Vestnik NMCKh im. N. I. Pirogova*. 2023; 18 (3): 66–70. (In Russ.).
DOI: 10.25881/20728255_2023_18_3_66.
12. *Семенцов К. В., Бояринов Д. Ю., Мянзелин М. Н., Кошелев Т. Е.* Современные подходы к оценке влияния механической желтухи на функциональное состояние печени. *Вестник НМХЦ им. Н. И. Пирогова*. 2024; 19 (1): 110–114. *Sementsov K. V., Boyarinov D. Yu., Myanzelin M. N., Koshelev T. E.* Modern approaches to the assessment of the impact of mechanical jaundice on the functional

state of the liver. *Bulletin of Pirogov National Medical & Surgical Center = Vestnik NMCKh im. N. I. Pirogova*. 2024; 19 (1): 110–114. (In Russ.).
DOI: 10.25881/20728255_2023_19_1_110.
13. *Eguchi A., Iwasa M.* The role of elevated liver-type fatty acid-binding proteins in liver diseases. *Pharm Res*. 2021; 38 (1): 89–95.
DOI: 10.1007/s11095-021-02998-x. PMID: 33534129.
14. *Abdulaziz B. A., Abdu S. A., Amin A. M., El Menyawi A. K. A. H., Ahmed A., Khalil M. A., Halim W. A. A.* Assessment of liver fatty acid binding protein (L-FABP) as a diagnostic marker in non-alcoholic fatty liver disease. *Open Journal of Gastroenterology*. 2019; 9: 113–124.
DOI: 10.4236/ojgas.2019.96014.
15. *Gökçen P., Çakmak E., Adali G., Doğan H. O., Yildiz S., Ozturk O., Doğanay H. L., et al.* Liver fatty acid binding protein: is it an early diagnostic and prognostic marker in liver damage? *Medical Science and Discovery*. 2021; 8 (4): 213–218.
DOI: 10.36472/msd.v8i4.516.
16. *Камышников В. С.* Клинико-лабораторная диагностика заболеваний печени. 3-е изд. М.: МЕДпресс-информ; 2019. *Kamyshnikov V. S.* Clinical and laboratory diagnostics of liver diseases. 3d ed. M.: MEDpress-inform; 2019. (In Russ.).
17. *Elmes M. W., Prentis L. E., McGoldrick L.L., Giuliano C. J., Sweeney J. M., Joseph O. M., Che J., et al.* FABP1 controls hepatic transport and biotransformation of △9-THC. *Sci Rep*. 2019; 9 (1): 7588.
DOI: 10.1038/s41598-019-44108-3.
PMID: 31110286.
18. *Buechler C., Aslanidis C.* Role of lipids in pathophysiology, diagnosis and therapy of hepatocellular carcinoma. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2020; 1865 (5): 158658.
DOI: 10.1016/j.bbalip.2020.158658.
PMID: 32058031.
19. *Kulkarni A. V., Sharma M., Kumar P., Simhadri V., Sowmya T. R., Mitnala S., Reddy D. N., et al.* Adipocyte fatty acid-binding protein as a predictor of outcome in alcohol-induced acute-on-chronic liver failure. *J Clin Exp Hepatol*. 2021; 11 (2): 201–208.
DOI: 10.1016/j.jceh.2020.07.010.
PMID: 33746445.
20. *Aimaitijiang M., Wu T.-T., Zheng Y.-Y., Hou X.-G., Yang H., Yang Y., Xie X.* Serum 5'-nucleotidase as a novel predictor of adverse clinical outcomes after percutaneous coronary intervention in patients with coronary artery disease. *Rev Cardiovasc Med*. 2024; 25 (1): 17.
DOI: 10.31083/j.rcm2501017. PMID: 39077643.
21. *Habib S., Shaikh O. S.* Approach to jaundice and abnormal liver function test results. In book: Zakim and Boyer's Hepatology. 7th ed: Elsevier; 2018: 99–116.
DOI: 10.1016/B978-0-323-37591-7.00007-0.
22. *Кишкун А. А.* Руководство по лабораторным методам диагностики. М.: ГЭОТАР-Медиа; 2014. *Kishkun A. A.* Manual of laboratory diagnostic methods. *Moscow: GEOTAR-Media*; 2014. (In Russ.).
23. *Xue X.-M., Liu Y.-Y., Chen X.-M., Tao B.-Y., Liu P., Zhou H.-W., Zhang C., et al.* Pan-cancer analysis identifies NT5E as a novel prognostic biomarker on cancer-associated fibroblasts associated with unique tumor microenvironment. *Front Pharmacol*. 2022; 13: 1064032.
DOI: 10.3389/fphar.2022.1064032.
PMID: 36569293.
24. *Галеева Н. В.* Активность фермента 5`-нуклеотидазы у больных хроническим гепатитом С с обострением естественного течения болезни и его терапевтическая коррекция. *Практическая Медицина*. 2020; 18 (4): 97–102. *Galeeva N. V.* Activity level of 5`-nucleotidase enzyme in patients with chronic hepatitis C with an exacerbation of the disease natural course and its therapeutic correction. *Practical Medicine = Prakticheskaya Meditsina*. 2020; 18 (4): 97–102. (In Russ.).
25. *Li M., Qin J., Xiong K., Jiang B., Zhang T.* Review of arginase as a promising biocatalyst: characteristics, preparation, applications and future challenges. *Crit Rev Biotechnol*. 2022; 42 (5): 651–667.
DOI: 10.1080/07388551.2021.1947962.
PMID: 34612104.
26. *Kaneko J. J., Harvey J. W., Bruss M. L.* Clinical biochemistry of domestic animals. 6th ed: Academic Press; 2008.
DOI: 10.1016/B978-012396305-5/50032-4.
27. *Al-Khateeb R., Prpic J.* Hyaluronic acid: the reason for its variety of physiological and biochemical functional properties. *Applied Clinical Research, Clinical Trials and Regulatory Affairs*. 2019; 6 (2): 112–159.
DOI: 10.2174/2213476X06666190405094637.
28. *Younesi S., Parsian H.* Diagnostic accuracy of glycoproteins in the assessment of liver fibrosis: a comparison between laminin, fibronectin, and hyaluronic acid. *Turk J Gastroenterol*. 2019; 30 (6): 524–531.
DOI: 10.5152/tjg.2019.17339. PMID: 31144658.
29. *Chen Z., Ma Y., Cai J., Sun M., Zeng L., Wu F., Zhang Y., et al.* Serum biomarkers for liver fibrosis. *Clin Chim Acta*. 2022; 537: 16–25.
DOI: 10.1016/j.cca.2022.09.022. PMID: 36174721.

30. *Matsumoto T., Aoki T., Shimizu T., Park K. H., Shiraki T., Sakuraoka Y., Mori S., Iso Y., et al.* Prognostic significance of preoperative hyaluronic acid level in patients with hepatocellular carcinoma. *HPB: (Oxford)*. 2022; 24 (4): 525–534.
DOI: 10.1016/j.hpb.2021.09.001.
PMID: 34654620.

Received 14.12.2025
Accepted 11.03.2025
Accepted in press 24.03.2025

https://doi.org/10.15360/1813-9779-2025-2-2546

Predictors of Adverse Outcomes in Acute Poisoning in Children

Maxim A. Udaltsov[1,2], Konstantin V. Pshenisnov[2]*, Yuri S. Alexandrovich[2], Vitaly A. Kaziakhmedov[2], Vyacheslav E. Ironosov[2,3], Galina P. Tikhova[4]

[1] Turner G.I. National Medical Research Center for Children's Traumatology and Orthopedics, Ministry of Health of the Russia, 64–68 Parkovaya Str., Pushkin, 196603 St. Petersburg, Russia
[2] St. Petersburg State Pediatric Medical University, Ministry of Health of Russia, 2 Litovskaya Str, 194100 Saint-Petersburg, Russia
[3] City Hospital № 14, 19/9 Kosinova Str.,198099 St. Petersburg, Russia
[4] Petrozavodsk State University, 33 Lenina pr., 185910 Petrozavodsk, Karelia Republic, Russia

For citation: *Maxim A. Udaltsov, Konstantin V. Pshenisnov, Yuri S. Alexandrovich, Vitaly A. Kaziakhmedov, Vyacheslav E. Ironosov, Galina P. Tikhova.* Predictors of Adverse Outcomes in Acute Poisoning in Children. *Obshchaya Reanimatologiya = General Reanimatology.* 2025; 21 (2): 25–33. https://doi.org/10.15360/1813-9779-2025-2-2546 [In Russ. and Engl.]

***Correspondence to:** Konstantin V. Pshenisnov, Psh_k@mail.ru

Summary

Poisoning is one of the most common causes for hospitalization of pediatric patients, often requiring admission to an intensive care unit (ICU).

Aim. To identify predictors of adverse outcomes in children with acute poisoning requiring ICU care.

Materials and Methods. A single-center, observational, retrospective study was conducted involving 262 children with severe poisoning. The median age was 15 [13-16] years. Patients were divided into two groups based on the clinical course of the poisoning: favorable and unfavorable. Hospitalization outcomes included duration of mechanical ventilation (MV), length of ICU stay, presence of complications (aspiration syndrome, seizures, etc.), and in-hospital mortality.

Results. The presence of toxic hepatitis/pancreatitis on admission increased the odds of adverse outcome by 4.63-fold, acute kidney injury by 5.32-fold, the need for MV by 14.34-fold, and aspiration pneumonia by 19.23-fold. The most significant markers of adverse outcomes during ICU care included shock (odds ratio OR=4.35), coagulopathy (OR=9.94), and hypocoagulation (OR=29.4). For assessing the severity of multiple organ dysfunction syndrome (MODS) in children with acute intoxication, the Marshall J. C. criteria showed the highest prognostic value (AUROC=0.894; sensitivity = 87.0%; specificity = 81.9%). A mathematical model was developed to predict the likelihood of adverse outcome in acute poisoning in children. The model includes 13 parameters: presence of pneumonia and seizures, need for MV, systolic and mean arterial pressure, catecholamine index, hemoglobin concentration, red and white blood cell counts, blood pH and glucose levels, SpO_2/FiO_2 ratio, and international normalized ratio (INR). The model demonstrated high predictive accuracy (accuracy=0.938; sensitivity=94.2%; specificity=92.5%; AUROC=0.981).

Conclusion. Impaired consciousness, severe hypoxemia, coagulopathy and acute liver failure are the main markers of severe acute poisoning in children.

Keywords: poisoning, children, intensive care unit, prognosis, outcome.

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

Funding. The study was conducted as part of a research project at St. Petersburg State Pediatric Medical University, Ministry of Health of Russia, without sponsorship.

Information about the authors:
Maxim A. Udaltsov: http://orcid.org/0000-0003-1054-9702
Konstantin V. Pshenisnov: http://orcid.org/0000-0003-1113-5296
Yuri S. Alexandrovich: http://orcid.org/0000-0002-2131-4813
Vitaly A. Kaziakhmedov: http://orcid.org/0000-0002-7243-2852
Vyacheslav E. Ironosov: http://orcid.org/0000-0002-2723-067X
Galina P. Tikhova: http://orsid.org/0000-0003-1128-9666

Introduction

Poisoning by toxic substances and drugs remains one of the most common causes of emergency department visits and intensive care unit (ICU) admissions in both adult and pediatric populations [1–5].

In recent years, there has been a steady increase in the number of pediatric cases of acute exogenous poisoning requiring intensive care [6–9]. The most common poisonings in children involve neurotoxic agents, nonsteroidal anti-inflammatory drugs (NSAIDs), and cardiovascular drugs [10]. Among neuroactive substances, benzodiazepine overdoses predominate, while paracetamol is the leading NSAID involved, reflecting its widespread use in pediatric medicine [10, 11].

Narcotic and psychotropic drug poisoning has emerged as a critical global public health challenge [9]. According to the World Health Organization

(WHO), 1 in 17 people aged 15–64 years used such substances in 2021. Reported cases will increase by 23% between 2011 (240 million) and 2021 (296 million), affecting 5.8% of the global population in this age group [9].

Each year in the United States, approximately 50,000 children present to emergency departments after unintentionally ingesting potentially toxic substances, with approximately 9,000 requiring hospitalization. Among children under the age of five, opioids are the leading cause of fatal poisonings. The proportion of opioid-related poisoning deaths has risen sharply, accounting for 52.2% of pediatric poisoning deaths in 2018, compared with 24.1% in 2005 [10, 12].

Li et al. (2021) note that while the incidence of accidental pediatric poisoning has decreased in recent years, the mortality rate has remained unchanged. In children aged 0–5 years, the risk of a fatal outcome is equivalent whether the toxic agent is a pharmaceutical or non-pharmaceutical substance. However, in older children, poisoning by non-pharmaceutical toxicants is associated with significantly higher mortality: the odds ratio increases to 2.38 (95% CI, 1.58–3.58) for children aged 6–12 years and to 3.04 (95% CI, 2.51–3.69) for adolescents (13–19 years) [13].

Of particular concern is the increase in suicide attempts involving pharmaceuticals, which accounted for 40.63% of fatal poisonings in children aged 6–12 years and 48.66% in adolescents (13–19 years), especially those with behavioral disorders. Non-pharmaceutical poisons were involved in 31.15% of suicide-related fatal poisonings in the 13–19 age group [13–15].

M. Junuzovic et al. (2022) reported that poisoning as a method of suicide occurred in 4% of pediatric cases [16]. These findings are consistent with observational studies identifying drugs as the most common cause of serious poisoning in children [17–20].

Cannabis-based products remain the most widely used substances worldwide, with 219 million users (4.3% of the global adult population) in 2021. Approximately 60 million people used opioids for non-medical purposes, including 31.5 million who used opiates — the main cause of fatal overdoses [9, 21, 22].

Recent studies highlight a steady increase in pediatric cannabis derivative poisonings associated with legalization in several countries. However, research on treatment protocols and family education for these patients remains critically limited [21–23].

In particular, few studies have evaluated outcomes or predictors of poor prognosis in severe pediatric poisonings. Early identification of high-risk patients upon admission to the ICU could significantly improve outcomes, underscoring the rationale for this study.

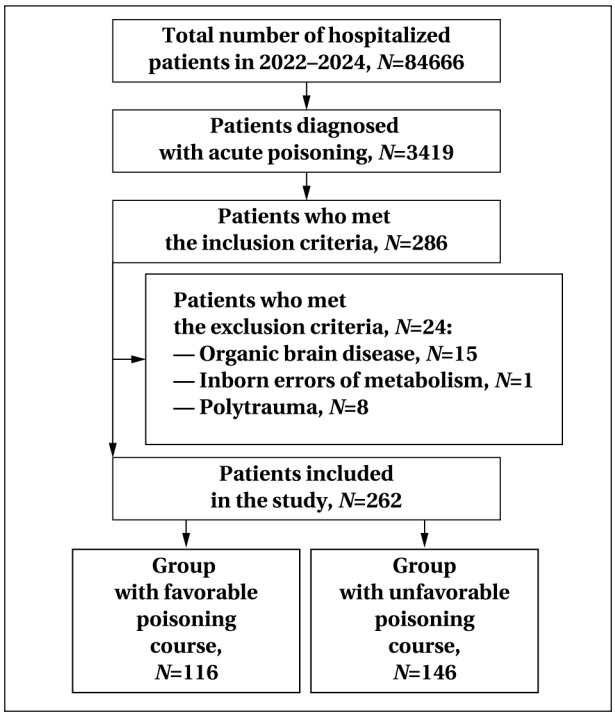

Fig. 1. Patient selection flowchart.

The study aim was to identify risk factors and predictors of unfavorable course in children with acute poisoning requiring intensive care.

Materials and Methods

We conducted a single-center, observational, retrospective study approved by the local ethics committee of the St. Petersburg State Pediatric Medical University, Russian Ministry of Health (Protocol No. 19/02, dated November 17, 2022).

Inclusion criteria

- Age 0–18 years
- Severe intoxication
- Impaired consciousness (stupor or coma)
- Need for intensive care treatment

Exclusion Criteria

- Organic brain disease
- Inborn errors of metabolism
- Genetic diseases
- Polytrauma

The study included 262 children (148 boys [56.5%] and 114 girls [43.5%]) aged 0–18 years who were admitted to the Department of Anesthesiology, Resuscitation and Intensive Care at Filatov Children's City Clinical Hospital No. 5 (2022–2024) (Fig. 1).

The most frequent poisoning agents were:

- Methadone (24.0%)
- Sedatives-hypnotics such as neuroleptics, tricyclic antidepressants, GHB precursors, anticonvulsants (24.0%)
- Ethanol (22.0%)
- Psychoactive substances such as cannabinoids, amphetamines, synthetic cannabinoids («spice»), hallucinogenic mushrooms (18.0%)

• Other substances such as muscle relaxants (baclofen, tizanidine), cardiovascular drugs (propafenone, clonidine, propranolol, cinnarizine), decongestants (naphazoline), antihistamines (cetirizine, diphenhydramine), antiemetics (dimenhydrinate, metoclopramide), hemorheologic agents (pentoxifylline), NSAIDs (acetaminophen), local anesthetics (lidocaine, benzocaine), cyanide (12.0%).

All patients underwent

• comprehensive clinical and laboratory evaluation

• toxicologic screening (blood and urine) to identify toxicants

To verify the diagnosis of acute respiratory distress syndrome (ARDS), the SpO_2/FiO_2 ratio and the oxygenation index (OI) were calculated. The OI was calculated using the following formula [5]:

$$OI=(MAP\times FiO_2\times 100\%)/PaO_2.$$

The catecholamine index was used to assess the intensity of catecholamine support. It was calculated according to the following formula [114]:

Catecholamine index = Dopamine (μg/kg/min) + Dobutamine (μg/kg/min) + Epinephrine (μg/kg/min) + Norepinephrine (μg/kg/min).

Patients were divided into two groups based on their clinical and laboratory status: those with a favorable course of poisoning (*N*=116) and those with an unfavorable course (*N*=146). Classification was based on seven severity criteria:

- Multiple organ dysfunction
- Seizures
- Need for mechanical ventilation
- Coagulopathy (prothrombin index <67%)
- Acidosis with pH <7.25
- Lactate concentration >2.5 mmol/L
- SpO_2/FiO_2 ratio < 300

Patients with five or more of these criteria were assigned to the unfavorable course group.

The hospitalization outcomes studied included the duration of mechanical ventilation, length of stay in the ICU, the presence of complications (such as aspiration syndrome, seizures, and others), and in-hospital mortality. In-hospital mortality was considered the primary endpoint, while all other endpoints were considered secondary.

For statistical analysis, direct access to electronic medical records was obtained through the medical information system, and all necessary frequency and quantitative data were available. Descriptive statistics were used throughout the analysis. Absolute and relative frequencies were calculated for binary and categorical variables. For continuous variables, median and interquartile range *(Q1–Q3)* were reported. The Shapiro–Wilk test was used to assess normality of data distribution. Differences in continuous variables between two independent groups were analyzed using the Mann–Whitney *U* test. Associations between continuous and binary variables were assessed by calculating odds ratios (OR) with their 95% confidence intervals (95% CI). For categorical variables with outcome frequencies less than 5 in any of the groups, Fisher's exact test was used.

Regression analysis and prognostic model development were based on univariate and multivariate logistic regression because the dependent variable was binary. Predictor selection was optimized using stepwise logistic regression with Akaike's information criterion ($\triangle AIC < 0.1$). The model initially included 28 clinical and laboratory variables (e.g., presence of arrhythmias, systolic, diastolic, and mean arterial pressure, heart rate, etc.). A total of 15 iterations were performed to define the final set of predictors.

Collinearity among potential predictors was assessed by correlation analysis based on variable types and distribution characteristics. Pearson's correlation coefficient was used for parametric variables, Spearman's rank correlation for nonparametric data, and Pearson's contingency coefficient for categorical variables. Predictors with statistically significant correlations greater than 0.5 with several other variables (i. e., accounting for more than 25% of the common variance) were excluded from the model.

Estimation of regression coefficients was performed using maximum likelihood, implemented via the glm function for binomial distribution and the MASS package for stepwise logistic regression in the R programming environment. To evaluate the predictive performance of clinical and laboratory variables, scoring systems, and the final model, ROC analysis was performed, including ROC curve construction and calculation of AUROC, accuracy, sensitivity, and specificity. The optimal cutoff point was determined using the Youden index (*J*-index) in MedCalc software.

For all statistical tests, regression and correlation coefficients, and odds ratios, the significance threshold was set at $P<0.05$. All tests were performed as two-tailed. All regression analyses were performed in *R* using dedicated libraries (MASS, ROCR, meta) and custom R scripts. Figure 2 was generated in *R* using the graphical functions of the meta package.

Results

The median age of the children included in the study was 15.0 years [IQR: 13.0–16.0]. The distribution of participants by sex and age is shown in Table 1. The majority of patients (70.0%) were between 14 and 18 years of age. There was a significantly higher proportion of boys compared to girls (43.5% vs. 26.3%).

The overall mortality rate was 0.76% (*N*=2), observed exclusively in the group of patients with an unfavorable course of poisoning; no deaths occurred in those with a favorable course (*P*=0.505).

Patients with an unfavorable course had a significantly longer time to regain consciousness (21.0 vs. 12.2 hours; $P<0.001$), duration of mechanical ventilation (2.0 vs. 0 days; $P<0.001$), and ICU stay (3.2 vs. 1.0 days; $P<0.001$).

Table 1. Distribution of patients by age and sex, *N* (%).

Age (years)	Boys, *N* (%)	Girls, *N* (%)	Total, *N* (%)
<1 year	1 (0.4)	1 (0.4)	2 (0.8)
1–3	11 (4.2)	17 (6.5)	28 (11.0)
3–7	11 (4.2)	10 (3.8)	21 (8.0)
7–10	4 (1.5)	1 (0.4)	5 (2.0)
11–14	7 (2.7)	16 (6.1)	23 (9.0)
14–18	114 (43.5)	69 (26.3)	183 (70.0)
Total	**148 (56.5)**	**114 (43.5)**	**262 (100.0)**

Table 2. Clinical and laboratory status on the first day of ICU treatment and during the entire stay in the ICU according to poisoning characteristics, *N* (%) or *Me (Q1–Q3)*.

Parameter	Values in groups		*P value*
	Favorable course, *N*=116	Unfavorable course, *N*=146	
Age, years	15 [4–16]	15 [14–16]	0.001
Sex			
Boys	61 (52.6)	87 (59.6)	<0.001
Girls	55 (47.4)	59 (40.4)	
Mechanical ventilation	8 (6.9)	123 (84.2)	<0.001
Acute kidney injury on day 1 in ICU	3 (2.6)	18 (12.3)	0.004
Toxic hepatitis/pancreatitis on day 1 in ICU	7 (6.0)	33 (22.6)	<0.001
Arrhythmia on day 1 in ICU	13 (11.2)	17 (11.6)	0.952
Pneumonia on day 1 in ICU	2 (1.7)	35 (24.0)	<0.001
Seizures on day 1 in ICU	7 (6.03)	22 (15.1)	0.021
Seizures during entire ICU stay	7 (6.03)	22 (15.1)	0.021
Hypocoagulation during entire ICU stay	3 (2.6)	64 (43.8)	<0.001
Coagulopathy during entire ICU stay	12 (10.3)	78 (53.4)	<0.001
Thrombocytopenia during entire ICU stay	4 (3.4)	20 (13.7)	0.004
Shock during entire ICU stay	6 (5.2)	28 (19.2)	<0.001
Anemia during entire ICU stay	5 (4.3)	21 (14.4)	0.006
Acute liver failure during entire ICU stay	11 (9.5)	43 (29.5)	0.005
Acute kidney injury during entire ICU stay	6 (5.2)	20 (13.7)	0.022
PEMOD score, points	3 [2–3]	5 [4–7]	0.001
PELOD score, points	1 [1–1]	11 [2–21]	0.001
MOD score by Marshall criteria, points	0 [0–0]	2 [1–3]	0.001
pSOFA score, points	3 [3–4]	6 [4–7]	0.001
GCS score, points	8.5 [7–10]	6 [5–9]	0.001
Glasgow-Pittsburgh score, points	28 [25.5–29]	20 [15–26]	0.001
FOUR score, points	12 [11–12]	7 [4–11]	0.001
Laboratory parameters			
Leukocytes, $\times 10^9$/L	11.45 [9.10–14.95]	14.55 [10–21]	0.001
Glucose, mmol/L	6.3 [5.5–7.5]	7.2 [6.0–10.7]	0.001
Urea, mmol/L	4.1 [3.4–5.0]	4.9 [3.7–5.9]	0.001
Creatinine, μmol/L	70 [47–82]	80 [61–113]	<0.001
Alanine aminotransferase (ALT), U/L	15 [13–18]	16 [12–29]	0.042
Aspartate aminotransferase (AST), U/L	29 [23–34]	37 [27–54.5]	<0.001
Creatine phosphokinase (CPK), U/L	173.5 [113–276]	204.5 [124–408]	0.044
Acid-base balance parameters			
pH	7.33 [7.30–7.36]	7.26 [7.19–7.33]	<0.001
Base deficit, mmol/L	–3.4 [–5.0–(–1.5)]	–4.6 [–8.0–(–2.0)]	<0.001
Lactate, mmol/L	2.2 [1.6–3.3]	3.0 [1.9–5.0]	<0.001
SpO_2/FiO_2 ratio	471 [466–476]	250 [200–330]	<0.001
Coagulation parameters			
Prothrombin index, %	85 [78–93]	75.5 [60–83.5]	<0.001
INR	1.17 [1.08–1.23]	1.23 [1.17–1.36]	<0.001

Note. PELOD — Paediatric Logistic Organ Dysfunction; PEMOD — Pediatric Multiple Organ Dysfunction Score; pSOFA — Paediatric Sequential Organ Failure Assessment; INR — International Normalized Ratio; MOD — Multiple Organ Dysfunction; GCS — Glasgow Coma Scale; FOUR — Full Outline of UnResponsiveness Score.

Among patients with a favorable course, only 25% remained unconscious after thirteen hours of treatment, while over 50% of patients in the unfavorable group were still unconscious at that time. By twenty hours, 50% of patients in the unfavorable group had regained consciousness; however, even after forty-seven hours, 25% remained unconscious. In contrast, nearly all patients with a favorable course had regained consciousness by that time.

The unfavorable course of acute poisoning was associated with significantly higher scores on all multiple organ dysfunction scales, decompensated acidosis, marked base deficit, and hyperlactatemia. These patients also had a decreased SpO_2/FiO_2 ratio and an increased INR,

Table 3. Prognostic significance of clinical and laboratory parameters in assessing the likelihood of unfavorable course.

Parameter	Significance					
	Area under the curve (AUC)	*P*	*J*-Index	Optimal cutoff value	Sensitivity (%)	Specificity (%)
FiO_2	0.852	<0.001	0.71	>0.3	70.87	100
SpO_2/FiO_2	0.853	<0.001	0.69	<300	69.2	100
Oxygenation index	0.838	<0.001	0.54	>3	64.5	88.89
pH	0.742	<0.001	0.41	⩽7.26	53.2	87.8
PTI	0.721	<0.001	0.33	⩽69.5	35.0	98.1
pCO_2	0.714	<0.001	0.35	>52	42.96	92.17
INR	0.697	<0.001	0.31	>1.17	74.1	57.3
AST	0.682	<0.001	0.32	>37	49.3	82.9
Creatinine	0.654	<0.001	0.26	>86	45.1	81.4
Glucose	0.643	<0.001	0.26	>7.6	47.6	78.3
Lactate	0.626	<0.001	0.24	>2.5	62.4	61.7
Albumin	0.578	0.043	0.13	⩽39.4	31.4	81.3
Potassium	0.584	0.018	0.19	>4.6	35.3	84.4
Leukocytes	0.625	<0.001	0.27	>15.2	48.6	78.5

Note. FiO_2 — Fraction of inspired oxygen; PTI — Prothrombin index; pCO_2 — Partial pressure of carbon dioxide in blood; INR — International normalized ratio; AST — Aspartate aminotransferase.

Table 4. Discriminatory power of multiple organ failure scoring systems in assessing the severity of multiple organ dysfunction in children with severe acute poisoning during the first 24 hours in the intensive care unit.

Scoring System	Significance					
	AUROC	*P*	*J*-Index	Optimal cutoff value	Sensitivity (%)	Specificity (%)
Marshall criteria	0.894	<0.001	0.69	>0	87.0	81.9
PELOD	0.831	<0.001	0.63	>1	83.6	79.3
PEMOD	0.849	<0.001	0.64	>3	77.4	87.1
pSOFA	0.837	<0.001	0.59	>4	65.1	93.9

Note. PELOD — Paediatric Logistic Organ Dysfunction; PEMOD — Pediatric Multiple Organ Dysfunction Score; pSOFA — Paediatric Sequential Organ Failure Assessment.

with all differences reaching statistical significance (Table 2).

The prognostic value of the clinical and laboratory parameters on admission to the ICU was assessed using ROC analysis (Table 3).

Among all oxygenation parameters, the SpO_2/FiO_2 ratio had the highest prognostic value. The severity of acid-base disturbances was more strongly associated with blood pH than with lactate level. Among the metabolic markers, aspartate aminotransferase, creatinine, and glucose showed the greatest discriminatory power, whereas albumin served only as an indirect indicator of overall disease severity.

The criteria proposed by J. Marshall (Table 4) showed the highest prognostic value for assessing the severity of multiple organ dysfunction in children with acute poisoning.

Toxic hepatitis or pancreatitis at the time of admission was associated with a 4.55-fold increase in the risk of an unfavorable course of acute poisoning [95% CI, 1.93–10.71], while acute kidney injury conferred a 5.29-fold increase in risk [95% CI, 1.52–18.45]. The need for mechanical ventilation markedly elevated the risk, with an odds ratio of 72.19 [95% CI, 31.0–168.1], and the presence of aspiration pneumonia was associated with a 14.14-fold increase in risk [95% CI, 3.32–60.1] (Table 5).

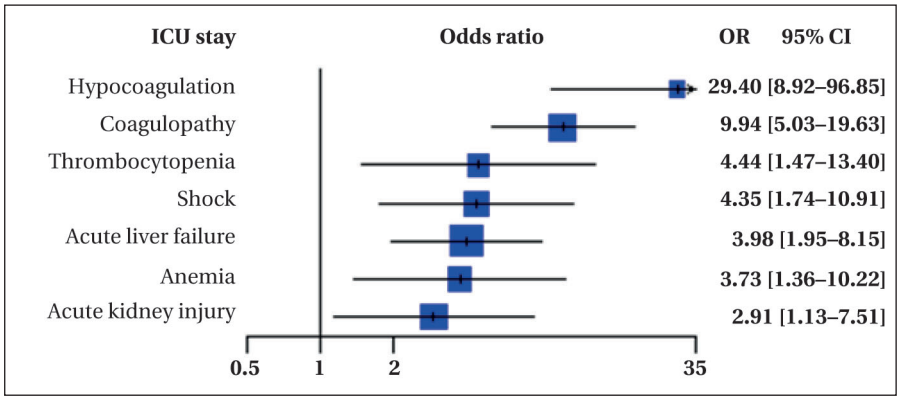

Fig. 2. Odds ratios for unfavorable poisoning course based on clinical and laboratory parameters throughout the ICU treatment period.

Shock (OR=4.35; 95% CI, 1.74–10.91), coagulopathy (OR=9.94; 95% CI, 5.03–19.63), and hypocoagulation (OR=29.4; 95% CI, 8.92–96.85) observed during treatment in the ICU were the most significant markers reflecting disease severity and increasing the likelihood of an unfavorable course (Fig. 2).

Based on the identified risk factors, a multivariate

Table 5. Odds ratios for unfavorable course in children with acute poisoning based on clinical and laboratory status on admission to the ICU.

Parameter	Odds Ratio (OR)	95% Confidence Interval (CI)
Mechanical ventilation	72.19	31.0–168.1
Pneumonia	14.14	3.32–60.1
Acute kidney injury	5.29	1.52–18.45
Toxic hepatitis / pancreatitis	4.55	1.93–10.71
INR >1.17	3.41	2.0–5.78
Leukocytes >15.2 × 10^9/L	3.36	1.95–5.8
Creatinine >86 µmol/L	3.34	1.91–5.82
Glucose >7.6 mmol/L	3.27	1.90–5.64
Potassium >4.6 mmol/L	3.18	1.75–5.76
Lactate >2.5 mmol/L	2.77	1.67–4.58
Seizures	2.73	1.14–6.72
Cardiac arrhythmias	1.04	0.49–2.25

logistic regression model was developed to predict an unfavorable course of acute poisoning in children, taking into account the patient's clinical and laboratory status (Table 6).

The coefficients for the variables pH and INR were reported as per 1 unit of measurement. Actually, these parameters vary within a range of 0.01 units, so the odds ratios calculated per whole unit yield extremely large or small values. In order to assess the true impact of these parameters on the risk of serious course, it was necessary to adjust them to plausible ranges (Table 7).

The presented model has the following characteristics: a cutoff of 0.481, a prognostic accuracy of 93.8% [95% CI, 90.9–96.7], a sensitivity of 94.2% [95% CI, 90.4–98.0], a specificity of 92.5% [95% CI, 87.7–97.3] and an AUROC of 0.981 (Fig. 3).

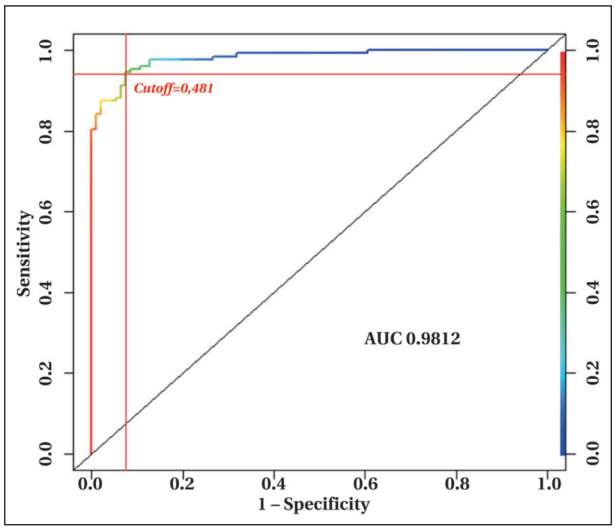

Fig. 3. ROC curve of the predictive model for unfavorable course in severe pediatric poisoning cases.

Table 7. Odds ratios for actual pH and INR ranges.

Parameter	pH (per 0.01 unit)	INR (per 0.01 unit)
Coefficient	–0.195	0.158
Standard Error	0.054	0.039
Z-score	–3.56	4.06
P value	<0.001	<0.001
Odds Ratio	0.82	1.17
95% CI (Lower)	0.74	1.09
95% CI (Upper)	0.92	1.27

Discussion

The most common complications of severe acute poisoning in children include coagulopathy, toxic damage to the liver and pancreas, and aspiration of gastric contents. However, a favorable outcome is observed in the majority of cases, with the duration of hospitalization not exceeding seven days. Fatal outcomes were observed in only two cases in the present study, which is consistent with global statistics.

The primary markers of severity on admission to the ICU, indicating a high likelihood of complications, were the need for invasive mechanical ventilation, aspiration pneumonia, and signs of acute liver and kidney injury.

When discussing risk factors for adverse outcomes in severe acute poisoning in children, it is important to emphasize that the most significant

Table 6. Data set analysis using multiple logistic regression.

Parameter	Coefficient	Standard error	*Z*-score	*P value*	Adjusted OR	95% CI lower	95% CI upper
Intercept	143.72	43.52	3.02	0.001	—	—	—
Need for mechanical ventilation	2.35	0.91	2.60	<0.001	10.49	1.76	62.40
Systolic blood pressure	–0.09	0.06	–1.52	0.129	0.91	0.81	1.03
Mean arterial pressure	0.18	0.08	2.10	0.036	1.20	1.02	1.40
Pneumonia	2.88	1.80	1.61	0.106	17.81	0.53	594.90
Seizures	2.02	1.00	2.01	0.044	7.54	1.06	53.52
Hemoglobin	–0.06	0.03	–1.85	0.047	0.94	0.89	1.00
RBC	1.77	0.99	1.80	0.071	5.87	0.84	40.87
WBC	–0.11	0.06	–2.08	0.037	0.90	0.80	1.01
Catecholamine index	–0.14	0.08	–1.68	0.094	0.87	0.74	1.02
Glucose	0.29	0.14	2.01	0.045	1.34	1.02	1.76
pH	–19.58	5.49	–3.56	<0.001	—	—	—
SpO_2/FiO_2 ratio	–0.027	0.005	–5.38	<0.001	0.97	0.96	0.98
INR	15.88	3.91	4.06	<0.001	—	3701.15	—

Note. Odds ratio for unfavorable course = exp (143.72 + 2.35 × [Mechanical Ventilation Need] – 0.09 × [Systolic BP] + 0.18 × [MAP] + 2.88 × [Pneumonia] + 2.02 × [Seizures] – 0.06 × [Hemoglobin] + 1.77 × [RBC] – 0.11 × [WBC] – 0.14 × [Catecholamine Index] + 0.29 × [Glucose] – 19.58 × [pH] – 0.027 × [SpO_2/FiO_2] + 15.88 × [INR]).

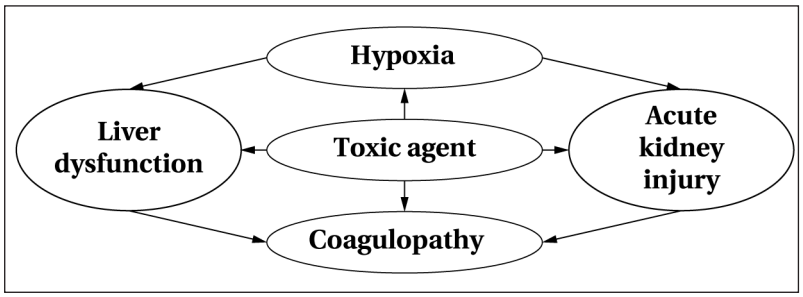

Fig. 4. The deadly quartet in acute pediatric poisoning (original illustration by the authors).

factors include hypocoagulation, shock, acute liver dysfunction or failure, and acute kidney injury — especially when these complications occur within the first 24 hours of treatment. These findings are consistent with data reported by other investigators [10, 24–27].

In a study of adults, S. T. Chang et al. found that acute kidney injury occurred in 66% of methanol poisoning cases and increased the risk of in-hospital mortality by approximately 20-fold [25].

Y. Atighi et al. demonstrated that in children with acute methadone poisoning, predictors of complications and adverse outcomes include respiratory distress and severe depression of consciousness [26].

The most common causes of fatal outcomes in acute pediatric poisoning are mixed-origin hypoxia, acute liver injury, and renal damage. These conditions lead to hemostatic dysfunction and coagulopathy, which exacerbate each other and form a «deadly quartet» (Fig. 4) — a concept analogous to the lethal triad observed in polytrauma.

In conclusion, maximizing early, targeted, pathogenesis-based therapy to address these pathologic syndromes can significantly improve outcomes, reduce complication rates, and minimize deaths in pediatric acute poisoning [1, 24, 28–30].

Conclusion

Impaired consciousness, severe hypoxemia, coagulopathy, acute liver failure, and renal injury are the primary markers of severity in acute pediatric poisoning.

Risk factors for adverse course include SpO_2/FiO_2 ratio <300 (sensitivity 69.2%, specificity 100%), oxygenation index > 3 (sensitivity 69.2%, specificity 100%), INR > 1.17 (sensitivity 74.1%, specificity 57.3%), lactate level > 2.5 mmol/L (sensitivity 62.4%, specificity 61.7%).

A mathematical model for predicting adverse outcomes in acute pediatric poisoning that incorporates 13 key homeostasis parameters (such as need for mechanical ventilation, catecholamine index, SpO_2/FiO_2, pH, international normalized ratio) demonstrates high predictive power (AUROC=0.981; sensitivity 94.2%, specificity 92.5%) and accuracy (93.8%).

References

1. *Александрович Ю. С., Пшениснов К. В., Гордеев В. И.* Интенсивная терапия критических состояний у детей. СПб.: Н-Л; 2014: 976. *Alexandrovich Yu. S., Pshenisnov K. V., Gordeev V. I.* Intensive care of critical conditions in children. SPb.: N-L; 2014: 976. (in Russ.). ISBN 978-5-94864-164-0.
2. *Пшениснов К. В., Александрович Ю. С.* Эпидемиология критических состояний у детей мегаполиса. *Анестезиология и реаниматология*. 2017; 62 (6): 463–467. *Pshenisnov K. V., Alexandrovich Yu. S.* Megapolis epidemiology of critical conditions in children. *Russ J Anesthesiol Reanimatol = Anesteziologiya i Reanimatologiya*. 2017; 62 (6): 463–467. (in Russ.). DOI: 10.18821/0201-7563-2017-62-6-463-467.
3. *Land M. E., Wetzel M., Geller R. J., Kamat P. P., Grunwell J. R.* Analysis of 207,543 children with acute opioid poisonings from the United States National Poison Data System. *Clin Toxicol (Phila)*. 2020; 58 (8): 829–836. DOI: 10.1080/15563650.2019.1691731. PMID: 31856616.
4. *Torrents R., Picot C., Glaizal M., Courne M.-A., Schmitt C., Richard N., Simon N., et al.* Child poisonings with methadone in France: a 6-year prospective national survey since the availability of capsules in 2008. *Clin Toxicol (Phila)*. 2015; 53 (8): 819–22. PMID: 26243461.
5. *Farah R., Cole R. J., Holstege C. P.* Increasing severity of medical outcomes and associated substances in cases reported to United States poison centers. *Clin Toxicol (Phila)*. 2024; 62 (4): 248–255. DOI: 10.1080/15563650.2024.2337897. PMID: 38634480.
6. *Gholami N., McDonald R., Farnaghi F., Yazdi M. H., Zamani N., Hassanian-Moghaddam H.* Fatal outcome in acutely poisoned children with hospitalization: a 10-year retrospective study from Tehran, Iran. *Pediatr Emerg Care*. 2022; 38 (2): e659–e663. DOI: 10.1097/PEC.0000000000002429. PMID: 33848098.
7. *Corlade-Andrei M., Nedelea P. L., Ionescu T. D., Rosu T. S., Hauta A., Grigorasi G. R., Blaga T., et al.* Pediatric emergency department management in acute poisoning-a 2-year retrospective study. *J Pers Med*. 2023; 13 (1): 106. DOI: 10.3390/jpm13010106. PMID: 36675767.
8. *Hemmati M., Tohidi M. R., Mohammadi A., Jahanpour F., Andayeshgar B., Fallah S.* Poisoning in children and adolescents in Kermanshah city, Iran. *BMC Pediatr*. 2024; 24 (1): 135. DOI: 10.1186/s12887-024-04631-3. PMID: 38383350.
9. World Drug Report 2023. Электронный ресурс. https://www.unodc.org/res/WDR- 023/WDR23_Exsum_ fin_DP.pdf. accessed 26 April 2024.
10. *Berg S. E., McCann S. D.* Pediatric toxicology: an updated review. *Pediatr Ann*. 2023; 52 (4): e139-e145. DOI: 10.3928/19382359-20230208-05. PMID: 37036778.
11. *Aleksandrovich Yu. S., Pshenisnov K. V., Kaziakhmedov V. A., Lodyagin A. N., Udaltcov M. A., Kozubov M. Y., Storozhuk O. D.* Acetaminophen poisoning: a cause of acute liver failure in pediatrics (clinical case). *J Emerg Med Trauma Surg Care*. 2020; 7: 039. DOI: 10.24966/ETS-8798/100039.
12. American Academy of Pediatrics: 10 ways to prevent poisoning in young children. Электронный ресурс. https://www.aap.org/en/news-room/news-releases/ health-safety-tips/american-academy-of-pediatrics-offers-tips-on-poison-prevention-in-your-home/. Accessed 26 April 2024.
13. *Li H., Dodd-Butera T., Beaman M. L., Pritty M. B., Heitritter T. E., Clark R. F.* Trends in childhood poison exposures and fatalities: a retrospective secondary data analysis of the 2009-2019 U.S. national poison data system annual reports. *Pediatr Rep*. 2021; 13 (4): 613–623. DOI: 10.3390/pediatric13040073. PMID: 34842797.
14. *Froberg B. A., Morton S. J., Mowry J. B., Rusyniak D. E.* Temporal and geospatial trends of adolescent intentional overdoses with suspected suicidal intent reported to a state poison control center. *Clin Toxicol (Phila)*. 2019; 57 (9): 798–805. DOI: 10.1080/15563650.2018.1554186. PMID: 30696297.
15. *Горьковая И. А., Рождественский В. И., Титова В. В.* Суицидальный риск у подростков с девиантным поведением с разным уровнем жизнестойкости. *Педиатр*. 2024; 15 (1): 101–108. *Gorkova I. A., Rozhdestvensky V. I., Titova V. V.* Suicidal risk in adolescents with deviant behavior with different levels of resilience. *Pediatrician = Pediatr*. 2024; 15 (1): 101–108. (in Russ.). DOI: 10.17816/PED151101-108.
16. *Junuzovic M., Lind K. M. T., Jakobsson U.* Child suicides in Sweden, 2000-2018. *Eur J Pediatr*. 2022; 181 (2): 599–607. DOI: 10.1007/s00431-021-04240-7. PMID: 34476611.
17. *Lee J., Fan N.-C., Yao T. C., Hsia S.-H., Lee E.-P., Huang J.-L., Wu H.-P.* Clinical spectrum of acute poisoning in children admitted to the pediatric emergency department. *Pediatr Neonatol*. 2019; 60 (1): 59–67.

DOI: 10.1016/j.pedneo.2018.04.001.
PMID: 29748113.

18. *Park J. M.* Clinical features of children with drug poisoning in a single emergency department in Goyang, Korea. *Pediatric Emergency Medicine Journal*. 2023; 10 (1): 23–30.
DOI: 10.22470/pemj.2022.00619.
19. *Khan M., Solomon F., Izu A., Bengura P., Okudo G., Maroane B., Lala N., et al.* The burden of poisoning in children hospitalised at a tertiary-level hospital in South Africa. *Front Public Health*. 2023; 11: 1279036.
DOI: 10.3389/fpubh.2023.1279036.
PMID: 37927861.
20. *Alghadeer S., Alrohaimi M., Althiban A., Kalagi N. A., Balkhi B., Khan A. A.* The patterns of children poisoning cases in community teaching hospital in Riyadh, Saudi Arabia. *Saudi Pharm J*. 2018; 26 (1): 93–97.
DOI: 10.1016/j.jsps.2017.10.007.
PMID: 29379339.
21. *Gaudet L. A., Hogue K., Scott S. D., Hartling L., Elliott S. A.* Acute pediatric cannabis intoxication: a scoping review. *J Child Health Care*. 2024; 28 (1): 196–214.
DOI: 10.1177/13674935221099158.
PMID: 35532228.
22. *Conerney C., Steinmetz F., Wakefield J., Loveridge S.* Cannabis and children: risk mitigation strategies for edibles. *Front Psychiatry*. 2024; 15: 1285784.
DOI: 10.3389/fpsyt.2024.1285784.
PMID: 38380122.
23. *Myran D. T., Tanuseputro P., Auger N., Konikoff L., Talarico R., Finkelstein Y.* Pediatric hospitalizations for unintentional cannabis poisonings and all-cause poisonings associated with edible cannabis product legalization and sales in Canada. *JAMA Health Forum*. 2023; 4 (1): e225041.
DOI: 10.1001/jamahealthforum.2022.5041.
PMID: 36637814.
24. *Лужников Е. А., Суходолова Г. Н., Коваленко Л. А., Чугунова О. Л.* Токсикология в педиатрии. Руководство для врачей. М.: «ГЭОТАР-Медиа»; 2023: 336. *Luzhnikov E. A., Sukhodolova G. N., Kovalenko L. A., Chugunova O. L.* Toxicology in pediatrics. A manual for doctors. Moscow: GEOTAR-Media; 2023: 336. (in Russ.). ISBN 978-5-9704-6576-9, 978-5-9704-7510-2 t.
25. *Chang S.-T., Wang Y.-T., Hou Y.-C., Wang I.-K., Hong H.-H., Weng C.-H., Huang W.-H., et al.* Acute kidney injury and the risk of mortality in patients with methanol intoxication. *BMC Nephrol*. 2019; 20 (1): 205.
DOI: 10.1186/s12882-019-1404-0.
PMID: 31170938.
26. *Atighi Y., Eizadi-Mood N., Mansourian M., Zamani A., Saffaei A., Sabzghabaee A. M.* Predictive factors of treatment outcomes for hospital care in children with acute methadone poisoning. *J Res Pharm Pract*. 2018; 7 (4): 200–204.
DOI: 10.4103/jrpp.JRPP_16_141.
PMID: 30622988.
27. *Паршина Н. В., Данилова Л. А., Дехтярева Н. С.* Гиперлактатемия и лактат-ацидоз в практике педиатра. *Педиатр*. 2021; 12 (3): 51–61. *Parshina N. V., L. Danilova L. A., Dekhtyareva N. S.* Hyperlactatemia and lactate acidosis in the practice of pediatricians. *Pediatrician = Pediatr*. 2021; 12 (3): 51–61. (in Russ.).
DOI: 10.17816/PED12351-61.
28. *Маркова И. В., Афанасьев В. В., Цыбулькин Э. К.* Клиническая токсикология детей и подростков. в 2 томах. СПб.: Специальная references; 1999: 400. *Markova I. V., Afanasyev V. V., Tsybulkin E. K.* Clinical toxicology of children and adolescents. in 2 volumes. St. Petersburg: Special literature; 1999: 400. (in Russ.). ISBN 5-89720-006-8.
29. *Александрович Ю., Пшениснов К.* Инфузионные антигипоксанты при критических состояниях у детей. *Общая реаниматология*. 2014; 10 (3): 59–74. *Alexandrovich Yu., Pshenisnov K.* Infusion antihypoxants in children with critical conditions. *General Reanimatology = Obshchaya Reanimatologiya*. 2014; 10 (3): 59–74. (in Russ.&Eng.).
DOI: 10.15360/1813-9779-2014-3-59-74.
30. *Lavonas E. J., Akpunonu P. D., Arens A. M., Babu K. M., Cao D., Hoffman R. S., Hoyte C. O., et al.; American Heart Association.* 2023 American Heart Association focused update on the management of patients with cardiac arrest or life-threatening toxicity due to poisoning: an update to the American heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2023; 148 (16): e149-e184.
DOI: 10.1161/CIR.0000000000001161.
PMID: 37721023.

Received 11.01.2025
Accepted 28.02.2025
Accepted in press 24.03.2025

https://doi.org/10.15360/1813-9779-2025-2-2523

Nitric Oxide as a Nephroprotective Agent in Cardiac Surgery

Alexander M. Boyko*, Nikolai O. Kamenshchikov, Yuri K. Podoksenov, Maria L. Dyakova, Yulia S. Svirko, Anna M. Gusakova, Elena B. Kim, Dmitry S. Panfilov, Boris N. Kozlov

Research Institute for Cardiology, Tomsk National Research Medical Center, Russian Academy of Sciences, 111-A Kievskaya Str., 634012 Tomsk, Russia

For citation: *Alexander M. Boyko, Nikolai O. Kamenshchikov, Yuri K. Podoksenov, Maria L. Dyakova, Yulia S. Svirko, Anna M. Gusakova, Elena B. Kim, Dmitry S. Panfilov, Boris N. Kozlov.* Nitric Oxide as a Nephroprotective Agent in Cardiac Surgery. *Obshchaya Reanimatologiya = General Reanimatology.* 2025; 21 (2): 34–41. https://doi.org/10.15360/1813-9779-2025-2-2523 [In Russ. and Engl.]

***Correspondence to:** Alexander M. Boyko, boiko.cardio@yandex.ru

Summary

Aim. To evaluate the efficacy of perioperative nitric oxide (NO) administration in reducing the incidence of acute kidney injury (AKI) during hemiarch surgery for nonsyndromic ascending aortic aneurysms under cardiopulmonary bypass and hypothermic circulatory arrest (HCA).

Materials and Methods. A single-blind, prospective, randomized, controlled study included 80 patients older than 18 years who underwent hemiarch aortic surgery with HCA for nonsyndromic ascending aortic aneurysms between 2020 and 2023. Patients were randomized (1:1) into two groups: the NO group (who received perioperative NO at 80 ppm) and the control group (who received standard perioperative management without NO administration). The primary endpoint was the incidence of AKI according to KDIGO criteria. Secondary endpoints included biomarker levels of subclinical renal injury and clinical outcomes.

Results. Postoperatively, the incidence of AKI was 25% in the NO group compared to 50% in the control group (OR=0.26; 95% CI: 0.10–0.69; P=0.036). Patients in the NO group had significantly lower levels of urinary neutrophil gelatinase-associated lipocalin (uNGAL, P=0.03) and cystatin C (P<0.001) 4 hours after surgery. In addition, the length of stay in the intensive care unit (ICU) was significantly shorter in the NO group (P=0.03) compared to the control group.

Conclusion. Perioperative NO therapy at 80 ppm during hemiarch aortic surgery with HCA reduces the incidence of acute kidney injury, lowers the levels of kidney injury biomarkers (uNGAL and cystatin C), and shortens the ICU stay.

Keywords: nitric oxide; acute kidney injury; nephroprotection; aortic aneurysm; circulatory arrest

Conflict of interest. The authors declare no conflict of interest. Some results have been published in the Proceedings of the Congress of the Federation of Anesthesiologists and Reanimatologists and Russian Forum of Anesthesiologists and Reanimatologists (RFAR-2024), St. Petersburg. 2024: 25. https://cdn.congressfar.ru/140/material.pdf (In Russ.).

Funding. The study was conducted as part of the basic research project «Organ Protection with Nitric Oxide in Cardiovascular Surgery: Technological Support (Synthesis and Delivery Devices), Mechanisms of Protective Effects, and Impact on Clinical Outcomes» (No. 122123000017-3).

Information about the authors:
Alexander M. Boyko: http://orcid.org/0000-0002-2408-8874
Nikolai O. Kamenshchikov: http://orcid.org/0000-0003-4289-4439
Yuri K. Podoksenov: http://orcid.org/0000-0002-8939-2340
Maria L. Dyakova: http://orcid.org/0000-0001-9353-7234
Yulia S. Svirko: http://orcid.org/0000-0002-2258-3564
Anna M. Gusakova: http://orcid.org/0000-0002-3147-3025
Elena B. Kim: http://orcid.org/0009-0001-5610-3506
Dmitry S. Panfilov: http://orcid.org/0000-0003-2201-350X
Boris N. Kozlov: http://orcid.org/0000-0002-0217-7737

Introduction

The rising prevalence of ascending aortic disease over the past decade has inevitably led to an increase in the number of surgical procedures. According to the literature, there are 9–16 cases of thoracic aortic aneurysm per 100,000 population per year [1–3], with the ascending aorta accounting for 60% of these aneurysms [4, 5]. The preferred treatment for thoracic aortic aneurysms is surgical repair with cardiopulmonary bypass (CPB) and hypothermic circulatory arrest (HCA) [6]. However, this approach has been associated with serious complications such as persistent neurological deficits, myocardial infarction, respiratory failure, and acute kidney injury (AKI) [7]. AKI associated with ascending aortic reconstructive surgery is a common complication with an incidence of up to 77.6% [8–12], and it has a negative impact on both short-term surgical outcomes and long-term prognosis [13]. The development of nephroprotective strategies as part of the preoperative management of thoracic aortic aneurysm surgery remains a pressing issue.

Nitric oxide (NO) is a pleiotropic molecule that plays an important role in protecting the kidney from ischemia-reperfusion injury. The use of NO to slow the progression of AKI appears to be a promising strategy [14]. However, current data on the potential use of NO for renoprotection in patients undergoing ascending aortic surgery with HCA are limited [15].

The aim of this study was to test the hypothesis that the administration of exogenous nitric oxide during hemiarch aortic surgery under hypothermic circulatory arrest can protect the kidneys.

Materials and Methods

To investigate the nephroprotective properties of nitric oxide (NO), we conducted a single-center, prospective, randomized, controlled trial (approved by the Ethics Committee of the Research Institute of Cardiology, Tomsk National Research Medical Center, Protocol No. 260, February 2, 2024).

The study was conducted in the laboratory of intensive care medicine. A total of 80 patients who underwent surgery in the Department of Cardiovascular Surgery of the Research Institute of Cardiology, a branch of Tomsk National Research Medical Center of the Russian Academy of Sciences (Research Institute of Cardiology, Tomsk NRMC) in 2020–2023 were included in the study.

The inclusion criteria were

- age ⩾18 years
- presence of nonsyndromic ascending aortic aneurysms
- elective aortic hemiarch repair under circulatory arrest and moderate hypothermia (30–32°C)
- signed informed consent to participate in the study.

Patients were excluded from the study if they met any of the following criteria:

- Chronic kidney disease (glomerular filtration rate [GFR] < 60 mL/min/1.73 m²)
- Need for emergency surgery
- Critical preoperative condition (preoperative need for mechanical ventilation, inotropic or vasopressor support, or mechanical circulatory support)
- Need for repeat cardiac surgery or extended surgical procedures (aortic root reconstruction, thoracic aortic replacement using the «frozen elephant trunk» technique)
- Absolute contraindications to NO therapy (congenital or acquired methemoglobinemia)
- Relative contraindications to NO therapy (coagulation disorder, intracranial hemorrhage, severe left ventricular failure classified as NYHA III–IV)
- Acute massive perioperative hemorrhage.

All patients were randomly assigned in a 1:1 ratio to two groups: the main group (NO group, in which perioperative administration of NO at a concentration of 80 ppm was administered, *N*=40) and the comparison group (standard perioperative care group, in which NO was not administered, *N*=40). Randomization was performed using sealed opaque envelopes. The envelopes were prepared before patient enrollment began, and their number corresponded to the calculated sample size. Each envelope contained a single code word: «NO» or «Control». On the morning of surgery, one envelope was randomly selected and opened by the anesthesiologist, and the contents of the envelope were not disclosed. The selection of patients for the study is shown in Fig. 1.

The administration of nephrotoxic drugs (contrast media, amphotericin, and/or aminoglycosides) within 48 hours before surgery was excluded.

Anesthetic support was performed according to the standardized protocol adopted at the clinic. Premedication, administered to all patients on arrival in the operating room, included opioid analgesics, antihistamines, and benzodiazepines. Induction of anesthesia was performed with propofol (1.5–3.0 mg/kg) and fentanyl (3.0–5.0 mcg/kg). Neuromuscular blockade was achieved with vecuronium bromide at a dose of 0.1 mg/kg. Anesthesia was maintained with sevoflurane (1.9–3.1 vol%), and propofol (3.0–5.0 mg/kg/h) and fentanyl (3–5 mcg/kg/h) were used during mechanical perfusion.

Mechanical ventilation (MV) was performed with the Primus ventilator (Dräger, Germany) in controlled mandatory ventilation (CMV) mode with

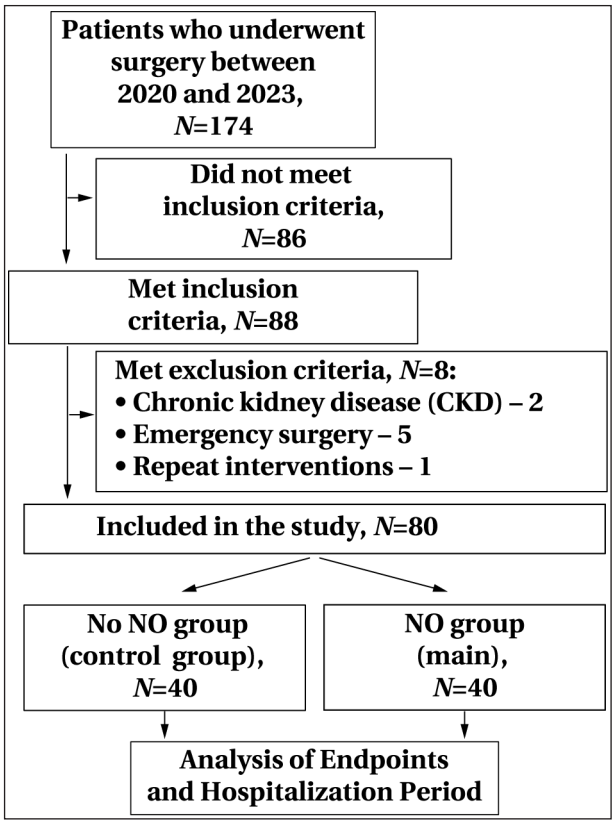

Fig. 1. Flowchart of patient selection for the study.

volume control, with a tidal volume of 6–7 mL/kg, a respiratory rate of 12–14 breaths per minute, a FiO_2 of 0.35 (increased as needed), and a positive end-expiratory pressure (PEEP) of 5 cm H_2O.

To monitor vital parameters, standard controls were performed: continuous ECG analysis, invasive monitoring of arterial and central venous pressure, pulse oximetry, nasopharyngeal and rectal temperature measurements using the Infinity Delta XL monitor (Dräger, Germany). Invasive arterial pressure measurements and blood samples for laboratory gas composition analysis were obtained by catheterization of both radial (or brachial) arteries (using a 20G arterial cannula, B Braun, Germany). For central venous pressure (CVP) monitoring, inotropic and infusion-transfusion therapy, the superior vena cava was catheterized via the right internal jugular vein with a 12F central venous catheter (Certofix; B Braun, Germany). The depth of sedation during general anesthesia was controlled by BIS monitoring, maintaining the index between 60 and 40. Cerebral oximetry (rSO_2, %) was monitored using near-infrared spectroscopy on an Invos 5100 device (Somanetics Corp.).

Cardiopulmonary bypass (CPB) was performed in non-pulsatile mode using a Stockert machine (Stockert Ins., Germany) with Skipper disposable membrane oxygenators (Eurosets, Italy). Perfusion index was maintained at 2.5 L/min/m². Hypocoagulation was achieved just before the start of CPB with a dose of heparin (3 mg/kg), controlled by the activated clotting time (target value >450 seconds). CPB was started in the following order: «brachiocephalic trunk — right atrium», after which the patient was «cooled» and an aortic clamp was applied. Selective pharmacological crystalloid cardioplegia was performed with the «Custodiol» solution (GmbH, Germany). The cardioplegia solution was infused for 6–8 minutes (according to the manufacturer's recommendations). The target body temperature in the rectal probe was maintained at 30–32°C. Once this temperature was reached, aortic occlusion distal to the left subclavian artery was performed, followed by induction of hypothermic circulatory arrest (HCA) with unilateral brain perfusion (perfusion flow rate 10 mL/kg/min). A hemiarch thoracic aortic replacement was performed. After completion of the distal anastomosis, CPB was discontinued and warming was started with artificial and parallel circulation. When body temperature reached 37°C, patients were weaned from CPB.

To inactivate the effects of heparin, a 1:1 solution of protamine sulfate was administered. To inhibit fibrinolysis, tranexamic acid was administered in a bolus dose of 10 mg/kg, followed by an infusion of 1–2 mg/kg/h until the end of surgery.

In the study, a sample of the plasma-chemical synthesis system for nitric oxide «TIANOKS» (RFNC-VNIIEF, Sarov, Russia) was used. This system was used for inhalation delivery of NO in the concentration of 80 ppm, and the concentration of NO in the gas-air mixture supply line was monitored. After tracheal intubation and transition to mechanical ventilation, NO was delivered through a connector with a Luer adapter embedded in the breathing circuit. The gas-air mixture was then passed through an absorber containing calcium hydroxide to remove nitrogen dioxide (NO_2). A gas sampling line to monitor the NO/NO_2 concentration in the inhaled mixture was placed as close to the patient as possible in the inspiratory limb of the circuit. In addition to inhaled NO delivery, NO was also delivered to the extracorporeal circuit at a concentration of 80 ppm after CPB was initiated and the calculated perfusion flow rate was achieved. Two ¼-inch Luer adapter connectors were inserted into the main gas-air supply line: NO was delivered through the proximal connector, and gas was sampled to monitor the fractional concentration of NO/NO_2 through the distal connector. The connector of the NO delivery line with a bacterial filter was placed as close as possible to the oxygenator of the CPB machine. During the period of hypothermic circulatory arrest, NO delivery was stopped (Fig. 2).

After the CPB machine was turned off, NO delivery continued at the same dose through the modified breathing circuit for 6 hours after surgery.

The primary endpoint of the study was the incidence of acute kidney injury (KDIGO criteria). Secondary endpoints were: duration of mechanical ventilation, cases of acute cerebrovascular event (ACVE) during the inpatient treatment phase, length of stay in the ICU, length of hospital stay, and urinary biochemical markers of acute kidney injury (uNGAL, cystatin C).

Intraoperative parameters such as duration of CPB, surgical procedure, and time of cardiac and circulatory arrest were monitored and recorded.

Acute kidney injury (AKI) was diagnosed according to the KDIGO criteria [16]: an increase in serum creatinine (SCr) ⩾0.3 mg/dL (⩾26.5 μmol/L) within 48 hours, or an increase in SCr ⩾1.5 times the baseline value (if known or assumed to have occurred within the previous 7 days), or a urine output rate <0.5 mL/kg/h over 6 hours. SCr levels were monitored for 7 days after surgery.

Levels of uNGAL and cystatin C (markers of AKI) were determined in urine samples. Urine was collected after bladder catheterization and 4 hours after the end of surgery. The urine was then centrifuged at 1500±3 rpm for 10 minutes and frozen at –20°C. The concentrations of uNGAL and cystatin C were measured using an enzyme-linked immunosorbent assay (ELISA) method (Hycult Biotech, Uden, The Netherlands) on a Sunrise analyzer (Tecan, Mannedorf, Switzerland).

Statistical data analysis was performed using Statistica 10.0 software (StatSoft, Inc, USA). The Shapiro–Wilk test was used to assess the normality

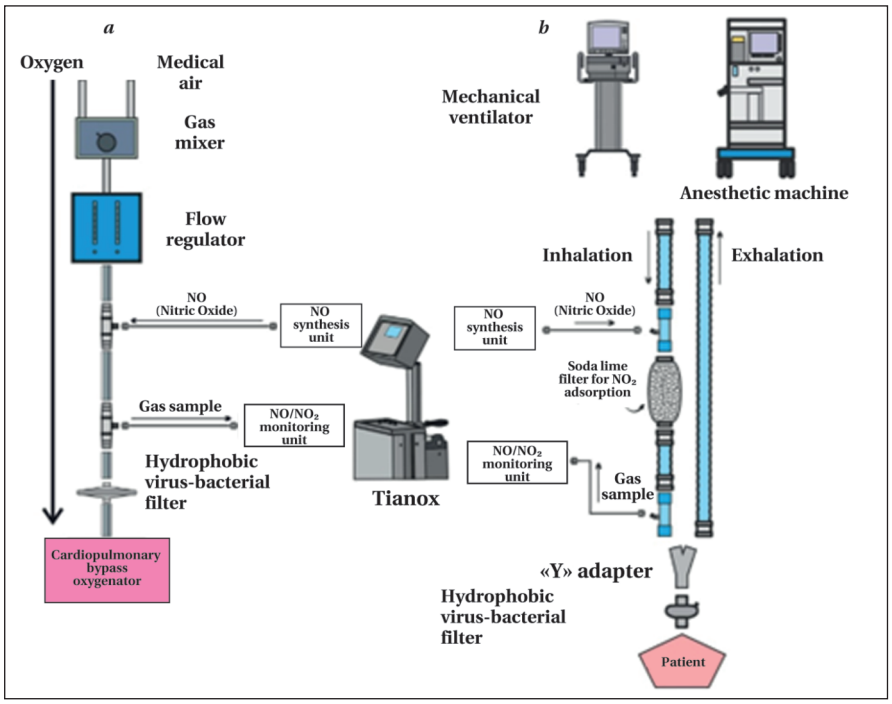

Fig. 2. Scheme of nitric oxide delivery.
Note. *a* — NO delivery to the cardiopulmonary bypass machine oxygenator; *b* — NO delivery to the mechanical ventilation system.

of the distribution of the variables. For non-normal distributions, quantitative data were expressed as median and 25th and 75th percentiles (*Me* [25; 75]), and categorical data were expressed as *N* (%). Quantitative parameters were analyzed using the Mann–Whitney *U* test for two independent samples. Fisher's exact test or χ^2 test was used to compare nominal variables in independent groups. Differences were considered statistically significant at $P<0.05$, with a two-tailed *P* value. Sample size calculation was based on a preliminary pilot study of 16 patients (8 patients in each group). The incidence of AKI was 20% in the NO group and 50% in the control group without NO administration. The required sample size for each group with alpha = 0.05, power = 0.8, and the observed proportions was 39 patients.

Results and Discussion

The groups were comparable with respect to the main clinical characteristics. Patient characteristics are shown in Table 1.

An analysis of intraoperative data and early postoperative period was performed in the study groups. The groups were comparable in terms of duration of cardiopulmonary bypass, surgery, and cardiac and circulatory arrest (Table 2).

The incidence of AKI was 25% in the NO group and 50% in the group without NO administration (RR=0.5; AR=0.25; 95% CI: 0.10–0.69; *P*=0.036) [17].

Table 1. Clinical and demographic characteristics of patients, *Me* [25; 75] or *N* (%).

Parameter	Values in groups		*P value*
	without NO (*N*=40)	NO (*N*=40)	
Age, years	67 [58; 72]	61 [52; 67]	0.06
Men	28 (70)	24 (60)	0.35
BMI, kg/m²	28.4 [26.0; 32.1]	29.0 [24.7; 31.1]	0.54
LVEF, %	64 [61; 68]	63 [58; 68]	0.56
CHD	22 (55)	16 (40)	0.18
Previous MI	4 (10)	2 (5)	0.67
Hypertension	36 (90)	30 (75)	0.14
Diabetes mellitus	3 (7.5)	7 (17.5)	0.18
Creatinine, μmol/L	87.0 [77.5; 95.5]	86.0 [74.0; 98.0]	0.76
GFR, mL/min/1.73 m²	81.0 [63.5; 92.5]	77.0 [64.0; 89.5]	0.91
Ascending aorta diameter, mm	50.0 [48.0; 54.5]	50.0 [48.5; 52.0]	1

Note. BMI — body mass index; LVEF — left ventricular ejection fraction; CHD — coronary heart disease; MI — myocardial infarction; GFR — glomerular filtration rate.

Table 2. Perioperative period characteristics, *Me* [25; 75] or *N* (%).

Parameter	Values in groups		*P value*
	without NO (*N*=40)	NO (*N*=40)	
Duration of circulatory arrest, min	18 [17; 20]	18 [16; 21]	0.74
Duration of cardiac arrest, min	101 [81; 135]	99.5 [82; 135]	0.59
CPB, min	140 [115; 166]	125 [105; 162]	0.20
Duration of surgery, min	360 [310; 370]	320 [285; 380]	0.15
ACVE	0	1 (2.5)	0.32
Myocardial infarction	1 (2.5)	0	0.32
Duration of lung ventilation, hours	12 [7; 18]	11 [7; 15]	0.85
Length of stay in the ICU, days	2 [1; 5]	1 [1; 2]	0.03
Length of hospital stay, days	20 [15; 28]	19 [14; 22]	0.23

Note. CPB — cardiopulmonary bypass; ACVE — acute cerebrovascular event.

Table 3. Urinary biomarker concentrations of AKI markers, *Me* [25; 75].

Parameter, ng/mL	Values in groups		*P value*
	without NO (*N*=40)	NO (*N*=40)	
	uNGAL		
Baseline	1.02 [0.61; 1.34]	1.03 [0.76; 1.08]	0.76
4 hours post-op	3.52 [2.72; 6.42]	1.85 [1.66; 3.82]	0.03
	Cystatin C		
Baseline	1.66 [1.17; 3.90]	1.54 [0.58; 3.77]	0.84
4 hours post-op	100.79 [80.06; 117.23]	45.02 [34.04; 73.41]	<0.001

Note. uNGAL — neutrophil gelatinase-associated lipocalin.

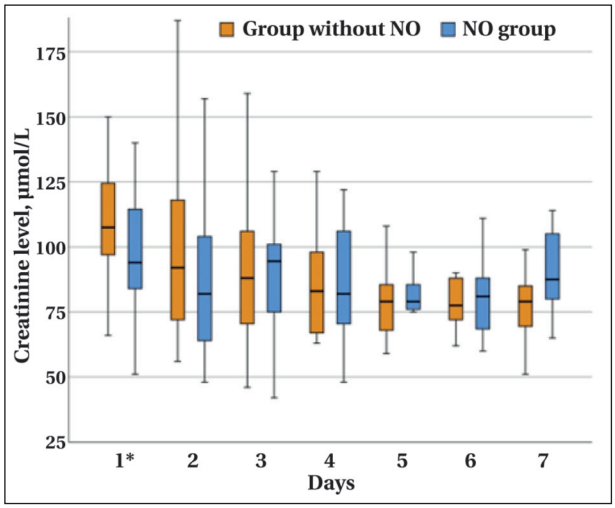

Fig. 3. Changes in serum creatinine level, *Me* [25; 75].
Note. * *P*=0.02.

The changes in creatinine concentration are shown in Fig. 3.

In the NO group, lower levels of uNGAL and cystatin C were observed 4 hours after surgery compared to the group without NO administration (*P*=0.03 and *P*<0.001, respectively) (Table 3).

No significant differences were found between the groups in the incidence of stroke, myocardial infarction, duration of mechanical ventilation, or length of hospital stay (Table 2). However, the NO group showed a reduction in ICU length of stay (*P*=0.03) (Table 2).

Throughout the study, NO_2 levels did not exceed the clinically acceptable threshold of 3 ppm.

A statistically significant reduction in the incidence of AKI according to KDIGO criteria was observed with perioperative NO administration. Previous clinical studies have shown that patients undergoing cardiac surgery experience impaired endogenous NO homeostasis and a hemolysis-associated NO-deficient state [18, 19]. Restoring NO levels and increasing its bioavailability is a promising nephroprotective strategy, as supported by several experimental studies [20–24]. According to a meta-analysis by J. Wang et al. [19], NO administration reduces the postoperative risk of AKI in cardiac surgery patients by 20%. Our results are consistent with the existing literature [25, 26].

Four hours after surgery, urinary uNGAL levels were lower in the NO group compared to patients who did not receive NO (*P*=0.03), indicating less pronounced renal injury. uNGAL is considered one of the most extensively studied biomarkers of AKI associated with cardiac surgery and is often referred to as a «troponin-like» biomarker in the laboratory diagnosis of AKI.

De Geus et al. [27] developed the CSA-NGAL score, a renal tubular injury scale based on NGAL levels in urine or plasma. In a study by E. A. Mostafa et al. [28], a positive correlation was observed between the severity of renal injury according to the CSA-NGAL score (cardiac surgery-associated neutrophil gelatinase-associated lipocalin scale) and AKI severity according to KDIGO criteria.

A meta-analysis by M. Haase et al. [29] confirmed NGAL as a sensitive and specific biomarker for AKI, a finding further supported by the meta-analysis by F. Zhou et al. [30]. In addition, a study by O. Dymova et al. [31] in patients undergoing thoracic aortic surgery with cardiopulmonary bypass highlighted the high prognostic value of NGAL in assessing AKI risk just hours after surgery.

Research suggests that urinary NGAL changes not only serve as an effective early diagnostic marker of AKI, even before the loss of excretory renal function, but also help to assess treatment efficacy and disease severity [31]. Thus, the data suggest that urinary NGAL measurement can be used for early diagnosis of AKI in the immediate postoperative period.

In our study, urinary cystatin C levels were also lower in the NO group four hours after surgery (p < 0.001), further confirming less pronounced renal injury with perioperative NO administration. Cystatin C is considered a promising biomarker for AKI, as its levels reflect changes in GFR and can be effectively used to predict AKI, especially in combination with NGAL [32–34].

According to a meta-analysis, cystatin C had the highest AUC value for predicting AKI and showed greater specificity compared to other biomarkers studied [35].

Perioperative NO administration has a nephroprotective effect in hemiarch aortic surgery performed under hypothermic circulatory arrest, as evidenced by the observed reduction in urinary uNGAL and cystatin C levels, indicating a lower in-

cidence of clinically manifest AKI and milder subclinical AKI.

These findings are of practical importance; however, further studies with larger patient cohorts are recommended to determine the optimal NO concentration and duration of administration to reduce the incidence of AKI in hemiarch aortic surgery under hypothermic circulatory arrest.

Study Limitations. This was a single-center study with a relatively small cohort of patients and no assessment of long-term outcomes. Local protocols for anesthesia management, CPB, CA, and surgical techniques and postoperative care may have influenced the results. In addition, the study protocol was not registered.

Conclusion

Perioperative administration of NO at a concentration of 80 ppm during hemiarch aortic replacement under hypothermic circulatory arrest has a nephroprotective effect. This is supported by a reduced incidence of acute kidney injury, changes in urinary biomarkers of subclinical kidney injury (uNGAL and cystatin C), and a shorter stay in the intensive care unit.

References

1. *Clouse W. D., Hallett J. W. Jr, Schaff H. V., Gayari M. M., Ilstrup D. M., Melton L. J.* 3rd. Improved prognosis of thoracic aortic aneurysms: a population-based study. *JAMA.* 1998; 280 (22): 1926–1929. DOI: 10.1001/jama.280.22.1926. PMID: 9851478.
2. *Olsson C., Thelin S., Ståhle E., Ekbom A., Granath F.* Thoracic aortic aneurysm and dissection: increasing prevalence and improved outcomes reported in a nationwide population-based study of more than 14,000 cases from 1987 to 2002. *Circulation.* 2006; 114 (24): 2611–2618. DOI: 10.1161/CIRCULATIONAHA.106.630400. PMID: 17145990.
3. *Downey R. T., Aron R. A.* Thoracic and thoracoabdominal aneurysms: etiology, epidemiology, and natural history. *Anesthesiol Clin.* 2022; 40 (4): 671–683. DOI: 10.1016/j.anclin.2022.08.011. PMID: 36328622.
4. *Ortega-Loubon C., Tamayo E., Jorge-Monjas P.* Cardiac surgery-associated acute kidney injury: current updates and perspectives. *J Clin Med.* 2022; 11 (11): 3054. DOI: 10.3390/jcm11113054. PMID: 35683442.
5. *Isselbacher E. M.* Thoracic and abdominal aortic aneurysms. *Circulation.* 2005; 111 (6): 816–828. DOI: 10.1161/01.CIR.0000154569.08857.7A. PMID: 15710776.
6. *Zhou Z., Cecchi A. C., Prakash S. K., Milewicz D. M.* Risk factors for thoracic aortic dissection. *Genes (Basel).* 2022; 13 (10): 1814. DOI: 10.3390/genes13101814. PMID: 36292699.
7. *Козлов Б. Н., Панфилов Д. С., Базарбекова Б. А., Сондуев Э. Л., Бойко А. М.* Непосредственные результаты хирургического лечения аневризмы восходящей аорты в сочетании со стенотическим поражением аортального клапана. *Сибирский журнал клинической и экспериментальной медицины.* 2023; 38 (3): 135–142. *Kozlov B. N., Panfilov D. S., Bazarbekova B. A., Sonduev E. L., Boyko A. M.* The immediate results of surgical treatment of an ascending aortic aneurysm in conjuction with a stenotic lesion of the aortic valve. *Siberian Journal of Clinical and Experimental Medicine = Sibirskiy Zhurnal Eksperimentalnoy i Klinicheskoy Meditsiny.* 2023; 38 (3): 135–142. (in Rus.). DOI: 10.29001/2073-8552-2022-424.
8. *Gambardella I., Gaudino M., Lau C., Munjal M., Di Franco A., Ohmes L. B., Hameedi F., et al.* Contemporary results of hemiarch replacement. *Eur J Cardiothorac Surg.* 2017; 52 (2): 333–338. DOI: 10.1093/ejcts/ezx071. PMID: 28387791.
9. *Amano K., Takami Y., Ishikawa H., Ishida M., Tochii M., Akita K., Sakurai Y., et al.* Lower body ischaemic time is a risk factor for acute kidney injury after surgery for type A acute aortic dissection. *Interact Cardiovasc Thorac Surg.* 2020; 30 (1): 107–112. DOI: 10.1093/icvts/ivz220. PMID: 31501854.
10. *Wu H. B., Ma W. G., Zhao H. L., Zheng J., Li J. R., Liu O., Sun L. Z.* Risk factors for continuous renal replacement therapy after surgical repair of type A aortic dissection. *J Thorac Dis.* 2017; 9 (4): 1126–1132. DOI: 10.21037/jtd.2017.03.128. PMID: 28523169.
11. *Wang J., Yu W., Zhai G., Liu N., Sun L., Zhu J.* Independent risk factors for postoperative AKI and the impact of the AKI on 30-day postoperative outcomes in patients with type A acute aortic dissection: an updated meta-analysis and meta-regression. *J Thorac Dis.* 2018; 10 (5): 2590–2598. DOI: 10.21037/jtd.2018.05.47. PMID: 29997920.
12. *Ghincea C. V., Reece T. B., Eldeiry M., Roda G. F., Bronsert M. R., Jarrett M. J., Pal J. D., et al.* Predictors of acute kidney injury following aortic arch surgery. *J Surg Res.* 2019; 242: 40–46. DOI: 10.1016/j.jss.2019.03.055. PMID: 31063910.
13. *Arnaoutakis G. J., Vallabhajosyula P., Bavaria J. E., Sultan I., Siki M., Naidu S., Milewski R. K., et al.* The impact of deep versus moderate hypothermia on postoperative kidney function after elective aortic hemiarch repair. *Ann Thorac Surg.* 2016; 102 (4): 1313–1321. DOI: 10.1016/j.athoracsur.2016.04.007. PMID: 27318775.
14. *Kamenshchikov N. O., Duong N., Berra L.* Nitric oxide in cardiac surgery: a review article. *Biomedicines.* 2023; 11 (4): 1085. DOI: 10.3390/biomedicines11041085. PMID: 37189703.
15. *Kamenshchikov N. O., Anfinogenova Y. J., Kozlov B. N., Svirko Y. S., Pekarskiy S. E., Evtushenko V. V., Lugovsky V. A., et al.* Nitric oxide delivery during cardiopulmonary bypass reduces acute kidney injury: a randomized trial. *J Thorac Cardiovasc Surg.* 2022; 163 (4): 1393–1403.e9. DOI: 10.1016/j.jtcvs.2020.03.182. PMID: 32718702.
16. *Kellum J. A., Lameire N. KDIGO AKI Guideline Work Group.* Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care.* 2013; 17 (1): 204. DOI: 10.1186/cc11454. PMID: 23394211.
17. Сборник тезисов *Съезд Федерации анестезиологов и реаниматологов, Форум анестезиологов и реаниматологов России (ФАРР-2024)*, СПб: 2024: 25. *Collection of abstracts Congress of the Federation of anesthesiologists and reanimatologists, Forum of anesthesiologists and reanimatologists of Russia (FARR-2024)*, SPb: 2024: 25. https://cdn.congressfar.ru/140/material.pdf. (in Russ.).
18. *Arellano D. L.* Acute kidney injury following cardiothoracic surgery. *Crit Care Nurs Clin North Am.* 2019; 31 (3): 407–417. DOI: 10.1016/j.cnc.2019.05.008. PMID: 31351558.
19. *Wang J., Cong X., Miao M., Yang Y., Zhang J.* Inhaled nitric oxide and acute kidney injury risk: a meta-analysis of randomized controlled trials. *Ren Fail.* 2021; 43 (1): 281–290. DOI: 10.1080/0886022X.2021.1873805. PMID: 33494652.
20. *Minneci P. C., Deans K. J., Zhi H., Yuen P. S., Star R. A., Banks S. M., Schechter A. N., et al.* Hemolysis-associated endothelial dysfunction mediated by accelerated NO inactivation by decompartmentalized oxyhemoglobin. *J Clin Invest.* 2005; 115 (12): 3409–17. DOI: 10.1172/JCI25040. PMID: 16294219.
21. *Troncy E., Francoeur M., Salazkin I., Yang F., Charbonneau M., Leclerc G., Vinay P., Blaise G.* Extra-pul-

monary effects of inhaled nitric oxide in swine with and without phenylephrine. *Br J Anaesth*. 1997; 79 (5): 631–640.
DOI: 10.1093/bja/79.5.631. PMID: 9422904.

22. *Ross J. T., Robles A. J., Mazer M. B., Studer A. C., Remy K. E., Callcut R. A.* Cell-free hemoglobin in the pathophysiology of trauma: a scoping review. *Crit Care Explor*. 2024; 6 (2): e1052.
DOI: 10.1097/CCE.0000000000001052.
PMID: 38352942.
23. *Kamenshchikov N. O., Diakova M. L., Podoksenov Y. K., Churilina E. A., Rebrova T. Y., Akhmedov S. D., Maslov L. N., et al.* Potential mechanisms for organoprotective effects of exogenous nitric oxide in an experimental study. *Biomedicines*. 2024; 12 (4): 719.
DOI: 10.3390/biomedicines12040719.
PMID: 38672075.
24. *Те М. А., Каменщиков Н. О., Подоксенов Ю. К., Мухомедзянов А. В., Маслов Л. Н., Козлов Б. Н.* Влияние донации оксида азота на выраженность митохондриальной дисфункции почечной ткани при моделировании искусственного кровообращения: экспериментальное исследование. *Вестник интенсивной терапии им. А. И. Салтанова*. 2023; 4: 176–184. *Te M. A., Kamenshchikov N. O., Podoksenov Yu. K., Mukhomedzyanov A. V., Maslov L. N., Kozlov B. N.* The effect of nitric oxide donation on the severity of mitochondrial dysfunction to the renal tissue in cardiopulmonary bypass simulation: an experimental study. *Ann Crit Care = Vestnik Intensivnoy Terapii im AI Saltanova*. 2023; 4: 176–184. (in Russ.).
DOI: 10.21320/1818-474X-2023-4-176-184.
25. *Hu J., Spina S., Zadek F., Kamenshchikov N. O., Bittner E. A., Pedemonte J., Berra L.* Effect of nitric oxide on postoperative acute kidney injury in patients who underwent cardiopulmonary bypass: a systematic review and meta-analysis with trial sequential analysis. *Ann Intensive Care*. 2019; 9 (1): 129.
DOI: 10.1186/s13613-019-0605-9. PMID: 31754841.
26. *Yan Y., Kamenshchikov N., Zheng Z., Lei C.* Inhaled nitric oxide and postoperative outcomes in cardiac surgery with cardiopulmonary bypass: a systematic review and meta-analysis. *Nitric Oxide*. 2024; 146: 64–74.
DOI: 10.1016/j.niox.2024.03.004. PMID: 38556145.
27. *de Geus H. R., Ronco C., Haase M., Jacob L., Lewington A., Vincent J. L.* The cardiac surgery-associated neutrophil gelatinase-associated lipocalin (CSA-NGAL) score: A potential tool to monitor acute tubular damage. *J Thorac Cardiovasc Surg*. 2016; 151 (6): 1476–1481.
DOI: 10.1016/j.jtcvs.2016.01.037. PMID: 26952930.
28. *Mostafa E. A., Shahin K. M., El Midany A. A. H., Hassaballa A. S., El-Sokkary I. N., Gamal M. A., Elsaid M. E., et al.* Validation of cardiac surgery-associated neutrophil gelatinase-associated lipocalin score for prediction of cardiac surgery-associated acute kidney injury. *Heart Lung Circ*. 2022; 31 (2): 272–277.
DOI: 10.1016/j.hlc.2021.05.084. PMID: 34219024.
29. *Haase M., Bellomo R., Devarajan P., Schlattmann P., Haase-Fielitz A.; NGAL Meta-analysis Investigator Group.* Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis*. 2009; 54 (6): 1012–1024.
DOI: 10.1053/j.ajkd.2009.07.020. PMID: 19850388.
30. *Zhou F., Luo Q., Wang L., Han L.* Diagnostic value of neutrophil gelatinase-associated lipocalin for early diagnosis of cardiac surgery-associated acute kidney injury: a meta-analysis. *Eur J Cardiothorac Surg*. 2016; 49 (3): 746–755.
DOI: 10.1093/ejcts/ezv199. PMID: 26094017.
31. *Дымова О. В., Еременко А. А., Минболатова Н. М.* Нейтрофильный желатиназа-ассоциированный липокалин (UNGAL) в ранней диагностике и прогнозировании острого почечного повреждения, СПОН и исходов лечения у кардиохирургических пациентов. *Анестезиология и реаниматология*. 2017; 62 (5): 347–351. *Dymova O. V., Eremenko A. A., Minbolatova N. M.* The value of neutrophilic gelatinase-associated lipocalin (UNGAL) in the early diagnosis and prognosis of acute renal injury, MOSF and outcomes in cardiosurgical patients. *Russ J Anesthesiol Reanimatol = Anesteziologiya i Reanimatologiya*. 2017; 62 (5): 347–351. (in Russ.).
DOI: 10.18821/0201-7563-2017-62-5-347-351.
32. *Wen Y., Parikh C. R.* Current concepts and advances in biomarkers of acute kidney injury. *Crit Rev Clin Lab Sci*. 2021; 58 (5): 354–368.
DOI: 10.1080/10408363.2021.1879000.
PMID: 33556265.
33. *Schrezenmeier E. V., Barasch J., Budde K., Westhoff T., Schmidt-Ott K. M.* Biomarkers in acute kidney injury — pathophysiological basis and clinical performance. *Acta Physiol (Oxf)*. 2017; 219 (3): 554–572.
DOI: 10.1111/apha.12764. PMID: 27474473.
34. *Pode Shakked N., de Oliveira M. H. S., Cheruiyot I., Benoit J. L., Plebani M., Lippi G., Benoit S. W., et al.* Early prediction of COVID-19-associated acute kidney injury: are serum NGAL and serum Cystatin C levels better than serum creatinine? *Clin Biochem*. 2022; 102: 1–8.
DOI: 10.1016/j.clinbiochem.2022.01.006.
PMID: 35093314.
35. *Lan H., Liu X., Yang D., Zhang D., Wang L., Hu L.* Comparing diagnostic accuracy of biomarkers for acute kidney injury after major surgery: a PRISMA systematic review and network meta-analysis. *Medicine (Baltimore)*. 2023; 102 (40): e35284.
DOI: 10.1097/MD.0000000000035284.
PMID: 37800811.

Received 19.10.2024
Accepted 14.02.2025
Accepted in press 20.03.2025

https://doi.org/10.15360/1813-9779-2025-2-2532

Intensive Care for Acute Liver Failure in Pediatric Practice (Review)

Georgy A. Avakyan, Yuri V. Bykov*, Alexander N. Obedin

Stavropol State Medical University, Ministry of Health of Russia,
310 Mira Str., 355017 Stavropol, Russia

For citation: *Georgy A. Avakyan, Yuri V. Bykov, Alexander N. Obedin.* Intensive Care for Acute Liver Failure in Pediatric Practice (Review). *Obshchaya Reanimatologiya = General Reanimatology.* 2025; 21 (2): 42–54. https://doi.org/10.15360/1813-9779-2025-2-2532 [In Russ. and Engl.]

***Correspondence to:** Yuri V. Bykov, yubykov@gmail.com

Summary

Acute liver failure (ALF) is a rare pathologic syndrome in pediatric practice with a high risk of multiple organ failure and death. Despite extensive research on risk factors and clinical manifestations, there are no standardized critical care protocols for ALF in children and adolescents. Anesthesiologists and intensivists face significant challenges in the diagnosis and prevention of ALF.

The aim of this review is to analyze the main triggers, etiology, pathogenesis, clinical manifestations and both specific and supportive treatment approaches for ALF in pediatric intensive care units.

The Cochrane Library, PubMed, Medscape and Library.ru databases were used to conduct a systematic search and analysis of the scientific literature using the keywords «acute liver failure, children and adolescents, hepatic encephalopathy, cerebral edema, extracorporeal methods, liver transplantation». A total of 81 sources were selected for review. Inclusion criteria were studies that described the pathogenesis, clinical manifestations, diagnosis and treatment of ALF in the pediatric intensive care unit. Exclusion criteria were studies that focused on the diagnosis and treatment of ALF in adult patients.

This review summarizes the most common etiologic factors and clinical presentations of ALF based on the child's age, as well as the diagnostic tools used in the pediatric intensive care unit. It also focuses on the primary supportive and disease-specific management strategies for ALF in the ICU, taking into account the unique physiological characteristics of pediatric patients.

Conclusion. Infectious and idiopathic causes are the most common etiologies of ALF, leading to hyperammonemia, inflammatory response, and hepatocyte death. The primary clinical manifestations of ALF in children vary with age and include jaundice, abdominal pain, nausea, vomiting, and encephalopathy. Specific treatment in the intensive care unit focuses on correcting fluid and electrolyte imbalances, administering antibacterial therapy, and providing enteral nutrition. Supportive therapy is aimed at stabilizing vital organ function, implementing extracorporeal treatment methods, and performing liver transplantation when indicated.

Keywords: acute liver failure; children and adolescents; hepatic encephalopathy; cerebral edema; extracorporeal methods; liver transplantation

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

Information about the authors:
Georgy A. Avakyan: http://orcid.org/0009-0006-7630-5734
Yuri V. Bykov: http://orcid.org/0000-0003-4705-3823
Alexander N. Obedin: http://orcid.org/0000-0002-9990-7272

Introduction

Acute liver failure (ALF) is a rare condition in pediatric practice that can rapidly progress to multiple organ failure with fatal outcome [1–7]. It is characterized by acute hepatocellular injury in the absence of pre-existing liver disease [1, 2, 8, 9]. The exact incidence of ALF in children remains unknown, but is estimated to range from 1 to 10 cases per million people per year in all age groups (including adults), with a mortality rate of approximately 5–10% [1, 10–14]. Notably, ALF is observed more frequently in children aged 1 to 5 years than in other pediatric age groups [15].

In adults, ALF is defined by severe liver dysfunction manifested by jaundice and coagulopathy, accompanied by the development of hepatic encephalopathy (HE) within eight weeks of symptom onset [1]. However, among young children, challenges in accurately assessing mental status and establishing the precise duration of illness limit the applicability of this definition [1, 16].

A generally accepted definition of pediatric ALF was formulated in 1999, characterizing it as a «rare multisystem disorder characterized by severe hepatic dysfunction, with or without hepatic encephalopathy, associated with hepatocellular necrosis in the absence of pre-existing chronic liver disease» [2, 13, 17].

Biochemical criteria for the diagnosis of ALF in children should include at least one of the following [1, 4, 10]:

- An international normalized ratio (INR) >1.5 that is not corrected with vitamin K administration in the presence of hepatic encephalopathy (HE).
- An INR>2.0 that does not respond to vitamin K supplementation, even in the absence of HE.

Management of this rare yet complex syndrome requires a comprehensive diagnostic eval-

uation, as well as continuous monitoring, prognostication, and treatment of the multiple organ failure that often develops as a secondary complication of ALF [1, 6, 8]. Diagnostic criteria for ALF in children vary according to age and clinical presentation, necessitating pediatric-specific intensive care algorithms that differ from those used in adults [1, 2, 4, 9, 13].

The importance of this review is underscored by the rarity of ALF in the pediatric ICU and the limited awareness among anesthesiologists and intensivists regarding emergency management strategies for this patient population.

The aim of this review is to examine the major triggers, etiopathogenesis, clinical manifestations, and both specific and supportive treatment approaches for ALF in pediatric intensive care practice.

Materials and Methods

A systematic search and analysis of the scientific literature was performed using the Cochrane Library, PubMed, Medscape, and Library.ru databases. The search was conducted using the following keywords: «acute liver failure, children and adolescents, hepatic encephalopathy, brain edema, extracorporeal therapies, liver transplantation».

The search yielded 350 publications from international and national journals published between 2014 and 2024. Studies were included in the review if they provided data on the pathogenesis, clinical presentation, diagnosis, and treatment strategies in pediatric intensive care. Articles that focused on the clinical characteristics, diagnosis, and ICU management of adult patients were excluded. After screening, 81 studies directly related to the objectives of this review were selected for analysis.

Etiology and Pathogenesis

Acute liver failure in children and adolescents is a potentially life-threatening condition caused by a variety of factors, making its accurate diagnosis and treatment difficult [10, 18]. The etiology of ALF varies depending on the child's age, geographic region, and socioeconomic status [17, 19]. Infectious causes are the most common etiology of ALF in developing countries, whereas undetermined causes are more common in Europe and North America [13, 15, 19–22].

In neonates, ALF may result from conditions such as gestational alloimmune liver disease, herpes simplex virus infection, and metabolic disorders [21, 22]. In adolescents, common causes include drug-induced liver injury (with acetaminophen overdose accounting for over 75% of ALF cases), ingestion of toxic Amanita phalloides mushrooms, herbal and dietary supplements, and autoimmune diseases [1, 2, 9, 15, 23].

Certain causes of ALF are specific to the pediatric population. These include metabolic disorders such as type 1 tyrosinemia, mitochondrial cytopathies, galactosemia, hereditary fructose intolerance, and genetic disorders such as neonatal hemochromatosis [7]. In addition, autoimmune hepatitis, acute leukemia, Wilson's disease, and Reye's syndrome are well recognized causes of pediatric ALF [7, 17].

Despite diagnostic advances, a substantial proportion of ALF cases (35–45%) remain of unknown etiology (indeterminate ALF), particularly in children aged 1 to 5 years [4, 9, 10, 17, 24–27].

Despite the diverse etiology of pediatric acute liver failure (PALF), the underlying mechanisms of hepatocellular injury and regeneration share common pathways regardless of the initiating factor. The interplay between innate and adaptive immune mechanisms plays a central role in this process [17]. Damage to individual hepatocytes triggers an integrated stress response (ISR), leading to increased activation of caspases and NF-κB, as well as Fas ligation [28, 29].

The pathophysiological cascade underlying ALF is primarily driven by two key mechanisms [30]. The first is the development of hyperammonemia due to the inability of the liver to produce urea [30, 31]. The second mechanism is hepatocyte necrosis, which results in the release of large amounts of degradation proteins such as damage-associated molecular patterns (DAMPs), including DNA and RNA fragments, S-100 proteins, hyaluronan, and purine metabolites [30].

This release of DAMPs triggers a proinflammatory response in intrahepatic macrophages, leading to systemic circulation of these molecules, which in turn activate monocytes and macrophages, resulting in further secretion of proinflammatory cytokines [30]. The excessive accumulation of DAMPs contributes to a clinical syndrome similar to septic shock, which is exacerbated by severe HE and cerebral edema (CE) [32].

Clinical Manifestations

The clinical presentation of PALF is highly variable and often atypical [3]. Symptoms vary depending on the underlying cause and the age of the child [33–35]. The most common signs include jaundice, abdominal pain, nausea, vomiting, and generalized weakness [10, 15].

In newborns, the clinical presentation is closely related to the etiology of neonatal liver failure, so that early symptoms are nonspecific and often limited to changes in general condition such as lethargy, weight loss, and vomiting [33–35]. Jaundice is not always present, especially in cases of inborn errors of metabolism [33–35]. Hepatic encephalopathy, which may manifest as behavioral changes such as irritability and sleep-wake disturbances, typically

occurs in later stages and is particularly difficult to diagnose in newborns [33–35]. Seizures may indicate meningoencephalitic brain involvement or be associated with hypoglycemia [33–35]. Hepatomegaly is common in neonatal ALF, whereas splenomegaly and ascites are uncommon [33–35].

In infants and older children, ALF often begins with a prodromal phase characterized by malaise, nausea, and anorexia [33–35]. Jaundice is a common sequela, but may be absent, particularly in the presence of metabolic disorders or toxic liver injury, making clinical diagnosis difficult [33–35]. Other signs include hepatomegaly, ascites, and cerebral edema (CE) [36]. While ascites is more typical of chronic liver disease, it can occasionally be seen in ALF, particularly in Budd-Chiari syndrome [36]. A characteristic hepatic odor on breath may be subtle or absent [33, 36].

Coagulopathy is a characteristic feature of ALF [37]. Although spontaneous bleeding may occur, primarily in the gastrointestinal tract [33–35], clinically significant bleeding is observed in less than 5% of patients, and spontaneous intracranial hemorrhage is diagnosed in less than 1% of children [37, 38]. Severe hypoglycemia is common and can lead to seizures if left untreated [33–35].

HE in children is classified into four stages [33]:

- Stage 1: Behavioral changes without altered consciousness, along with sleep disturbances (sleepiness, insomnia, or disrupted sleep-wake cycles in neonates).
- Stage 2: Disorientation, marked drowsiness, and inappropriate behavior.
- Stage 3: Stupor with weak response to pain and auditory stimuli.
- Stage 4: Coma with decorticate posturing [33].

HE may be absent despite severe liver dysfunction or may develop over hours, days, or weeks after the onset of ALF [33–35].

The most common cause of mortality in ALF is CE, which leads to intracranial hypertension (ICH) and ischemic brain injury [37]. Triggers of CE include hypoxia, systemic hypotension, and decreased cerebral perfusion pressure, all of which result from increased ammonia levels and excessive glutamine production in the brain [37]. Pathologic pupillary reflexes, muscle rigidity, and decerebrate posturing indicate the presence of ICH [37]. ALF often results in multisystem organ dysfunction, with acute kidney injury (AKI) and acute respiratory failure (ARF) being among the most common early complications [36].

The major complications of ALF in children and adolescents are summarized in Table.

Diagnosis

All children suspected of having ALF must undergo an immediate evaluation to determine the underlying cause and assess the severity of liver injury and dysfunction [1, 39]. A thorough history should be obtained, focusing on the onset of hepatic symptoms, changes in mental status, exposure to infectious agents, blood transfusions, medication use, and any family history of liver or autoimmune disease [1]. A comprehensive physical examination, including a detailed neurological assessment, is essential [1].

CBC, absolute platelet count, prothrombin time (PT) with international normalized ratio (INR), coagulation factors V and VII, blood glucose, and serum electrolytes (potassium, sodium, calcium, and phosphate) should be checked every 12 hours [37, 40]. Serum bilirubin, AST/ALT, alkaline phosphatase, albumin, and globulin should also be assessed routinely [37, 40]. Blood and urine cultures and chest radiography are essential to identify potential sources of infection [37, 39, 40]. Cranial computed tomography (CT) should be performed in children with grade 3–4 HE to exclude intracranial hemorrhage and CE [37]. Continuous monitoring of clinical and biochemical parameters is necessary until the child's condition stabilizes [41].

Recommended monitoring includes

1. Continuous monitoring of hemoglobin oxygen saturation (SpO_2).
2. Assessment of vital signs (respiratory rate, heart rate, blood pressure) every 4 hours; more frequently in hemodynamically unstable children.

Table. Common complications of acute liver failure (ALF) in children [2].

System	Complications
Brain	• Hepatic encephalopathy • Cerebral edema
Blood	• Coagulopathy • Aplastic anemia
Gastrointestinal	• Ascites • Gastrointestinal bleeding • Pancreatitis
Urinary	• Hypovolemia • Hepatorenal syndrome
Metabolic	• Hypokalemia, hypophosphatemia, hypoglycemia • Acid-base disorders
Immune	• Bacterial infection and sepsis
Cardiovascular	• Pulmonary edema • Hypovolemia • Shock

3. Hourly neurological examination for 12 hours, including assessment of consciousness level.

4. Regular monitoring of electrolytes, glucose levels, and arterial blood gas analysis.

5. Daily coagulation studies and complete blood count.

6. Daily liver size measurements (palpation and ultrasonography).

7. Twice weekly monitoring of cholesterol, urea, creatinine, calcium, and phosphate levels.

Intensive Therapy

The management of PALF is complex due to the risk of multi-organ dysfunction and requires a multidisciplinary approach [1]. Close collaboration between anesthesiologists, intensivists, pediatricians, hepatologists, neurologists, nephrologists, and hematologists is essential [1].

Children with worsening coagulopathy and/or altered mental status must be admitted to the ICU for continuous neurological, cardiorespiratory, and laboratory monitoring, as PALF can deteriorate rapidly [1, 39, 42]. ICU admission is indicated if INR >1.5 with evidence of HE or if INR >4 without HE [40].

After initial assessment and stabilization, management should focus on the identification and treatment of complications [23, 36]. Venous access is required for fluid administration, acid-base balance correction, and electrolyte maintenance [37, 41]. If consciousness deteriorates to coma, endotracheal intubation should be performed to protect the airway and prevent aspiration [37].

Fluid Therapy and Electrolyte Correction

Metabolic, electrolyte, and acid-base disturbances are common in PALF and require careful monitoring and correction [1, 39, 43]. Fluid support is essential for patients who are unable to receive adequate enteral nutrition [44]. Intravenous fluid therapy should be started at ¾ of the calculated daily requirement to prevent fluid overload [40, 41, 45]. Overhydration can lead to pulmonary edema, ascites, and CE, while underhydration increases the risk of hepatorenal syndrome, acute tubular necrosis, worsening HE, and arterial hypotension [45].

Balanced crystalloids are the preferred fluid choice for ALF [44]. The initial fluid solution in hemodynamically stable patients consists of 10% glucose with sodium (0.5–1.0 mmol/kg) and potassium (2–3 mmol/kg) [40, 45]. Lactated Ringer's solution should be avoided as it may worsen lactic acidosis and contribute to CE [40].

Hypoglycemia occurs due to impaired glycogenolysis and gluconeogenesis and requires continuous glucose infusion at a rate of 10–15 mg/kg/min [37, 39, 45, 46]. Intravenous lipid emulsions can be used for caloric support, but fat metabolism may be impaired in certain conditions that lead to ALF (e. g., mitochondrial diseases) [47].

Plasma concentrations of sodium, potassium, phosphate, calcium, and magnesium are often low and require careful correction [1]. Hyponatremia and hypokalemia may occur as a result of aggressive fluid therapy, ascites, and AKI when diuretics are used [1, 39]. It is very important to avoid hyponatremia to avoid exacerbation of CE [39]. Serum phosphate levels should be monitored and corrected as hypophosphatemia can be severe [37, 45, 48].

Severe symptomatic cases of hypophosphatemia require intravenous administration of *P* when the serum level is <1.0 mg/dL (or <0.32 mmol/L); oral preparations should be started when the serum phosphate exceeds 2.0 mg/dL (or 0.48 mmol/L).

Sodium phosphate and potassium phosphate preparations with an equivalent phosphate content of 0.011 g/mL are commonly used according to the following scheme [37, 45, 48]:

— If serum P < 1.0 mg/dL: 0.6 mmol/kg intravenously over 6 hours;

— If serum P 1.0–1.7 mg/dL: 0.4 mmol/kg intravenously over 6 hours;

— If serum P 1.7–2.2 mg/dL: 0.2 mmol/kg intravenously over 6 hours.

Hypocalcemia and hypomagnesemia are common in ALF and require timely correction [39]. For hypocalcemia, oral calcium supplementation is indicated for mild cases (asymptomatic, with serum calcium >1.9 mmol/L), whereas intravenous administration of calcium gluconate is required for severe cases (serum calcium <1.9 mmol/L) [39]. Hypomagnesemia should be treated with slow intravenous infusion of magnesium sulfate (25% $MgSO_4$) administered under close clinical and hemodynamic monitoring. In pediatric patients, the recommended dose of 25% $MgSO_4$ is 25–50 mg/kg (0.2–0.4 mEq/kg), with a maximum single dose of 2 g administered over 1–5 minutes [39].

Enteral Nutrition

ALF is a hypercatabolic state characterized by negative nitrogen balance and increased caloric expenditure, which increases energy requirements in children by approximately 20% [43]. The goals of enteral nutrition in ALF include providing adequate calories to limit protein catabolism, maintaining euglycemia, and ensuring adequate protein delivery without inducing hyperammonemia [1, 39]. However, the lack of randomized controlled trials (RCTs) has resulted in the absence of standardized, evidence-based nutritional guidelines for pediatric ALF. Instead, most nutritional protocols are based on approaches used in the management of chronic liver disease or cirrhosis [1, 49, 50].

To reduce complications such as CE, enteral nutrition should utilize high-calorie formulas that minimize the administration of free water. Recommended daily caloric intake targets are 50–80 kcal/kg/day for older children and 120–160 kcal/kg/day for neonates and infants less than one year of age [40, 49, 51]. When selecting enteral formulas for patients with ALF, products such as Nutrien Hepa are beneficial. These formulas contain medium-chain triglycerides (MCTs), which are efficiently metabolized without storage in adipose tissue or accumulation in the liver [52].

The target blood glucose concentration during enteral nutrition should be maintained between 110–130 mg/dL [40]. Children should receive approximately 1.5–1.9 g/kg of protein per day, while neonates of normal birth weight require 3.0–3.3 g/kg/day [40].

Antibacterial Therapy

Recommendations for the prophylactic use of antibacterial agents in children and adolescents with ALF remain uncertain [51]. Several RCTs in adults have examined the role of prophylactic antibiotics in liver failure, but the results remain inconclusive [53]. The lungs and kidneys are the most common sites of bacterial infection, with gram-positive cocci (staphylococci, streptococci) and gram-negative enterobacteria being the most commonly isolated pathogens [54]. Empiric therapy with broad-spectrum antibiotics is indicated in children with sepsis or worsening HE [37, 51].

Anesthetics and Muscular Blocking Agents

Sedatives, analgesics, and neuromuscular blocking agents are important components of the intensive care management of children with ALF in the ICU, especially if mechanical ventilation is required [39]. Data on pharmacologic agents that can be used for sedation and/or analgesia in children with ALF are limited, but drugs with short duration of action are preferred [1, 39]. The use of sedatives in agitated, spontaneously breathing children with ALF should be carefully considered, balancing the potential benefits of reducing agitation with tranquilizers against the risk of worsening HE [1, 39].

Benzodiazepines and propofol may worsen encephalopathy by increasing gamma-aminobutyric acid (GABA) neurotransmission in the brain [1, 39]. In addition, benzodiazepines may have prolonged sedative effects in the setting of impaired liver function and should be avoided [39]. Recovery time in children after propofol administration is significantly shorter than with benzodiazepines, and propofol may provide some neuroprotection by reducing cerebral blood flow and intracranial pressure [1, 39, 55]. Concomitant use of opioid analgesics may reduce the required anesthetic doses [1, 39]. Opioid analgesics with a shorter half-life, such as fentanyl or remifentanil, are preferred [39]. If neuromuscular blockade is used, vecuronium and rocuronium should be avoided as they are metabolized in the liver [56]. Atracurium and cisatracurium are the preferred neuromuscular blockers in children with ALF on mechanical ventilation because of their short duration of action [56].

Symptomatic Therapy and Correction of Brain Dysfunction

Cerebral dysfunction is the most important predictor of outcome in PALF [1]. Early recognition of neurological deterioration allows timely initiation of intensive therapy and minimizes mortality [1]. Seizures increase cerebral oxygen demand and may exacerbate CE in children with ALF [41]. Phenytoin has been used in adults with ALF to control seizures, but no clear benefit of its use in preventing BE has been demonstrated [37, 41].

Hepatic Encephalopathy

Early diagnosis and intensive therapy in ALF are crucial to prevent the onset and progression of HE [1, 39]. It is necessary to perform frequent neurological examinations and to minimize the influence of exogenous noise and pain factors [1, 39]. Children with HE greater than grade 2 should undergo endotracheal intubation for airway protection due to decreased level of consciousness and assisted ventilation. [1, 37, 39]. Elevating the head of the bed by 20–30° helps improve CSF drainage [1, 37, 39]. Fever and chills can lead to increased intracranial pressure and should be treated promptly, avoiding the prescription of acetaminophen, which is hepatotoxic [1, 39]. The use of antibiotics such as rifaximin and neomycin is a widely used strategy to reduce ammonia production in the treatment of HE, but RCTs confirming their efficacy in PALF are currently lacking [46, 51]. In HE, rifaximin is given at a dose of 400 mg every 8 hours to children over 12 years of age [57]. Lactulose is given at a dose of 0.3–0.4 ml/kg orally or rectally 3–4 times/day for the treatment of HE; alternatively, lactilol 30–40 g/day or sodium benzoate at a dose of 250 mg/kg/day may be used [40]. L-ornithine-l-aspartate (LOLA) and l-ornithine-phenylacetate (LOPA), as major components of ammonia deamination, are currently being investigated for use as agents to reduce ammonia production in ALF [1]. Promising results have been reported in an adult study [51]; however, there are no data on their use in PALF [58].

Intracranial Hypertension and Cerebral Edema

The goal in the treatment of ICH and CE is to reduce ICP while maintaining cerebral perfusion

pressure (the difference between ICP and mean arterial pressure), which helps prevent hypoxic brain injury [1]. Osmotic agents such as mannitol and hypertonic saline (HS) are among the primary treatments for CE [1, 37, 59]. Mannitol is used as a first-line treatment for elevated ICP in children with ALF [1, 46]. It works by increasing serum osmolality, thereby facilitating the passage of water from neurons into the bloodstream [1, 39]. Mannitol also reduces blood viscosity, resulting in vasoconstriction and a decrease in cerebral blood volume [39]. The drug is recommended to be administered intravenously as a bolus at a dose of 0.25–1.0 g/kg, with the possibility of one or two repeated doses as long as serum osmolality remains below 320 mOsm/L [1, 46]. In children, it is recommended only for acute ICP elevation and should not be used prophylactically [1, 39]. Most information on the use of mannitol has been extrapolated from the adult literature, and there are no RCTs evaluating its efficacy in PALF [1, 39].

HS (3-30%) is a second-line agent that reduces intracranial pressure by decreasing brain water content via an osmotic effect and improves cerebral blood flow by reducing edema [39, 60, 61]. The advantages of HS include an increase in serum osmolarity without the hemodynamic side effects observed with the use of mannitol [39]. A 3% HS is administered at a dose of 2–6 mL/kg, followed by 0.1–1.0 mL/kg/hour (administration should be stopped if serum sodium concentration exceeds 155 mOsm/L or osmolality exceeds 360 mOsm/L) [40, 62]. HS has been studied as a therapeutic agent to prevent elevated intracranial pressure in adult patients with ALF; however, its use as a treatment for elevated ICP in this disease has not been studied in children [39, 63, 64]. Importantly, HS administration is associated with electrolyte imbalance, hyperchloremic metabolic acidosis, worsening coagulopathy, deep vein thrombosis, and increased risk of bleeding [61].

Management of Cardiovascular Dysfunction

ALF is associated with elevated cytokine levels leading to hyperdynamic circulatory failure [39]. In most cases, peripheral vasodilation develops, often accompanied by low mean arterial pressure (MAP) [39]. The first-line treatment for relative hypovolemia is to restore adequate intravascular volume by fluid resuscitation [39]. In cases of massive blood loss, transfusion of blood components is indicated [45]. If arterial hypotension persists despite adequate fluid resuscitation, vasopressor therapy should be initiated [1, 39].

Vasopressors are essential to maintain MAP within or above the physiologic range to ensure adequate renal and cerebral perfusion [37]. In adults, norepinephrine is the preferred agent because it optimally improves peripheral organ perfusion while minimizing tachycardia and preserving splanchnic circulation [51]. Although RCTs in PALF are lacking, norepinephrine is considered a rational first-line vasopressor in volume-refractory hyperdynamic circulatory failure because it helps maintain adequate central perfusion pressure in children [1, 39, 46].

Vasopressin and its analogues may be used as adjunctive therapy in children who do not respond to norepinephrine and fluid resuscitation. If the norepinephrine infusion exceeds 3 μg/kg/min without achieving the target MAP, vasopressin may be started at 0.0001 IU/kg/min to augment the pressor effect [1, 40].

Focused cardiac ultrasound is a valuable tool for rapid assessment of myocardial function, particularly in the evaluation of cardiac output and diagnosis of fluid overload in hemodynamically unstable pediatric patients. This method can be integrated with clinical assessment to differentiate the etiology of shock and guide decisions regarding fluid administration, vasopressor use, inotropic support, and other therapeutic interventions [65].

Management of Respiratory Dysfunction

Children with ALF may develop acute respiratory failure (ARF) due to sepsis, fluid overload-induced pulmonary edema, pulmonary hemorrhage, or acute respiratory distress syndrome (ARDS) [1, 37, 39]. Endotracheal intubation and mechanical ventilation (MV) may be required in ALF-associated ARF due to these causes or to protect the airway in cases of progressive HE [66].

Ventilation strategies in ALF should be both lung and neuroprotective, especially in the presence of elevated ICP [39]. The standard of care for ventilated pediatric patients with elevated ICP includes maintaining normocapnia and preventing hypoxemia [1]. Low tidal volumes (3–6 mL/kg) and moderately elevated positive end-expiratory pressure (PEEP>6 cm H_2O) are recommended to maintain adequate oxygenation (SpO_2>94%) [39, 40]. Excessively high levels of PEEP may increase intrahepatic and intracranial pressures, so minimally effective PEEP should be used to achieve adequate oxygenation [5, 40].

Hyperventilation may be used as an emergency measure to reduce elevated ICP refractory to mannitol therapy. However, prolonged hyperventilation should be avoided in pediatric patients due to its potential adverse effects [1, 39].

Management of Renal Dysfunction

Acute kidney injury (AKI) in the setting of ALF may develop due to hypovolemia, acute tubular necrosis, or hepatorenal syndrome [37]. Preventive strategies focus on maintaining adequate fluid balance, avoiding volume overload, minimizing the

use of nephrotoxic drugs or intravenous contrast, and ensuring optimal renal perfusion pressure [1, 67]. Renal replacement therapy (RRT) is considered an important intervention in patients awaiting liver transplantation (LT) [37]. However, the criteria for initiating RRT in pediatric ALF remain poorly defined [68, 69]. Continuous RRT is generally preferred to intermittent hemodialysis in critically ill patients because it minimizes hemodynamic instability and reduces the risk of ICP elevation [1, 37]. The decision to initiate RRT in children and adolescents is based on the severity of renal impairment and associated metabolic and electrolyte imbalances [1]. AKI typically resolves either after RRT when liver function is restored or after LT [70–72].

Management of Hematologic Disorders

In ALF, hepatic synthesis of coagulation factors (II, V, VII, IX, and X) is impaired, leading to fibrinolytic abnormalities and hemostasis disorders [73]. Correction of hemodynamic disorders should be guided by clear clinical indications, taking into account not only standard coagulation tests but also thromboelastography (TEG) or rotational thromboelastometry (ROTEM) parameters [74].

There are only two scenarios that require active correction of coagulopathy and thrombocytopenia. First, if ICP monitoring is required, the administration of fresh frozen plasma (FFP), cryoprecipitate, and platelets should be considered based on the degree of coagulopathy. Second, if there is significant active bleeding, coagulation abnormalities must be corrected in addition to local hemostatic measures to control the source of bleeding [75].

Routine correction of coagulopathy in PALF is not recommended except in cases of active bleeding or before invasive procedures [1, 33, 37, 76]. Transfusion of platelets, FFP, and cryoprecipitate may be used when indicated [33, 37].

FFP is given at a dose of 15–20 mL/kg every 6 hours or 3–5 mL/kg/hour intravenously in cases of bleeding [40]. However, FFP infusion alone may not be sufficient to correct severe coagulopathy and carries the risk of fluid overload [1]. Recombinant factor VIIa (80 mcg/kg) is recommended when FFP fails to normalize PT INR to acceptable levels or when volume overload is a concern [40, 77]. It is important to note that administration of recombinant factor VIIa increases the risk of thrombosis [37].

Platelet transfusion is indicated when the platelet count falls below 50,000/mm³ before an invasive procedure or prophylactically when the platelet count falls below 20,000/mm³ [40]. Vitamin K is used to correct coagulopathy at a dose of 0.2 mg/kg intravenously (maximum dose 10 mg) [33, 40].

FFP and/or platelet transfusions carry risks, including transfusion-related lung injury (TRALI) and volume overload, and may mask a rising INR, which is an important prognostic marker in ALF [1]. Thromboelastography is considered a superior method to assess bleeding risk in ALF, but its routine use in pediatric patients remains limited due to availability issues [78].

Gastrointestinal Management

The use of H_2-receptor antagonists or proton pump inhibitors (PPIs) is recommended for the prevention of stress-induced gastrointestinal bleeding in children with ALF admitted to the ICU [1, 33, 37]. Sucralfate (10–15 mg/kg orally every 6 hours) or omeprazole (10 mg/kg twice daily) are preferred for prophylaxis of gastric bleeding [33, 40].

A small proportion of children with ALF may develop ascites, for which spironolactone is the diuretic of choice [66].

Specific Treatment Based on ALF Etiology

For children with ALF due to acetaminophen toxicity, activated charcoal and prompt administration of N-acetylcysteine (NAC) are indicated [37, 40]. The oral NAC regimen consists of a loading dose of 140 mg/kg followed by 70 mg/kg every 4 hours for 17 doses [40]. The intravenous NAC protocol includes an initial dose of 150 mg/kg diluted in 200 mL 5% dextrose infused over 15 minutes, followed by 50 mg/kg over the next 4 hours and 100 mg/kg over the next 15 hours [40].

Patients with suspected Amanita phalloides mushroom poisoning require gastric lavage, activated charcoal, and intravenous penicillin-G at a dose of 1 g/kg/day [37].

For ALF associated with hepatitis A or E, supportive care remains the mainstay of treatment, as specific antiviral therapies have not been established [37, 40]. Patients with acute or reactivated hepatitis B should receive nucleotide analogues (entecavir or tenofovir) for at least six months [37, 40]. Children with suspected autoimmune hepatitis should be treated with intravenous methylprednisolone at a dose of 60 mg/day [37, 40].

For chronic hepatitis E, interferon and ribavirin therapy may be considered [40]. Children with herpes simplex virus (HSV) hepatitis or ALF caused by varicella-zoster virus (VZV) should receive intravenous acyclovir at a dose of 5–10 mg/kg every 8 hours [37]. Patients with cytomegalovirus (CMV)-induced hepatitis should be treated with intravenous ganciclovir at a dose of 5 mg/kg every 12 hours [37, 40].

Extracorporeal Treatment Modalities

Several extracorporeal liver support systems have been studied in pediatric patients with ALF to determine their potential impact on clinical outcomes [45]. These methods include albumin dialysis, plasmapheresis, bioartificial liver support

systems (using human hepatoblastoma cells), and molecular adsorbent recirculation systems (MARS), each of which has demonstrated varying degrees of efficacy [79–81].

In adult patients with ALF, high-volume plasma exchange (HVPE) has been shown to exert beneficial effects by removing hepatotoxic substances from the circulation while enhancing liver regeneration [30, 82]. However, data on its efficacy in pediatric ALF remain limited. Although HVPE may improve coagulation parameters, there is no conclusive evidence to support its role in improving neurological outcomes or facilitating spontaneous recovery [45].

Most RCTs in pediatric patients suggest that plasmapheresis, sometimes in combination with other extracorporeal therapies, may serve as a «therapeutic bridge» to LT [83]. Plasmapheresis has been associated with a reduction in multi-organ dysfunction and HE, while increasing survival in the absence of LT [72, 84].

Despite its theoretical advantages, MARS has not demonstrated significant clinical benefit in pediatric ALF [85]. Limited studies, including a cohort of 20 children undergoing MARS therapy, have reported improvements in biochemical markers such as ammonia, bilirubin, and creatinine levels, with good overall tolerability of the procedure [86]. However, further RCTs are needed to determine whether this modality provides meaningful clinical benefit in pediatric patients [45].

Liver Transplantation

The decision to proceed with LT in children with ALF is urgent when the likelihood of spontaneous recovery is extremely low and before the development of irreversible neurological or respiratory complications [87]. A progressive increase in serum aminotransferases, coupled with worsening coagulopathy, indicates progressive liver necrosis and the potential need for LT [37].

Currently, the Model for End-Stage Liver Disease (MELD) score is used to assess transplant eligibility in PALF patients, replacing the Child-Pugh classification [33, 88].

In some cases, the decision-making process for LT can take several hours to days [89]. Many centers prefer to list patients for transplantation while continuing ICU management and further diagnostic evaluation within the first 24–48 hours [89]. Prior to the introduction of LT, mortality in PALF was 70–95% [89]. However, with the advent of transplantation, mortality has decreased to 11% [90]. Currently, up to 10.3% of all pediatric liver transplants are performed for ALF [90]. Given the success of living-donor liver transplantation (LDLT) in PALF, this approach should be actively considered for children listed for transplantation, particularly in multidisciplinary centers where LDLT is feasible [89].

A major limitation of LT is the shortage of viable donor organs and the need for lifelong immunosuppressive therapy to prevent graft rejection [91]. Hepatocyte transplantation (HT) has emerged as a promising alternative to LT, either as a potential replacement therapy or as a bridge treatment until a donor liver becomes available. HT involves the infusion and engraftment of human hepatocytes, typically from organs unsuitable for whole organ transplantation, into the recipient's liver parenchyma to temporarily restore liver function [89].

Conclusion

Pediatric acute liver failure (PALF) is a rare and life-threatening condition that many anesthesiologists and intensivists rarely encounter. As a result, optimizing its management remains a challenge that can negatively impact the quality of emergency care. Increased awareness and education about PALF are essential to improve outcomes. In addition, more clinical research is needed to advance therapeutic strategies, including the development of novel approaches such as hepatocyte transplantation.

References

1. *Bhatt H., Rao G. S.* Management of acute liver failure: a pediatric perspective. *Curr Pediatr Rep.* 2018; 6 (3): 246–257. DOI: 10.1007/s40124-018-0174-7. PMID: 32288972.
2. *Mandato C., Vajro P.* Pediatric acute liver failure. *Pediatr Rep.* 2023; 15 (3): 426–430. DOI: 10.3390/pediatric15030039. PMID: 37489413.
3. *Ming H., He Y., Xu H. M.* Advancements in the diagnosis and treatment of pediatric acute liver failure. (Chinese). *Zhongguo Dang Dai Er Ke Za Zhi.* 2024; 26 (2): 194–200. DOI: 10.7499/j.issn.1008-8830.2309015. PMID: 38436319.
4. *Deep A., Tissieres P.* Editorial: Acute liver failure in children. *Front Pediatr.* 2024: 12: 1402119. DOI: 10.3389/fped.2024.1402119. PMID: 38633329.
5. *Jagadisan B., Dhawan A.* Letter to the Editor: Pediatric acute liver failure management-view from the other side of the pond. *Liver Transpl.* 2023; 29 (6): E9-E10. DOI: 10.1097/LVT.0000000000000101. PMID: 36789651.
6. *Mishra S., Pallavi P.* Diagnosis and management of pediatric acute liver failure: ESPGHAN and NASPGHAN 2022. *Indian Pediatr.* 2022; 59 (4): 307–311. PMID: 35410966.
7. *Coilly A., Samuel D.* Paediatric acute liver failure: confirm the outbreak, find the cause and explore the mechanisms. *United European Gastroenterol J.* 2022; 10 (8): 789–790. DOI: 10.1002/ueg2.12306. PMID: 36094884.
8. *Hegarty R., Thompson R. J.* Genetic aetiologies of acute liver failure. *J Inherit Metab Dis.* 2024; 47 (4): 582–597. DOI: 10.1002/jimd.12733. PMID: 38499319.
9. *Putra J., Ng V. L., Perez-Atayde A. R.* Pediatric acute liver failure: a clinicopathological Pperspective. *Pediatr Dev Pathol.* 2022; 25 (4): 361–379. DOI: 10.1177/10935266211067893. PMID: 35356839.
10. *Deep A., Alexander E. C., Bulut Y., Fitzpatrick E., Grazioli S., Heaton N., Dhawan A.* Advances in medical management of acute liver failure in children: promoting native liver survival. *Lancet Child Adolesc Health.* 2022; 6 (10): 725–737. DOI: 10.1016/S2352-4642(22)00190-0. PMID: 35931098
11. *Kim W. R., Lake J. R., Smith J. M.* OPTN/SRTR 2017 annual data report: liver. *Am J Transplant.* 2019; 19 (Suppl 2): 184–283. DOI: 10.1111/ajt.15276. PMID: 30811890.
12. *Kwong A. J., Ebel N. H., Kim W. R., Lake J. R., Smith J. M., Schladt D. P., Skeans M., et al.* OPTN/SRTR 2020 annual data report: liver. *Am J Transplant.* 2022; 22: 204–309. DOI: 10.1111/ajt.16978. PMID: 35266621.
13. *Kaya S., Ekşi Bozbulut N.* Therapeutic plasma exchange in children with acute and acuteon-chronic liver failure: a single-center experience. *Exp Clin Transplant.* 2024; 22 (Suppl 1): 88–95. DOI: 10.6002/ect.MESOT2023.O12. PMID: 38385381.
14. *de Kleine R. H., Lexmond W. S., Buescher G., Sturm E., Kelly D., Lohse A. W., Lenz D., et al.* Severe acute hepatitis and acute liver failure of unknown origin in children: a questionnaire-based study within 34 paediatric liver centres in 22 European countries and Israel, April 2022. *Euro Surveill.* 2022; 272200369. DOI: 10.2807/1560-7917.ES.2022.27.19.2200369. PMID: 35551705.
15. *Kaliciński P., Grenda R., Szymczak M., Pietraszek P., Pawłowska J.* Multidisciplinary management of children with acute liver failure — Report on 104 children treated in single center. *Pediatr Transplant.* 2024; 28 (1): e14654. DOI: 10.1111/petr.14654. PMID: 37983943.
16. *Taylor S. A., Whitington P. F.* Neonatal acute liver failure. *Liver Transpl.* 2016; 22 (5): 677–85. DOI: 10.1002/lt.24433. PMID: 26946058.
17. *Mann J. P., Lenz D., Stamataki Z., Kelly D.* Common mechanisms in pediatric acute liver failure. *Trends Mol Med.* 2023; 29 (3): 228–240. DOI: 10.1016/j.molmed.2022.11.006. PMID: 36496278.
18. *Deep A., Tissieres P.* Editorial: Acute liver failure in children. *Front Pediatr.* 2024: 12: 1402119. DOI: 10.3389/fped.2024.1402119. PMID: 38633329.
19. *Amatya P., Kapalavai S. K., Deep A., Sankaranarayanan S., Krupanandan R., Sadasivam K., Ramachandran B.* Pediatric acute liver failure: sn experience of a pediatric intensive care unit from resource limited settings. *Front Pediatr.* 2022; 10: 956699. DOI: 10.3389/fped.2022.956699. PMID: 36120651.
20. *Силивончик Н. Н., Гавриленко Д. И.* «Острая-нахроническую» печеночная недостаточность. *Гепатология и гастроэнтерология.* 2018; 2 (2): 154–159. *Silivonchik N. N., Gavrilenko D. I.* «Acute-to-chronic» liver failure. *Hepatology and Gastroenterology = Gepatologija i Gastrojenterologija.* 2018; 2 (2): 154–159. (in Russ.)
21. *Kramarov S., Yevtushenko V., Seriakova I., Voronov O., Kyrytsia N., Zakordonets L. V., Shadrin V., et al.* A case report of acute liver failure in a child with hepatitis a virus and Epstein-Barr virus coinfection on the background of autoimmune sclerosing cholangitis. *Int Med Case Rep J.* 2024: 17: 801–807. DOI: 10.2147/IMCRJ.S477802. PMID: 39355258.
22. *Mieli-Vergani G., Vergani D., Czaja A. J., Manns M. P., Krawitt E. L., Vierling J. M., Lohse A. W., Montano-Loza A. J., et al.* Autoimmune hepatitis. *Nat. Rev. Dis. Primers.* 2018; 4: 18017. DOI: 10.1038/nrdp.2018.17. PMID: 29644994.
23. *Samanta A., Poddar U.* Pediatric acute liver failure: current perspective in etiology and management. *Indian J Gastroenterol.* 2024; 43 (2): 349–360. DOI: 10.1007/s12664-024-01520-6. PMID: 38466551.
24. *Lenz D., Jørgensen M. H., Kelly D., Cardinale V., Geerts A., Costa I. G., Fichtner A., et al.* Etiology and outcome of adult and pediatric acute liver failure in Europe. *J Pediatr Gastroenterol Nutr.* 2023; 77: 115–120. DOI: 10.1097/MPG.0000000000003777. PMID: 36930963.
25. *Di Giorgio A., Gamba S., Sansotta N., Nicastro E., Colledan M., D'antiga L.* Identifying the aetiology of acute liver failure is crucial to impact positively on outcome. *Children.* 2023; 10: 733. DOI: 10.3390/children10040733. PMID: 37189982.
26. *Бакулин И. Г., Абациева М. П., Белоусова Л. Н., Медведев Ю. В., Немцова Е. Г.* Острая печеночная

недостаточность — диагностические и прогностические проблемы. *Фарматека*. 2018; 9: 23–29. *Bakulin I. G., Abatsieva M. P., Belousova L. N., Medvedev Yu. V., Nemtsova E. G.* Acute liver failure — diagnostic and prognostic problems. *Pharmateca = Farmateka*. 2018; 9: 23–29. (in Russ.) DOI: 10.18565/pharmateca.2018.9.18-23.

27. *Alonso E. M., Horslen S. P., Behrens E. M., Doo E.* Pediatric acute liver failure of undetermined cause: a research workshop. *Hepatology*. 2017; 65: 1026–1037. DOI: 10.1002/hep.28944. PMID: 27862115.
28. *Schwabe R. F., Luedde T.* Apoptosis and necroptosis in the liver: a matter of life and death. *Nat Rev Gastroenterol. Hepatol*. 2018; 15: 738–752. DOI: 10.1038/s41575-018-0065-y. PMID: 30250076.
29. *Rao J., Zhang C., Wang P., Lu L., Qian X., Qin J., Pan X., et al.* C/EBP homologous protein (CHOP) contributes to hepatocyte death via the promotion of ERO1α signalling in acute liver failure. *Biochem J*. 2015; 466: 369–378. DOI: 10.1042/BJ20140412. PMID: 25387528.
30. *Larsen F. S.* Low-volume plasma exchange to treat children with acute liver failure. *J Clin Exp Hepatol*. 2023; 13 (2): 191–192. DOI: 10.1016/j.jceh.2023.01.015. PMID: 36950484.
31. *Paine C., Pichler R.* How we treat hyperammonemia in acute liver failure. *Clin J Am Soc Nephrol*. 2024; 19 (2): 254–256. DOI: 10.2215/CJN.0000000000000350. PMID: 37847521.
32. *Bernal W., Wendon J.* Acute liver failure. *N Engl J Med*. 2013; 369: 2525–2534. DOI: 10.1056/NEJMra1208937. PMID: 24369077.
33. Интенсивная терапия острой печёночной недостаточности у детей и подростков: учеб. пособие. *Быков Ю. В., Обедин А. Н., Волков Е. В., Зинченко О. В., Яцук И. В., Муравьёва А. А., Фишер В. В. и др.* Ставрополь: Изд-во СтГМУ; 2024: 76. Intensive care of acute liver failure in children and adolescents: a tutorial. *Bykov Yu. V., Obedin A. N., Volkov E. V., Zinchenko O. V., Yatsuk I. V., Muravyova A. A., Fisher V. V. et al.* Stavropol: Publishing house of StGMU; 2024: 76. (in Russ.).
34. *Shanmugam N. P., Bansal S., Greenough A., Verma A., Dhawan A.* Neonatal liver failure: aetiologies and management. State of the art. *Eur J Pediatr*. 2011; 170 (5): 573–581. DOI: 10.1007/s00431-010-1309-1. PMID: 20886352.
35. *Лебединский К. М.* Острая печеночноклеточная недостаточность: патогенез и возможности коррекции. *Практическая онкология*. 2024; 25 (2): 102–110. *Lebedinsky K. M.* Acute hepatocellular failure: pathogenesis and possibilities of correction. *Practical Oncology = Prakticheskaja Onkologija*. 2024; 25 (2): 102–110. (in Russ.). DOI: 10.31917/2502102.
36. *Sabapathy D. G., Desai M. S.* Acute liver failure in children. *Pediatr Clin North Am*. 2022; 69 (3): 465–495. DOI: 10.1016/j.pcl.2022.02.003. PMID: 35667757.
37. *Shah N. J., Royer A., John S.* Acute liver failure. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2025. PMID: 29493996.
38. *Abimannane A., Deepthi B., Bhowmick R., Parameswaran N.* Clinical profile and outcomes of children with acute liver failure in a tertiary care center in South India: a retrospective study. *Pediatr Gastroenterol Hepatol Nutr*. 2024; 27 (1): 43–52. DOI: 10.5223/pghn.2024.27.1.43. PMID: 38249636.
39. *Lutfi R., Abulebda K., Nitu M. E., Molleston J. P., Bozic M. A., Subbarao G.* Intensive care management of pediatric acute liver failure. *J Pediatr Gastroenterol Nutr*. 2017; 64 (5): 660–670. DOI: 10.1097/MPG.0000000000001441. PMID: 27741059.
40. *Kundan M., Gupta T., Sandeep G.* Acute liver failure. *Journal of Pediatric Critical Care*. 2019; 6 (5): 67–74. DOI: 10.21304/2019.0605.00535.
41. *Bhatia V., Lodha R.* Intensive care management of children with acute liver failure. *Indian J Pediatr*. 2010; 77 (11): 1288–1295. DOI: 10.1007/s12098-010-0167-1. PMID: 20799075.
42. *Lal B. B., Khanna R., Sood V., Alam S., Nagral A., Ravindranath A., Kumar A., et al.* Diagnosis and management of pediatric acute liver failure: consensus recommendations of the Indian Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ISPGHAN). *Hepatol Int*. 2024; 18 (5): 1343–1381. DOI: 10.1007/s12072-024-10720-3. PMID: 39212863.
43. *Лукашик С. П., Карпов И. А.* Острая печеночная недостаточность у взрослых. *Клиническая микробиология и антимикробная химиотерапия*. 2019; 21 (1): 46–55. *Lukashik S. P., Karpov I. A.* Acute liver failure in adults. *Clinical Microbiology and Antimicrobial Chemotherapy = Klinicheskaja Mikrobiologija i Antimikrobnaja Himioterapija*. 2019; 21 (1): 46–55. (in Russ.).
44. *Mekeirele M. M. M., Wilmer A.* Fluid Management in Liver Failure. In: Rational use of intravenous fluids in critically ill patients. 2023: 411–425. *SpringerLink*. DOI: 10.1007/978-3-031-42205-8_21.
45. *Squires J. E., Alonso E. M., Ibrahim S. H., Kasper V., Kehar M., Martinez M., Squires R. H.* North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Position Paper on the diagnosis and management of pediatric acute liver failure. *J Pediatr Gastroenterol Nutr*. 2022; 74 (1): 138–158. DOI: 10.1097/MPG.0000000000003268. PMID: 34347674.
46. *Yang X., Liu X., Wang L., Xu J., Wen J.* Hypoglycemia on admission in patients with acute on chronic liver failure: a retrospective cohort analyzing the current situation, risk factors, and associations with prognosis. *Ann Palliat Med*. 2023; 12 (1): 163–170. DOI: 10.21037/apm-22-1422. PMID: 36747390.
47. *Zou Y. G., Wang H., Li W. W., Dai D. L.* Challenges in pediatric inherited/metabolic liver disease: focus on the disease spectrum, diagnosis and management of relatively common disorders. *World J Gastroenterol*. 2023; 29 (14): 2114–2126. DOI: 10.3748/wjg.v29.i14.2114. PMID: 37122598.
48. *Zechner C., Adams-Huet B., Gregory B., Neyra J. A., Rule J. A., Li X., Rakela J., et al.* Hypophosphatemia in acute liver failure of a broad range of etiologies is associated with phosphaturia without kidney damage or phosphatonin elevation. *Transl Res*. 2021: 238: 1–11. DOI: 10.1016/j.trsl.2021.07.003. PMID: 34298149.
49. *Abenavoli L., Maurizi V., Boccuto L., Di Berardino A., Giostra N., Santori P., Scarcella M. L., et al.* Nutri-

tional support in acute liver failure. *Diseases*. 2022; 10 (4): 108.
DOI: 10.3390/diseases10040108. PMID: 36412602.
50. *Hasse J. M., DiCecco S. R.* Enteral nutrition in chronic liver disease: translating evidence into practice. *Nutr Clin Pract.* 2015; 30: 474–87.
DOI: 10.1177/0884533615591058. PMID: 26113562.
51. *Stravitz R. T., Fontana R. J., Karvellas C., Durkalski V., McGuire B., Rule J. A., Tujios S., et al.* Future directions in acute liver failure. *Hepatology*. 2023; 78 (4): 1266–1289.
DOI: 10.1097/HEP.0000000000000458.
PMID: 37183883.
52. *Стец В. В., Половников С. Г., Журавлев А. Г., Шестопалов А. Е.* Нутритивно-метаболическая коррекция в интенсивной терапии перитонита. *Раны и раневые инфекции. Журнал имени проф. Б. М. Костюченка*. 2016; 3 (1): 25–31. *Stets V. V., Polovnikov S. G., Zhuravlev A. G., Shestopalov A. E.* Nutritional and metabolic correction in intensive care of peritonitis. *Wounds and Wound Infections. The prof. B. M. Kostyuchenok Journal = Rany i Ranevye Infekcii. Zhurnal imeni prof. B. M. Kostjuchjonka*. 2016; 3 (1): 25–31. (in Russ.).
53. *Karvellas C. J., Cavazos J., Battenhouse H., Durkalski V., Balko J., Sanders C., Leeet W. M., et al.* Effects of antimicrobial prophylaxis and blood stream infections in patients with acute liver failure: a retrospective cohort study. *Clin Gastroenterol Hepatol.* 2014; 12 (11): 1942–9.e1.
DOI: 10.1016/j.cgh.2014.03.011. PMID: 24674942.
54. *Dong Y., Sun D., Wang Y., Du Q., Zhang Y., Han R., Teng M., et al.* Evaluation of the current guidelines for antibacterial therapy strategies in patients with cirrhosis or liver failure. *BMC Infect Dis.* 2022; 22 (1): 23.
DOI: 10.1186/s12879-021-07018-2. PMID: 34983426.
55. *Liu C. C., Chen I. W., Liu P. H., Wu J. Y., Liu T. H., Huang P. Y., Yu C. H., et al.* Efficacy of propofol-based anesthesia against risk of brain swelling during craniotomy: a meta-analysis of randomized controlled studies. *J Clin Anesth.* 2024: 92: 111306.
DOI: 10.1016/j.jclinane.2023.111306.
56. *Shalimar S., Acharya S. K.* Management in acute liver failure. *J Clin Exp Hepatol.* 2014; 5 (1): 104–115.
DOI: 10.1016/j.jceh.2014.11.005. PMID: 26041950.
57. *Заболотских И. Б., Громова Е. Г., Кузовлев А. Н., Лебединский К. М., Лубнин А. Ю., Осовских В. В., Синьков С. В. с соавт.* Периоперационное ведение взрослых пациентов с сопутствующими заболеваниями печени. Методические рекомендации. Анестезиология и реаниматология. 2022; 3: 5–24. *Zabolotskikh I. B., Gromova E. G., Kuzovlev A. N., Lebedinsky K. M., Lubnin A. Yu., Osovskikh V. V., Sinkov S. V., et al.* Perioperative management of patients with concomitant liver diseases. Guidelines. *Russian Journal of Anesthesiology and Reanimatology = Anesteziologiya i Reanimatologiya*. 2022; 3: 5–24. (in Russ.).
DOI: 10.17116/anaesthesiology20220315.
58. *Lee W. M., Stravitz T. R., Fontana R. J.* Safety and tolerability of Ornithine Phenylacetate to lower ammonia in Acute Liver Failure: Preliminary report of the STOP-ALF Trial. *Hepatology.* 2015; 62 (suppl): 319A.
59. *Бойко А. В., Лукашевич Н. В.* Механизмы развития и медикаментозная терапия отека головного мозга при спонтанном внутримозговом кровоизлиянии. *Медицинские новости*. 2022; (7): 42–45. *Boyko A. V., Lukashevich N. V.* Mechanisms of development and drug therapy of cerebral edema after spontaneous intracerebral hemorrhage. *Medical News = Medicinskie Novosti*. 2022; (7): 42–45. (in Russ.).
60. Диабетический кетоацидоз в педиатрической практике: учеб. пособие. *Быков Ю. В., Обедин А. Н., Волков Е. В., Зинченко О. В., Яцук И. В., Муравьёва А. А., Фишер В. В.* Ставрополь: Изд-во СтГМУ, 2023: 60. Diabetic ketoacidosis in pediatric practice: textbook. *Bykov Yu. V., Obedin A. N., Volkov E. V., Zinchenko O. V., Yatsuk I. V., Muravyova A. A., Fisher V. V.* Stavropol: Publishing house of StGMU; 2023: 60. (in Russ.).
61. *Mason A., Malik A., Ginglen J. G.* Hypertonic fluids. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2023. PMID: 31194351.
62. *Webster D. L., Fei L., Falcone R. A., Kaplan J. M.* Higher-volume hypertonic saline and increased thrombotic risk in pediatric traumatic brain injury. *J Crit Care*. 2015; 30: 1267–1271.
DOI: 10.1016/j.jcrc.2015.07.022. PMID: 26307005.
63. *Tujios S., Stravitz R. T., Lee W. M.* Management of acute liver failure: update 2022. *Semin Liver Dis.* 2022; 42 (3): 362–378.
DOI: 10.1055/s-0042-1755274. PMID: 36001996.
64. *Kochanek P. M., Carney N., Adelson P. D., Ashwal S., Bell M. J., Bratton S., Carson S., et al.* Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents–second edition. *Pediatr Crit Care Med.* 2012; 13 (suppl 1): S1–82.
DOI: 10.1097/PCC.0b013e31823f435c.
PMID: 22217782.
65. *Burton L., Bhargava V., Kong M.* Point-of-care ultrasound in the pediatric intensive care unit. *Front Pediatr*. 2022: 9: 830160.
DOI: 10.3389/fped.2021.830160. PMID: 35178366.
66. *Fernández J., Bassegoda O., Toapanta D., Bernal W.* Acute liver failure: a practical update. *JHEP Rep.* 2024; 6 (9): 101131.
DOI: 10.1016/j.jhepr.2024.101131. PMID: 39170946.
67. *Leventhal T. M., Liu K. D.* What a nephrologist needs to know about acute liver failure. *Adv Chronic Kidney Dis.* 2015; 22 (5): 376–381.
DOI: 10.1053/j.ackd.2015.06.006. PMID: 26311599.
68. *Cardoso F. S., Gottfried M., Tujios S., Olson J. C., Karvellas C. J.* Continuous renal replacement therapy is associated with reduced serum ammonia levels and mortality in acute liver failure. *Hepatology.* 2018; 67 (2): 711–720.
DOI: 10.1002/hep.29488. PMID: 28859230.
69. *Jalanko H., Pakarinen M.* Combined liver and kidney transplantation in children. *Pediatr Nephrol (Berlin, Germany)*. 2014; 29 (5): 805–814.
DOI: 10.1007/s00467-013-2487-7. PMID: 23644898.
70. *Nadim M. K., Sung R. S., Davis C. L., Andreoni K. A., Biggins S. W., Danovitch G. M., Feng S., et al.* Simultaneous liver-kidney transplantation summit: current state and future directions. *Am J Transplant.* 2012;

12 (11): 2901–2908.
DOI: 10.1111/j.1600-6143.2012.04190.x.
PMID: 22822723.

71. *Ankawi G., Neri M., Zhang J., Breglia A., Ricci Z., Ronco C.* Extracorporeal techniques for the treatment of critically ill patients with sepsis beyond conventional blood purification therapy: the promises and the pitfalls. *Crit Care.* 2018; 22: 262.
DOI: 10.1186/s13054-018-2181-z. PMID: 30360755.
72. *Vo L. T., Do V. C., Trinh T. H., Vu T., Nguyen T. T.* Combined therapeutic plasma exchange and continuous renal replacement therapy in children with Dengue-associated acute liver failure and shock syndrome: single-center cohort from Vietnam. *Pediatr Crit Care Med.* 2023; 24 (10): 818–828.
DOI: 10.1097/PCC.0000000000003304.
PMID: 37310173.
73. *Кабанов М. Ю., Семенцов К. В., Бояринов Д. Ю., Мянзелин М. Н., Беликова М. Я., Алексеев В. В.* Трудности оценки тяжести дисфункции печени при механической желтухе. *Анналы хирургической гепатологии.* 2021; 26 (2): 129–136. *Kabanov M. Yu., Sementsov K. V., Boyarinov D. Yu., Myanzelin M. N., Belikova M. Ya., Alekseev V. V.* Difficulties in assessing the severity of liver dysfunction for obstructive jaundice. *Annals of HPB Surgery = Annaly` Khirurgicheskoy Gepatologii.* 2021; 26 (2): 129–136. (in Russ.).
DOI: 10.16931/1995-5464.2021-2-129-136.
74. *Kim A., Niu B., Woreta T., Chen P. H.* Clinical considerations of coagulopathy in acute liver failure. *J Clin Transl Hepatol.* 2020; 8 (4): 407–413.
DOI: 10.14218/JCTH.2020.00058. PMID: 33447524.
75. *European Association for the Study of the Liver.* EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. *J Hepatol.* 2017; 66 (5): 1047–1081.
DOI: 10.1016/j.jhep.2016.12.003. PMID: 28417882.
76. *Заболотских И. Б., Проценко Д. Н. (ред.).* Интенсивная терапия: национальное руководство: в 2-х томах Т. II. 2-е издание, переработанное и дополненное М.: ГЭОТАР-Медиа; 2020: 1072. *Zabolotskikh I. B., Protsenko D. N. (eds.).* Intensive care: National guidelines: in 2 volumes, vol. II. 2nd edition, revised and expanded Moscow: GEOTAR-Media; 2020: 1072. (in Russ.). ISBN 978-5-9704-5018-5.
77. *Pan J. J., Fontana R. J.* CAQ Corner: acute liver failure management and liver transplantation. *Liver Transpl.* 2022; 28 (10): 1664–1673.
DOI: 10.1002/lt.26503. PMID: 35574981.
78. *Agarwal B., Wright G., Gatt A., Riddell A., Vemala V., Mallett S., Chowdary P., et al.* Evaluation of coagulation abnormalities in acute liver failure. *J Hepatol.* 2012; 57 (4): 780–786.
DOI: 10.1016/j.jhep.2012.06.020. PMID: 22735303.
79. *Zoica B. S., Deep A.* Extracorporeal renal and liver support in pediatric acute liver failure. *Pediatr Nephrol.* 2021; 36: 1119–1128.
DOI: 10.1007/s00467-020-04613-4. PMID: 32500250.
80. *Jain V., Dhawan A.* Extracorporeal liver support systems in paediatric liver failure. *J Pediatr Gastroenterol Nutr.* 2017; 64: 855–863.
DOI: 10.1097/MPG.0000000000001500.
PMID: 28248208.
81. *Ибадов Р. А., Исмаилов Е. Л., Ибрагимов С. Х.* Применение экстракорпоральных систем протезирования функций печени при острой декомпенсированной печеночной недостаточности. *Общая реаниматология.* 2021; 17 (4): 12–21. *Ibadov R. A., Ismailov Ye. L., Ibragimov S. Kh.* The use of extracorporeal liver support systems in acute decompensated liver failure. *General Reanimatology = Obshchaya Reanimatologiya.* 2021; 17 (4): 12–21. (in Russ&Eng.).
DOI: 15360/1813-9779-2021-4-12-21.
82. *Кутепов Д. Е., Пасечник И. Н., Сальников П. С.* Возможности экстракорпоральных методов лечения печеночной недостаточности. *Хирургия. Журнал им. Н. И. Пирогова.* 2014; 2: 55–58. *Kutepov D. E., Pasechnik I. N., Salnikov P. S.* The opportunities for extracorporeal treatment of liver failure. *Pirogov Russian Journal of Surgery = Khirurgiya. Zhurnal im. N. I. Pirogova.* 2014; 2: 55–58. (in Russ.).
83. *Arikan A. A., Srivaths P., Himes R. W., Pekkucuksen N. T., Lam F., Nguyen N., Miloh T., et al.* Hybrid extracorporeal therapies as a bridge to pediatric liver transplantation. *Pediatr Crit Care Med.* 2018; 19: e342–9.
DOI: 10.1097/PCC.0000000000001546.
PMID: 29652753.
84. *Larsen F. S., Schmidt L. E., Bernsmeier C.* High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. *J Hepatol.* 2016; 64: 69–78.
DOI: 10.1016/j.jhep.2015.08.018. PMID: 26325537.
85. *Hanish S. I., Stein D. M., Scalea J. R., Essien E. O., Thurman P., Hutson W. R., Bartlett S. T.,* et al. Molecular adsorbent recirculating system effectively replaces hepatic function in severe acute liver failure. *Ann Surg.* 2017; 266: 677–684.
DOI: 10.1097/SLA.0000000000002361.
PMID: 28692474.
86. *Lexmond W. S., Van Dael C. M., Scheenstra R., Goorhuis J. F., Sieders E., Verkade H. J., Van Rheenen P. F., et al.* Experience with molecular adsorbent recirculating system treatment in 20 children listed for high-urgency liver transplantation. *Liver Transpl.* 2015; 21: 369–80.
DOI: 10.1002/lt.24037. PMID: 25366362.
87. *Alnagar A. M., Hakeem A. R., Daradka K., Kyrana E., Methga M., Palaniswamy K., Rajwal S.,* et al. Long-term outcomes of pediatric liver transplantation in acute liver failure vs end-stage chronic liver disease: a retrospective observational study. *World J Transplant.* 2023; 13 (3): 96–106.
DOI: 10.5500/wjt.v13.i3.96. PMID: 36968135.
88. *Венцловайте Н. Д., Ефремова Н. А., Горячева Л. Г., Герасимова О. А.* Трансплантация печени у детей: опыт последних десятилетий, актуальные проблемы и пути их решения. *Детские инфекции.* 2020; 19 (2): 52–57. *Venslovayte N. D., Efremova N. A., Goriacheva L. G., Gerasimova O. A.* Liver transplantation in children: the experience of last decades, current problems and solutions. *Children Infections = Detskie Infekcii.* 2020; 19 (2): 52–57. (in Russ.).
DOI: 10.22627/2072-8107-2020-19-2-52-57.
89. *Bartlett J. M., Yanni G., Kwon Y., Emamaullee J.* Pediatric acute liver failure: reexamining key clinical

features, current management, and research prospects. *Liver Transpl*. 2022; 28 (11): 1776–1784. DOI: 10.1002/lt.26500. PMID: 35557028.

90. *Kim W. R., Lake J. R., Smith J. M., Skeans M. A., Schladt D. P., Edwards E. B., Harper A. M., et al.* OPTN/SRTR 2015 Annual Data Report: liver. *Am J Transplant*. 2017; 17: 174–251. DOI: 10.1111/ajt.14126. PMID: 28052604.

91. *Nulty J., Anand H., Dhawan A.* Human hepatocyte transplantation: three decades of clinical experience and future perspective. *Stem Cells Transl Med*. 2024; 13 (3): 204–218. DOI: 10.1093/stcltm/szad084. PMID: 38103170.

Received 21.11.2024
Accepted 25.02.2025
Accepted in press 25.02.2025

https://doi.org/10.15360/1813-9779-2025-2-2554

Clinical Application of Xenon in Subanesthetic Concentrations (Review)

Mikhail E. Politov*, Sofia V. Podprugina, Elizaveta N. Zolotova, Pavel V. Nogtev, Yulia S. Agakina, Svetlana G. Zhukova, Andrey G. Yavorovsky

I. M. Sechenov First Moscow State Medical University, Ministry of Health of Russia,
8 Trubetskaya Str., Bldg. 2, 119991 Moscow, Russia

For citation: *Mikhail E. Politov, Sofia V. Podprugina, Elizaveta N. Zolotova, Pavel V. Nogtev, Yulia S. Agakina, Svetlana G. Zhukova, Andrey G. Yavorovsky.* Clinical Application of Xenon in Subanesthetic Concentrations (Review). *Obshchaya Reanimatologiya = General Reanimatology.* 2025; 21 (2): 55–67. https://doi.org/10.15360/1813-9779-2025-2-2554 [In Russ. and Engl.]

***Correspondence to:** Mikhail E. Politov, politov.mikhail@gmail.com

Summary

Xenon is considered to be the safest general anesthetic agent with organ-protective properties. In subanesthetic doses, it is recognized as a promising therapeutic agent in various medical fields.

The aim of this review was to systematically summarize scientific data on the potential therapeutic use of xenon for organ system protection outside the context of anesthetic support during surgery and perioperative analgesia.

Publications were searched in the databases PubMed, Google Scholar, Cochrane Library, and eLIBRARY.RU from August to September 2024. A total of 33 publications on the clinical use of inhaled xenon for therapeutic purposes from 2002 to 2023 were selected, including 12 randomized controlled trials (RCTs), 8 prospective controlled studies, 2 prospective comparative studies, 6 prospective uncontrolled studies, and 2 clinical observations. An additional 32 publications were used to discuss various aspects related to the topic of the review.

Conclusion. The literature review showed that inhaled xenon at subanesthetic doses has potential neuroprotective, cardioprotective, and therapeutic effects for the treatment of addictive and neurotic disorders, as well as oncologic and pulmonary conditions. Despite some promising results, the number of RCTs remains limited, and the existing studies have methodological limitations, small sample sizes, and a high risk of systematic error. Definitive conclusions regarding the clinical efficacy and safety of inhaled xenon require further large-scale randomized trials.

Keywords: xenon; xenon inhalation; therapeutic use of xenon; neuroprotection; stroke; traumatic brain injury; cardioprotection; myocardial infarction; withdrawal syndrome; neurotic disorders; oncology; chronic pain syndrome; organ protection

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

Information about the authors:
Mikhail E. Politov: http://orcid.org/0000-0003-0623-4927
Sofia V. Podprugina: http://orcid.org/0009-0002-9614-7877
Elizaveta N. Zolotova: http://orcid.org/0000-0002-1608-6131
Pavel V. Nogtev: http://orcid.org/0000-0002-5553-0880
Yulia S. Agakina: http://orcid.org/0000-0002-3556-2703
Svetlana G. Zhukova: http://orcid.org/0000-0001-5468-3183
Andrey G. Yavorovsky: http://orcid.org/0000-0001-5103-0304

Introduction

Xenon has been used in anesthesia since the late 20th century. It does not undergo metabolic transformation and is eliminated unchanged by respiration.

Xenon anesthesia is associated with faster induction and emergence, absence of respiratory, renal, and hepatic toxicity, and less pronounced hemodynamic changes compared with other anesthetic agents (both inhalational and intravenous) [1–4]. Extensive research on xenon has demonstrated its ability to protect organs from injury.

Large systematic reviews [5–7] have described the main mechanisms underlying the organoprotective effects of xenon:

— Inhibition of glutamate receptors (NMDA, AMPA, and kainate), preventing excitotoxic damage during ischemia-reperfusion injury.

— Activation of potassium channels (TREK-1, KATP), resulting in reduced neuronal excitability and neuroprotective effects.

— Modulation of intracellular signaling pathways (PI3K/Akt, MAPK, RISK and SAFE) that attenuate apoptosis and myocardial injury.

— Regulation of transcription factors (CREB, HIF-1α) that enhance the expression of cytoprotective and anti-apoptotic genes.

— Modulation of serotonergic, cholinergic and dopaminergic systems, which explains its influence on anesthesia and mental and emotional states.

The identified mechanisms of action, along with experimental data, support the recognition of xenon not only as a general anesthetic but also as a standalone pharmacological agent with the potential to reduce tissue injury, provide analgesia, modulate mental and emotional state, and

exhibit a relatively favorable safety profile at subanesthetic doses.

This review aims to consolidate the scientific evidence on the potential therapeutic applications of xenon for organ protection in different systems of the body.

Materials and Methods

The literature search was conducted using international and Russian databases of scientific publications, including PubMed, Google Scholar, Cochrane Library, and eLIBRARY.RU. Search queries were formulated between August 1, 2024, and September 1, 2024, using combinations of the following key terms: «xenon therapy,» «xenon inhalation,» «subanesthetic xenon,» as well as their Russian equivalents («ксенон терапия», «субанестетические дозы ксенона», «ингаляции ксенона»). Additional terms specifying the therapeutic applications of xenon were also included, such as «neuroprotection», «cardioprotection», «pain management», «oncology», «lung diseases», «нейропротекция», «кардиопротекция», «онкология».

Selection criteria required studies to be original clinical research focusing on the therapeutic effects of inhaled xenon at subanesthetic concentrations. Articles were excluded if they examined only xenon as an anesthetic agent, as were review articles and experimental (preclinical) studies.

Manual reference screening of selected publications was performed to identify additional relevant sources. In addition, semantic search techniques using artificial intelligence models (Semantic Scholar, Research Rabbit, and Neurosearch on eLIBRARY.RU) were used to identify additional studies that met the inclusion criteria.

As a result of the selection process, 65 publications were included in the review. Of these, 33 studies focused on the clinical use of inhaled xenon for therapeutic purposes between 2002 and 2023, including 12 randomized controlled trials, 8 prospective controlled studies, 2 prospective comparative studies, 6 prospective uncontrolled studies, and 2 clinical case reports (Table 1). An additional 32 publications were used to discuss various aspects related to the review topic.

Therapeutic Applications of Xenon for Neuroprotection

Systematic reviews and meta-analyses of preclinical studies [5, 8, 9] have shown that xenon has significant neuroprotective effects in several models of acute brain injury, including cardiac arrest, traumatic brain injury, and stroke. The greatest improvements in both short- and long-term neurological outcomes were observed when xenon was administered after the initial injury (postconditioning), even when treatment was delayed up to 2–3 hours after ischemic brain injury.

The neuroprotective effect of xenon was dose-dependent, with higher concentrations (50–75%) providing greater benefit than lower concentrations (15–37.5%).

A key factor in the safe use of xenon in brain injury is its effect on cerebral perfusion. Studies have shown that xenon inhalation can cause a dose-dependent increase in intracranial pressure [10, 11]. In patients with pre-existing elevated intracranial pressure, high concentrations of xenon may reduce cerebral perfusion. However, subanesthetic doses (30–32%) did not cause clinically significant changes in cerebral blood flow [12] or intracranial pressure [13].

The first studies on the neuroprotective effects of xenon were conducted by Finnish researchers in patients with post-hypoxic encephalopathy following out-of-hospital cardiac arrest. These studies investigated the effects of xenon on both the cardiovascular system [14, 15] and the central nervous system [16].

In the randomized controlled XeHypotheCA trial, R. Laitio and colleagues [16] investigated the effect of xenon on white matter injury in 110 coma patients after cardiac arrest. The xenon group (*N*=55) received 40% xenon inhalation combined with therapeutic hypothermia (33°C), while the control group (*N*=55) received hypothermia alone for 24 hours. Global fractional anisotropy coefficient, an indicator of white matter integrity, was 3.8% higher in the xenon group (95% CI, 1.1–6.4%), suggesting less white matter damage. However, clinical outcomes were not significantly different between groups, with a six-month mortality rate of 27.7% in the xenon group versus 34.5% in the control group (*P*=0.053). To further evaluate the efficacy of this approach, the authors initiated a large multicenter trial, XePOHCAS (NCT03176186, clinicaltrials.gov), which enrolled 1,436 patients.

The combined effects of xenon inhalation and hypothermia have also been studied in neonatal brain injury. Small studies by D. Azzopardi (*N*=14) [17] and J. Dingley et al. (*N*=14) [18] showed that inhaled xenon at concentrations of 30–50% effectively suppressed seizure activity in neonates. However, abrupt discontinuation of xenon therapy was associated with seizure recurrence. When xenon was gradually withdrawn over 40 minutes, seizure activity did not recur [18]. A similar anticonvulsant effect was reported in a clinical case of a five-year-old child with super-refractory status epilepticus [19].

To further evaluate the neuroprotective properties of xenon, D. Azzopardi and colleagues conducted a randomized controlled trial with two parallel groups [20]. The study included 92 neonates (gestational age 36–43 weeks) with signs of severe encephalopathy and abnormal electroencephalo-

graphic activity. The investigators compared two groups: one receiving standard therapeutic hypothermia alone (*N*=46) and the other receiving hypothermia combined with 30% inhaled xenon for 24 hours (*N*=46). There were no significant differences in brain injury between the groups based on MRI findings. The authors concluded that delayed administration of xenon in combination with hypothermia did not reduce neuronal injury, possibly due to the late initiation of treatment (median onset was 10.0 hours after birth) and the severity of the initial cerebral insult.

In a randomized controlled pilot study, O. Grebenchikov and colleagues [21] investigated the effects of short-term xenon sedation in patients with acute ischemic stroke. The study included mechanically ventilated patients with a Glasgow Coma Scale (GCS) score of less than 12, a Full Outline of UnResponsiveness (FOUR) score of less than 13, and a National Institutes of Health Stroke Scale (NIHSS) score of greater than 15. Immediately after endotracheal intubation, patients in the intervention group received 6 hours of inhalation sedation with 40% xenon, while the control group received propofol.

On admission, the median GCS score was 10 (IQR 10–11) in the xenon group and 10.5 (IQR 9–12) in the control group (*P*=0.721). By day 8, a significant difference had emerged: 13 (IQR 11–15) in the xenon group versus 7 (IQR 6–8) in the control group (*P*=0.026). Improvements in the FOUR score were observed as early as day 2: 14 (IQR 12–15) in the xenon group versus 12 (IQR 10–13) in the control group (*P*=0.038), with further divergence by day 8: 14 (IQR 13–15) versus 8 (IQR 7–8) (*P*=0.026). NIHSS neurological deficit was also significantly lower in the xenon group on day 8: 24 (IQR 12–27) compared to 34 (IQR 34–34) in the control group (*P*=0.007).

In the xenon group, the level of the neuronal injury marker S100b decreased from 0.188 (0.172–0.201) to 0.098 (0.075–0.116) ng/mL. In contrast, the control group showed an increase from 0.196 (0.158–0.213) to 0.396 (0.368–0.418) ng/mL, resulting in a fourfold increase by day 8 (*P*=0.007).

However, the publication [21] has several limitations, including lack of data on time to hospital admission, use of thrombolytic therapy or thrombectomy, and comorbidities, as well as lack of between-group comparisons. These omissions introduce a risk of systematic bias and weaken the validity of conclusions regarding the effects of xenon.

In a randomized controlled trial, A. Shpichko and colleagues [22, 23] investigated the effects of inhalational xenon sedation on the level of consciousness and spastic activity in patients with chronic disorders of consciousness (vegetative state or minimally conscious state) after severe traumatic brain injury (TBI) [22]. They also evaluated the changes of biomarkers related to neuroinflammation, neuronal injury, and neurogenesis [23]. In the intervention group (*N*=12), participants received daily 30-minute sessions of 30% xenon inhalation for 7 days. The control group (*N*=12) received an oxygen-air gas mixture.

On day 3, the xenon group showed a reduction in inflammatory markers (IL-6 and AGP), although the differences were not statistically significant. This may be due to the inherently low levels of neuroinflammation in the chronic phase of chronic disorder of consciousness (typically beyond 28 days post TBI). In support of this, S100b levels remained very low in both groups (<0.005 pg/mL).

A significant increase in the level of brain-derived neurotrophic factor (BDNF) was observed in the xenon group — 0.1271 (0.046; 0.2695) pg/mL vs. 0.054 (0.021; 0.093) pg/mL in the control group (*P*=0.04), which may indicate activation of neuronal regeneration [23].

Consciousness was assessed using the Coma Recovery Scale-Revised (CRS-R) [24]. In the control group, scores changed minimally from 8 (6; 10) to 9 (7; 11) (*P*>0.05). In contrast, the xenon group showed a marked improvement, with scores increasing from 9 (7; 10) to 15 (12; 17) (*P*=0.021); the between-group difference was statistically significant (*P*=0.038). Xenon therapy did not exert a substantial effect on spastic activity, although a transient reduction in muscle tone was observed during sessions [22].

With respect to the effect of xenon anesthesia on the incidence of cognitive impairment, a meta-analysis by Y.-S. Yang et al. [25] did not reveal any significant advantage in reducing the frequency of postoperative neurocognitive disorders. However, the authors emphasized the need for further research.

Taken together, these findings suggest that during the acute phase of brain injury, xenon may reduce neuroinflammation and neuronal excitability, thereby decreasing the risk of spreading depolarization [26]. In later stages, its effects appear to involve inhibition of apoptosis and promotion of neuronal recovery mechanisms [8]. While xenon's neuroprotective properties appear promising, current evidence remains insufficient to draw definitive conclusions. Ongoing studies, such as the XePOHCAS trial, are expected to provide a more comprehensive understanding. Furthermore, a large-scale investigation of xenon use in patients with subarachnoid hemorrhage (Xe-SAH [27]) is currently underway, with preliminary results anticipated by 2027. These studies may significantly enhance the current understanding of xenon's therapeutic potential in neuroprotection.

Therapeutic Use of Xenon for Cardioprotection

The cardioprotective effects of xenon, particularly its ability to reduce the extent of ischemic

myocardial injury, have been demonstrated in various experimental models. Administration of xenon resulted in a significant reduction in the size of myocardial necrosis zones [5]. These studies used subanesthetic concentrations, taking into account the high minimum alveolar concentration (MAC) values observed in experimental animals (pigs ≈119% [28], rats ≈161%, mice ≈95% [29]).

A study by O. Arola et al. [14] investigated the effects of xenon inhalation on the cardiovascular system in comatose patients after out-of-hospital cardiac arrest. In this RCT, patients in the main group (*N*=16) received xenon inhalation (47% for 25.5 hours) combined with therapeutic hypothermia, while the control group (*N*=20) received hypothermia alone. The incidence of serious adverse events, including in-hospital mortality, status epilepticus, and acute kidney injury, was comparable between groups. Notably, the xenon group required lower cumulative doses of norepinephrine (2.95 mg vs. 5.30 mg; *P*=0.06) and had a lower heart rate (*P*=0.04). The 72-hour increase in troponin T levels was also lower in the xenon group: 0.08 μg/L compared with 0.62 μg/L in the hypothermia-only group (median difference –0.52 μg/L; 95% CI, –1.72 to –0.06 μg/L; *P*=0.04).

These findings were subsequently confirmed by the same group of authors in a larger study (*N*=110) XeHypotheCA described previously [16]. In addition to assessing changes in brain tissue, the authors also investigated the effect of xenon on ischemic myocardial injury [15]. In the group receiving 40% xenon inhalation for 24 hours, a significant reduction in troponin levels at 72 hours was observed compared to the control group (adjusted mean difference: 0.66; 95% CI, –1.16 to –0.16; *P*=0.01). This xenon-induced reduction in troponin T concentration was independent of the primary intervention (percutaneous coronary intervention). An increase in troponin T from baseline to any time point was a significant predictor of 6-month mortality in both groups.

Building on this, A. Saraste and colleagues [30] used the same xenon and hypothermia protocol in patients after out-of-hospital cardiac arrest and evaluated echocardiographic changes after 24 hours of exposure. A significantly higher left ventricular ejection fraction (LVEF) was observed in the xenon group (*N*=17) compared to controls (*N*=21): 50±10% vs. 42±10%, *P*=0.014. Global longitudinal systolic strain was also significantly better in the xenon group (–14.4±4.0% vs. –10.5±4.0%, *P*=0.006). Prolonged xenon inhalation improved longitudinal strain in nonischemic myocardial segments. No significant between-group differences were found for diastolic function parameters.

Thus, xenon inhalation combined with therapeutic hypothermia was associated with less myocardial injury [14, 15] and greater improvement in left ventricular systolic function compared with hypothermia alone in patients resuscitated from out-of-hospital cardiac arrest [30].

A clinical study by I. Molchanov et al. [31] investigated the effect of xenon inhalation on the course of acute coronary syndrome (ACS). The main group included 20 patients (16 with acute myocardial infarction and 4 with unstable angina) who received xenon inhalation (25–50%, 20–40 minutes per session) in addition to standard therapy. The control group consisted of 15 patients (11 with AMI, 4 with unstable angina). The inhalation course lasted 3 to 5 days. Xenon had no effect on blood pressure or heart rate. However, according to noninvasive hemodynamic monitoring (bioimpedance), the last inhalation session was associated with an increase in cardiac index from 2.90±0.6 to 3.25±0.9 L/min/m² and a decrease in systemic vascular resistance (SVR) from 1389.5±158.2 to 1290.2±149.1 dyn×s/cm^{-5}×m². Echocardiographic assessment also showed a significant reductionin pulmonary artery systolic pressure from 33.41±3.22 to 29.84±1.69 mmHg (*P*<0.05).

The authors reported a more pronounced reduction in biomarkers of myocardial injury on day 3, as well as a reduction in hypercoagulability as assessed by thromboelastography in the xenon-treated group. However, the study was limited by its observational design, lack of hemodynamic data in the control group, and lack of between-group comparisons of myocardial injury markers. In addition, the potential effect of standard anticoagulant therapy on hemostatic parameters was not considered. These factors make it difficult to interpret the therapeutic efficacy of xenon in this context.

A study by V. Potievskaya et al [32] investigated the effects of xenon inhalation on the cardiovascular system. No significant changes were observed on the ECG, including QTc interval duration or repolarization processes. QTc prolongation was observed only in the control group. No arrhythmias were reported. Analysis of hemodynamic parameters showed a similar, clinically insignificant decrease in both systolic and diastolic blood pressure in both groups, with no effect on heart rate.

Regarding the cardioprotective effects of xenon in the context of anesthesia, a large randomized controlled trial (*N*=492) conducted by J. Hofland et al. [33] found that xenon anesthesia during coronary artery bypass grafting (CABG) had a cardioprotective profile comparable to that of sevoflurane and more pronounced than that of propofol. However, the clinical significance of these differences remains uncertain.

In conclusion, xenon therapy appears to be safe for patients with cardiovascular disease. It may provide benefits by reducing myocardial reperfusion injury and exerting anti-inflammatory effects. However, further randomized controlled trials are needed to assess its impact on clinical outcomes.

Use of Xenon in the Treatment of Addictive Disorders

Studies on the intensive treatment of severe alcohol and drug withdrawal syndromes have highlighted the organoprotective properties of xenon. S. Naumov et al. [34] showed that xenon inhalation reduced cortisol levels (from 504.9±35.4 to 409.6±40.0 nmol/L) and growth hormone levels (from 7.15±0.72 to 1.75±0.9 ng/mL) and stabilized blood glucose levels, indicating an anti-stress effect. In addition, an improvement in liver function was observed, as evidenced by a decrease in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activity.

O. Strepetova [35] reported that in moderate to severe alcohol intoxication, xenon inhalation not only reduced the incidence and duration of hyperactive delirium (6.1±0.7 days vs. 8.7±2.1 days in the control group, P=0.018), but also shortened the duration of mechanical ventilation. In addition, patients receiving xenon required lower doses of vasopressors and positive inotropic agents (P=0.003).

Several studies have shown that xenon administration accelerates cognitive recovery and enhances its neuroprotective properties [36–38]. B. Tsygankov reported a trend toward cerebral hemodynamic normalization in patients undergoing xenon therapy [39]. When used as part of the intensive treatment of severe withdrawal syndrome, xenon reduced the need for anxiolytics and antipsychotics, thereby reducing the risk of adverse effects associated with standard therapy, such as neuroleptic syndrome, excessive sedation, and orthostatic disturbances [39]. In addition, a significant reduction in depressive symptoms has been observed [36].

Evidence suggests that xenon plays a dual role in the treatment of addictive disorders: in addition to its organoprotective effects, it modulates neurotransmitter systems involved in addictive behavior by blocking NMDA receptors [40]. S. Shamov found that xenon inhalation not only accelerated the resolution of psychopathological symptoms in patients with alcohol and drug dependence, but also significantly reduced pathological craving for these substances [36, 37]. Xenon therapy resulted in the disappearance of hallucinations, the alleviation of delusions, and the normalization of sleep patterns. Patients also reported reductions in pain, irritability, anxiety, and tremors. By the 6th to 10th session of xenon therapy, all patients (N=80) experienced a complete cessation of drug cravings, while 71.4% of the control group (N=35) continued to experience cravings until days 11–15 [34].

Similarly, A. Kuznetsov and colleagues reported a more rapid reduction in alcohol craving, improved sleep quality, reduced anxiety, and increased mood stability in the xenon group compared to controls (P<0.05) [39].

Although studies suggest the efficacy of xenon in the treatment of opioid and alcohol dependence [34–39, 41], a closer analysis reveals several methodological limitations, including the lack of randomization, control group comparisons, and detailed effect size analysis. These factors weaken the reliability of the findings and highlight the need for additional high-quality RCTs.

Xenon in the Treatment of Neurotic Disorders

Neurotic disorders are characterized by chronic and recurrent episodes of anxiety, stress and emotional instability. While pharmacological treatments such as antidepressants, anxiolytics, and antipsychotics are commonly used, their adverse side effects have stimulated interest in alternative therapies, including xenon inhalation therapy.

A study by A. Dobrovolsky et al. [42] evaluated the efficacy of xenon therapy in panic disorder (PD). Patients were divided into two groups: those with PD alone (N=42) and those with PD and comorbid psychiatric disorders (N=39), the majority of whom had depression. All participants received xenon inhalation therapy (15–30%) for 6–7 sessions. At baseline, both groups had high levels of anxiety on the Self-Rating Anxiety Scale (SAS) (72.7 and 64.1, respectively), which decreased significantly to 36.5 and 46.8 after one month. This anxiolytic effect was maintained at the six-month follow-up. Similarly, Hospital Anxiety and Depression Scale for Anxiety (HADS-A) scores indicated «clinically significant anxiety» at baseline (17.7 and 19.0, respectively), which normalized by the end of treatment. Regarding depression, the prevalence of «clinical depression» in the second group (assessed by HADS-D) decreased from 92.3% to 46.2%. Subjectively, 52.4% of patients in the first group and 12.8% in the second group reported improvements on the Clinical Global Impression (CGI) Scale. These findings suggest a potential role for xenon therapy in the treatment of panic disorder, but further RCTs comparing it with standard psychotropic therapies are needed to establish its efficacy.

A study by T. S. Sabinina et al. [43] investigated the effects of xenon therapy on seven severely traumatized children — five injured in a terrorist attack and two by dog bites — suffering from intractable pain and acute stress disorder (ASD). Xenon oxygen inhalation (15–30%) was administered between days 13 and 14 post-injury in sessions lasting 15–20 minutes, for a total of 3–12 sessions per patient.

During inhalation therapy, significant reductions in BIS index (from 95.5 to 86.5), Ramsay Sedation Scale scores (from 5.5 to 2.7), and pain intensity (from 4.1 to 1.1 points, P<0.05) were observed. After two sessions, analgesic consumption was reduced by half. Pain relief required an average of

five sessions, phantom pain resolution required 12 sessions, and sleep disturbances were alleviated after three sessions.

The authors concluded that xenon therapy is highly effective in treating persistent pain and ASD in children with severe trauma. However, the lack of a control group receiving standard therapy limits the ability to assess the true effect size.

Early intervention for ASD is critical to preventing the development of post-traumatic stress disorder (PTSD), which is diagnosed when symptoms persist for more than four weeks after a traumatic event. PTSD symptoms can last for months or even years and include intrusive memories, avoidance of trauma-related reminders, negative changes in cognition and mood, and hyperarousal [44].

A study by T. Igoshina et al. [45-47] evaluated the efficacy of xenon therapy in the treatment of neurotic disorders in 40 men (aged 30–42) working in high-risk occupations. The control group (N=20) received standard care, including psychotherapy, physiotherapy, nootropics, antidepressants, and benzodiazepines. In the experimental group (N=20), patients additionally underwent 10 sessions of xenon inhalation therapy (20–30% concentration, 10–30 minutes per session). The intervention group showed EEG normalization characterized by restoration of alpha rhythm and reduction of slow wave activity, indicating improved brain function. Statistically significant reductions in somatic complaints (GBB scale) by 66%, anxiety (HARS) by 70% and depression (BDI) by 55% were observed compared to baseline (P<0.05). Improvements were less pronounced in the control group at 35%, 26% and 30%, respectively. Patients reported subjective improvement after 3–4 sessions.

A separate study by F. Shvetsky et al. [48] investigated the effects of xenon therapy on stress levels in anesthesiologists and intensive care physicians after night shifts (N=30). A 3-minute inhalation of a 30% xenon-oxygen mixture resulted in a significant reduction in anxiety scores (Spielberger State-Trait Anxiety Inventory): in 50% of physicians with moderate baseline anxiety, scores decreased from 37.5±1.4 to 30.0±2.3 points (P<0.05), while in 17% of those with high anxiety, scores decreased from 45.0±2.2 to 39.0±1.4. In addition, significant improvements were observed in heart rate variability parameters (increased SDNN, RMSSD, and pNN50), indicating increased parasympathetic activity. However, no significant changes in stress hormone levels were found, probably due to their initially low baseline concentrations.

Experimental data [49] and clinical studies support the potential use of xenon therapy in the treatment of panic disorder, stress-related disorders, PTSD, anxiety, and depression. However, the lack of RCTs dedicated to this topic limits conclusions regarding the efficacy of xenon.

Therapeutic Use of Xenon in Oncology

Improving the quality of life of cancer patients, especially during chemotherapy, is assisted by «supportive care» aimed at preventing and treating pain syndrome, nausea and vomiting, gastrointestinal complications, and psycho-emotional issues, among others. The use of xenon may enhance the effectiveness of supportive therapy.

The effects of xenon in reducing the toxic effects of chemotherapeutic agents were studied by L. Nikolaev et al. [50]. Female breast cancer patients undergoing highly emetogenic chemotherapy were divided into two groups. The control group (N=36) received standard antiemetic therapy, while the experimental group (N=40) additionally received xenon inhalation at a concentration of 30% during their chemotherapy cycles. Acute vomiting occurred in 5% of patients in the xenon group compared to 16-47% in the control group (P<0.001). The incidence of delayed vomiting differed only in the fourth cycle (45% vs. 58%, P<0.001). Anticipatory vomiting was less frequent in the xenon group — 22% compared to 72% in the control group (P<0.001). Most patients in the experimental group reported that nausea and vomiting did not significantly interfere with their daily life, as measured by the FLIE questionnaire (P<0.001). General condition as assessed by the Karnofsky scale was 94% in the experimental group compared to 67% in the control group.

Y. Sidorenko and colleagues [51] investigated the effects of xenon inhalation on the symptoms of premature surgical or pharmacological menopause, such as irritability, depression, and anxiety. The study included 30 women of reproductive age (39.4±3.7 years) with locally advanced cervical cancer. Starting on the third day after hysterectomy, participants underwent a five-day course of xenon inhalation, with the xenon concentration gradually increasing from 15–16% to 20–22% and the exposure time decreasing from 20 to 10 minutes. EEG results showed normalization of cortical brain activity. Neuropsychological tests showed a reduction in anxiety and fatigue, and an improvement in sleep and work performance in 82–98% of patients.

A similar effect of xenon on the mental and emotional state of women with newly diagnosed breast cancer was observed in a study by RD. ozenko and colleagues [52]. After mastectomy, the experimental group (N=30) received a five-day course of xenon inhalation, while the control group (N=30) received standard therapy. On day 10, the experimental group showed a 2.6-fold improvement in overall well-being, a 2.3-fold reduction in depression, and a 1.9-fold reduction in anxiety (P<0.05), as assessed by the ESAS and MOS-SF-36 questionnaires. Physical health (89.2±2.2%) and mental health (81.2±3.2%) scores were significantly higher in the xenon group than in the control group (70.7±1.7%

and 75.3±1.5%, respectively, $P<0.05$). EEG results showed a decrease in beta rhythm power, an increase in slow rhythms, and an increase in alpha rhythm, suggesting a reduction in psychological stress.

The potent analgesic properties of xenon make it a valuable option for painful procedures that do not require deep sedation, such as endoscopic and dental interventions [53, 54]. Inhaled xenon is emerging as a promising component of multimodal analgesia. For example, in a study by T. Sabinina [43], xenon inhalation helped alleviate a persistent pain syndrome in patients with severe trauma.

The role of xenon in pain management in oncological patients was studied by V. Potievskaya [55, 32, 56]. RCTs conducted in 2021 [55] and 2023 [56] examined its effects on acute postoperative pain. Patients undergoing abdominal oncologic surgery (N=31) received inhalations of a 25±5% xenon-oxygen mixture for 10 minutes, while the placebo group (N=29) received 50% oxygen. Pain intensity, assessed by visual analog scale (VAS), decreased in 90.3% of patients immediately after inhalation ($P<0.01$) and in 80.6% after 30 minutes ($P<0.05$), compared to 37.9% and 27.4% in the placebo group, respectively. The duration of analgesia was significantly longer in the xenon group, lasting 5 (4–8.75) hours versus 1 (0–3) hours in the placebo group (P=0.0003). Electrical neurostimulation data showed an increased pain threshold immediately after inhalation ($P<0.01$) and 30 minutes later ($P<0.05$). In addition, pupillometry revealed correlations between autonomic nervous system activity and pain severity, suggesting a modulatory effect of xenon therapy.

Neuroinflammation and brain neuronal sensitization play a key role in the development of chronic pain, leading to increased neuronal excitability and hypersensitivity [57]. A human volunteer study [58] demonstrated that xenon inhibits the increased activity in the sensorimotor and insular regions of the brain observed during repeated pain stimulation, thereby preventing the progression to chronic pain.

A RCT by V. Potievskaya et al [32] included 95 oncology patients with chronic pain syndrome. In the intervention group (N=48), patients underwent seven sessions of inhalation with a 50% xenon-oxygen mixture. A statistically significant reduction in pain intensity as measured by the numerical rating scale (NRS) was observed — from 50 (40; 60) to 40 (25; 50) points ($P<0.05$) — while no significant changes were observed in the control group.

A larger study on the use of xenon for chronic pain was conducted by G. Abuzarova and colleagues [59]. This RCT included 131 oncology patients with moderate to severe chronic pain syndrome. The intervention group (N=66) received standard therapy along with 30-minute inhalations of a 50% xenon-oxygen mixture for seven days. Thirty minutes after inhalation, the median pain reduction on NRS was 19.0 mm in the xenon group compared to 4.0 mm in the placebo group ($P<0.001$). The difference remained significant two weeks after treatment: 15.0 mm vs. 0.0 mm ($P<0.001$). A reduction in the daily dose of thiamazole was also observed in the xenon group, from 210.9±31.3 mg to 150.1±28.3 mg.

Seven patients (5.3%) reported mild adverse events, with nausea and vomiting being the most common (five cases). One patient reported dizziness, excessive sleepiness, and pain.

Thus, the use of xenon as part of a comprehensive treatment approach for oncology patients may contribute to improved quality of life by alleviating chemotherapy-induced nausea and vomiting, managing mental and emotional distress, and reducing acute pain in chronic pain syndromes. However, further studies are needed to confirm these effects. In addition, xenon's potential to stimulate hematopoiesis [60] and its reported organoprotective properties may help mitigate the harmful effects of radiation and chemotherapy, but this also requires further investigation.

Therapeutic Use of Xenon in Pulmonary Disease

Xenon is the densest of all gases and its inhalation may increase airway resistance. However, a study in healthy volunteers found that a high concentration of xenon-oxygen mixture had no significant effect on airway compliance or transpulmonary pressure gradient [61]. Therefore, xenon inhalation is considered relatively safe and may be explored as a potential therapeutic agent for various inflammatory lung conditions. However, it may exacerbate conditions associated with bronchial obstruction.

To date, no randomized controlled trials have been conducted in this area. V. Udut and colleagues [62] reported a case of xenon therapy in a patient with ARDS due to COVID-19. After five days of inhalation of 70% xenon, the patient showed a decrease in heart rate and respiratory rate and an increase in SpO_2. Laboratory tests demonstrated a reduction in inflammatory markers: C-reactive protein decreased from 102.1 to 11.37 mg/L, D-dimer from 620 to 460 ng/mL, and leukocyte count from 14 to 6.4×10^9/L. Computed tomography (CT) scans showed a reduction in lung damage from 45% to 15%.

Further experimental studies by the same research group identified key mechanisms of xenon's therapeutic effects, including anti-inflammatory and angioprotective properties, modulation of hemostasis, and restoration of surfactant activity [63–65].

Conclusion

Our review of the literature highlights the significant therapeutic potential of inhaled xenon in several medical fields, including neuroprotection,

cardioprotection, oncology, pulmonary disease, and the treatment of addictive and neurotic disorders (Table). However, despite more than 30 years of clinical research, the number of high-quality publications based on RCTs remains limited.

To date, only 12 RCTs and 8 prospective controlled studies (without explicit randomization) have investigated the medical use of xenon. Many of these studies are limited by small sample sizes and a high risk of bias, reducing the ability to draw definitive conclusions about the clinical efficacy of xenon.

To fully evaluate the therapeutic potential of xenon and its impact on long-term clinical outcomes, further large-scale randomized trials are needed. Their results could significantly expand our understanding of xenon therapy targets and its potential applications in modern medicine.

Table. Clinical Use of Inhaled Xenon in Subanesthetic Doses.

Study	Design*	Diagnosis	Exposure	Key Effects of Xenon
Use of xenon for neuroprotection				
Azzopardi D., 2013 [17]	Prospective uncontrolled, *N*=14	Perinatal encephalopathy	30% xenon, 24 hours	Anticonvulsant effect
Dingley J., 2014 [18]	Prospective uncontrolled, *N*=14	Perinatal encephalopathy	25–50% xenon, 3–18 hours	Anticonvulsant effect
Azzopardi D., 2016 [20]	RCT, *N*=92	Perinatal encephalopathy	30% xenon, 24 hours	No significant effect on brain damage
Laitio R., 2016 (XeHypotheCA Trial) [16]	RCT, *N*=110	Out-of-hospital cardiac arrest	40% xenon, 24 hours	Reduced white matter damage, lower 6-month mortality (*P*=0.053)
Lazarev V., 2019 [19]	Case study, *N*=1	Refractory status epilepticus	60% xenon	Anticonvulsant effect
Grebenchikov O., 2022 [21]	RCT, *N*=24	Ischemic stroke	40% xenon, 6 hours	Improved consciousness (GCS, FOUR), reduced neurological deficit (NIHSS)
Shpichko A., 2023 [22, 23]	RCT, *N*=24	Chronic disorders of consciousness, consequences of severe TBI	30% xenon, 30 minutes, 7 days	Restoration of consciousness (CRS-R), increased BDNF (marker of neuronal regeneration)
Use of xenon for cardioprotection				
Molchanov I., 2012 [31]	Prospective controlled, *N*=35	Acute coronary syndrome	25–50% xenon, 20–40 minutes, 3–5 days	Reduced myocardial damage markers, improved hemodynamics
Arola O., 2013 [14]	RCT, *N*=36	Out-of-hospital cardiac arrest	40% xenon, 24 hours	Reduced troponin T levels at 72 hours
Arola O., 2017 (XeHypotheCA Trial) [15]	RCT, *N*=110	Out-of-hospital cardiac arrest	40% xenon, 24 hours	Reduced troponin T levels at 72 hours
Saraste A., 2021 [30]	RCT, *N*=38	Out-of-hospital cardiac arrest	40% xenon, 24 hours	Increased left ventricular ejection fraction, improved systolic deformation
Use of xenon in the treatment of addictive disorders				
Naumov S., 2002 [34]	Prospective comparative, *N*=30	Opioid addiction, acute withdrawal syndrome	50% xenon, 2–3 min, 17 sessions (7 days)	Reduced cortisol, growth hormone, glucose, aminotransferase activity; increased TSH and thyroxine; alleviation of withdrawal symptoms
Shamov S., 2006 [36]	Prospective controlled, *N*=80	Opioid withdrawal syndrome	50% xenon, 40 minutes, 9–10 sessions	Pain relief, reduced affective, asthenic, and behavioral disorders, improved psycho-emotional state
Shamov S., 2007 [37]	Prospective controlled, *N*=101	Acute encephalopathy in patients with substance dependence	50% xenon, 7–10 sessions, 5 days	Rapid reduction of psychiatric and somatovegetative disturbances, no adverse effects on hemodynamics or respiration
Kuznetsov A., 2007 [41]	Prospective controlled, *N*=138	Alcohol withdrawal syndrome	Subanesthetic doses of xenon, frequency of sessions based on symptoms	Reduced alcohol craving, earlier resolution of withdrawal symptoms, improved cognitive function
Tsygankov B., 2013 [39]	Prospective controlled, *N*=120	Alcohol and opioid dependence, withdrawal syndrome, encephalopathy of various etiologies	33% xenon ($Xe:O_2$ = 1:2), 5–7 minutes, 7–12 sessions, 5 days	Reduced anxiety, depression, cognitive impairment, improved EEG and REG parameters, normalized cerebral hemodynamics, reduced need for opioid analgesics and tranquilizers

Table. Clinical Use of Inhaled Xenon in Subanesthetic Doses.

Study	Design*	Diagnosis	Exposure	Key Effects of Xenon
Utkin S., 2014 [38]	Prospective comparative, *N*=78	Opioid withdrawal syndrome	25% xenon, 10 days, 20 minutes per session	Reduced severity of withdrawal symptoms, no psychopharmacological side effects
Strepetova O., 2014 [35]	Prospective controlled, *N*=137	Alcohol disorders: withdrawal syndrome, delirium, coma	25–30% xenon, 10–15 minutes, 6 days	Reduced sedative medication doses, lower frequency of complications (delirium, coma), faster recovery of consciousness, improved cognitive functions
Use of xenon in the treatment of neurotic disorders				
Igoshina T., 2013–2014 [45, 46]	Prospective controlled, *N*=40	Neurotic disorders in high-risk profession individuals	20–30% xenon, 10–30 minutes, 10 sessions	Reduced anxiety, depression, improvement in EEG parameters
Shvetski F., 2016 [48]	Prospective uncontrolled, *N*=30	Chronic stress and fatigue in anesthesiologists and intensivists	70% xenon, 3 minutes, flow rate 3.5–5.5 L/min	Reduced anxiety levels, improved heart rate variability, increased cardiovascular functional reserves, improved sleep quality
Dobrovolskiy A., 2017 [42]	Prospective uncontrolled, *N*=81	Panic disorder	15–30% xenon, 6–7 sessions	Reduced anxiety according to SAS and HADS-T scales
Sabinina T., 2019 [43]	Prospective uncontrolled, *N*=7	Severe trauma, acute stress disorder, persistent pain syndrome	15–30% xenon, 15–20 minutes, 3–12 sessions	Reduced acute pain, improved sleep, reduction in acute stress disorder, alleviation of phantom pain, normalization of psycho-emotional state
Use of xenon in the treatment of neoplastic diseases				
Nikolaev L., 2014 [50]	RCT, *N*=76	Breast cancer, chemotherapy	30% xenon, 30–40 minutes during chemotherapy sessions	Reduced frequency of acute nausea and vomiting, reduced anticipatory vomiting, improved quality of life
Sidorenko Yu., 2019 [51]	Prospective uncontrolled, *N*=30	Cervical cancer, surgical menopause	12–22% xenon, 10–20 minutes, 5 sessions every other day	Normalization of EEG, reduced anxiety, depression, fatigue, improved sleep, appetite, work capacity, increased activity and optimism
Rozenko D., 2021 [52]	RCT, *N*=60	Breast cancer, surgical treatment	15–22% xenon, 10–25 minutes, 5 sessions	Reduced depression, anxiety, weakness, sleep disturbances; normalization of EEG
Potievskaya V., 2022 [32]	RCT, *N*=95	Chronic pain syndrome in cancer patients	50% xenon, 8–10 minutes, 7 sessions	Reduced intensity of chronic pain, no significant impact on cardiovascular system
Potievskaya V., 2021, 2023 [55, 56]	RCT, *N*=60	Acute postoperative pain in cancer patients	25% xenon, 10 minutes	Reduced pain intensity on VAS, increased pain threshold, decreased analgesic use
Abuzarova G., 2020 [59]	RCT, *N*=131	Chronic pain in cancer patients	50% xenon, 8–9 minutes, 7 sessions	Reduced intensity of chronic pain, decreased daily consumption of tramadol and NSAIDs
Use of xenon in the treatment of pulmonary conditions				
Udut V., 2021 [62]	Clinical case, *N*=1	Acute respiratory distress and neuro-psychiatric disorder in COVID-19	70% xenon, 1 minute, once per day, 5-day course	Increased oxygen saturation, reduced dyspnea, normalized respiratory rhythm, decreased anxiety, depression, and insomnia, improved lung tissue structure on CT

Note. RCT — randomized controlled trial; PTSD — post-traumatic stress disorder; VAS — visual analog scale; ARDS — acute respiratory distress syndrome; CT — computed tomography; NSAIDs — non-steroidal anti-inflammatory drugs; EEG — electroencephalogram; REG — rheoencephalogram. * — many publications do not specify the study design; in such cases, the type of study was determined based on the description of the study. ** — the study describes a control group, but the primary endpoints were not compared between groups.

References

1. *Xia Y., Fang H., Xu J., Jia C., Tao G., Yu B.* Clinical efficacy of xenon versus propofol: a systematic review and meta-analysis. *Medicine*. 2018; 97 (20): e10758. DOI: 10.1097/MD.0000000000010758. PMID: 29768360.
2. *Law L. S. C., Lo E. A. G., Gan T. J.* Xenon anesthesia: a systematic review and meta-analysis of randomized controlled trials. *Anesth. Analg.* 2016; 122 (3): 678. DOI: 10.1213/ANE.0000000000000914. PMID: 26273750.
3. *Hou B., Li F., Ou S., Yang L., Zhou S.* Comparison of recovery parameters for xenon versus other inhalation anesthetics: systematic review and meta-analysis. *J. Clin. Anesth.* 2016; 29: 65–74. DOI: 10.1016/j.jclinane.2015.10.018. PMID: 26897451.
4. *Лисиченко И. А., Гусаров В. Г.* Выбор метода анестезиологического обеспечения у пациентов пожилого и старческого возраста при ортопедических вмешательствах (обзор). *Общая реаниматология*. 2022; 18 (3): 45–58.
5. *De Deken J., Rex S., Monbaliu D., Pirenne J., Jochmans I.* The Efficacy of Noble Gases in the Attenuation of Ischemia Reperfusion Injury: A Systematic Review and Meta-Analyses. *Crit. Care Med.* 2016; 44 (9): e886-e896. DOI: 10.1097/CCM.0000000000001717. PMID: 27071065.
6. *McGuigan S., Marie D. J., O'Bryan L. J., Flores F. J., Evered L., Silbert B., Scott D. A.* The cellular mechanisms associated with the anesthetic and neuroprotective properties of xenon: a systematic review of the preclinical literature. *Front. Neurosci.* 2023; 17: 1225191. DOI: 10.3389/fnins.2023.1225191.
7. *Anna R., Rolf R., Mark C.* Update of the organoprotective properties of xenon and argon: from bench to bedside. *ICMx*. 2020; 8 (1): 11. DOI: 10.1186/s40635-020-0294-6. PMID: 32096000.
8. *Liang M., Ahmad F., Dickinson R.* Neuroprotection by the noble gases argon and xenon as treatments for acquired brain injury: a preclinical systematic review and meta-analysis. *Br. J. Anaesth.* 2022; 129 (2): 200–218. DOI: 10.1016/j.bja.2022.04.016. PMID: 35688658.
9. *Ершов А. В., Крюков И. А., Антонова В. В., Баева А. А.* Влияние ксенона на активность гликоген-синтазы киназы-3β в перифокальной зоне ишемического инсульта. *Общая реаниматология*. 2023; 19 (2): 60–67. https://doi.org/10.15360/1813-9779-2023-2-2274
10. *Рылова А. В., Беляев А. Ю., Лубнин А. Ю.* Влияние ксенона на мозговой кровоток у нейрохирургических пациентов без внутричерепной гипертензии. *Анестезиология и реаниматология*. 2013; (4): 4–9.
11. *Рылова А. В., Гаврилов А. Г., Лубнин А. Ю., Потапов А. А.* Внутричерепное и церебральное перфузионное давление у нейрохирургических пациентов во время анестезии ксеноном. *Анестезиология и реаниматология*. 2014; (4): 19–25.
12. *Васильев С. В., Владимиров С. А.* Критерии безопасности воздействия субнаркотических доз ксенона на церебральную гемодинамику у пациентов с ишемическими поражениями ЦНС. *J. Siberian Med. Sci.* 2014; (6): 41.
13. *Marion D. W., Crosby K.* The Effect of Stable Xenon on ICP. *J. Cereb. Blood Flow Metab.* 1991; 11 (2): 347–350. DOI: 10.1038/jcbfm.1991.69. PMID: 1997507.
14. *Arola O. J., Laitio R. M., Roine R. O., Grönlund J., Saraste A., Pietilä M., Airaksinen J., Perttilä J., Scheinin H., Olkkola K. T., Maze M., Laitio T. T.* Feasibility and cardiac safety of inhaled xenon in combination with therapeutic hypothermia following out-of-hospital cardiac arrest. *Crit. Care Med.* 2013; 41 (9): 2116–2124. DOI: 10.1097/CCM.0b013e31828a4337. PMID: 23896830.
15. *Arola O., Saraste A., Laitio R., Airaksinen J., Hynninen M., Bäcklund M., Ylikoski E., Wennervirta J., Pietilä M., Roine R. O., Harjola V. P., Niiranen J., Korpi K., Varpula M., Scheinin H., Maze M., Vahlberg T., Laitio T.* Inhaled xenon attenuates myocardial damage in comatose survivors of out-of-hospital cardiac arrest: the xe-hypotheca trial. *J. Am. Coll. Cardiol.* 2017; 70 (21): 2652–2660. DOI: 10.1016/j.jacc.2017.09.1088. PMID: 29169472.
16. *Laitio R., Hynninen M., Arola O., Virtanen S., Parkkola R., Saunavaara J., Roine R. O., Grönlund J., Ylikoski E., Wennervirta J., Bäcklund M., Silvasti P., Nukarinen E., Tiainen M., Saraste A., Pietilä M., Airaksinen J., Valanne L., Martola J., Silvennoinen H., Scheinin H., Harjola V. P., Niiranen J., Korpi K., Varpula M., Inkinen O., Olkkola K. T., Maze M., Vahlberg T., Laitio T.* Effect of inhaled xenon on cerebral white matter damage in comatose survivors of out-of-hospital cardiac arrest: a randomized clinical trial. *JAMA*. 2016; 315 (11): 1120. DOI: 10.1001/jama.2016.1933. PMID: 26978207.
17. *Azzopardi D., Robertson N. J., Kapetanakis A., Griffiths J., Rennie J. M., Mathieson S. R., Edwards A. D.* Anticonvulsant effect of xenon on neonatal asphyxial seizures. *Arch. Dis. Child. Fetal Neonatal Ed.* 2013; 98 (5): F437-F439. DOI: 10.1136/archdischild-2013-303786. PMID: 23572341.
18. *Dingley J., Tooley J., Liu X., Scull-Brown E., Elstad M., Chakkarapani E., Sabir H., Thoresen*

M. Xenon ventilation during therapeutic hypothermia in neonatal encephalopathy: a feasibility study. *Pediatrics.* 2014; 133 (5): 809–818. DOI: 10.1542/peds.2013-0787. PMID: 24777219.
19. *Lazarev V. V., Golubev B. I., Brusov G. P., Tsypin L. E.* Xenon in the treatment of superrefractory status epilepticus. Case report. *Ann. Crit. Care.* 2019; (4): 123–127. DOI: 10.21320/1818-474X-2019-4-123-127.
20. *Azzopardi D., Robertson N. J., Bainbridge A., Cady E., Charles-Edwards G., Deierl A., Fagiolo G., Franks N. P., Griffiths J., Hajnal J., Juszczak E., Kapetanakis B., Linsell L., Maze M., Omar O., Strohm B., Tusor N., Edwards A. D.* Moderate hypothermia within 6 h of birth plus inhaled xenon versus moderate hypothermia alone after birth asphyxia (TOBY-Xe): a proof-of-concept, open-label, randomised controlled trial. *Lancet Neurol.* 2016; 15 (2): 145–153. DOI: 10.1016/s1474-4422 (15)00347-6. PMID: 26708675.
21. *Гребенчиков О. А., Евсеев А. К., Кулабухов В. В., Кузовлев А. Н., Петриков С. С., Рамазанов Г. Р., Хусаинов Ш. Ж., Черпаков Р. А., Шабанов А. К., Шпичко А. И.* Нейропротективные эффекты ингаляционной седации ксеноном в сравнении с внутривенной седацией пропофолом при тяжелом ишемическом инсульте. *Журнал им. Н. В. Склифосовского «Неотложная медицинская помощь».* 2022; 11 (4): 561–572. DOI: 10.23934/2223-9022-2022-11-4-561-572.
22. *Шпичко А. И., Кузовлев А. Н., Черпаков Р. А., Шпичко Н. П., Гребенчиков О. А., Евсеев А. К., Шабанов А. К., Петриков С. С.* Новая стратегия лечения пациентов с длительным нарушением сознания с применением ксенона. Проспективное пилотное исследование. *Журнал им. Н. В. Склифосовского «Неотложная медицинская помощь».* 2022; 11 (4): 592–599. DOI: 10.23934/2223-9022-2022-11-4-592-599.
23. *Шпичко А. И., Черпаков Р. А., Шабанов А. К., Евсеев А. К., Горончаровская И. В., Гребенчиков О. А.* Эффекты ксенона в отношении маркеров нейровоспаления. Проспективное пилотное исследование. *Журнал им. Н. В. Склифосовского «Неотложная медицинская помощь».* 2023; 12 (2): 250–258. DOI: 10.23934/2223-9022-2023-12-2-250-258.
24. *Mochalova E. G., Legostaeva L. A., Zimin A. A., Yusupova D. G., Sergeev D. V., Ryabinkina Y. V., Bodien Y., Suponeva N. A., Piradov M. A.* The Russian version of Coma Recovery Scale-revised — a standardized method for assessment of patients with disorders of consciousness. *Zh. Nevrol. Psikhiatr. Im. S.S. Korsakova.* 2018; 118 (3): 25. DOI: 10.17116/jnevro20181183225-3. PMID: 29798977.
25. *Yang Y. S., Wu S. H., Chen W. C., Pei M. Q., Liu Y. B., Liu C. Y., Lin S., He H. F.* Effects of xenon anesthesia on postoperative neurocognitive disorders: a systematic review and meta-analysis. *BMC Anesthesiol.* 2023; 23 (1): 366. DOI: 10.1186/s12871-023-02316-5. PMID: 37946114.
26. *Белкин А. А., Зислин Б. Д., Аврамченко А. А., Алашеев А. М., Сельский Д. В., Громов В. С., Доманский Д. С., Инюшкин С. Н., Почепко Д. В., Рудник Е. И., Солдатов А. С.* Синдром острой церебральной недостаточности как концепция нейрореаниматологии. *Анестезиология и реаниматология.* 2008; (2): 4–8.
27. *Laaksonen M., Rinne J., Rahi M., Posti J. P., Laitio R., Kivelev J., Saarenpää I., Laukka D., Frösen J., Ronkainen A., Bendel S., Långsjö J., Ala-Peijari M., Saunavaara J., Parkkola R., Nyman M., Martikainen I. K., Dickens A. M., Rinne J., Valtonen M., Saari T. I., Koivisto T., Bendel P., Roine T., Saraste A., Vahlberg T., Tanttari J., Laitio T.* Effect of xenon on brain injury, neurological outcome, and survival in patients after aneurysmal subarachnoid hemorrhage — study protocol for a randomized clinical trial. *Trials.* 2023; 24 (1): 417. DOI: 10.1186/s13063-023-07432-8. PMID: 37337295.
28. *Hecker K. E., Horn N., Baumert J. H., Reyle-Hahn S. M., Heussen N., Rossaint R.* Minimum alveolar concentration (MAC) of xenon in intubated swine. *Br. J. Anaesth.* 2004; 92 (3): 421–424. DOI: 10.1093/bja/aeh077. PMID: 14742330.
29. *Koblin D. D., Fang Z., Eger E. I., Laster M. J., Gong D., Ionescu P., Halsey M. J., Trudell J. R.* Minimum alveolar concentrations of noble gases, nitrogen, and sulfur hexafluoride in rats: helium and neon as nonimmobilizers (nonanesthetics). *Anesth. Analg.* 1998; 87 (2): 419–424. DOI: 10.1213/00000539-199808000-00035.
30. *Saraste A., Ballo H., Arola O., Laitio R., Airaksinen J., Hynninen M., Bäcklund M., Ylikoski E., Wennervirta J., Pietilä M., Roine R. O., Harjola V. P., Niiranen J., Korpi K., Varpula M., Scheinin H., Maze M., Vahlberg T., Laitio T.* Effect of Inhaled Xenon on Cardiac Function in Comatose Survivors of Out-of-Hospital Cardiac Arrest — A Substudy of the Xenon in Combination With Hypothermia After Cardiac Arrest Trial. *Crit. Care Explor.* 2021; 3 (8): e0502. DOI: 10.1097/CCE.0000000000000502. PMID: 34345828.
31. *Молчанов И. В., Потиевская В. И., Пулина Н. Н., Шебзухова Е. Х.* Лечение больных с острым коронарным синдромом ингаляциями ксенона. *ДокторРу.* 2012; 10 (78): 35–40.
32. *Potievskaya V. I., Abuzarova G. R., Sarmanaeva R. R., Loboda A. V., Potievskiy M. B.,*

Kuznetsov S. V., Kaprin A. D. Effect of xenon-oxygen inhalations on functional status of cardiovascular system in oncological patients suffering chronic pain syndrome. *Issled Prakt Med (Print)*. 2022; 9 (3): 52–66.
DOI: 10.17709/2410-1893-2022-9-3-4.

33. *Hofland J., Ouattara A., Fellahi J. L., Gruenewald M., Hazebroucq J., Ecoffey C., Joseph P., Heringlake M., Steib A., Coburn M., Amour J., Rozec B., Liefde I., Meybohm P., Preckel B., Hanouz J. L., Tritapepe L., Tonner P., Benhaoua H., Roesner J. P., Bein B.* Effect of xenon anesthesia compared to sevoflurane and total intravenous anesthesia for coronary artery bypass graft surgery on postoperative cardiac troponin release. *Anesthesiology*. 2017; 127 (6): 918–933.
DOI: 10.1097/ALN.0000000000001873.
34. *Наумов С. А., Шписман М. Н., Наумов А. В., Лукинов А. В., Тупицын М. В., Вовк С. М.* Роль ксенона в лечении опийной наркомании. *Вопросы наркологии*. 2002; (6): 13–17.
35. *Стрепетова О. В.* Успешный опыт применения ксенона в комплексе интенсивного лечения алкогольных расстройств. *Медицина неотложных состояний*. 2014; 7 (62): 88–94.
36. *Шамов С. А., Цыганков Б. Д., Доненко В. Е., Клячин А. И., Тюнева А. И.* Использование ксенона для купирования острого абстинентного синдрома при лечении больных наркотической зависимостью. *Наркология*. 2006; 5 (6): 46–52.
37. *Шамов С. А., Давлетов Л. А., Цыганков Д. Б., Шуляк Ю. А.* Применение ксенона в комплексном лечении психических и соматоневрологических расстройств при острой энцефалопатии у пациентов с зависимостью от психоактивных веществ. *Наркология*. 2007; 6 (1): 38–44.
38. *Уткин С. И., Атамурадов И. Б., Винникова М. А., Захаров М. В., Деревлев Н. Н., Литвинская И. И., Вишневский С. А., Потапов А. В., Потапов С. В.* Ксенон в терапии опийного абстинентного синдрома. *Вопросы наркологии*. 2014; (4): 13–28.
39. *Tzigankov B. D., Shamov S. A., Rykhletskiy P. Z., Davletov L. A.* The possibilities of xenon application in complex therapy of psycho-pathologic disorders in patients of narcologic profile. *Russ. Med. J.* 2013; 19 (4): 11–14.
DOI: 10.17816/rmj38066.
40. *Fluyau D., Revadigar N., Pierre C. G.* Clinical benefits and risks of N-methyl-D-aspartate receptor antagonists to treat severe opioid use disorder: a systematic review. *Drug Alcohol Depend*. 2020; 208: 107845.
DOI: 10.1016/j.drugalcdep.2020.107845.
PMID: 31978670.
41. *Кузнецов А. В., Шамов С. А., Цыганков Д. Б.* Опыт применения лечебного ксенонового наркоза в комплексной терапии больных алкогольной зависимостью в период абстинентных и постабстинентных расстройств. *Российский медицинский журнал*. 2007; (6): 19–22.
42. *Dobrovolsky A., Ichim T. E., Ma D., Kesari S., Bogin V.* Xenon in the treatment of panic disorder: an open label study. *J. Transl. Med*. 2017; 15 (1): 137.
DOI: 10.1186/s12967-017-1237-1.
PMID: 28610592.
43. *Sabinina T. S., Bagaev V. G., Amcheslavsky V. G., et al.* First experience with xenon in treatment of severe trauma in children. *Medicinskij alfavit*. 2019; 2 (31): 41–45.
DOI: 10.33667/2078-5631-2019-2-31(406)-41-45.
44. *Васильева А. В., Караваева Т. А., Лукошкина Е. П., Радионов Д. С.* Основные подходы к диагностике и терапии посттравматического стрессового расстройства. *Обозрение психиатрии и медицинской психологии им. В. М. Бехтерева*. 2022; 56 (4): 107–111.
DOI: 10.31363/2313-7053-2022-4-107-111.
45. *Игошина Т. В.* Коррекция связанных со стрессом невротических расстройств методом ингаляции субнаркотических доз ксенона в условиях санатория. *Кремлевская медицина. Клинический вестник*. 2013; (4): 37–42.
46. *Игошина Т. В., Котровская Т. И., Бубеев Ю. А., Счастливцева Д. В., Потапов А. В.* Применение ингаляции субнаркотических доз ксенона в санаторном лечении посттравматических стрессовых расстройств. *Авиакосмическая и экологическая медицина*. 2014; 48 (5): 58–63.
47. *Бубеев Ю. А., Игошина Т. В., Котровская Т. И.* Коррекция связанных со стрессом расстройств у лиц опасных профессий в условиях клинического санатория. *Экстремальная деятельность человека*. 2016; (3): 25–30.
48. *Шветский Ф. М., Потиевская В. И., Смольников П. В., Чижов А. Я.* Коррекция функционального состояния врачей анестезиологов-реаниматологов ингаляциями ксенона. *Вестник Российского университета дружбы народов. Серия: Экология и безопасность жизнедеятельности*. 2016; (4): 96–104.
49. *Стряпко Н. В., Сазонтова Т. Г., Потиевская В. И., Хайруллина А. А., Вдовина И. Б., Куликов А. Н., Архипенко Ю. В., Молчанов И. В.* Адаптационный эффект многократного применения ксенона. *Общая реаниматология*. 2014; 10 (2): 50–56.
50. *Николаев Л. Л., Петрова М. В., Болихова Н. А., Добровольская Н. Ю., Потапов А. В.* Ксенон как компонент терапии сопровождения при химиотерапии больных раком молочной железы. *Эффективная фармакотерапия*. 2014; (57): 6–9.

51. *Сидоренко Ю. С., Кит О. И., Попова Н. Н., Арапова Ю. Ю., Шихлярова А. И., Моисеенко Т. И., Меньшенина А. П., Ващенко Л. Н., Росторгуев Э. Е., Попов И. А., Гончарова А. С.* Роль ЦИС в ингибировании посткастрационного синдрома у больных раком шейки матки репродуктивного возраста на основе программируемых режимов ксенонтерапии. *Вопросы онкологии.* 2019; 65 (5): 708–714.
52. *Розенко Д. А., Шихлярова А. И., Ващенко Л. Н., Попова Н. Н., Арапова Ю. Ю., Арджа А. Ю., Коробов А. А.* Нейропсихологические особенности пациенток репродуктивного возраста с диагнозом рак молочной железы на этапе хирургического лечения с применением ксенон-кислородной терапии. *Исследования и практика в медицине.* 2021; 8 (3): 10–20. DOI: 10.17709/2410-1893-2021-8-3-1.
53. *Потиевская В. И., Шветский Ф. М.* Процедурная седация ксеноном при диагностической эзофагогастродуоденоскопии. *Вестник интенсивной терапии.* 2017; (4): 42–46.
54. *Давыдова Н. С., Наумов С. А., Костромитина Г. Г., Собетова Г. В., Еремин В. С., Рабинович С. А., Бабиков А. С.* Кислородно-ксеноновые ингаляции в поликлинической практике. *Поликлиника.* 2013; (5–2): 48–51.
55. *Potievskaya V. I., Shvetskiy F. M., Sidorov D. V., Lozhkin M. V., Potievskiy M. B., Abuzarova G. R., Sarmanaeva R. R., Kuznetsov S. V., Alekseeva G. S.* Assessment of xenon effect on postoperative pain syndrome severity in oncological patients: a randomized study. *Ann. Crit. Care.* 2021; (3): 140–150. DOI: 10.21320/1818-474X-2021-3-140-150.
56. *Potievskaya V. I., Shvetskiy F. M., Varchenko N. N., Gankin K. A., Potievskiy M. B., Alekseeva G. S., Khorovyan A. M.* Effect of xenon-oxygen inhalations on psychovegetative component of pain syndrome after abdominal surgery in cancer patients. *Russ. J. Anaesthesiol. Reanimatol.* 2023; (4): 56. DOI: 10.17116/anaesthesiology202304156.
57. *Овечкин А. М.* Хронический послеоперационный болевой синдром — подводный камень современной хирургии. *Регионарная анестезия и лечение острой боли.* 2016; 10 (1): 5–18.
58. *Adolph O., Köster S., Georgieff M., Bäder S., Föhr K. J., Kammer T., Herrnberger B., Grön G.* Xenon-induced changes in CNS sensitization to pain. *NeuroImage.* 2010; 49 (1): 720–730. DOI: 10.1016/j.neuroimage.2009.08.034. PMID: 19703572.
59. *Абузарова Г. Р., Хороненко В. Э., Сарманаева Р. Р., Кузнецов С. В.* Рандомизированное двойное слепое плацебо-контролируемое исследование ингаляций ксенона в терапии хронической боли в онкологии. *Вестник интенсивной терапии им. А. И. Салтанова.* 2020; (4): 48–57.
60. *Stoppe C., Ney J., Brenke M., Goetzenich A., Emontzpohl C., Schälte G., Grottke O., Moeller M., Rossaint R., Coburn M.* Sub-anesthetic Xenon Increases Erythropoietin Levels in Humans: A Randomized Controlled Trial. *Sports Med.* 2016; 46 (11): 1753–1766. DOI: 10.1007/s40279-016-0505-1. PMID: 26939898.
61. *Schaefer M. S., Treschan T. A., Gauch J., Neukirchen M., Kienbaum P.* Influence of xenon on pulmonary mechanics and lung aeration in patients with healthy lungs. *Br. J. Anaesth.* 2018; 120 (6): 1394–1400. DOI: 10.1016/j.bja.2018.02.064. PMID: 29793604.
62. *Udut V. V., Naumov S. A., Evtushenko D. N., Udut E. V., Naumov S. S., Zyuz'kov G.N.* A case of xenon inhalation therapy for respiratory failure and neuropsychiatric disorders associated with COVID-19. *EXCLI J.* 2021; 20: 1517. DOI: 10.17179/excli2021-4316. PMID: 34924901.
63. *Udut V. V., Naumov S. A., Udut E. V., Naumov S. S., Evtushenko D. N., Chumakova O. N., Zyuz'kov G.N.* Mechanisms of the Effects of Short-Term Inhalations of Xe and O_2 Gas Mixture in the Rehabilitation of Post-COVID Ventilation Failure. *Bull. Exp. Biol. Med.* 2022; 172 (3): 364–367. DOI: 10.1007/s10517-022-05393-7. PMID: 35001305.
64. *Evtushenko D. N., Fateev A. V., Naumov S. A., Udut E. V., Naumov S. S., Udut V. V.* Xenon-Induced Recovery of Functional Activity of Pulmonary Surfactant (In Silico Study). *Bull. Exp. Biol. Med.* 2023; 176 (2): 260–267. DOI: 10.1007/s10517-024-06006-1. PMID: 38194069.
65. *Fedorova E. P., Filonova M. V., Churin A. A., Sandrikina L. A., Fomina T. I., Neupokoeva O. V., Shepeleva N. V., Nikiforov P. E., Naumov S. A., Udut E. V., Naumov S. S., Udut V. V.* Effect of Xe/O_2 Inhalation on Hemostasis in Experimental Thromboplastin Pneumonitis. *Bull. Exp. Biol. Med.* 2024; 176 (6): 731–735. DOI: 10.1007/s10517-024-06098-9. PMID: 38904932.

Received 06.02.2025
Accepted 14.03.2025
Accepted in press 28.03.2025

https://doi.org/10.15360/1813-9779-2025-2-27-02

Ethical Imperatives for Harmonizing Brain Death Standards in the United States and Globally

Calixto Machado[1]*, Jose J. Sanchez[2], Beata Drobna Saniova[3], Michal Drobný[3], Arthur Schiff[4]

[1] Institute of Neurology and Neurosurgery, Department of Clinical Neurophysiology,
29 y D Vedado, 10400 La Habana, Cuba
[2] Better Call Agency,
1545 NW 15th Street Road, Miami, FL 33125, USA
[3] Clinic of Anaesthesiology and Intensive Medicine, Comenius University in Bratislava,
Jessenius Faculty of Medicine and University Hospital in Martin,
2 Kollarova Str., 03659 Martin, Slovak Republic
[4] Northside Hospital Gwinnett,
500 Medical Center Blvd, Suite 350, Lawrenceville, GA 30046, USA

For citation: *Calixto Machado, Jose J. Sanchez, Beata Drobna Saniova, Michal Drobný, Arthur Schiff.* Ethical Imperatives for Harmonizing Brain Death Standards in the United States and Globally. *Obshchaya Reanimatologiya = General Reanimatology.* 2025; 21 (2): 67–71. https://doi.org/10.15360/1813-9779-2025-2-27-02 [In Engl.]

***Correspondence to:** Calixto Machado, cmachado180652@gmail.com

Summary

The determination of brain death/death by neurological criteria (BD/DNC) is a critical medical and legal process. The Uniform Determination of Death Act (UDDA) provides a legal framework, yet significant state-by-state inconsistencies persist in its interpretation and implementation. These disparities create ethical concerns related to justice, patient autonomy, informed consent, and public trust in medical determinations of death.

This paper argues for urgently harmonizing BD/DNC criteria across the United States and globally to uphold ethical medical practice, ensure consistency in end-of-life care, and preserve public confidence in the organ donation system.

Ethical considerations are examined, including fairness in healthcare access, respect for religious and cultural beliefs, and the implications for organ procurement policies. The call for national and international standardization aligns with bioethical principles and medical best practices, aiming to reinforce ethical and legal integrity in BD/DNC determination.

Keywords: brain death; death by neurological criteria; medical ethics; justice; public trust; legal standards; global health policy; organ donation; informed consent

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

Information about the authors:
Machado Calixto: https://orcid.org/0000-0002-0539-5844
Saniova Drobna Beata: https://orcid.org/0000-0002-0833-9493
Drobný Michal: https://orcid.org/0000-0001-9312-558X

Introduction

Brain death/death by neurological criteria (BD/DNC), as defined by the UDDA, requires the irreversible cessation of all brain functions, including the brainstem. However, state-level variability in BD/DNC determination has created inconsistencies that undermine the ethical foundation of death determination. These inconsistencies result in unequal treatment of patients based on geographical location, affecting their legal status and eligibility for organ donation. Furthermore, international standards for BD/DNC vary widely, further complicating the definition and acceptance of brain death [1–10].

This paper explores this fragmentation's ethical dilemmas and calls for standardized national and global guidelines.

Challenges in Brain Death Diagnosis

The diagnosis of BD/DNC relies on clinical assessments that evaluate the absence of brainstem reflexes, irreversible coma, and the inability to breathe independently. Additional confirmatory tests, such as cerebral blood flow studies or electroencephalography, may be used when inconclusive clinical exams. However, discrepancies exist in how these tests are applied across jurisdictions, contributing to ethical and legal uncertainties [6, 11–13].

Some key challenges in BD/DNC diagnosis include:

- Variability in required clinical examinations and confirmatory tests between states and countries.
- Differences in physician training and expertise in BD determination.
- Ethical concerns regarding misdiagnosis, particularly in patients with complex neurological conditions.
- Religious and cultural objections to BD that further complicate standardization efforts.

Ethical Issues in BD/DNC Determination [8, 9, 14–17]

1. Justice and Equity — The principle of justice demands that all patients be treated equally, yet

current BD/DNC criteria vary by state and country. Patients and families in different jurisdictions may receive different determinations of death, leading to inequities in care and access to organ transplantation.

2. Autonomy and Informed Consent — Many families struggle with BD diagnoses, particularly when state laws and hospital policies differ. Lack of uniform communication and inconsistent criteria compromise informed consent, leaving families uncertain about their loved one's medical status.

3. Public Trust and Legitimacy — Public confidence in BD/DNC is critical, particularly in organ donation. The presence of varying state and international criteria risks eroding trust in medical professionals and the ethical integrity of brain death determinations, potentially impacting organ donation rates.

4. Religious and Cultural Considerations — Ethical concerns arise when diverse religious and cultural beliefs are not uniformly considered in BD/DNC protocols. The lack of a standardized approach can lead to unnecessary conflicts between medical teams and families who dispute BD determinations on cultural or religious grounds.

5. Legal and Policy Implications — The legal definition of death should be coherent and consistently applied. The variation among states and countries challenges the credibility of BD as a legal and medical standard, opening the door for legal disputes and further ethical ambiguities.

The Need for National and Global Standardization: Harmonizing BD/DNC standards across all U.S. states and internationally is an ethical imperative to protect patients, families, and the medical community. National and global guidelines should ensure that BD determination is scientifically rigorous, ethically justified, and legally enforceable [18–22].

Key recommendations include:

- Adoption of a single, national BD/DNC standard to ensure consistency in death determination across U.S. states.
- Development of international BD/DNC guidelines under organizations such as the World Health Organization (WHO) to facilitate global alignment on BD criteria.
- Strengthening communication and transparency in BD diagnoses to improve public trust.
- Considering cultural and religious perspectives in BD determinations to uphold ethical inclusivity.
- Enhancing medical education and physician training to ensure accurate and ethical BD diagnoses worldwide.

Discussion

The ethical necessity of standardizing BD/DNC criteria extends beyond national borders. Countries such as Japan, Israel, and some Muslim-majority nations have different approaches to BD due to cultural, religious, or legal reasons — this global diversity challenges medical professionals and policymakers seeking a unified approach. The absence of universal BD standards complicates international organ donation efforts, raises ethical dilemmas regarding patient rights, and fuels skepticism toward BD determinations. The global medical community must engage in interdisciplinary discussions to achieve greater harmonization of BD/DNC policies, ensuring ethical and legal consistency across borders [19, 21, 23–25].

Conclusion

The ethical challenges posed by inconsistent BD/DNC criteria demand immediate attention. A nationally and internationally unified approach to BD determination aligns with justice, transparency, and medical integrity principles. Standardizing BD/DNC guidelines will enhance ethical medical practice, ensure fairness in healthcare decisions, and reinforce public confidence in determining death and organ donation systems. The time has come for a comprehensive, evidence-based, and globally accepted BD/DNC determination framework.

References

1. *Allemang B., Patton M., Greer K., Pinston K., Farias M., Schofield K., Samuael S.,* et al. Development of the Strengths, Skills, and Goals Matrix: a tool for facilitating strengths-based adolescent and young adult engagement in research. *Res Involv Engagem*. 2023; 9 (1): 89. DOI: 10.1186/s40900-023-00502-w.
2. *Berkowitz I. D., Garret J.* Should the brain death exam with apnea test require surrogate informed consent? No. The U. D.DA revision series. *Neurology*. 2023; 101 (5): 218–220. DOI: 10.1212/WNL.0000000000207343. PMID: 37429709.
3. *Barnes E., Greer D.* Inconsistency in brain death determination should not be tolerated. *AMA J Ethics*. 2020; 22 (12): E1027-1032. DOI: 10.1001/amajethics.2020.1027. PMID: 33419503.
4. *Lewis A., Kirschen M.P, Greer D. M.* Author response: pediatric and adult brain death/death by neurologic criteria consensus guideline: report of the AAN Guidelines Subcommittee, AAP, CNS, and SCCM. *Neurology*. 2024; 102 (9): e209370. DOI: 10.1212/WNL.0000000000209370. PMID: 38648607.
5. *Bernat J. L.* Author response: challenges to brain death in revising the uniform determination of Death Act: the UDDA revision series. *Neurology*.2024; 102 (1): e208045. DOI: 10.1212/WNL.0000000000208045. PMID: 38165387.
6. *Machado C.* Reader response: challenges to brain death in revising the uniform determination of death act: the UDDA revision series. *Neurology*. 2024; 102 (1): e208044. DOI: 10.1212/WNL.0000000000208044. PMID: 38165388
7. *Machado C.* Reader response: What is the ideal brain criterion of death? Nonclinical considerations: the UDDA revision series. *Neurology*. 2024; 102 (9): e209286. DOI: 10.1212/WNL.0000000000209286. PMID: 38621220.
8. *Landau D., Kirschen M. P., Greer D., Lewis A.* States do not delineate the «Accepted Medical Standards» for brain death/death by neurologic criteria determination. *Neurocrit Care*. 2025. DOI: 10.1007/s12028-024-02209-6. PMID: 39849222.
9. *Johnson L. S.M.* Philosophical, medical, and legal controversies about brain death. Elements in bioethics and neuroethics. Cambridge University Press; 2024: 84. DOI: 10.1017/9781009323352
10. *Kowalski K., Marschollek J., Nowakowska-Kotas M., Budrewicz S.* The impact of clinical education on knowledge and attitudes towards brain death among Polish medical students — a cross-sectional study. *BMC Med Educ*. 2023; 23 (1): 669. DOI: 10.1186/s12909-023-04637-y. PMID: 37710211.
11. *Junga A., Kockwelp P., Valkov D., Schulze H., Bozdere P., Hätscher O., Ahrens H., et al.* Teach the unteachable with a virtual reality (VR) brain death scenario — 800 students and 3 years of experience. *Perspect Med Educ*. 2025; 14 (1): 44–54. DOI: 10.5334/pme.1427. PMID: 39897616.
12. *Amiri M., Fisher P. M., Raimondo F., Sidaros A., Hribljan M. C., Othman M. H., Zibrandtsen I., et al.* Multimodal prediction of residual consciousness in the intensive care unit: the CONNECT-ME study. *Brain*. 2023; 146 (1): 50–64. DOI: 10.1093/brain/awac335. PMID: 36097353.
13. *Taran S., Gros P., Gofton T., Boyd G., Briard J. M., Chassé M., Singh J. M.* The reticular activating system: a narrative review of discovery, evolving understanding, and relevance to current formulations of brain death. *Can J Anaesth*. 2023; 70 (4): 788–795. DOI: 10.1007/s12630-023-02421-6. PMID: 37155119.
14. *Rizk A. A., Farhani N., Shankar J.* Computed tomography perfusion for the diagnosis of brain death: a technical review. *Can J Neurol Sci*. 2024; 51 (2): 173–178. DOI: 10.1017/cjn.2023.242. PMID: 37462465.
15. *Murphy N. B., Shemie S. D., Capron A., Truog R. D. Nakagawa T., Healey A., Gofton T., et al.* Advancing the scientific basis for determining death in controlled organ donation after circulatory determination of death. *Transplantation*. 2024; 108 (11): 2197–2208. DOI: 10.1097/TP.0000000000005002. PMID: 38637919.
16. *Diaz-Cobacho G., Molina-Perez A., Rodriguez-Arias D.* Death pluralism: a proposal. *Philos Ethics Humanit Med*. 2023; 18 (1): 10. DOI: 10.1186/s13010-023-00139-3. PMID: 37528432.
17. *Eisenberg L. R.* Disputes over diagnosing death: is it ethical to test for death by neurologic criteria over parental objection? *Am J Bioeth*. 2023; 23 (1): 86–87. DOI: 10.1080/15265161.2023.2146408. PMID: 36594995.
18. *Lewis A.* Should the revised uniform determination of death act address objections to the use of neurologic criteria to declare death? *Neurocrit Care*. 2022; 37 (2): 377–385. DOI: 10.1007/s12028-022-01567-3. PMID: 35854082.
19. *Lewis A., Kitamura E.* The intersection of neurology and religion: a survey of hospital chaplains

on death by neurologic criteria. *Neurocrit Care*. 2021; 35 (2): 322–334.
DOI: 10.1007/s12028-021-01252-x.
PMID: 34195896.

20. *Afif I. N., Goldberg A. J., Zhao H., O'Shaughnessy G. D., Kling S. M., Nathan H. M., Hasz R. D.,* et al. Formal training improves resident understanding and communication regarding brain death/death by neurologic criteria. *J Surg Educ*. 2022; 79 (1): 198–205.
DOI: 10.1016/j.jsurg.2021.08.018.
PMID: 34507909.
21. *Lewis A., Kitamura E., Padela A. I.* Allied Muslim healthcare professional perspectives on death by neurologic criteria. *Neurocrit Care* 2020; 33 (2): 347–357.
DOI: 10.1007/s12028-020-01019-w.
PMID: 32556858.
22. *Lewis A. A* Survey of multidenominational rabbis on death by neurologic criteria. *Neurocrit Care*. 2019; 31 (2): 411–418.
DOI: 10.1007/s12028-019-00742-3.
PMID: 31218638.
23. *Atabekov T. A., Sazonova S. I., Khlynin M. S., Muslimova E.F., Krivolapov S.N., Kurlov I.O., Rebrova T.Yu., et al.* Predictors of appropriate therapies delivered by the implantable cardioverter-defibrillator in patients with coronary artery disease during long-term period. *Int J Cardiovasc Imaging*. 2024; 40 (9): 1863–1874.
DOI: 10.1007/s10554-024-03172-1.
PMID: 38963590.
24. *Damaiyanti M., Amir H., Cahyani D.D, Alhidayat N.S., Afrianti N., Rahmiati C., Hastuti H., et al.* Improving caregiver preparedness in the care transition of stroke patients: a scoping review. *J Med Life*. 2023; 16 (12): 1723–1731.
DOI: 10.25122/jml-2023-0142. PMID: 38585525.
25. *Ferhatoglu M. F., Ferhatoglu S. Y.* A Holistic assessment of organ transplantation activities, scientific productivity on brain death in Islamic countries, and comparison of the outcomes with the United Nations Development statistics. *J Relig Health*. 2021; 60 (2): 774–786.
DOI: 10.1007/s10943-020-01157-7.
PMID: 33415604.

Received 27.02.2025
Accepted 18.03.2025
Accepted in press 25.03.2025

Instructions for Authors of the General Reanimatology Journal

Based on the **Brief Author Guidelines for Preparing and Formatting Scholarly Papers in Journals Indexed in International Scientific Databases**, edited by Olga Kirillova and published under the auspices of ASEP (Association of Scientific Editors and Publishers) and RRIEPL (Russian Research Institute of Economics, Politics, and Law in Science and Technology) in 2019; the **CSE's White Paper on Promoting Integrity in Scientific Journal Publications** (2012 Update); the **ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals** (December 2016); and the *EASE Guidelines for Authors and Translators* (available at **https://ease.org.uk/guidelines-toolkits/**).

Version Dated February 2023

When submitting a manuscript to the General Reanimatology journal, the authors guarantee that:

— the manuscript has not been previously published in another journal;

— the manuscript is not currently reviewed for publication in another journal;

— the manuscript does not contain any confidential information;

— all co-authors agree with publication of the current version of the article.

Instructions for the Authors Before Submitting the Manuscript

Before submitting a manuscript for review, make sure that the file contains all the necessary information in Russian or English, lists all sources of information (references), has a full set of figures and tables, all citations are properly formatted.

The editorial board of the «General Resuscitation» journal recommends that authors use the following checklists and charts developed by international health organizations in preparing manuscripts and other materials (**EQUATOR, Enhancing the Quality and Transparency of Health Research, https://www.equator-network.org/reporting-guidelines/; SWIHM, Scientific Writing in Health & Medicine https://www.swihm.com/course/**):

When preparing papers reporting the results of randomized clinical trials, **«CONSORT 2010 checklist of information to include when reporting a randomized trial»**, **https://www.equator-network.org/reporting-guidelines/consort/**, should be used.

When preparing papers reporting the results of non-experimental research, **«The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies»**, **https://www.equator-network.org/reporting-guidelines/strobe/**, should be used.

When preparing a systematic review, **«PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)»**, **https://www.equator-network.org/reporting-guidelines/prisma/**, should be used. Additionally, we recommend the following outline for the abstract (summary): scope of the problem (1–3 sentences from the introduction); aim of the review (the same wording in the summary and in the introduction); number of sources, criteria and databases of source selection; specific issues considered according to the highlighted subheadings in the body of the review); limitations of the research on the topic; conclusion (an abridged version of the conclusion from the body of the review).

When preparing a clinical case report/series, **«The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development»**, **https://www.care-statement.org/checklist/**, or **SWIHM** 2019 recommendations should be used. Russian language form can be found at **www.reanimatology.com** → Section «Authors Guidelines» → Case Report Writing Template for Authors.

When preparing papers reporting the results of qualitative research, **SRQR (Standards for reporting qualitative research)**, **https://www.equator-network.org/reporting-guidelines/srqr/**, should be used.

Full version at www.reanimatology.com

Main information for the manuscript submission

PARAMETER	INSTRUCTIONS
Limitations	
Initial submission	One file in the Word format in Russian for Russian-speaking authors in English for non-Russian-speaking authors, including: — the title of the paper; — full names of all authors; — affiliations of all authors; — IDs of profiles in the scientific databases for each author; — the text of all sections of the paper; — tables, figures, photos with captions and notes; — references; — conflict of interest; — information of study funding; — acknowledgements (optional); — authors' contribution (preferably)
The length of the manuscript	Original manuscript — about 40,000 characters with spaces; Short communication — should not exceed 2,500 words; Review, meta-analysis — 25,000–40,000 characters with spaces
Front page information	
Title of the paper	Should not exceed 15 words
Information about authors	Full name (Peter A. Johnson), author profile ID in the research database(s) for each author (e-Library/RSCI (Rus), ORCID, Scopus, WoS researcher ID if available)
Affiliations	Full name and postal address of the organizations with zip code
Corresponding author	Full name, e-mail address, phone number
The paper outline and references	
Summary (abstract)	250–300 words. Sections: scope of the problem (introduction/background), aim, material and methods, results, conclusion
Highlights (main messages as text or infographics, an optional section following the summary)	1–3 messages in graphic or text form (no more than 40 words per each text message)
Key words	6–8 words listed with a semicolon (;), without a dot at the end
Body of the paper	Sections: introduction (background), material and methods, results, discussion, conclusion
Supplementary information sections	Conflict of interest, funding of the study should follow the Keywords paragraph. Acknowledgements (optional) and authors' contribution (preferably) should be placed at the end of the paper
Illustrations, including tables	Original paper — up to 8; Short communication — no more than 3; Review — up to 8
References	Dating: 70% should be published within the last 5 years, of them at least 30% within the last 3 years. Number: Original paper — 25–45; Short communication — 10–25; Review — 80–120. Format: please see the «References Formatting» section, www.reanimatology.com
Formatting	
Font	Times New Roman, 12 points. The section titles should be typed in bold
Spacing and Indentation	Line spacing — 1.5; Interval before and after the paragraph — none; Interval between sections — one extra spacing; First line indent — 1.25 cm
Fields	2.5 cm on all sides
Page numbering	In the lower right corner

NobiliXe®

КОМПЛЕКС ТЕРАПЕВТИЧЕСКИЙ
КСЕНОНОВЫЙ

ИнертГаз
Медикал

Единственная в мире **автоматическая** станция для проведения терапевтических процедур медицинским ксеноном с целью лечения острых и хронических болевых синдромов, обезболивания, лечебных и диагностических манипуляций

Свойства ксенона:

- Не является химически синтезированным веществом
- Без запаха, без вкуса, не раздражает дыхательные пути
- Не обладает ни общей, ни специфической токсичностью
- Не подвергается метаболизму в организме, полностью выводится через легкие
- Оказывает быстрое терапевтическое воздействие на организм
- В терапевтических, субнаркозных концентрациях обладает анальгетическим, анксиолитическим, нейро- и кардиопротективным эффектами
- Не вызывает аллергических реакций и совместим с любыми фармпрепаратами
- Внесён ВАДА в список запрещённых препаратов в связи с его доказанным влиянием на функциональные резервы организма и повышением толерантности к физическим нагрузкам
- Вызывает у пациента приятные ощущения после процедуры

Xe 54
Ксенон

КсенОкс® 50

- Первый в мире **терапевтический** препарат на основе ксенона и кислорода
- Может применяться врачами **любой** специальности для анальгезии
- Совместим с имеющимся оборудованием для проведения ингаляций ксенон-кислородными газовыми смесями
- Относится к группе АТХ N02 - **Анальгетики**

Показания к применению:

- Терапия острой и хронической боли умеренной и сильной интенсивности
- Анальгезия у онкологических пациентов при хроническом болевом синдроме средней и тяжелой степени

ingasgroup.ru
+7 495 123 45 91
+7 906 711 00 55
sales@ingasgroup.ru