



[www.reanimatology.com](http://www.reanimatology.com)  
ISSN 2411-7110 (online)

# GENERAL REANIMATOLOGY

SCIENTIFIC-AND-PRACTICAL JOURNAL

**ОБЩАЯ РЕАНИМАТОЛОГИЯ**  
научно-практический журнал

**Volume 22**

**Том 22**

**№ 4**

---

## Information from the AI Use Policy

**Dear Authors,**

Please note the following:

Beginning in August 2026, authors are required to disclose the use of AI tools during manuscript preparation when submitting manuscripts to the journal «General Reanimatology».

Information regarding the use or non-use of AI should be provided at the end of the «Materials and Methods» section, following the description of statistical data processing methods, under the subsection «Information on the Use of Artificial Intelligence».

This subsection specifies:

1. The AI model(s) and software version(s) used.
2. The sections of the article (including illustrations and references) and the technical tasks (such as style refinement, translation, etc.) in which AI was used.
3. The main instructions provided to the AI (the core prompts).

A copy (or copies) of the full prompt(s) must be provided upon request by the reviewer or editor if clarification of the logical structure of the AI-generated text is required.

**The use of AI is not permitted in formulating the research  
and/or practical objectives of the work, discussing the results,  
or drawing conclusions.**

If the authors prepared the article materials without the use of AI, the relevant subsection should state: «Artificial intelligence was not used in the preparation of this article».

**Sincerely,  
Editors of the «General Reanimatology» Journal**

## GENERAL REANIMATOLOGY OBSSHCHAYA 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 «Obsshchaya 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:

© «Emergency Medicine» Fund, Member of the Association of Scientific Editors and Publishers (ASEP), Moscow, Russia



Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology, Moscow, Russia

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»

### EDITORS

**Viktor V. MOROZ, Editor-in-Chief, MD, PhD, DSci, Professor, Corr. Member of RAS, Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (Moscow, Russia)**

**Artem N. KUZOVLEV, Deputy Editor-in-Chief, MD, DSci, Professor, V. A. Negovsky Research Institute of Reanimatology, Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (Moscow, Russia)**

**Arkady M. GOLUBEV, Deputy Editor-in-Chief, MD, PhD, DSci, Professor, Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (Moscow, Russia)**

**Vladimir T. DOLGIH, Deputy Editor-in-Chief, MD, PhD, DSci, Professor, V. A. Negovsky Scientific Research Institute of General Reanimatology, Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (Moscow, Russia)**

**Dmitry A. OSTAPCHENKO, Scientific Editor, MD, PhD, DSci, N. I. Pirogov Moscow City Hospital №1 (Moscow, Russia)**

**Vladimir M. PISAREV, Scientific Editor, MD, PhD, DSci, Professor, V. A. Negovsky Scientific Research Institute of General Reanimatology, Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (Moscow, Russia)**

### EDITORIAL BOARD

**Soheyl BAHRAMI, Professor, PhD, The International Federation of Shock Society (IFSS), Ludwig Boltzmann Institute of Experimental and Clinical Traumatology (Vienna, Austria)**

**Andrey E. BAUTIN, MD, V. A. Almazov National Medical Research Center (St. Petersburg, Russia)**

**Leo L. BOSSAERT, MD, Professor, Board of Advisory Committee, European Resuscitation Council University of Antwerpen (Belgium)**

**Gennady A. BOYARINOV, MD, PhD, DSci, Professor, Privolzhsky Research Medical University (Nizhniy Novgorod, Russia)**

**Jean-Louis VINCENT, Professor, Erasme Hospital, Universite Libre de Bruxelles (Belgium)**

**Andrey V. GRECHKO, PhD, DSci, Professor, Member of RAS, Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (Moscow, Russia)**

**Evgeny V. GRIGORYEV, MD, PhD, DSci, Professor, Corr. Member of RAS, Research Scientific Institute of Clinical Studies of complex problems of cardiovascular diseases, Siberian Branch, RAS (Kemerovo, Russia)**

## ОБЩАЯ РЕАНИМАТОЛОГИЯ OBŠAÂ 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», член Ассоциации научных редакторов и издателей (АНРИ), 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

### РЕДАКТОРЫ

**В. В. МОРОЗ, главный редактор, член-корр. РАН, профессор, Федеральный научно-клинический центр реаниматологии и реабилитологии (г. Москва, Россия)**

**А. Н. КУЗОВЛЕВ, заместитель главного редактора, д. м. н., профессор, НИИ общей реаниматологии им. В. А. Неговского ФНКЦ РР (г. Москва, Россия)**

**А. М. ГОЛУБЕВ, заместитель главного редактора, д. м. н., профессор, НИИ общей реаниматологии им. В. А. Неговского ФНКЦ РР (г. Москва, Россия)**

**В. Т. ДОЛГИХ, заместитель главного редактора, д. м. н., профессор, НИИ общей реаниматологии им. В. А. Неговского ФНКЦ РР (г. Москва, Россия)**

**Д. А. ОСТАПЧЕНКО, научный редактор, д. м. н., Городская клиническая больница № 1 им. Н. И. Пирогова (г. Москва, Россия)**

**В. М. ПИСАРЕВ, научный редактор, д. м. н., профессор, НИИ общей реаниматологии им. В. А. Неговского ФНКЦ РР (г. Москва, Россия)**

### РЕДАКЦИОННАЯ КОЛЛЕГИЯ

**С. БАРАМИ, профессор, Международное общество по изучению шока, Институт экспериментальной и клинической травматологии им. Л. Больцмана (г. Вена, Австрия)**

**А. Е. БАУТИН, д. м. н., Национальный медицинский исследовательский центр им. В. А. Алмазова (г. Санкт-Петербург, Россия)**

**Л. БОССАРТ, профессор, Консультативный комитет Европейского совета по реанимации (г. Антверпен, Бельгия)**

**Г. А. БОЯРИНОВ, д. м. н., профессор, Приволжский исследовательский медицинский университет (г. Нижний Новгород, Россия)**

**Ж.-Л. ВИНСЕНТ, профессор, Больница Эрасме Университета Либре (г. Брюссель, Бельгия)**

**А. В. ГРЕЧКО, Академик РАН, профессор, Федеральный научно-клинический центр реаниматологии и реабилитологии (г. Москва, Россия)**

**Е. В. ГРИГОРЬЕВ, член-корр. РАН, д. м. н., профессор, НИИ комплексных проблем сердечно-сосудистых заболеваний СО РАН (г. Кемерово, Россия)**

**Agzam Sh. ZHUMADILOV**, MD, Professor, National Coordination Center for Emergency Medicine (Astana, Kazakhstan)  
**Igor B. ZABOLOTSKIY**, MD, PhD, DSci, Professor, Kuban State Medical University (Krasnodar, Russia)  
**Michael N. ZAMYATIN**, MD, PhD, DSci, Professor, Institute for Advanced Medical Studies, N. I. Pirogov National Medical Surgical Center, Ministry of Health of Russia (Moscow, Russia)  
**Bernd SAUGEL**, MD, Professor, University Medical Center Hamburg-Eppendorf, Hamburg, Germany  
**Nikolai A. KARPUN**, MD, PhD, DSci, City Hospital № 68 (Moscow, Russia)  
**Mikhail Yu. KIROV**, MD, DSci, Professor, Corr. Member of RAS, Northern State Medical University (Arkhangelsk, Russia)  
**Igor A. KOZLOV**, MD, PhD, DSci, Professor, M. F. Vladimirovsky Moscow Regional Research Clinical Institute (Moscow, Russia)  
**Patrick M. KOCHANNEK**, MD, FCCM, Professor, P. Safar Center for Resuscitation Research, University of Pittsburgh School of Medicine (USA)  
**Giovanni LANDONI**, MD, Associate Professor, Vita-Salute San Raffaele, Milan, Italy  
**Konstantin M. LEBEDINSKY**, MD, DSci, Professor, I. I. Mechnikov North-Western Medical University (St. Petersburg, Russia)  
**Jerry P. NOLAN**, Professor, Royal United Hospital (Bath, UK)  
**Svetlana A. PEREPELITSA**, MD, DSci, I. Kant Baltic Federal University (Kaliningrad, Russia)  
**Sergey S. PETRIKOV**, DSci, Professor, Member of RAS, N. V. Sklifosovsky Research Institute of Emergency Medicine, Moscow City Health Department (Moscow, Russia)  
**Vasily I. RESHETNYAK**, MD, PhD, DSci, Professor, Russian University of Medicine, Ministry of Health of Russia (Moscow, Russia)  
**Vladislav V. RIMASHEVSKY**, MD, PhD, Associate Professor, Belarusian State Medical University (Minsk, Belarus)  
**Djurabay M. SABIROV**, DSci, Professor, Tashkent Institute of Postgraduate Medical Education (Tashkent, Uzbekistan)  
**Beata D. SANIOVA**, MD, PhD, DSci, Professor, University Hospital (Martin, Slovak Republic)  
**Natalia D. USHAKOVA**, MD, PhD, DSci, Professor, Rostov Cancer Research Institute, (Rostov-on-Don, Russia)

**Mikhail Ya. YADGAROV**, Statistical Data Reviewer, PhD, MD with advanced diploma in computer science, I. V. Pryanikov Scientific Research Institute of Rehabilitology, Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (Moscow, Russia)  
**Petr A. POLYAKOV**, Statistical Data Reviewer, I. V. Pryanikov Scientific Research Institute of Rehabilitology, Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (Moscow, Russia)  
**Oksana N. SYTNIK**, Translator and Bibliographer, PhD, V. A. Negovsky Scientific Research Institute of General Reanimatology, Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (Moscow, Russia)  
**Natalya V. GOLUBEVA**, Managing Editor, PhD, V. A. Negovsky Scientific Research Institute of General Reanimatology, Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (Moscow, Russia)

**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](http://www.aov.ru)

**Contacts:**

25 Petrovka Str., Bldg. 2, 107031 Moscow, Russia.

Tel. +7-495-694-17-73.

E-mail: [journal\\_or@mail.ru](mailto:journal_or@mail.ru);

Web: [www.reanimatology.com](http://www.reanimatology.com)

**Open Access Journal under a Creative Commons**

**Attribution 4.0 License**

**Subscription:**

Index 46338, refer to catalog of «Книга-Сервис»

**Signed for printing:** 08.09.2026

**А. Ш. ЖУМАДИЛОВ**, д. м. н., профессор, Национальный координационный центр экстренной медицины (г. Астана, Казахстан)  
**И. Б. ЗАБОЛОТСКИХ**, д. м. н., профессор, Кубанский государственный медицинский университет (г. Краснодар, Россия)  
**М. Н. ЗАМЯТИН**, д. м. н., профессор, Институт усовершенствования врачей Национального медико-хирургического Центра им. Н. И. Пирогова Минздрава России (г. Москва, Россия)  
**Б. ЗАУТЕЛЬ**, д. м. н., профессор, клиника анестезиологии-реаниматологии Гамбургского Университета (г. Гамбург, Германия)  
**Н. А. КАРПУН**, д. м. н., Городская клиническая больница № 68 (г. Москва, Россия)  
**М. Ю. КИРОВ**, член-корр. РАН, д. м. н., профессор, Северный Государственный медицинский Университет (г. Архангельск, Россия)  
**И. А. КОЗЛОВ**, д. м. н., профессор, Московский областной научно-исследовательский клинический институт им. М. Ф. Владимирского (г. Москва, Россия)  
**П. КОХАНЕК**, профессор, Центр исследований проблем реаниматологии им. П. Сафара, Университет Питтсбурга (г. Питтсбург, США)  
**Дж. ЛАНДОНИ**, профессор, Университет Вита-Салуте Сан Раффаэле (г. Милан, Италия)  
**К. М. ЛЕБЕДИНСКИЙ**, д. м. н., профессор, Северо-Западный медицинский университет им. И. И. Мечникова (г. Санкт-Петербург, Россия)  
**Д. П. НОЛАН**, профессор, Королевский объединенный госпиталь (г. Бат, Великобритания)  
**С. А. ПЕРЕПЕЛИЦА**, д. м. н., Балтийский Федеральный университет им. И. Канта (г. Калининград, Россия)  
**С. С. ПЕТРИКОВ**, Академик РАН, д. м. н., профессор, Научно-исследовательский институт скорой помощи им. Н. В. Склифосовского Департамента здравоохранения г. Москвы, (Москва, Россия)  
**В. И. РЕШЕТНЯК**, д. м. н., профессор, Российский Университет Медицины Минздрава России (г. Москва, Россия)  
**В. В. РИМАШЕВСКИЙ**, д. м. н., доцент, Белорусский Государственный медицинский университет (г. Минск, Беларусь)  
**Д. М. САБИРОВ**, д. м. н., профессор, Ташкентский институт усовершенствования врачей (г. Ташкент, Узбекистан)  
**Б. Д. САНИОВА**, д. м. н., профессор, Университетский госпиталь (г. Мартин, Словакия)  
**Н. Д. УШАКОВА**, д. м. н., профессор, Научно-исследовательский онкологический институт (г. Ростов-на-Дону, Россия)

**М. Я. ЯДГАРОВ**, рецензент методов статистической

обработки данных, к. м. н., НИИ реабилитологии

им. проф. И. В. Пряникова ФНКЦ РР (г. Москва, Россия)

**П. А. ПОЛЯКОВ**, рецензент методов статистической

обработки данных, НИИ реабилитологии

им. проф. И. В. Пряникова ФНКЦ РР (г. Москва, Россия)

**О. Н. СЫТНИК**, переводчик и библиограф, к. м. н.,

НИИ общей реаниматологии им. В. А. Неговского

ФНКЦ РР (г. Москва, Россия)

**Н. В. ГОЛУБЕВА**, ответственный секретарь, к. б. н.,

НИИ общей реаниматологии им. В. А. Неговского

ФНКЦ РР (г. Москва, Россия)

**Оригинал-макет:** Н. В. Голубева

**Верстка:** С. В. Шишков

**Типография:** отпечатано в ООО «Авансд солюшнз».

119071, г. Москва, Ленинский пр-т, д. 19, стр. 1. [www.aov.ru](http://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](mailto:journal_or@mail.ru);

сайт: [www.reanimatology.com](http://www.reanimatology.com)

**Доступ к контенту:** открытый под лицензией Creative

Commons Attribution 4.0 License

**Подписка и распространение:** индекс издания по ката-

логу «Книга-Сервис» — 46338.

Цена свободная

**Подписано в печать:** 08.09.2026

## CONTENTS

## СОДЕРЖАНИЕ

## CLINICAL STUDIES

## КЛИНИЧЕСКИЕ ИССЛЕДОВАНИЯ

- Assessment of Comorbidity in Patients with Chronic Disorders of Consciousness 4  
*Liudmila A. Legostaeva, Natalya A. Suponeva, Olga A. Kirichenko, Dmitry V. Sergeev, Ksenia A. Yatsko, Artem D. Kolokoltsev, Anton A. Bormin, Yulia. V. Ryabinkina, Michael A. Piradov*

- Ultrasound-Derived Diaphragmatic Function Indices Predict Weaning Outcomes in Surgical Intensive Care Unit Patients (Prospective Observational Study) 12  
*Tran Viet Duc, Vu Hoang Phuong, Nguyen Huu Tu*

## FOR PRACTITIONER

## ПРАКТИКУЮЩЕМУ ВРАЧУ

- Early Ultrasound Diagnosis of Post-Operative Microaspiration and Pneumonia (Case Report) 22  
*Ivan S. Shcheparev, Boris A. Teplykh, Darya N. Rostovceva*
- Effect of Octenidine Dihydrochloride on Gingival Inflammation, Dental Plaque, and Xerostomia in Patients Receiving Respiratory Support 28  
*Irina A. Ruslyakova, Ekaterina A. Zakharova, Yulia A. Mironova, Ilja S. Chertsov, Elvina Z. Shamsutdinova, Alexey V. Silin*

## EXPERIMENTAL STUDIES

## ЭКСПЕРИМЕНТАЛЬНЫЕ ИССЛЕДОВАНИЯ

- Effect of Hypothermia on the Expression of Brain Injury Marker Proteins in the Presence of Interleukin-6 and Anoxia *in vitro* 38  
*Artem A. Ivkin, Elena D. Khilazheva, Evgeniy V. Grigoriev, Angelina I. Mosyagina*

## REVIEWS &amp; SHORT COMMUNICATIONS

## ОБЗОРЫ И КРАТКИЕ СООБЩЕНИЯ

- Concept of Infectious Perioperative Risk (Analytical Review) 47  
*Ekaterina I. Glushko, Nikita V. Trembach, Alexey A. Noskov, Igor B. Zabolotskikh*
- Impact of Frailty on Outcomes and Management of Older and Very Old Patients in the Intensive Care Unit (Review) 62  
*Ainagul Zh. Bayalieva, Veronica R. Davydova*

## Assessment of Comorbidity in Patients with Chronic Disorders of Consciousness

Liudmila A. Legostaeva\*, Natalya A. Suponeva\*, Olga A. Kirichenko, Dmitry V. Sergeev, Ksenia A. Yatsko, Artem D. Kolokoltsev, Anton A. Bormin, Yulia V. Ryabinkina, Michael A. Piradov

Russian Center for Neurology and Neuroscience,  
80 Volokolamskoe Shosse, 125367 Moscow, Russia

**For citation:** Liudmila A. Legostaeva, Natalya A. Suponeva, Olga A. Kirichenko, Dmitry V. Sergeev, Ksenia A. Yatsko, Artem D. Kolokoltsev, Anton A. Bormin, Yulia V. Ryabinkina, Michael A. Piradov. Effect of Octenidine Dihydrochloride on Gingival Inflammation, Dental Plaque, and Xerostomia in Patients Receiving Respiratory Support. *Obshchaya Reanimatologiya = General Reanimatology*. 2026; 22 (4): 4–11. <https://doi.org/10.15360/1813-9779-2026-4-2558> [In Russ. and Engl.]

\*✉ Liudmila A. Legostaeva, milalegostaeva@gmail.com; Natalya A. Suponeva, nasu2709@mail.ru

### Summary

Presence and decompensation of comorbid conditions can directly affect levels of wakefulness and consciousness in patients with chronic disorders of consciousness (DoC). Identifying and thorough assessment of comorbid conditions and concurrent diseases is a decisive step in diagnosing signs of consciousness, monitoring changes over time, and making prognoses in patients with DoC.

**Objective.** To assess the incidence and severity of comorbid conditions in patients with chronic DoC using the Comorbidities Coma Scale (CoCoS).

**Materials and Methods.** At the Russian Center of Neurology and Neurosciences, we conducted a retrospective review of the medical records of 52 patients with chronic DoC of various etiologies (31 men, 21 women; traumatic etiology,  $n=18$ ; non-traumatic etiology,  $n=34$ ). To determine the type of DoC, all patients were independently assessed twice by two investigators using the Coma Recovery Scale–Revised (CRS–R). To account for the severity and nature of brain injury, we analyzed etiology (traumatic/non-traumatic), time since injury, and the baseline CRS–R score as an integrated measure of neurological deficit. Comorbid status was assessed using the CoCoS scale.

**Results.** Different types of stomas as life-sustaining medical devices (tracheostomy, gastrostomy, and suprapubic cystostomy) in 100%, and joint disorders in 98% were identified as predominant comorbid conditions in patients with chronic DoC. Less common comorbid conditions included urinary tract infections (71.15%), kidney diseases (57.69%), pressure ulcers (53.85%), infectious respiratory diseases (46.15%), malnutrition (38.46%), anemia (30.77%), fractures of bones and skull (28.85%), hydrocephalus (13.46%), and paroxysmal autonomic activity (13.25%). Comorbidity of moderate severity was identified in one patient (1.96%); all others were classified as mild. When stratified by etiology, no significant differences in the total CoCoS score were found between the traumatic and non-traumatic groups ( $p>0.05$ ). No correlation was observed between CRS–R and CoCoS scores in the overall sample ( $p=0.051$ ,  $R=0.227$ ); similar results were obtained in the subgroup analyses (traumatic:  $p=0.43$ ,  $R=0.19$ ; non-traumatic:  $p=0.28$ ,  $R=0.21$ ).

**Conclusion.** The analysis revealed a high prevalence of medical devices used to support vital functions and prevent joint contractures, reflecting apparent dependence of patients with chronic DoC on technical support and care. In most cases, the comorbidity burden was mild, indicating a relatively compensated somatic status. The absence of a significant correlation between the level of consciousness and comorbidity burden suggests that, in cases of mild comorbidity, somatic disorders are not the determining factor masking conscious activity. These findings underscore the need for an interdisciplinary approach to the management of such patients and the mandatory quantitative assessment of structural brain damage, otherwise it is impossible to distinguish the contribution of primary brain injury from that of concomitant pathology into development of chronic DoC.

**Keywords:** comorbidity; chronic disorders of consciousness; unresponsive wakefulness syndrome; vegetative state; minimally conscious state; comorbidity assessment scale for unresponsive patients; Comorbidities Coma Scale.

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

### Информация об авторах / Information about the authors:

Легостаева Людмила Александровна / Liudmila A. Legostaeva, <https://orcid.org/0000-0001-7778-6687>

Супонева Наталья Александровна / Natalya A. Suponeva, <https://orcid.org/0000-0003-3956-6362>

Кириченко Ольга Андреевна / Olga A. Kirichenko, <https://orcid.org/0000-0002-7119-9841>

Сергеев Дмитрий Владимирович / Dmitry V. Sergeev, <https://orcid.org/0000-0002-9130-1292>

Яцко Ксения Александровна / Ksenia A. Yatsko, <https://orcid.org/0000-0002-3014-4350>

Колокольцев Артем Дмитриевич / Artem D. Kolokoltsev, <https://orcid.org/0000-0002-3782-3284>

Бормин Антон Александрович / Anton A. Bormin, <https://orcid.org/0000-0001-6224-8595>

Рябинкина Юлия Валерьевна / Yulia V. Ryabinkina, <https://orcid.org/0000-0001-8576-9983>

Пирадов Михаил Александрович / Michael A. Piradov, <https://orcid.org/0000-0002-6338-0392>

## Introduction

Group of patients with chronic disorders of consciousness (CDoC) includes patients with severe brain injury whose condition is characterized by the return of the sleep-wake cycle with complete or partial absence of consciousness. Depending on the presence or absence of signs of conscious activity, patients with CDoC can be divided into two major groups: patients in a vegetative state (VS), or unresponsive wakefulness syndrome (UWS), in whom there are no signs of goal-directed behavior, indicating the absence of consciousness; and patients in a minimally conscious state (MCS), who show inconsistent but clearly distinguishable signs of awareness of themselves or their environment [1–5].

At present, predicting recovery of consciousness in patients with CDoC is a challenging task due to the extreme variability of brain injury, compounded by the presence of concomitant somatic pathology and the diagnostic difficulty of identifying signs of conscious activity [6–10]. A patient's comorbid condition in CDoC may be caused both by the initial brain injury and by the subsequent development of the pathological process [11–13]. Somatic complications and chronic comorbid diseases have a direct impact on survival, recovery of consciousness, and functional independence in patients with CDoC [7, 9, 14–18].

A correlation has been identified between a decline in the quality of detectable signs of conscious activity and the presence of clinical somatic complications or severe comorbidities leading to reduced behavioral reactivity [6,8,9,19,20]. The most common pathologies involve the respiratory, urinary, and cardiovascular systems; however, the full range of somatic problems is much broader and, without exaggeration, encompasses nearly all body systems and organs [7, 16].

There are numerous tools for assessing comorbidity in various patient groups, mainly those with oncologic or age-related diseases. A quantitative, standardized assessment can provide insight into the impact of comorbid conditions on prognosis and outcomes (for example, the Kaplan-Feinstein scale, the ICED, the Charlson Comorbidity Index (CCI), and the Geriatric Index) [7, 21–23].

However, the range of comorbid conditions seen in CDoC significantly sets these scales apart from those used for other complex disorders. Important aspects that affect the assessment of consciousness in CDoC may be overlooked, while those that are common in other diseases may be absent or rare in patients with CDoC, making their evaluation redundant and time-consuming [9]. Such comorbid conditions that occur more often in CDoC than in other diseases may include seizures, hydrocephalus, heterotopic ossification, and several others [7, 21, 24, 25].

Development of a standardized scale focused on clinical characteristics and needs of patients with CDoC, and capable of improving the management of comorbid conditions, became necessary to clearly identify additional factors affecting the diagnosis, prognosis, and outcomes of CDoC. Such a scale was developed in 2019 at the University of L'Aquila (Italy) — the Comorbidity Coma Scale (CoCoS). Implementing this scale can improve not only the objectivity and reliability of results, but also the quality of care provided to patients with CDoC [26].

The validation group for international scales and questionnaires at the Research Center of Neurology, a federal state budgetary scientific institution, decided to conduct a two-stage study on the linguistic and cultural adaptation and validation of this scale. The first stage involved linguistic and cultural adaptation, after which the scale was given the Russian title «Comorbidity Assessment Scale for Unresponsive Patients». The second stage was validation of the scale, during which its psychometric properties were determined (inter-rater and test-retest reliability), and its sensitivity and validity were established [27, 28].

The aim of this study was to assess the comorbid status of patients with CDoC using the CoCoS scale.

## Materials and Methods

The study was conducted at the Research Center of Neurology as a retrospective cohort analysis of medical records of patients with CDoC (VS or MCS) who were treated between 2014 and 2021.

**Inclusion criteria:** diagnosis of VS or MCS, and a traumatic or non-traumatic brain injury that occurred at least 4 weeks earlier.

**Exclusion criteria:** incomplete medical records, inability to verify CoCoS categories, and absence of CRS-R/CoCoS data.

The study included medical records from 52 patients (31 men, 21 women) with CDoC of traumatic ( $n=18$ ) and nontraumatic ( $n=34$ ) etiology. Non-traumatic injuries included hypoxic-ischemic encephalopathy and cerebrovascular disease.

The median age in the overall group was 32 (25–48) years; in the group with traumatic CNS injury, 25 (22–32) years; and in the group with non-traumatic injury, 32 (25–48) years. The median time since injury was 32.5 (20.0–71.3) weeks in the overall sample; 25 (12.0–52.0) weeks for non-traumatic injury; and 56 (32.8–98.8) weeks for traumatic injury.

To verify the level of consciousness (LOC), the Coma Recovery Scale–Revised (CRS-R) was used (mean, 6.6 in the VS group and 15.4 in the MCS group). Because the study was retrospective, CRS-R scores were extracted from medical records, which contained the results of two examinations conducted by independent investigators as part of routine clinical practice. No quantitative neuroimaging as-

assessment of the severity of brain injury (e. g., the DAI scale or lesion volume) was performed, which is a limitation of the study.

The comorbidity status was assessed retrospectively using the validated CoCoS scale, which includes 24 categories (Fig. 1).

Two qualified neurologists who had completed specialized training independently filled out the CoCoS form based on the pooled data from the medical records: notes from specialist examinations, results of laboratory and instrumental tests (ECG, ultrasound, CT, etc.), as well as consultants' reports. To assess inter-rater reliability, the first and second physicians completed the initial form (designated A1 and B1, respectively). To assess intra-rater stability, the first physician completed CoCoS again after 24 hours (A2) and after 14 days (A3), each time reviewing the same source documents to eliminate the influence of memory and random factors.

Thus, the study design incorporated a retrospective inter-rater and retrospective within-subject assessment of comorbidity. The repeated assessments on days 1 and 14 did not reflect changes in patients condition over time; rather, they were used to determine the reliability of retrospective completion of the scale form. The initial data (CRS-R) were extracted only once, since they had already been recorded in the medical documentation: the initial examination was performed as soon as possible after hospital admission.

Each CoCoS category was assessed for severity based on objective clinical examination, laboratory and instrumental methods (ECG, ultrasonography,

CT, etc.), as well as the findings of relevant specialists. The total comorbidity burden was expressed as a score ranging from 0 to 72: mild, 1–24 scores; moderate, 25–48; severe, 49–72.

If more than two CoCoS categories could not be reliably assessed, the total score was not taken into account.

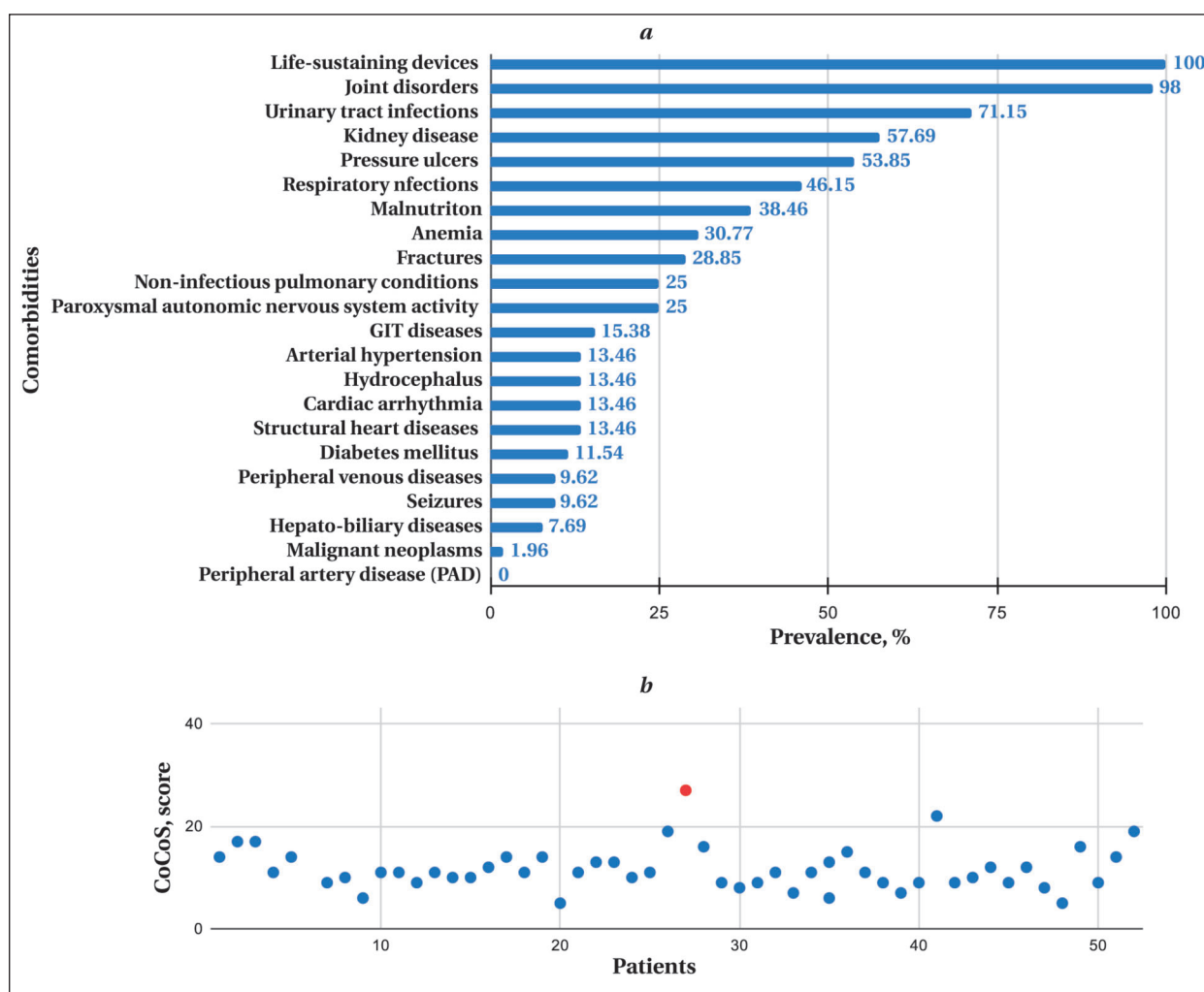
**Statistical analysis.** Statistica 13 software (StatSoft Inc., 2016) was used. The normality of the distribution of quantitative variables was assessed using the Shapiro–Wilk test. When the distribution deviated from normal and/or given the small size of the subgroups, nonparametric methods were applied. Quantitative variables were described as the median and interquartile range (*Me* [IQR]). Spearman's rank correlation coefficient was used for correlation analysis. Quantitative measures in two independent groups (by etiology: traumatic vs. nontraumatic; by diagnosis: VS vs. MCS) were compared using the Mann–Whitney *U* test. Pearson's chi-square test was used to compare the frequencies of binary categorical variables (presence/absence of each comorbid condition) between etiological groups; when the expected frequency in any cell of the contingency table was less than 5, Fisher's exact test was used. All statistical tests were two-sided, and differences were considered statistically significant at  $p < 0.05$ .

## Results

The study included medical data from 33 patients in VS (mCRS-R=6.6) and 19 patients in MCS (mCRS-R=15.4).

| RECORDING FORM                                                     |                                                             |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
|--------------------------------------------------------------------|-------------------------------------------------------------|-------------------------------------|--------------|-----------|---|---|---|---|---|---|---|---|----|----|----|
| Patient:                                                           |                                                             | Diagnosis:                          |              | Etiology: |   |   |   |   |   |   |   |   |    |    |    |
| Date of Acquired Severe Brain Injury:                              |                                                             | Assessment Date:                    |              |           |   |   |   |   |   |   |   |   |    |    |    |
| MONTHLY ASSESSMENT (from 0 to 3 points, as indicated in the Scale) |                                                             | Before Acquired Severe Brain Injury | On Admission | 1         | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| 1                                                                  | RESPIRATORY TRACT INFECTIONS                                |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 2                                                                  | URINARY TRACT INFECTIONS                                    |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 3                                                                  | NON-INFECTIOUS RESPIRATORY DISEASES                         |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 4                                                                  | ORGANIC HEART DISEASE (ischemic or non-ischemic etiology)   |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 5                                                                  | CARDIAC ARRHYTHMIAS IN THE ABSENCE OF ORGANIC HEART DISEASE |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 6                                                                  | ARTERIAL HYPERTENSION                                       |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 7                                                                  | DIABETES MELLITUS                                           |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 8                                                                  | PAROXYSMAL SYMPATHETIC HYPERACTIVITY                        |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 9                                                                  | PERIPHERAL ARTERY DISEASE                                   |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 10                                                                 | BRACHIOCEPHALIC ARTERY DISEASE                              |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 11                                                                 | PERIPHERAL VENOUS DISEASE                                   |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 12                                                                 | HEPATOBIILIARY SYSTEM DISEASES                              |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 13                                                                 | GASTROINTESTINAL TRACT DISEASES                             |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 14                                                                 | KIDNEY DISEASES                                             |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 15                                                                 | SEIZURES                                                    |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 18                                                                 | PRESENCE OF LIFE SUPPORT DEVICES                            |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 19                                                                 | ANEMIA                                                      |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 20                                                                 | JOINT DISEASES                                              |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 21                                                                 | MALIGNANT TUMORS                                            |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 22                                                                 | NUTRITIONAL DEFICIENCY                                      |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 22                                                                 | NUTRITIONAL DEFASER                                         |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| 24                                                                 | PRE-EXISTING DISABILITY                                     |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |
| Total Score                                                        |                                                             |                                     |              |           |   |   |   |   |   |   |   |   |    |    |    |

Fig. 1. Scale for assessing comorbid conditions in nonreactive patients [24, 25].



**Fig. 2. Prevalence of comorbidities (a, %) and distribution of patients with CDoC by severity of comorbid pathology (b, CoCoS). Note. b — blue — mild severity (1–24 scores, 98.1%,  $n=51$ ); red — moderate severity (25–48 scores, 1.9%,  $n=1$ ). Severe (49–72 scores) was not identified.**

According to the 24 CoCoS categories, the most common comorbid conditions were associated with the presence of life-sustaining devices (tracheostomy, gastrostomy, suprapubic cystostomy) in 100% of patients, with following after them joint disorders (stiffness, contractures) found in 51 patients (98%). The prevalence of the other conditions, in descending order, was as follows: urinary tract infections (71.15%), kidney disease (57.69%), pressure ulcers (53.85%), respiratory infections (46.15%), malnutrition (38.46%), anemia (30.77%), fractures of the skeletal bones and skull (28.85%), hydrocephalus (13.46%), paroxysmal autonomic nervous system activity (13.25%), and others (Fig. 2, a). A malignant neoplasm was recorded in only one case (1.96%), and no patient was found to have brachiocephalic artery pathology.

Severity stratification by CoCoS showed that only one patient (1.96%) had comorbid burden of moderate severity; all others exhibited mild comorbid burden (Fig. 2, b).

A comparison of the level of conscious activity (CRS-R score) and the severity of comorbid conditions (CoCoS score) in the overall sample showed a statistically insignificant correlation ( $p=0.051$ ,  $R=0.227$ ). When analyzed separately by etiology, no correlation was found in the traumatic group ( $p=0.43$ ,  $R=0.19$ ) or in the nontraumatic group ( $p=0.28$ ,  $R=0.21$ ). The median CoCoS score did not differ between the VS and MCS groups ( $p=0.34$ ).

The prevalence of comorbid conditions at different sites, according to the total CoCoS score, correlated with nontraumatic (hypoxic) etiology only in certain patient groups (for example, respiratory tract infections were more common in nontraumatic cases,  $p=0.04$ ); however, the overall CoCoS score did not differ between etiological groups ( $p=0.19$ ).

## Discussion

During a retrospective analysis of comorbid conditions and diseases in CDoC patients, numerous

components of VS and MCS patients' somatic status were identified and described in detail.

Attention to comorbid conditions in CDoC is driven by the fact that their destabilization directly affects the level of consciousness and wakefulness. A comprehensive, detailed analysis of concomitant conditions can facilitate the difficult diagnosis of signs of conscious activity [9]. Despite the abundance of scales capable of assessing comorbid status in various neurological disorders, none reflects the multidimensional complexity required to evaluate a patient with CDoC.

The results of our validation study [27] provide evidence-based support for the use of CoCoS in scientific research and everyday practice.

In the present study, no significant correlation was found between the LOC (CRS-R) and the comorbid conditions burden, assessed by CoCoS. This may suggest a relatively stable somatic status in patients with CDoC in the studied sample and absence of comorbidity substantial impact on assessed parameters of consciousness in patients with mild comorbidity burden. However, we acknowledge that the main factor determining the LOC is the severity and nature of the primary brain injury, which was not quantitatively assessed in this study (a standardized neuroimaging scale, such as a DAI scale for diffuse axonal injury or a volumetric lesion assessment, was not used). This was an important limitation of the study.

The diagnosed mild comorbidity burden did not indicate absence of concurrent conditions, but rather the extent to which they were compensated. A higher level of conscious activity did not correlate with the total number of comorbid conditions. Nevertheless, proper diagnosis and management of comorbid conditions may help reveal signs of consciousness and avoid diagnostic errors.

Most patients with CDoC required medical devices to sustain vital functions. High dependence on such devices is considered a predictor of a poor prognosis [15, 18]. High prevalence of tracheostomies, cystostomies, and other devices in the sample may explain the high rate of respiratory and urinary tract infections.

High rates of contractures and pressure sores are a consequence of motor dysfunction and immobility, but they may also indicate inadequate quality of care. The data obtained are consistent with findings reported in international studies [15, 21, 22]. Hyperactivity of the autonomic nervous system, often observed in patients with CDoC, can affect the accuracy of consciousness assessment [25, 29]: an increased heart and respiratory rates are often misinterpreted as an emotional response and false-positive signs of conscious activity.

Examination and assessment of a patient with CDoC require an objective instrumental and laboratory basis. The use of a standardized scale does not replace taking a medical history, but it does make it possible to establish the minimum set of factors needed to assess the patient's condition, match it with CDoC, avoid false conclusions, and formulate an appropriate prognosis and management plan [7, 30].

The practical use of the CoCoS scale in the day-to-day work of physicians caring for patients with CDoC can be implemented in several ways. First, a standardized assessment of comorbid conditions makes it possible to objectify the severity of the somatic burden at admission and to monitor changes in the patient's condition, which helps ensure timely treatment adjustments (for example, active decontamination of the tracheobronchial tree when a respiratory infection is identified, or meticulous skin care in the presence of pressure ulcers). Second, regular use of CoCoS as part of a comprehensive neuromonitoring protocol supports the differential diagnosis of changes in consciousness characteristics: a decline in behavioral responses caused by decompensation of the patient's somatic status (for example, fever, hypoxia, pain syndrome) can be distinguished from a true decline in the level of consciousness, thereby preventing diagnostic errors. Third, the total CoCoS score may serve as an additional criterion for prognosis and for planning patient transition, especially when deciding whether to transfer the patient to palliative care or rehabilitation units. It is recommended that CoCoS be included in the standard clinical assessment protocol for patients with CDoC alongside the CRS-R scale.

## Conclusion

A review of medical data from 52 patients with CDoC and retrospective assessment using CoCoS scale showed that the most common comorbid conditions were associated with the use of life-sustaining medical devices in addition to joint contractures, reflecting the patients' high dependence on technical support and care. The vast majority of cases were classified as mild comorbid conditions, indicating relatively compensated somatic status.

The absence of a significant correlation between the level of consciousness (CRS-R) and comorbid burden (CoCoS) suggests that, in cases of mild comorbidity burden, somatic status is not a determining factor masking signs of conscious activity. The key conclusion is the need for a separate quantitative assessment of the severity of the primary structural brain injury, otherwise it's impossible to distinguish the contribution of the underlying cerebral pathology from that of concomitant conditions.

## References

1. Posner J.B., Saper C.B., Schiff N.D., Claassen J., eds. Plum and Posner's diagnosis and treatment of stupor and coma. Fifth edition. Oxford University Press; 2019.
2. Пирадов М.А., Супонева Н.А., Вознюк И.А., Кондратьев А.Н., Щеголев А.В., Белкин А.А., Зайцев О.С. с соавт. Хронические нарушения сознания: терминология и диагностические критерии. Results первого заседания Российской рабочей группы по проблемам хронических нарушений сознания. *Анналы клинической и экспериментальной неврологии*. 2020; 14 (1): 5–16. Piradov M., Suponeva N.A., Voznyuk I.A., Kondratyev A.N., Shchegolev A.V., Belkin A.A., Zaitsev O.S., et al. Chronic disorders of consciousness: terminology and diagnostic criteria The results of the first meeting of the Russian Working Group for Chronic Disorders of Consciousness. *Annals of Clinical and Experimental Neurology=Annaly Klinicheskoy i Eksperimentalnoy Nevrologii*. 2020; 14 (1): 5–16. (in Russ.). DOI: 10.25692/ACEN.2020.1.1.
3. Кондратьева Е.А., Яковенко И.В. Вегетативное состояние: этиология, патогенез, диагностика и лечение. Москва: Медицина, ФГБУ «РНХИ им. проф. А.Л. Поленова»; 2014. Kondratyeva E.A., Yakovenko I.V. Vegetative state: etiology, pathogenesis, diagnostics, and treatment. Moscow: Medicine, Federal State Budgetary Institution «Russian Research Institute of Neurosurgery named after Professor A.L. Polenov»; 2014. (in Russ.).
4. Белкин А.А., Александрова Е.В., Ахутин Т.В., Белкин В.А., Бердникович Е.С., Быкова В.И., Варако Н.А. с соавт. Хронические нарушения сознания: клинические рекомендации Общероссийской общественной организации «Федерация анестезиологов и реаниматологов». *Вестник интенсивной терапии имени А. И. Салтанова*. 2023; 3: 7–42. Belkin A.A., Aleksandrova E.V., Akhutina T.V., Belkin V.A., Berdnikovich E.S., Bykova V.I., Varako N.A. et al. Chronic disorders of consciousness: guidelines of the All-Russian public organization «Federation of Anesthesiologists and Reanimatologists». *Annals of Critical Care*. 2023; 3: 7–42. (in Russ.). DOI: 10.21320/1818-474X-2023-3-7-42.
5. Teasdale G., Jennett B. Assessment of coma and impaired consciousness. *The Lancet*. 1974; 304 (7872): 81–84. DOI: 10.1016/S0140-6736 (74)91639-0.
6. Легостаева Л.А., Мочалова Е.Г., Супонева Н.А., Сергеев Д.В., Рябинкина Ю.В., Саморуков В.Ю., Домашенко М.А. с соавт. Сложности клинической диагностики хронических нарушений сознания и рекомендации по клинико-инструментальной оценке пациентов после их выхода из комы. *Анестезиология и реаниматология*. 2017; 62 (6): 449–456. Legostaeva L. A., Mochalova E.G., Suponeva N.A., Sergeev D.V., Ryabinkina Yu.V., Samorukov V.Yu., Domashenko M.A., et al. Difficulties in evaluation of chronic disorders of consciousness: approaches to clinical assessment and instrumental studies. *Russian Journal of Anaesthesiology and Reanimatology= Anesteziologiya i Reanimatologiya*. 2017; 62 (6): 449–456. (in Russ.). DOI: 10.18821/0201-7563-2017-62-6-449-456.
7. Estraneo A., Briand M.M., Noé E. Medical comorbidities in patients with prolonged disorder of consciousness: A narrative review. *NeuroRehabilitation*. 2024; 54 (1): 61–73. DOI: 10.3233/NRE-230130.
8. Lippert J., Guggisberg A.G. Diagnostic and therapeutic approaches in neurorehabilitation after traumatic brain injury and disorders of consciousness. *Clin Transl Neurosci*. 2023; 7 (3): 21. DOI: 10.3390/ctn7030021.
9. Saporito G., Gentili L., Cacchio A., Casalena A., Necozone S., Ricci A., Venturomi F, et al. Assessment of frequency and predictive value of comorbidities in patients with disorders of consciousness in the acute setting. *Neurotrauma Rep*. 2024; 5 (1): 267–276. DOI: 10.1089/neur.2023.0120. PMID: 38515549.
10. Saif M., Sharbatti S.A., Nemmar A., Kumar S.S., Prasad K., Khan A.M., Khadar I, et al. Outcomes of neurorehabilitation among patients with prolonged disorders of consciousness. *Cureus*. 2023; 15 (5): e38816. DOI: 10.7759/cureus.38816. PMID: 37303333.
11. Cortese M.D., Vatrano M., Arcuri F, Raso M.G., Tonin P, Calabro R.S., Riganello F Behavioral scales variability in patients with prolonged disorders of consciousness. *Neurol Sci*. 2023; 44 (9): 3107–3122. DOI: 10.1007/s10072-023-06812-x. PMID: 37087504.
12. Wang J., Hu X., Hu Z., Sun Z., Laureys S., Di H. The misdiagnosis of prolonged disorders of consciousness by a clinical consensus compared with repeated coma-recovery scale-revised assessment. *BMC Neurol*. 2020; 20 (1): 343. DOI: 10.1186/s12883-020-01924-9. PMID: 32919461.
13. Edlow B.L., Claassen J., Schiff N.D., Greer D.M. Recovery from disorders of consciousness: mechanisms, prognosis and emerging therapies. *Nat Rev Neurol*. 2021; 17 (3): 135–156. DOI: 10.1038/s41582-020-00428-x. PMID: 33318675.
14. Ganesh S., Guernon A., Chalcraft L, Harton B., Smith B., Louise-Bender Pape T. Medical comorbidities in disorders of consciousness pa-

- tients and their association with functional outcomes. *Arch Phys Med Rehabil.* 2013; 94 (10): 1899–1907.  
DOI: 10.1016/j.apmr.2012.12.026.  
PMID: 23735521.
15. Driessen D.M.F, Utens C.M.A., Ribbers P.G.M., Van Erp W.S., Heijenbrok-Kal M.H. Short-term outcomes of early intensive neurorehabilitation for prolonged disorders of consciousness: A prospective cohort study. *Ann Phys Rehabil Med.* 2024; 67 (5): 101838.  
DOI: 10.1016/j.rehab.2024.101838.  
PMID: 38830314.
  16. Whyte J., Nordenbo A.M., Kalmar K., Merges B., Bagiella E., Chang H., Yablon S., et al. Medical complications during inpatient rehabilitation among patients with traumatic disorders of consciousness. *Arch Phys Med Rehabil.* 2013; 94 (10): 1877–1883.  
DOI: 10.1016/j.apmr.2012.12.027.  
PMID: 23735519.
  17. Whyte J., Nakase-Richardson R., Hammond F.M., McNamee S., Giacino J.T., Kalmar K., Greenwald B.D., et al. Functional outcomes in traumatic disorders of consciousness: 5-year outcomes from the National Institute on Disability and Rehabilitation Research traumatic brain injury model systems. *Arch Phys Med Rehabil.* 2013; 94 (10): 1855–1860.  
DOI: 10.1016/j.apmr.2012.10.041.  
PMID: 23732164.
  18. Draghi F., Pancani S., De Nisco A., Romoli A.M., Maccanti D., Burali R., Grippo A., et al. Implications of the consciousness state on decannulation in patients with a prolonged disorder of consciousness. *Arch Phys Med Rehabil.* 2024; 105 (9): 1691–1699.  
DOI: 10.1016/j.apmr.2024.05.006.  
PMID: 38734048.
  19. Estraneo A., Masotta O., Bartolo M., Pistoia F., Perin C., Marino S., Lucca L., et al. Multi-center study on overall clinical complexity of patients with prolonged disorders of consciousness of different etiologies. *Brain Inj.* 2021; 35 (1): 1–7.  
DOI: 10.1080/02699052.2020.1861652.  
PMID: 33331792.
  20. Magliacano A., De Bellis F., Panico F., Sagliano L., Trojano L., Sandroni C., Estraneo A. Long-term clinical evolution of patients with prolonged disorders of consciousness due to severe anoxic brain injury: a meta-analytic study. *Eur J Neurol.* 2023; 30 (12): 3913–3927.  
DOI: 10.1111/ene.15899. PMID: 37246500.
  21. Pingue V., Mirando M., Cazzulani B., Bellaviti G., Saporiti F., Zanga C., Nardone A. Neck muscle spasticity in patients with disorder of consciousness: a pilot study. *Eur J Phys Rehabil Med.* 2024; 60 (3): 412–419. DOI: 10.23736/S1973-9087.24.08176-0. PMID: 38502553.
  22. Martens G., Laureys S., Thibaut A. Spasticity management in disorders of consciousness. *Brain Sci.* 2017; 7 (12): 162.  
DOI: 10.3390/brainsci7120162. PMID: 29232836.
  23. Zhang J., Wei R.-L., Peng G.-P., Zhou J.-J., Wu M., He F.-P., Pan G., et al. Correlations between diffusion tensor imaging and levels of consciousness in patients with traumatic brain injury: a systematic review and meta-analysis. *Sci Rep.* 2017; 7 (1): 2793.  
DOI: 10.1038/s41598-017-02950-3.  
PMID: 28584256.
  24. Van Kampen P.J., Martina J.D., Vos P.E., Hoedemaekers C.W.E., Hendricks H.T. Potential risk factors for developing heterotopic ossification in patients with severe traumatic brain injury. *Journal of Head Trauma Rehabilitation.* 2011; 26 (5): 384–391.  
DOI: 10.1097/HTR.0b013e3181f78a59.  
PMID: 21321512.
  25. Baguley I.J., Perkes I.E., Fernandez-Ortega J.-F., Rabinstein A.A., Dolce G., Hendricks H.T., Consensus Working Group. Paroxysmal sympathetic hyperactivity after acquired brain injury: consensus on conceptual definition, nomenclature, and diagnostic criteria. *J Neurotrauma.* 2014; 31 (17): 1515–1520.  
DOI: 10.1089/neu.2013.3301. PMID: 24731076.
  26. Pistoia F., Carolei A., Bodien Y.G., Greenfield S., Kaplan S., Sacco S., Pistarini C., et al. The Comorbidities Coma Scale (CoCoS): psychometric properties and clinical usefulness in patients with disorders of consciousness. *Front Neurol.* 2019; 10: 1042.  
DOI: 10.3389/fneur.2019.01042. PMID: 31681139.
  27. Супонева Н.А., Кириченко О.А., Яцко К.А., Зимин А.А., Легостаева Л.А., Сергеев Д.В., Юсупова Д.Г., с соавт. Шкала оценки сопутствующих заболеваний у ареактивных пациентов (CoCoS): оценка психометрических свойств. *Журнал им. Н.В. Склифосовского «Неотложная медицинская помощь».* 2023; 12 (2): 202–209. Suponeva N.A., Kirichenko O.A., Yatsko K.A., Zimin A.A., Legostayeva L.A., Sergeev D.V., Yusupova D.G., et al. The Comorbidities Coma Scale (CoCoS): assessment of psychometric properties. *Russian Sklifosovsky Journal «Emergency Medical Care» = Zhurnal im. N.V. Sklifosovskogo «Neotlozhnaya Meditsinskaya Pomoshch».* 2023; 12 (2): 202–209. (in Russ.).  
DOI: 10.23934/2223-9022-2023-12-2-202-209.
  28. Супонева Н.А., Пирадов М.А., Рябинкина Ю.В., Юсупова Д.Г., Зимин А.А., Кириченко О.А., Бузган Н.Г., с соавт. Шкала оценки сопутствующих заболеваний у ареактивных пациентов (CoCoS): лингвокультурная адаптация русскоязычной версии (сообщение). *Общая реаниматология.* 2022; 18 (2): 65–75. Suponeva N.A., Piradov M.A., Ryabinkina Yu. V.,

- Yusupova D.G., Zimin A.A., Kirichenko O.A., Buzgan N.G., et al.* Comorbidities Coma Scale (CoCoS): linguistic and cultural adaptation of the Russian-language version. *General Reanimatology= Obshchaya Reanimatologiya*. 2022; 18 (2): 65–75. (in Russ.&Eng.). DOI: 10.15360/1813-9779-2022-2-65-75.
29. *Zhang B., Huang K., Karri J., O'Brien K., Di-Tommaso C., Li S.* Many faces of the hidden souls: medical and neurological complications and comorbidities in disorders of consciousness. *Brain Sciences*. 2021; 11 (5): 608. DOI: 10.3390/brainsci11050608. PMID: 34068604.
30. *Fusco A, Galluccio C, Castelli L, Pazzaglia C., Pastorino R., Marafon D.P, Bernabei R., et al.* Severe acquired brain injury: prognostic factors of discharge outcome in older adults. *Brain Sci*. 2022; 12 (9): 1232. DOI: 10.3390/brainsci12091232. PMID: 36138968.
- Received 24.02.2025**  
**Accepted 08.07.2026**

# Ultrasound-Derived Diaphragmatic Function Indices Predict Weaning Outcomes in Surgical Intensive Care Unit Patients (Prospective Observational Study)

Tran Viet Duc<sup>1,2</sup>, Vu Hoang Phuong<sup>1,2\*</sup>, Nguyen Huu Tu<sup>1,2</sup>

<sup>1</sup> Department of Anesthesia and Critical care, Hanoi Medical University,

1 Ton That Tung, Kim Lien Ward, Ha Noi 100000, Vietnam

<sup>2</sup> Center of Anesthesiology, Critical care and Pain management, Hanoi Medical University Hospital,

1 Ton That Tung, Kim Lien Ward, Ha Noi 100000, Vietnam

**For citation:** Tran Viet Duc, Vu Hoang Phuong, Nguyen Huu Tu. Ultrasound-derived diaphragmatic function indices predict weaning outcomes in surgical intensive care unit patients (prospective observational study). *Obshchaya Reanimatologiya = General Reanimatology*. 2026; 22 (4): 12–21. <https://doi.org/10.15360/1813-9779-2026-4-2723> [In Engl.]

\*✉ Vu Hoang Phuong, [vuhoangphuong@hmu.edu.vn](mailto:vuhoangphuong@hmu.edu.vn)

## Summary

Conventional respiratory indices have limited accuracy for predicting weaning outcomes in critically ill surgical patients. Diaphragmatic ultrasound has emerged as a promising bedside tool for evaluating respiratory muscle function during liberation from mechanical ventilation.

**Aim.** To evaluate the predictive value of ultrasound-derived diaphragmatic function indices for weaning outcomes in surgical intensive care unit (ICU) patients and to compare their performance with conventional respiratory parameters.

**Methods.** This prospective observational study included mechanically ventilated adult patients undergoing spontaneous breathing trials (SBT) in a surgical ICU. Diaphragmatic excursion (DE) and diaphragm thickening fraction (DTF) were assessed by bedside ultrasound immediately before SBT initiation. Diaphragmatic rapid shallow breathing indices based on DE (DE-RSBI) and DTF (DTF-RSBI) were also calculated. Conventional respiratory parameters, including respiratory rate (RR), rapid shallow breathing index (RSBI), and PaO<sub>2</sub>/FiO<sub>2</sub> ratio (P/F), were recorded simultaneously. Predictive performance was evaluated using receiver operating characteristic (ROC) analysis and DeLong comparison tests. Multivariable logistic regression was performed to identify independent predictors of successful weaning.

**Results.** DE demonstrated the highest predictive performance for successful weaning, with an AUC of 0.793, followed by DTF (0.740) and DTF-RSBI (0.711). In contrast, RR and conventional RSBI showed limited discriminative ability, with AUC values close to 0.5. DeLong analysis demonstrated significantly greater AUC values for both DE and DTF compared with the P/F ratio and RSBI. The optimal cutoff values were > 1.26 cm for DE and > 16.3% for DTF. In multivariable analysis, lower APACHE II score, higher P/F ratio, and greater DE remained independently associated with successful weaning. Each 1 mm increase in DE was associated with a 66.6% increase in the odds of successful weaning (adjusted OR 1.67, 95% CI 1.31–2.12;  $p < 0.001$ ).

**Conclusion.** Ultrasound-derived diaphragmatic indices, particularly diaphragmatic excursion, demonstrated superior predictive performance compared with conventional respiratory parameters and may provide valuable adjunctive information during weaning assessment in surgical ICU patients.

**Keywords:** diaphragm; rapid shallow breathing index; surgical intensive care; ultrasound; ventilator weaning; predictive value

**Conflict of Interest.** The authors declare no conflict of interest related to this study.

**Funding.** This research received no external funding.

**Acknowledgements.** The authors appreciate the medical and nursing staff of Center of Anesthesiology, Critical Care and Pain Management, Hanoi Medical University Hospital for their support during patient enrollment and data collection.

**Information about the authors / Информация об авторах:**

Tran Viet Duc / Тран Вьет Дук, <https://orcid.org/0000-0002-9114-993X>

Vu Hoang Phuong / Ву Хоанг Фуонг, <https://orcid.org/0000-0003-3367-5787>

Nguyen Huu Tu / Нгуен Хуу Ту, <https://orcid.org/0000-0002-5283-0909>

## Introduction

Weaning from mechanical ventilation is a critical step in the management of critically ill patients, particularly in the surgical intensive care unit (ICU). Successful extubation is associated with shorter ICU stay, fewer ventilator-related complications, and reduced healthcare costs, whereas weaning failure leads to prolonged mechanical ventilation, increased respiratory morbidity, and higher mortality [1–3]. Despite

its importance, predicting weaning outcomes accurately in daily clinical practice remains challenging.

For decades, clinical and respiratory indices have been used to guide weaning decisions. The Rapid Shallow Breathing Index (RSBI), calculated as the respiratory rate divided by tidal volume (RR/VT), is the most widely applied parameter. However, its diagnostic performance is inconsistent. A systematic review by M. Karthika et al. [4] reported

that although RSBI demonstrates high sensitivity (0.80–0.97), its specificity ranges from 0.40 to 0.70, resulting in a significant number of false-positive results. These findings suggest that RSBI may be useful as a screening tool but has limited discriminative ability when used alone. Similarly, the  $\text{PaO}_2/\text{FiO}_2$  (P/F) ratio is frequently incorporated into readiness criteria for spontaneous breathing trials (SBT), with thresholds  $\geq 150$ –200 mmHg commonly considered acceptable under low PEEP conditions [5]. However, a meta-analysis by F. Torrini et al. [6], showed that although lower P/F values were statistically associated with extubation failure, their independent predictive value was weak to moderate. Although widely used, the P/F ratio reflects gas exchange rather than the patient's ability to sustain spontaneous breathing. Respiratory rate (RR) is another routinely monitored variable during SBT. Y. Okabe et al. [7] reported an AUC of approximately 0.82 for RR in predicting weaning outcomes, yet its predictive value remained inferior to parameters assessing respiratory mechanics more directly.

Increasing evidence indicates that diaphragm dysfunction plays a central role in weaning failure. E. C. Goligher et al. [8] documented diaphragm dysfunction in 29–64% of mechanically ventilated patients and demonstrated its association with prolonged ventilation and weaning failure. Importantly, patients may exhibit acceptable RSBI or RR values while still failing extubation due to impaired diaphragmatic contractility.

The increasing use of point-of-care ultrasound has enabled direct bedside assessment of diaphragmatic function. Among ultrasound-derived parameters, diaphragmatic excursion (DE) and diaphragm thickening fraction (DTF) are the most extensively investigated. In a meta-analysis by A. Le Neindre et al. [9], DE demonstrated moderate predictive performance for successful weaning, with a pooled sensitivity of 0.71, specificity of 0.80, and an AUC of approximately 0.82. DTF has shown even stronger diagnostic accuracy. A large meta-analysis by H. M. Parada-Gereda et al. [10] reported a pooled AUC around 0.87 for DTF, supporting its superiority over conventional respiratory indices such as RSBI. Combined parameters integrating respiratory pattern and diaphragmatic function, such as the diaphragmatic rapid shallow breathing index (D-RSBI:  $\text{RR}/\text{DE}$  or  $\text{RR}/\text{DTF}$ ), have also been proposed. Preliminary data indicated improved discriminative performance, with reported AUC values of 0.813–0.859 compared with 0.639 for conventional RSBI [11].

Despite these promising findings, most available evidence derives from heterogeneous ICU populations, and dedicated studies in surgical ICU patients remain limited. Postoperative factors such as residual anesthesia, pain, and transient diaphragmatic dysfunction may alter the mechanisms un-

derlying weaning failure in this population [12]. Moreover, few studies have simultaneously compared DE, DTF, combined indices, and conventional respiratory parameters within the same cohort. Therefore, further investigation is needed to clarify the predictive value of diaphragmatic ultrasound indices in surgical ICU patients and to determine whether these parameters provide incremental benefit over traditional weaning criteria. This study aimed to evaluate the predictive value of diaphragmatic ultrasound indices for weaning outcomes in surgical ICU patients and to compare their performance with conventional respiratory parameters (RSBI, RR, and  $\text{PaO}_2/\text{FiO}_2$  ratio).

## Materials and Methods

This study was carried out in accordance with the principles outlined in the Declaration of Helsinki. The study protocol was reviewed and approved by the Hanoi Medical University Institutional Ethical Review Board (Approval No. 1276/GCN-HMUIRB, April 22, 2024) and was registered at ClinicalTrials.gov (Identifier: NCT06321848). The requirement for direct participant consent was waived due to the fact that all patients were under mechanical ventilation at the time of enrollment; however, written informed consent was obtained from the participants' legally authorized representatives.

**Study design and setting.** This prospective observational study was conducted in the Center of Anesthesiology, Critical Care and Pain Management at Hanoi Medical University Hospital. Patient enrollment and data collection were performed between May 2024 and April 2026. Adult postoperative patients admitted to the surgical intensive care unit who required invasive mechanical ventilation were screened for eligibility. The inclusion criteria were age  $\geq 18$  years, postoperative patients undergoing mechanical ventilation via endotracheal tube, duration of invasive mechanical ventilation  $\geq 48$  hours, patients considered ready for weaning from mechanical ventilation. Patients were excluded if they had progressive neuromuscular diseases, chronic respiratory or cardiac diseases requiring long-term ventilatory support at home (e.g., severe chronic obstructive pulmonary disease or severe asthma), known diaphragmatic injury or prior diaphragmatic surgery, failure of a previous SBT, tracheostomy, refusal to participate by the patient or their legal representative.

The sample size was estimated based on the area under the receiver operating characteristic (AUC) curve using the method proposed by J. A. Hanley and B. J. McNeil [13]. The expected AUC value for diaphragm thickening fraction (DTF) was assumed to be 0.85 based on previous literature, with an estimated weaning failure rate of 25% [14]. With a type I error of 5% and study power of 80%, the

minimum required sample size was calculated to be 135 patients. To account for potential data loss, we planned to enroll at least 150 patients.

**Weaning readiness assessment.** Patients were evaluated daily for readiness to wean according to established guidelines for ventilator weaning [5]. Criteria included:

- Resolution or control of the underlying cause of respiratory failure.
- Body temperature  $<38^{\circ}\text{C}$  and hemoglobin  $\geq 8$  g/dL.
- Absence of significant electrolyte imbalance.
- Neurological status with Glasgow Coma Scale  $\geq 9$  and improvement after cessation of sedation.
- Hemodynamic stability with heart rate 60–100 beats/min and systolic blood pressure 90–160 mmHg without or with minimal vasopressor support.
- Adequate oxygenation with  $\text{PaO}_2/\text{FiO}_2 \geq 250$  mmHg,  $\text{FiO}_2 \leq 0.4$ , and  $\text{PEEP} \leq \text{cm H}_2\text{O}$ .

Eligible patients underwent a spontaneous breathing trial using pressure support ventilation with  $\text{PS} = 7$  cmH<sub>2</sub>O,  $\text{PEEP} = 5$  cmH<sub>2</sub>O, and  $\text{FiO}_2 = 0.40$  for 60 minutes.

If no signs of intolerance were observed, the SBT was considered successful and the patient was evaluated for extubation. In cases of intolerance, mechanical ventilation was resumed and the SBT was repeated after 24 hours if the patient again met weaning readiness criteria. After a successful SBT, extubation was performed when the patient demonstrated adequate airway protection, including effective cough and the ability to clear airway secretions. Airway patency was further assessed using the cuff leak test. Following extubation, patients received oxygen therapy via face mask at a flow rate of 5 L/min. Patients were monitored for 48 hours to determine extubation outcomes. Successful weaning was defined as the ability to maintain spontaneous breathing without ventilatory support for at least 48 hours after extubation. Weaning failure was defined as any of the following within 48 hours: failure of the spontaneous breathing trial; re-intubation or requirement for non-invasive ventilation due to intolerance signs.

Intolerance signs were defined by the occurrence of any of the following: respiratory distress (respiratory rate  $> 35$  breaths/min, oxygen saturation  $< 90\%$ , or increased work of breathing), cardiovascular instability (heart rate  $\geq 140$  beats/min, arrhythmia, or systolic blood pressure  $< 90$  or  $> 180$  mmHg), or neurological deterioration such as agitation or decreased level of consciousness.

**Diaphragm ultrasound assessment.** All diaphragm ultrasound examinations were performed by a single trained investigator with certification in critical care ultrasound to ensure measurement

consistency. Diaphragmatic ultrasound measurements were not used to guide clinical weaning decisions and clinicians responsible for weaning management were blinded to ultrasound-derived indices. Patients were placed in a semi-recumbent position with the head elevated at  $30^{\circ}$ . Diaphragmatic excursion (DE) was measured using a convex probe in the sub-costal view along the mid-clavicular line to visualize the right hemidiaphragm. M-mode ultrasound was used to record diaphragmatic motion across at least three respiratory cycles, and the maximal displacement from baseline was recorded [15, 16].

Diaphragm thickness was measured using a linear probe placed in the zone of apposition between the ninth and tenth intercostal spaces along the mid-axillary line. Diaphragm thickness during inspiration (DTi) and expiration (DTe) was measured over at least three respiratory cycles. Diaphragm thickening fraction (DTF) was calculated as:

$$\text{DTF} = (\text{DTi} - \text{DTe}) / \text{DTe} \times 100$$

The diaphragmatic rapid shallow breathing index based on diaphragmatic excursion (DE-RSBI) was calculated as the ratio of respiratory rate (RR) to diaphragmatic excursion (DE) measured by M-mode ultrasound ( $\text{RR}/\text{DE}$ , breaths/min/mm). In addition, a modified diaphragmatic rapid shallow breathing index based on diaphragm thickening fraction (DTF-RSBI) was calculated as RR divided by diaphragm thickening fraction ( $\text{RR}/\text{DTF}$ ) [11].

**Study variables and outcomes.** Baseline demographic and clinical characteristics, including age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II score, length of hospital stay, duration of stay in the surgical ICU, and duration of mechanical ventilation, were collected. The APACHE II score was calculated at the time of ICU admission.

Respiratory parameters, including tidal volume, respiratory rate, and the rapid shallow breathing index (RSBI), were recorded during the first three minutes of the spontaneous breathing trial (SBT). Arterial blood gas analysis was obtained immediately before initiation of the SBT, and the  $\text{PaO}_2/\text{FiO}_2$  ratio was subsequently calculated.

Diaphragmatic ultrasound measurements were performed at the beginning of the SBT. Diaphragmatic excursion (DE) and diaphragm thickening fraction (DTF) were measured, and derived indices including DE-RSBI and DTF-RSBI were calculated accordingly.

The primary outcome was overall weaning outcome, defined as successful maintenance of spontaneous breathing without ventilatory support for at least 48 hours after extubation. Secondary outcomes included: diagnostic accuracy of DE, DTF, DE-RSBI, and DTF-RSBI; independent predictors of successful weaning identified by multivariable logistic regression.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp.,

Armonk, NY, USA) and MedCalc, version 23.2 (MedCalc Software Ltd, Ostend, Belgium). Continuous variables were tested for normality using the Shapiro–Wilk test. Normally distributed variables were expressed as mean  $\pm$  standard deviation and compared using the student *t*-test, whereas non-normally distributed variables were presented as median (interquartile range) and compared using the Mann–Whitney *U* test. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test or Fisher's exact test when appropriate.

The predictive performance of diaphragmatic ultrasound indices and conventional respiratory parameters was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) was calculated with 95% confidence intervals. For variables in which lower values were associated with a higher probability of weaning success (e.g., RSBI), reverse coding was applied to ensure consistent directionality before ROC analysis. Optimal cut-off values were determined using Youden's index, and corresponding sensitivity, specificity, positive predictive value, and negative predictive value were calculated. Comparisons between AUCs were performed using the DeLong test.

Univariable logistic regression analysis was initially conducted to identify factors associated with weaning outcomes. Before multivariable model construction, correlations among age, APACHE II score, and SOFA score were assessed using Spearman's correlation analysis. Variables considered clinically relevant or showing potential association were entered into a multivariable logistic regression model to identify independent predictors of weaning failure. Results were reported as odds ratios (ORs) with 95% confidence intervals. A two-sided *p* value  $< 0.05$  was considered statistically significant.

## Results

A total of 160 patients were included in the study. Of these, 134 patients (83.8%) successfully completed the first SBT, whereas 26 patients (16.3%) failed the initial SBT. Among the 134 patients who successfully completed the first SBT, 21 (15.7%) subsequently developed extubation failure after initial ventilator liberation. Overall, successful weaning was ultimately achieved in 113 patients (70.6%), while 47 patients (29.4%) met the criteria for weaning failure (Fig. 1).

Baseline demographic and clinical characteristics were summarized in Table 1. Patients in the weaning failure group were older and had significantly higher APACHE II and SOFA scores compared with those in the weaning success group. Chronic obstructive pulmonary disease, diabetes mellitus, and chronic kidney disease were more common in the weaning failure group.

Hypertension was the most common comorbidity in the overall cohort. Emergency surgery ac-

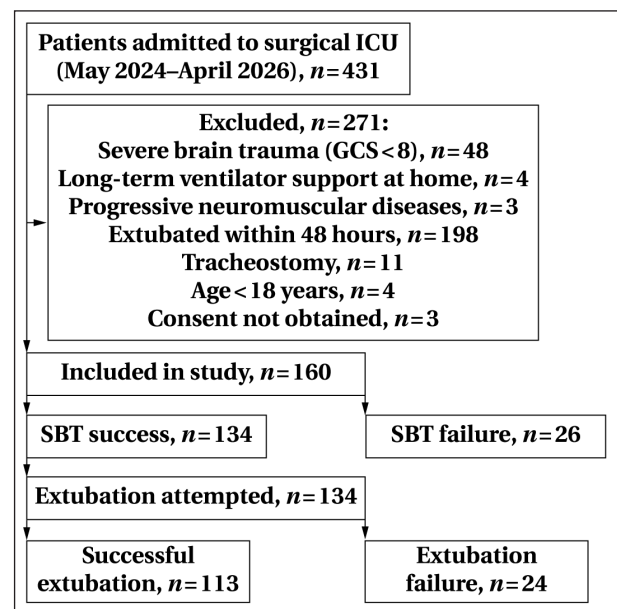


Fig. 1. Flowchart of patient enrollment and weaning outcomes.

counted for the majority of cases, and gastrointestinal surgery was the most frequently represented surgical category. No significant differences were identified in sex distribution, body mass index, operative characteristics, or duration of mechanical ventilation before the first spontaneous breathing trial between the two groups. However, patients with weaning failure had significantly longer SICU and hospital stays ( $p < 0.001$ ).

Among the 53 elective surgical patients, prolonged postoperative mechanical ventilation was mainly associated with neurological impairment, hemodynamic instability, respiratory insufficiency, sepsis, and the need for continued postoperative monitoring. Detailed information is provided in Supplementary Table S1.

Respiratory and diaphragmatic ultrasound indices according to weaning outcome are presented in Table 2. Patients with weaning failure had significantly lower  $\text{PaO}_2/\text{FiO}_2$  ratios immediately before SBT, lower diaphragmatic excursion and diaphragm thickening fraction values, and higher DE-RSBI and DTF-RSBI values compared with the weaning success group. In contrast, no significant difference in conventional RSBI and respiratory rate were observed between groups.

ROC curve analysis demonstrated moderate discriminative performance of diaphragmatic ultrasound-derived indices for predicting weaning outcomes (Fig. 2). DE showed the highest predictive accuracy (AUC 0.793), followed by DTF (AUC 0.740) and DTF-RSBI (AUC 0.711). In contrast, conventional respiratory parameters, including the  $\text{PaO}_2/\text{FiO}_2$  ratio, respiratory rate, and RSBI, showed lower predictive performance, with AUC values of 0.598, 0.543, and 0.532, respectively.

**Table 1. Baseline demographic and clinical characteristics according to weaning outcome.**

| Parameters                                    | Parameters value in groups |                            |                           | P-value                       |
|-----------------------------------------------|----------------------------|----------------------------|---------------------------|-------------------------------|
|                                               | Total,<br>n= 160           | Weaning<br>success, n= 113 | Weaning<br>failure, n= 47 |                               |
| Demographic and clinical characteristics      |                            |                            |                           |                               |
| Age, years                                    | 64.0 [56.0–74.0]           | 63.0 [54.0–70.5]           | 71.0 [62.0–77.0]          | <b>0.004<sup>b</sup></b>      |
| Male sex                                      | 100 (62.5)                 | 70 (61.9)                  | 30 (63.8)                 | 0.823 <sup>a</sup>            |
| APACHE II score                               | 10.0 [8.0–12.0]            | 9.0 [7.0–10.0]             | 13.0 [11.0–15.0]          | <b>&lt; 0.001<sup>b</sup></b> |
| SOFA score                                    | 2.0 [1.0–4.0]              | 2.0 [1.0–3.0]              | 3.0 [2.0–6.0]             | <b>&lt; 0.001<sup>b</sup></b> |
| Body mass index, kg/m <sup>2</sup>            | 21.7 [19.5–23.4]           | 21.9 [19.9–23.4]           | 21.4 [17.9–23.6]          | 0.140 <sup>b</sup>            |
| Surgical urgency                              |                            |                            |                           |                               |
| Elective surgery                              | 53 (33.1)                  | 37 (32.7)                  | 16 (34.0)                 | 0.874 <sup>a</sup>            |
| Emergency surgery                             | 107 (66.9)                 | 76 (67.3)                  | 31 (66.0)                 |                               |
| Surgical categories                           |                            |                            |                           |                               |
| Gastrointestinal surgery                      | 62 (38.8)                  | 44 (38.9)                  | 18 (38.3)                 | 0.504 <sup>c</sup>            |
| Neurosurgery                                  | 49 (30.5)                  | 32 (28.4)                  | 17 (36.2)                 |                               |
| Cardiovascular surgery                        | 27 (16.9)                  | 18 (15.9)                  | 9 (19.2)                  |                               |
| Trauma surgery                                | 6 (3.8)                    | 5 (4.4)                    | 1 (2.1)                   |                               |
| Soft tissue and skin infection surgery        | 16 (10.0)                  | 14 (12.4)                  | 2 (4.2)                   |                               |
| Comorbidities                                 |                            |                            |                           |                               |
| Hypertension                                  | 85 (53.1)                  | 55 (48.7)                  | 30 (63.8)                 | 0.080 <sup>a</sup>            |
| COPD                                          | 23 (14.4)                  | 12 (10.6)                  | 11 (23.4)                 | <b>0.036<sup>a</sup></b>      |
| Diabetes mellitus                             | 46 (28.7)                  | 27 (23.9)                  | 19 (40.4)                 | <b>0.035<sup>a</sup></b>      |
| Chronic kidney disease                        | 22 (13.8)                  | 11 (9.7)                   | 11 (23.4)                 | <b>0.022<sup>a</sup></b>      |
| Malignancy                                    | 32 (20.0)                  | 19 (16.8)                  | 13 (27.7)                 | 0.118 <sup>a</sup>            |
| ICU outcomes                                  |                            |                            |                           |                               |
| Length of SICU stay                           | 5.0 [4.0–7.0]              | 5.0 [4.0–6.0]              | 8.0 [6.0–12.0]            | <b>&lt; 0.001<sup>b</sup></b> |
| Length of hospital stay                       | 17.0 [12.0–24.8]           | 15.0 [11.0–21.0]           | 24.0 [16.0–34.0]          | <b>&lt; 0.001<sup>b</sup></b> |
| Duration of mechanical ventilation before SBT | 4.0 [3.0–5.0]              | 3.0 [3.0–4.0]              | 4.0 [4.0–5.0]             | 0.715 <sup>b</sup>            |

**Note.** Values are presented as number (%) or median [interquartile range]. For tables 1, 5: APACHE II — Acute Physiology and Chronic Health Evaluation. BMI — body mass index; COPD — Chronic Obstructive Pulmonary Disease; SICU — surgical intensive care unit; SOFA — Sequential Organ Failure Assessment. <sup>a</sup> — Chi-square test; <sup>b</sup> — Mann-Whitney *U*-test; <sup>c</sup> — Fisher exact test.

**Table 2. Comparison of respiratory and diaphragmatic ultrasound indices according to weaning outcome.**

| Indices                                             | Indices value in groups |                        | P-value <sup>a</sup> |
|-----------------------------------------------------|-------------------------|------------------------|----------------------|
|                                                     | Weaning success, n= 113 | Weaning failure, n= 47 |                      |
| PaO <sub>2</sub> /FiO <sub>2</sub> ratio before SBT | 352.0 [315.3–442.8]     | 340 [281.3–376.8]      | <b>0.041</b>         |
| Respiratory rate, min <sup>-1</sup>                 | 20 [16–24]              | 21 [18–24]             | 0.433                |
| RSBI, breaths/min/L                                 | 47.5 [37.8–56.1]        | 47.4 [35.6–62.2]       | 0.461                |
| DE, cm                                              | 1.5 [1.3–1.7]           | 1.2 [1.0–1.4]          | <b>&lt; 0.001</b>    |
| DTF, %                                              | 31.2 [24.2–50.2]        | 20.2 [9.8–33.3]        | <b>&lt; 0.001</b>    |
| DE-RSBI, breaths/min/cm                             | 13.3 [11.3–16.1]        | 16.2 [12.7–21.6]       | <b>&lt; 0.001</b>    |
| DTF-RSBI, breaths/min/%                             | 59.8 [41.0–89.1]        | 112.7 [56.8–212.6]     | <b>&lt; 0.001</b>    |

**Note.** Values are presented as median [interquartile range]. <sup>a</sup> — Mann-Whitney *U*-test. For tables 2–5: DE — diaphragmatic excursion; DTF — diaphragm thickening fraction; RSBI — rapid shallow breathing index.

Based on the results presented in Table 3, the optimal cutoff values for predicting successful weaning were  $> 1.26$  cm for DE,  $> 16.3\%$  for DTF,  $\leq 17.0$  for DE-RSBI, and  $\leq 124.7$  for DTF-RSBI. DE demonstrated the most balanced overall diagnostic performance, with a sensitivity of 83.2%, specificity of 61.7%, PPV of 83.9%, NPV of 60.4%, and the highest positive likelihood ratio ( $LR+ = 2.17$ ) among the ultrasound-derived parameters. In contrast, DTF and DTF-RSBI showed higher sensitivity and lower negative likelihood ratios ( $LR- = 0.19$  and  $0.20$ , respectively), suggesting greater ability to identify patients likely to achieve successful weaning, although with lower specificity. Combined diaphragmatic indices demonstrated intermediate diagnostic performance between conventional respiratory parameters and isolated diaphragmatic ultrasound measurements.

DeLong analysis demonstrated that both DE and DTF demonstrated significantly higher dis-

criminative performance than both the PaO<sub>2</sub>/FiO<sub>2</sub> ratio and RSBI. Combined diaphragmatic indices (DE-RSBI and DTF-RSBI) significantly outperformed RSBI alone but showed no significant difference compared with the PaO<sub>2</sub>/FiO<sub>2</sub> ratio.

Correlation analysis demonstrated a strong correlation between APACHE II and SOFA scores (Spearman's  $\rho = 0.745$ ,  $p < 0.001$ ), while age showed moderate correlations with APACHE II ( $\rho = 0.424$ ,  $p < 0.001$ ) and SOFA score ( $\rho = 0.338$ ,  $p < 0.001$ ). In multivariable logistic regression analysis (Table 5), lower APACHE II score, higher PaO<sub>2</sub>/FiO<sub>2</sub> ratio, and greater diaphragmatic excursion were independently associated with successful weaning. Each 1 mm increase in DE was associated with a 66.6% increase in the odds of successful weaning (adjusted OR 1.67, 95% CI 1.31–2.12;  $p < 0.001$ ). A sensitivity analysis was subsequently performed by additionally adjusting for COPD, diabetes mellitus, and chronic

**Table 3. Diagnostic performance of respiratory and diaphragmatic ultrasound indices for predicting successful weaning.**

| Variable                                        | AUC, 95% CI         | Optimal cutoff | Sensitivity, % | Specificity, % | PPV, % | NPV, % | LR+  | LR–  | P-value           |
|-------------------------------------------------|---------------------|----------------|----------------|----------------|--------|--------|------|------|-------------------|
| PaO <sub>2</sub> /FiO <sub>2</sub> ratio, mm Hg | 0.598 (0.518–0.675) | > 412.5        | 30.0           | 89.4           | 87.2   | 34.7   | 2.83 | 0.78 | <b>0.042</b>      |
| Respiratory rate, breaths/min                   | 0.543 (0.463–0.622) | ≤ 20           | 43.4           | 72.3           | 79.0   | 34.7   | 1.57 | 0.78 | 0.312             |
| RSBI, breaths/min/L                             | 0.532 (0.452–0.612) | ≤ 55.4         | 41.6           | 72.3           | 78.3   | 34.0   | 1.50 | 0.81 | 0.437             |
| DE, cm                                          | 0.793 (0.722–0.853) | > 1.26         | 83.2           | 61.7           | 83.9   | 60.4   | 2.17 | 0.27 | <b>&lt; 0.001</b> |
| DTF, %                                          | 0.740 (0.665–0.806) | > 16.3         | 91.2           | 46.8           | 80.5   | 68.9   | 1.71 | 0.19 | <b>&lt; 0.001</b> |
| DE-RSBI                                         | 0.674 (0.595–0.746) | ≤ 17.0         | 82.3           | 48.9           | 79.5   | 53.5   | 1.61 | 0.36 | <b>&lt; 0.001</b> |
| DTF-RSBI                                        | 0.711 (0.634–0.780) | ≤ 124.7        | 90.3           | 48.9           | 80.9   | 67.7   | 1.77 | 0.20 | <b>&lt; 0.001</b> |

**Note.** Optimal cutoff values were determined using the Youden index. *P*-values represent comparisons of ROC areas against the reference value of 0.5. For tables 3, 4: AUC — area under the receiver operating characteristic curve; CI — confidence interval. LR+ — positive likelihood ratio; LR– — negative likelihood ratio; NPV — negative predictive value; PPV — positive predictive value.

**Table 4. Comparison of areas under the ROC curves.**

| Comparison                                           | Difference in AUC | 95% CI        | P-value           |
|------------------------------------------------------|-------------------|---------------|-------------------|
| DE vs DTF                                            | 0.053             | –0.0583–0.164 | 0.350             |
| DE vs PaO <sub>2</sub> /FiO <sub>2</sub> ratio       | 0.195             | 0.0760–0.313  | <b>0.001</b>      |
| DTF vs PaO <sub>2</sub> /FiO <sub>2</sub> ratio      | 0.142             | 0.0153–0.267  | <b>0.028</b>      |
| DE-RSBI vs PaO <sub>2</sub> /FiO <sub>2</sub> ratio  | 0.076             | –0.0571–0.207 | 0.266             |
| DTF-RSBI vs PaO <sub>2</sub> /FiO <sub>2</sub> ratio | 0.113             | –0.0188–0.244 | 0.093             |
| DE vs RSBI                                           | 0.261             | 0.125–0.397   | <b>&lt; 0.001</b> |
| DTF vs RSBI                                          | 0.208             | 0.0666–0.350  | <b>0.004</b>      |
| DE-RSBI vs RSBI                                      | 0.142             | 0.013–0.271   | <b>0.001</b>      |
| DTF-RSBI vs RSBI                                     | 0.180             | 0.0567–0.303  | <b>0.004</b>      |

**Note.** DeLong test was used to compare correlated ROC curves.

**Table 5. Logistic regression analysis of factors associated with successful weaning.**

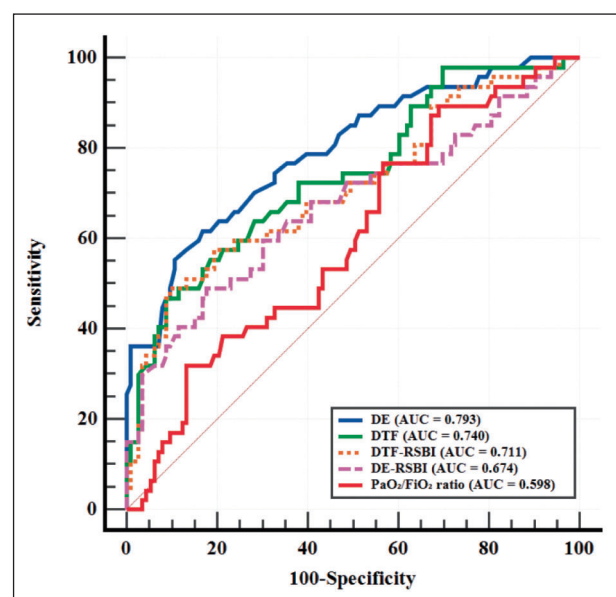
| Variable                                 | Univariable OR (95% CI) | P-value | Multivariable OR (95% CI) | P-value |
|------------------------------------------|-------------------------|---------|---------------------------|---------|
| APACHE II                                | 0.55 (0.45–0.67)        | < 0.001 | 0.53 (0.42–0.68)          | < 0.001 |
| PaO <sub>2</sub> /FiO <sub>2</sub> ratio | 1.01 (1.00–1.01)        | 0.023   | 1.01 (1.00–1.02)          | 0.03    |
| DE (per 1mm increase)                    | 1.56 (1.31–1.86)        | < 0.001 | 1.67 (1.31–2.12)          | < 0.001 |
| DTF (per 1% increase)                    | 1.06 (1.03–1.09)        | < 0.001 | —                         | —       |
| DE-RSBI                                  | 0.86 (0.79–0.93)        | < 0.001 | —                         | —       |
| DTF-RSBI                                 | 0.99 (0.98–0.99)        | < 0.001 | —                         | —       |

kidney disease. The results remained materially unchanged, with diaphragmatic excursion remained independently associated with successful weaning (adjusted OR 1.66 per 1-mm increase, 95% CI 1.30–2.11; *p* < 0.001) (Supplementary Table S2).

## Discussion

Among all evaluated parameters, DE demonstrated the highest predictive performance for successful weaning, with an AUC of 0.793, followed by DTF (AUC 0.740) and DTF-RSBI (AUC 0.711). In contrast, respiratory rate and conventional RSBI showed poor discriminative ability, with AUC values close to 0.5. Importantly, both DE and DTF significantly outperformed conventional respiratory parameters, including the PaO<sub>2</sub>/FiO<sub>2</sub> ratio and RSBI, on DeLong analysis.

DE demonstrated the most balanced diagnostic performance in our study, with a sensitivity of 83.2% and specificity of 61.7% at a cutoff value of > 1.26 cm, whereas DTF showed higher sensitivity but lower specificity. Additional diagnostic accuracy

**Fig. 2. ROC curve analysis of ultrasound-derived diaphragmatic indices for predicting successful weaning.**

metrics further supported these findings. Diaphragmatic excursion demonstrated the highest positive likelihood ratio among the evaluated ultrasound-derived parameters, suggesting greater usefulness for identifying patients likely to achieve successful weaning. In contrast, diaphragm thickening fraction yielded the lowest negative likelihood ratio, indicating a potentially greater ability to exclude successful weaning when values were below the optimal threshold. Nevertheless, all likelihood ratios remained within a moderate range, supporting the use of diaphragmatic ultrasound as an adjunct rather than a standalone decision-making tool during weaning assessment. These findings are comparable to previous studies and meta-analyses reporting good predictive accuracy of diaphragmatic ultrasound during weaning assessment [9]. Combined diaphragmatic indices also showed better performance than conventional RSBI alone, consistent with findings reported by S. Spadaro et al. and subsequent studies evaluating D-RSBI during spontaneous breathing trials [17]. Similar findings were subsequently reported by S. M. S. Mowafy et al. [18] and A. Abbas et al. [19], both of whom demonstrated superior diagnostic performance of D-RSBI compared with traditional RSBI in mechanically ventilated patients. However, in the present study, isolated diaphragmatic ultrasound measurements remained numerically superior to combined indices, suggesting that direct assessment of diaphragmatic mechanics may provide more robust physiologic information than composite respiratory parameters incorporating respiratory rate.

Importantly, diaphragmatic excursion remained independently associated with successful weaning after adjustment for APACHE II score and  $\text{PaO}_2/\text{FiO}_2$  ratio. Each 1 mm increase in DE was associated with a 66.6% increase in the odds of successful weaning, supporting the role of diaphragmatic ultrasound as an independent physiologic marker beyond conventional indices of disease severity and oxygenation. Similar findings have been reported in previous studies evaluating diaphragmatic ultrasound during weaning. G. Ferrari et al. demonstrated that reduced diaphragmatic excursion was independently associated with weaning failure in mechanically ventilated patients, highlighting the physiologic importance of diaphragmatic mobility during spontaneous breathing trials [20]. Likewise, E. DiNino et al. reported that diaphragmatic excursion assessed by bedside ultrasound was independently predictive of extubation success and provided incremental value beyond conventional respiratory indices [21].

The diagnostic performance of DE observed in our study is comparable to previous investigations evaluating diaphragmatic ultrasound during weaning assessment. Prior studies have reported AUC values

ranging from approximately 0.75 to 0.85 for DE and DTE, supporting the reproducibility of diaphragmatic ultrasound as a predictor of weaning outcomes across different ICU populations. The diagnostic performance of diaphragmatic ultrasound observed in the present study is consistent with previous investigations evaluating diaphragmatic function during weaning assessment. E. DiNino et al. [21] reported an AUC of approximately 0.79 for diaphragm thickening fraction in predicting extubation success, while M. J. Alam et al. [22] demonstrated AUC values of 0.83 for diaphragmatic excursion and 0.69 for diaphragm thickening fraction. These findings support the reproducibility of diaphragmatic ultrasound as a predictor of weaning outcomes across different ICU populations. Although the study included several surgical categories, all patients shared a common clinical context of prolonged postoperative mechanical ventilation. Patients were enrolled only after stabilization of the underlying condition, fulfillment of predefined readiness-to-wean criteria, and initiation of a standardized weaning protocol including spontaneous breathing trial and extubation assessment. In surgical ICU patients, postoperative pain, abdominal distension, residual sedation, and impaired chest wall mechanics may substantially affect diaphragmatic performance during spontaneous breathing [23, 24].

Although approximately one-third of the cohort underwent elective surgery, these patients were not representative of routine fast-track surgical populations. Most required prolonged postoperative mechanical ventilation because of ongoing neurological dysfunction, hemodynamic instability, respiratory complications, severe infection, or the need for intensive postoperative monitoring. Therefore, prolonged ventilation reflected the severity of postoperative critical illness rather than deviations from contemporary perioperative care pathways. Unlike conventional respiratory indices, diaphragmatic ultrasound provides direct assessment of inspiratory muscle function and respiratory mechanical reserve [25]. Because weaning failure is frequently related to respiratory muscle dysfunction rather than isolated impairment of oxygenation, diaphragmatic ultrasound-derived parameters may better reflect physiologic readiness for liberation from mechanical ventilation. Furthermore, prolonged mechanical ventilation itself may induce diaphragmatic weakness through ventilator-induced diaphragmatic dysfunction, further supporting the physiologic relevance of diaphragmatic ultrasound during weaning assessment.

An important finding of the present study is that preserved diaphragmatic excursion or thickening did not invariably translate into successful weaning. Although diaphragmatic ultrasound provides valuable information regarding diaphragmatic contrac-

tility, successful weaning depends on the integrated function of multiple organ systems. Some patients with favorable diaphragmatic ultrasound parameters nevertheless failed weaning because of non-diaphragmatic factors, including cardiovascular dysfunction, residual pulmonary abnormalities, impaired airway protection, excessive airway secretions, or neurological impairment. These conditions may increase respiratory workload or compromise the ability to maintain spontaneous breathing despite adequate diaphragmatic function. This observation highlights an important limitation of diaphragmatic ultrasound when used in isolation and supports its interpretation within a comprehensive clinical assessment. The predictive performance of diaphragmatic ultrasound is therefore likely to be greatest in patients whose weaning outcome is primarily determined by respiratory muscle function, whereas its accuracy may be reduced when weaning failure is driven predominantly by cardiac, pulmonary, neurological, or upper-airway factors. Because the present study was not powered for subgroup analyses, we were unable to identify specific surgical populations in which diaphragmatic ultrasound performs optimally. Further studies in more homogeneous surgical cohorts are warranted to better define the clinical settings in which diaphragmatic ultrasound provides the greatest predictive value.

An important consideration in interpreting our findings of this study is that structural pulmonary abnormalities were not systematically assessed as study variables. Conditions such as atelectasis, pleural effusion, pneumonia, or pul-

monary embolism may contribute to weaning failure independently of diaphragmatic dysfunction by increasing respiratory workload and impairing gas exchange. Therefore, diaphragmatic ultrasound indices should be interpreted within the broader clinical context and in conjunction with respiratory, hemodynamic, and radiological assessment. Future studies incorporating multimodal lung and diaphragm ultrasound assessment may provide a more comprehensive evaluation of weaning readiness.

There are many limitations in this research. First, this was a single-center study conducted exclusively in surgical ICU patients, which may limit generalizability to other ICU populations. Second, diaphragmatic ultrasound measurements were obtained at a single time point before spontaneous breathing trial initiation, and serial changes during the weaning process were not evaluated. Third, although ultrasound examinations were performed by experienced operators, diaphragmatic ultrasound remains operator dependent. Finally, the sample size was moderate, and larger multicenter studies are warranted to further validate these findings.

## Conclusion

Diaphragmatic ultrasound-derived indices, particularly diaphragmatic excursion, demonstrated superior predictive performance compared with conventional respiratory parameters and may provide valuable adjunctive information during weaning assessment in surgical ICU patients.

## Supplements

**Table S1. Primary clinical reasons for prolonged postoperative mechanical ventilation among elective surgical patients (*n* = 53).**

| Primary reason for prolonged mechanical ventilation | <i>n</i> (%) |
|-----------------------------------------------------|--------------|
| Neurological impairment                             | 18 (34.0)    |
| Hemodynamic instability                             | 14 (26.4)    |
| Respiratory insufficiency                           | 10 (18.9)    |
| Sepsis / septic shock                               | 1 (1.8)      |
| Ongoing sedation / postoperative monitoring         | 10 (18.9)    |

**Table S2. Sensitivity analysis of factors associated with successful weaning.**

| Variable                                    | Adjusted OR | 95% CI      | <i>P</i> -value |
|---------------------------------------------|-------------|-------------|-----------------|
| APACHE II score                             | 0.54        | 0.41–0.71   | < 0.001         |
| PaO <sub>2</sub> /FiO <sub>2</sub> ratio    | 1.008       | 1.001–1.015 | 0.032           |
| Diaphragmatic excursion (per 1-mm increase) | 1.66        | 1.30–2.11   | < 0.001         |
| COPD                                        | 2.20        | 0.51–9.54   | 0.292           |
| Chronic kidney disease                      | 1.46        | 0.41–5.21   | 0.556           |
| Diabetes mellitus                           | 0.93        | 0.28–3.12   | 0.904           |

## References

1. Engidaw MS, Tekeba B, Amare HT, Belay KA, Ayana Y, Liyew B. Incidence and predictors of extubation failure among adult intensive care unit patients in Northwest Amhara comprehensive specialized hospitals. *Scientific Reports* 2025; 15 (1): 20957. DOI: 10.1038/s41598-025-05625-6. PMID: 40594652.
2. Ha TS, Oh DK, Lee HJ, Chang Y, Jeong IS, Sim YS, et al. Liberation from mechanical ventilation in critically ill patients: Korean Society of Critical Care Medicine Clinical Practice Guidelines. *Acute Crit Care* 2024; 39 (1): 1–23. DOI: 10.4266/acc.2024.00052. PMID: 38476061.
3. Michels JD, Trudzinski FC, Bornitz F, Ewert R, Müller M, Trinkmann F, et al. Costs of Weaning Failure: A Prospective, Multicentre, Controlled, Non-Randomised, Interventional Study on Economic Implications for the German Health Care System. *Respiration* 2023; 102 (9): 813–820. DOI: 10.1159/000533333. PMID: 37619539.
4. Karthika M, Al Enezi FA, Pillai LV, Arabi YM. Rapid shallow breathing index. *Ann Thorac Med* 2016; 11 (3): 167–176. DOI: 10.4103/1817-1737.176876. PMID: 27512505.
5. Roberts KJ, Goodfellow LT, Battey-Muse CM, Hoerr CA, Carreon ML, Sorg ME, et al. AARC Clinical Practice Guideline: Spontaneous Breathing Trials for Liberation From Adult Mechanical Ventilation. *Respir Care* 2024; 69 (7): 891–901. DOI: 10.4187/respcare.11735. PMID: 38476061.
6. Torrini F, Gendreau S, Morel J, Carteaux G, Thille AW, Antonelli M, et al. Prediction of extubation outcome in critically ill patients: a systematic review and meta-analysis. *Critical Care* 2021; 25 (1): 391. DOI: 10.1186/s13054-021-03802-3. PMID: 34782003.
7. Okabe Y, Asaga T, Bekku S, Suzuki H, Kanda K, Yoda T, et al. Lung-thorax compliance measured during a spontaneous breathing trial is a good index of extubation failure in the surgical intensive care unit: a retrospective cohort study. *Journal of Intensive Care* 2018; 6 (1): 44. DOI: 10.1186/s40560-018-0313-9. PMID: 30083347.
8. Goligher JA, Dres M, Fan E, Rubenfeld GD, Scales DC, Herridge MS, et al. Mechanical Ventilation-induced Diaphragm Atrophy Strongly Impacts Clinical Outcomes. *Am J Respir Crit Care Med* 2018; 197 (2): 204–213. DOI: 10.1164/rccm.201703-0536OC. PMID: 28930478.
9. Le Neindre A, Philippart F, Luperto M, Wormser J, Morel-Sapene J, Aho SL, et al. Diagnostic accuracy of diaphragm ultrasound to predict weaning outcome: A systematic review and meta-analysis. *Int J Nurs Stud* 2021; 117: 103890. DOI: 10.1016/j.ijnurstu.2021.103890. PMID: 33588324.
10. Parada-Gereda HM, Tibaduiza AL, Rico-Mendoza A, Molano-Franco D, Nieto VH, Arias-Ortiz WA, et al. Effectiveness of diaphragmatic ultrasound as a predictor of successful weaning from mechanical ventilation: a systematic review and meta-analysis. *Crit Care* 2023; 27 (1): 174. DOI: 10.1186/s13054-023-04430-9. PMID: 37619539.
11. Song J, Qian Z, Zhang H, Wang M, Yu Y, Ye C, et al. Diaphragmatic ultrasonography-based rapid shallow breathing index for predicting weaning outcome during a pressure support ventilation spontaneous breathing trial. *BMC Pulm Med* 2022; 22 (1): 337. DOI: 10.1186/s12890-022-02133-5. PMID: 35450260.
12. Hu J, Guo R, Li H, Wen H, Wang Y. Perioperative Diaphragm Dysfunction. *J Clin Med* 2024; 13 (2). DOI: 10.3390/jcm13020519. PMID: 38476061.
13. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982; 143 (1): 29–36. DOI: 10.1148/radiology.143.1.7063747. PMID: 7063747.
14. Mohamed RSE, Mohamed ASE, Fathalah WF, Mohamed MF, Ahmed AA. The role of diaphragmatic ultrasound as a predictor of successful extubation from mechanical ventilation in respiratory intensive care unit. *The Egyptian Journal of Bronchology* 2021; 15 (1): 51. DOI: 10.1186/s43168-021-00095-6. PMID: 34782003.
15. Haaksma ME, Smit JM, Boussuges A, Demoule A, Dres M, Ferrari G, et al. EXpert consensus On Diaphragm UltraSonography in the critically ill (EXODUS): a Delphi consensus statement on the measurement of diaphragm ultrasound-derived parameters in a critical care setting. *Crit Care* 2022; 26 (1): 99. DOI: 10.1186/s13054-022-03975-5. PMID: 35450260.
16. Mahmoodpoor A, Fouladi S, Ramouz A, Shadvar K, Ostadi Z, Soleimanpour H. Diaphragm ultrasound to predict weaning outcome: systematic review and meta-analysis. *Anaesthesiol Intensive Ther* 2022; 54 (2): 164–174. DOI: 10.5114/ait.2022.117273. PMID: 35450260.
17. Spadaro S, Grasso S, Mauri T, Dalla Corte F, Alvisi V, Ragazzi R, et al. Can diaphragmatic ultrasonography performed during the T-tube trial predict weaning failure? The role

- of diaphragmatic rapid shallow breathing index. *Crit Care* 2016; 20 (1): 305.  
DOI: 10.1186/s13054-016-1479-y.  
PMCID: PMC5039882.
18. Mowafy SMS, Abdelgalel EF. Diaphragmatic rapid shallow breathing index for predicting weaning outcome from mechanical ventilation: Comparison with traditional rapid shallow breathing index. *Egyptian Journal of Anaesthesia* 2018.  
DOI: 10.1016/j.egja.2018.10.003.
  19. Abbas A, Embarak S, Walaa M, Lutfy SM. Role of diaphragmatic rapid shallow breathing index in predicting weaning outcome in patients with acute exacerbation of COPD. *Int J Chron Obstruct Pulmon Dis* 2018; 13: 1655–1661.  
DOI: 10.2147/copd.S161691.  
PMCID: PMC5967374.
  20. Ferrari G, De Filippi G, Elia F, Panero F, Volpelli G, Aprà F. Diaphragm ultrasound as a new index of discontinuation from mechanical ventilation. *Crit Ultrasound J* 2014; 6 (1): 8.  
DOI: 10.1186/2036-7902-6-8.  
PMCID: PMC4057909.
  21. DiNino E, Gartman EJ, Sethi JM, McCool FD. Diaphragm ultrasound as a predictor of successful extubation from mechanical ventilation. *Thorax* 2014; 69 (5): 423–427.  
DOI: 10.1136/thoraxjnl-2013-204111.  
PMID: 24365607.
  22. Alam MJ, Roy S, Iktidar MA, Padma FK, Nipun KI, Chowdhury S, et al. Diaphragm ultrasound as a better predictor of successful extubation from mechanical ventilation than rapid shallow breathing index. *Acute Crit Care* 2022; 37 (1): 94–100.  
DOI: 10.4266/acc.2021.01354.  
PMCID: PMC8918710.
  23. Sasaki N, Meyer MJ, Eikermann M. Postoperative respiratory muscle dysfunction: pathophysiology and preventive strategies. *Anesthesiology* 2013; 118 (4): 961–978.  
DOI: 10.1097/ALN.0b013e318288834f.  
PMID: 23429163.
  24. Dres M, Demoule A. Diaphragm dysfunction during weaning from mechanical ventilation: an underestimated phenomenon with clinical implications. *Crit Care* 2018; 22 (1): 73.  
DOI: 10.1186/s13054-018-1992-2.  
PMCID: PMC5861656.
  25. Umbrello M, Formenti P. Ultrasonographic Assessment of Diaphragm Function in Critically Ill Subjects. *Respir Care* 2016; 61 (4): 542–555.  
DOI: 10.4187/respcare.04412. PMID: 26814218.

Received 19.05.2026

Accepted 14.07.2026

## Early Ultrasound Diagnosis of Post-Operative Microaspiration and Pneumonia (Case Report)

Ivan S. Shcheparev\*, Boris A. Teplykh, Darya N. Rostovceva

N. I. Pirogov National Medical and Surgical Center, Ministry of Health of Russia,  
70 Nizhnyaya Pervomayskaya Str., 105203 Moscow, Russia

**For citation:** Ivan S. Shcheparev, Boris A. Teplykh, Darya N. Rostovceva. Early Ultrasound Diagnosis of Post-Operative Microaspiration and Pneumonia (Case Report). *Obshchaya Reanimatologiya = General Reanimatology*. 2026; 22 (4): 22–27. <https://doi.org/10.15360/1813-9779-2026-4-2696> [In Russ. and Engl.]

\*✉ Ivan S. Shcheparev, is22@list.ru

### Summary

Aspiration-related complications remain one of the most significant causes of early postoperative pneumonia, and microaspiration often occurs without symptoms and is not recognized at an early stage. The sensitivity of chest X-ray and CT (computed tomography) for the earliest changes is limited, creating a diagnostic «gap» in which lung ultrasound (LUS) may play a key role.

**Patient case presentation.** A 62-year-old patient with class III obesity (body mass index [BMI] 46.5 kg/m<sup>2</sup>), ASA class III, and a significant oncologic history experienced a prolonged (8-hour) neurosurgical procedure in the prone position. In the early postoperative period, after reintubation, she developed severe hypoxemia in the absence of specific changes on chest radiography or chest CT, while laboratory inflammatory markers were consistent with a nonspecific postoperative response. Lung ultrasound revealed a pattern atypical for atelectasis: multiple small (up to 1.5 cm<sup>2</sup>) subpleural consolidations scattered predominantly in the right lung, including nondependent areas, in the environment of preserved aeration of the surrounding tissue and a low lung ultrasound score.

**Diagnostic assessment and interventions.** The initial impression of atelectasis was revised in favor of early aspiration pneumonia, despite a «negative» CT scan. On serial ultrasound, there was a rapid increase in the number and size of subpleural consolidations, a rise in the total ultrasound score from 7 to 17, and the appearance of a right-sided pleural effusion, which prompted repeat CT and escalation of respiratory and antibiotic therapy. The repeat CT confirmed multiple areas of consolidation and hydrothorax; aspiration pneumonia was ultimately confirmed by bronchoscopy and bronchoalveolar lavage culture, which grew polymicrobial oral flora.

**Conclusion.** In the presented case, the specific lung ultrasound pattern and its progression preceded radiographic changes and made it possible to promptly suspect postoperative microaspiration as the cause of severe respiratory failure. Routine use of standardized lung ultrasound screening in high-risk patients may become a promising tool for the very early diagnosis of microaspiration, expediting the initiation of antimicrobial therapy.

**Keywords:** aspiration pneumonia; microaspiration; lung ultrasound examination

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

**Информация об авторах / Information about the authors:**

Щепарев Иван Сергеевич / Ivan S. Shcheparev, <https://orcid.org/0000-0002-0432-135X>

Теплых Борис Анатольевич / Boris A. Teplykh, <https://orcid.org/0000-0002-1784-9540>

Ростовцева Дарья Николаевна / Darya N. Rostovceva, <https://orcid.org/0009-0004-3048-3493>

### Introduction

Aspiration of contents from the oropharynx, stomach, or esophagus remains a significant complication of general anesthesia and the perioperative period [1], leading to a range of consequences from transient gas exchange disturbances to severe pneumonia and acute respiratory failure [2, 3]. In recent years, the phenomenon of microaspiration has attracted particular attention [4–6], as it can occur without marked regurgitation and may not manifest clinically until a day or more later presenting as early postoperative pneumonia [7]. Conventional imaging modalities (X-ray, computed tomography (CT)) have limited sensitivity in the earliest stages of aspiration injury [8–10] and may remain insufficiently informative during the first 24–48 hours [11, 12]. Under these conditions, lung ultrasound plays an increasingly important role, as it is highly sensitive to even minimal

increases in interstitial fluid and early emergence of subpleural foci of infiltration [13–15]. We present a clinical case of a patient at high anesthetic risk in whom specific ultrasound findings in the lungs allowed us to rule out the initial diagnosis of atelectasis and suspect early aspiration pneumonia at the «gray zone» stage of imaging and laboratory markers.

**Informed consent.** We obtained the patient's written informed consent to publish de-identified clinical case report and clinical and diagnostic data.

### Case Report

**Patient Information.** Patient T., 62 years old, was admitted for urgent surgery due to a solitary metastasis in the left cerebellar hemisphere, with a history of stage IIIA left breast cancer. Height: 160 cm; weight: 127 kg; body mass index (BMI): 46.5 kg/m<sup>2</sup> (class 3 obesity); ASA III. Concomitant conditions:

hypertension (stage 3, risk 4), stage I congestive heart failure, functional class II, incompetence of lower esophageal sphincter with reflux esophagitis, varicose veins and Post-Thrombotic Syndrome (PTS), and metabolic dysfunction-associated steatotic liver disease (MASLD). The patient was on azilsartan and chlorthalidone maintenance therapy. On admission: blood pressure 150/90 mm Hg, HR 89 bpm, RR 16 breaths per minute, SpO<sub>2</sub> 92% on room air; neurologically — unsteady gait, general weakness, headache.

**Timeline.** Admission to a hospital of a female patient with metastasis to the cerebellum.

**Day 0:** Neurosurgical trepanation (8 hours) under general anesthesia with mechanical ventilation in pressure-controlled ventilation (PCV) mode; initial tracheal extubation without signs of aspiration. End of Day 0 (transfer to the intensive care unit): sudden deterioration—ventricular tachycardia, seizures, impaired consciousness, re-intubation.

**Night 0–1:** Head CT scan showed no abnormalities; mechanical ventilation continued for 12 hours. Day 1: Tracheal extubation was attempted again followed by marked hypoxemia (SpO<sub>2</sub>=80%); chest X-ray showed no abnormalities; lung ultrasound—multiple subpleural consolidations, chest CT («fibrous bands/atelectasis»).

**Day 2:** Worsening hypoxemia, repeat lung ultrasound (LUS) yields an increased score — LUS 7→17, right-sided pleural effusion; repeat chest CT scan shows consolidations and hydrothorax. Bronchoscopy with bronchoalveolar lavage and subsequent bacteriological examination yields multibacterial flora, therefore empirical antibiotic therapy initiated instantly.

**Days 3–20:** prolonged mechanical ventilation (20 days totally).

**Day 26:** completion of intensive care, stabilization, discharge.

**Surgery and Anesthesia.** Cranial trepanation and microsurgical removal of the metastasis in the left suboccipital region and autologous bone graft reconstruction lasted 8 hours on the patient in prone position. Anesthesia: induction — propofol, fentanyl, rocuronium; maintenance — desflurane combined with fentanyl and repeated administration of a muscle relaxant; tracheal intubation via the mouth using an 8.0-mm-diameter tube, with no technical complications. Mechanical ventilation was performed in PCV mode at FiO<sub>2</sub> of 0.6 and positive end-expiratory pressure (PEEP) of 7 cm H<sub>2</sub>O, with a tidal volume of approximately 600 mL; the PaO<sub>2</sub>/FiO<sub>2</sub> ratio during surgery was 371 mm Hg, and no critical episodes of desaturation were observed. Upon completion of the procedure, the patient was awakened and extubated after muscle tone had been restored and adequate spontaneous breathing had been established; no immediate signs of regurgitation or aspiration were observed.

### Early postoperative period and deterioration.

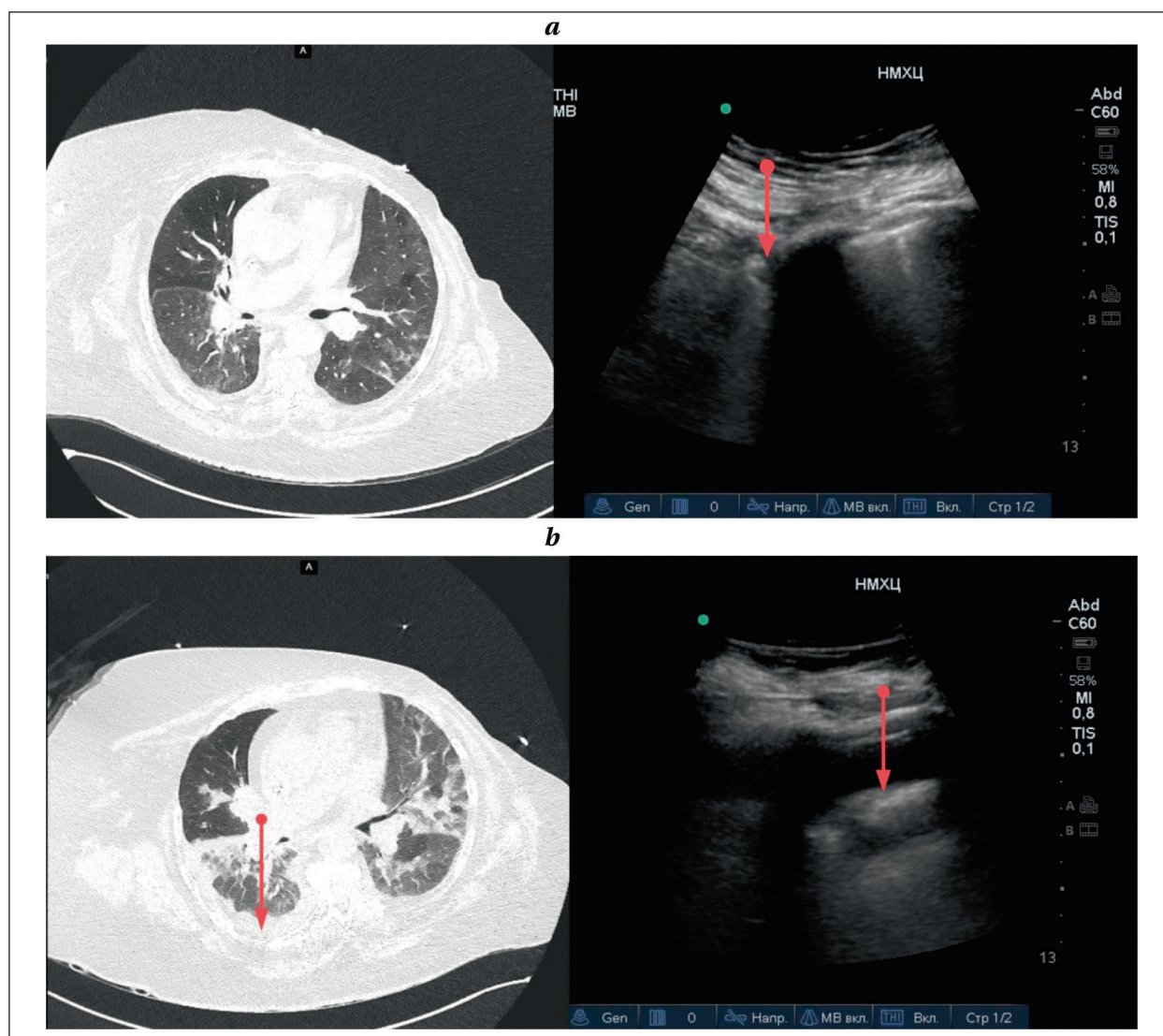
During transfer to the ICU, patient's condition suddenly deteriorated: she experienced a brief episode of ventricular tachycardia and seizures, followed by alteration of consciousness up to stupor and worsening respiratory failure. Emergency re-intubation was performed; laryngoscopy revealed no visible aspirated material in the airways. Brain CT scan was performed to rule out acute intracranial pathology; although no pathological changes were found. After 12 hours of mechanical ventilation the patient was extubated and instantaneously developed acute hypoxemia, SpO<sub>2</sub> dropped to 80% on room air requiring a continuous oxygen supply via a face mask at 10 L/min. Atelectasis of the basal lung fields was initially suggested with regard to residual respiratory depression, given the patient's obesity and long-lasting surgery. A chest X-ray revealed no conclusive pathology; laboratory markers of inflammation (C-reactive protein (CRP) 66 mg/L, procalcitonin 0.318 ng/mL) were considered nonspecific for the early postoperative period.

**Ultrasound examination of the lungs.** To identify the cause of respiratory failure, a lung ultrasound (LUS) was performed using the standard positions of the 12-zone protocol, with the total score calculated (Fig. a). Contrary to the expected pattern of compression atelectasis in the posterobasal, dependent regions, these areas remained aerated and did not contain marked consolidations. Instead, multiple small (up to 1.5 cm) subpleural consolidations were identified, spreading into continuous, confluent B-lines extending deeper into the lung, predominantly in the right lung, including the anterior and lateral segments, in the environment of preserved airiness in the surrounding tissue with few B-lines. This ultrasound pattern did not correspond to the typical presentation of compression atelectasis, which looks like a dynamic homogeneous, «tissue-like» consolidated mass floating within a pleural effusion in the dependent posterobasal segments.

**Chest CT.** To verify the LUS findings, a chest CT scan was performed using the angiographic mode. On the first day, the CT scan revealed no clear signs of pneumonia (Fig. a): only nonspecific areas of opacity were noted, interpreted as fibrous bands or subsegmental atelectasis, without convincing consolidation. No signs of pulmonary embolism were detected.

Thus, a contradictory situation arose: severe acute respiratory failure with a radiographically and CT-wise «clean» picture, where only specific ultrasound findings raised concerns regarding early aspiration.

**Changes in the LUS findings and a repeat CT scan.** On the second day after surgery, despite ongoing respiratory support, the patient developed a dry cough and worsening hypoxemia (PaO<sub>2</sub> —



**Figure.** Computed tomography and ultrasound images of the lungs on day 1 (*a*) and day 2 (*b*).

**Note.** *a* — CT revealed only nonspecific changes; ultrasound showed scattered subpleural consolidations (indicated by the arrow) with well-defined borders, homogeneous hypoechoic content, and broad confluent B-lines behind the consolidation in the aerated lung and an unchanged pleural line. *b* — The CT scan revealed multiple areas of involvement with consolidations and pleural effusion (indicated by the arrow); the ultrasound showed large, confluent consolidations and pleural effusion (indicated by the arrow).

39 mm Hg, SpO<sub>2</sub> — 72% on room air), while laboratory markers of inflammation remained moderately elevated. A repeat LUS revealed a negative trend: an increase in the number and size of subpleural consolidations with a tendency to coalesce, the spread of the ultrasound infiltration pattern to new areas, and the appearance of a right-sided pleural effusion (Fig. *b*); the total ultrasound score rose from 7 to 17. Given the progressive deterioration in gas exchange and the negative trend in the ultrasound findings, a repeat chest CT scan was performed, which revealed a significant increase in areas of consolidation and densification of lung tissue, as well as a right-sided hydrothorax (Fig. *b*).

**Diagnosis, treatment, and outcome.** Based on the compiled clinical data — clinical deterioration, a characteristic ultrasound pattern and its

progression, confirmed by a repeat CT scan — aspiration pneumonia was diagnosed. Bronchoscopy performed on the second day revealed diffuse inflammation of the bronchial mucosa; culture of bronchoalveolar lavage fluid revealed polymicrobial flora typical of the oral cavity (*Gemella haemolysans* 10<sup>6</sup> CFU/mL, *Streptococcus mitis/oralis* 10<sup>5</sup> CFU/mL, and others), which served as direct confirmation of the aspiration-related nature of the lung injury. An empirical antibiotic therapy (levofloxacin) was initiated, and was subsequently adjusted based on the results of microbiological testing, and invasive mechanical ventilation was continued due to the progression of respiratory failure. The total duration of mechanical ventilation was 20 days, and that of intensive care was 26 days; by the time of discharge, the patient's condition had sta-

bilized, and her respiratory function had returned to normal.

**The patient's perspective.** After completing a course of intensive care, the patient reported a significant improvement in her well-being and the disappearance of shortness of breath. In her words, «It was hard to breathe the first few days after being discharged from the ICU, but I gradually recovered». The patient expressed her gratitude for the timely diagnosis and treatment. She continues to receive outpatient follow-up care from an oncologist and a pulmonologist.

## Discussion

The presented case illustrates a typical diagnostic pitfall of the perioperative period: «silent» microaspiration mimicking expected atelectasis in an obese patient following a prolonged procedure [16–18]. The absence of obvious regurgitation during re-intubation, as well as the initially «clear» findings on X-ray and CT, reinforced the erroneous hypothesis of atelectasis. It was unclear at what stage the aspiration might have occurred [19–21]. Under these circumstances, lung ultrasound evolved from a routine imaging method into a key diagnostic tool, allowing us to propose an alternative hypothesis of aspiration pneumonia long before it was confirmed by CT and microbiological data. The most significant ultrasound findings indicating an atypical presentation were:

- Multiple small subpleural consolidations (up to 1.5 cm) with multiple confluent B-lines behind them, scattered, predominantly in the right lung, including areas independent of gravity, in an environment of preserved airiness in the surrounding lung tissue.
- Absence of the typical pattern of homogeneous compression atelectasis in the posterobasal, gravity-dependent regions [22].
- Rapid progression in the number and size of subpleural foci with a tendency to coalesce; an increase in the total LUS score from 7 to 17 over two days [22, 23].
- Development of a right-sided pleural effusion alongside with progressive hypoxemia [24].

This pattern is more consistent with focal inflammatory damage associated with the local exposure of aspirated oral contents than with the passive collapse of lung tissue characteristic of atelectasis [14]. This case highlights the limitations of CT as the «gold standard» for imaging in the very early stages following aspiration: the initial CT scan did not reveal convincing infiltrative changes, despite marked hypoxemia. This is consistent with the literature, which indicates that CT is more sensitive to established dense consolidation, whereas the early stages of interstitial edema and partial alveolar fluid filling may not be visualized [15]. Lung ultrasound, on the other hand, detects precisely these early

functional and morphological changes in the form of B-lines and subpleural consolidations, making it a valuable tool for dynamic bedside monitoring [15, 25]. In anesthesiology and critical care practice, such «silent» microaspiration events in high-risk patients (obesity, prolonged surgeries, neurosurgery, repeated tracheal intubation) may represent an underestimated cause of early postoperative pneumonia [2, 26]. Incorporation of standardized ultrasound screening for lung injuries (using an ultrasound scoring system and assessment of subpleural patterns) into routine monitoring protocol for such patients can:

- Reduce the likelihood of missing early signs of aspiration injury.
- Justify the need for early escalation of respiratory support and antibiotic therapy.
- Reduce the time lag between clinical manifestations and radiological confirmation of pneumonia.

## Limitations and future research directions.

This report is limited to a single clinical case, which does not allow for the extrapolation of findings to the entire patient population. The patient's specific clinical profile (severe obesity, neurosurgical intervention, and repeated tracheal intubation) may have influenced both the risk of aspiration and the characteristics of the ultrasound and CT findings. Nevertheless, this case report provides a clear hypothesis for prospective studies: assessing the specificity of the pattern of multiple subpleural consolidations for the early diagnosis of aspiration, standardizing the protocol for pulmonary ultrasound in the perioperative period, and determining whether the implementation of ultrasound screening can reduce the incidence of severe aspiration pneumonia and improve outcomes.

## Conclusion

In a high-risk patient following a prolonged neurosurgical procedure, the development of severe acute respiratory failure was initially attributed to pulmonary atelectasis, while chest X-rays, CT scans, and laboratory markers did not provide conclusive evidence of pneumonia. Only the specific LUS findings (multiple scattered subpleural consolidations with preserved air in the tissue and their rapid progression as the ultrasound score increased) suggested early aspiration pneumonia long before it became evident on CT and microbiological tests. This underscores the potential of LUS markers as a tool for the early diagnosis of postoperative microaspiration and, consequently, as a predictor of high risk for the development of aspiration pneumonia in at-risk patients. Standardizing ultrasound protocols and validating the identified patterns in larger studies appear to be a promising approach for reducing the incidence of severe respiratory complications in anesthesiology and critical care.

## References

1. Sun J., Wei G., Hu L., Liu C., Ding Z. Perioperative pulmonary aspiration and regurgitation without aspiration in adults: a retrospective observational study of 166,491 anesthesia records. *Ann Palliat Med.* 2021; 10 (4): 4037–4046. DOI: 10.21037/apm-20-2382. PMID: 33832306.
2. Sparn M.B., Widmann B., Pietsch U., Weitzendorfer M., Warschkow R., Steffen T. Risk factors and outcomes of postoperative aspiration pneumonia in abdominal surgery patients: An exact matching and weighting analysis. *Surgery.* 2021; 170 (5): 1432–1441. DOI: 10.1016/j.surg.2021.05.025. PMID: 34148710.
3. Fukuda T., Imai S., Shimoda S., Maruo K., Nakadera M., Horiguchi H. Aspiration pneumonia and anesthesia techniques in hip fracture surgery in elderly patients: a retrospective cohort study using administrative data. *J Orthop Surg.* 2022; 30 (1): 10225536221078622. DOI: 10.1177/10225536221078622. PMID: 35226565.
4. Degroote T., Jaillette E., Reignier J., Zerimech F., Girault C., Brunin G., Chiche A., et al; Micro-COPD study group. Is COPD associated with increased risk for microaspiration in intubated critically ill patients? *Ann Intensive Care.* 2021; 11 (1): 7. DOI: 10.1186/s13613-020-00794-1. PMID: 33428002.
5. Miao P., Zhang Y., Zhong A. Risk factors of aspiration occurrence with different feeding patterns in elderly intensive care unit patients: a cross-sectional study. *J Thorac Dis.* 2023; 15 (5): 2585–2600. DOI: 10.21037/jtd-23-430. PMID: 37324079.
6. Nseir S., Zerimech F., Jaillette E., Artru F., Balduyck M. Microaspiration in intubated critically ill patients: diagnosis and prevention. *Infect Disord Drug Targets.* 2011; 11 (4): 413–423. DOI: 10.2174/187152611796504827. PMID: 21679139.
7. D'Haese J., De Keukeleire T., Remory I., Van Rompaey K., Umbrain V., Poelaert J. Assessment of intraoperative microaspiration: does a modified cuff shape improve sealing? *Acta Anaesthesiol Scand.* 2013; 57 (7): 873–880. DOI: 10.1111/aas.12119. PMID: 23556486.
8. Mandell L.A., Niederman M.S. Aspiration pneumonia. *N Engl J Med.* 2019; 380 (7): 651–663. DOI: 10.1056/NEJMra1714562. PMID: 30763196.
9. Marik P.E. Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med.* 2001; 344 (9): 665–671. DOI: 10.1056/NEJM200103013440908. PMID: 11228282.
10. Raghavendran K., Nemzek J., Napolitano L.M., Knight P.R. Aspiration-induced lung injury. *Crit Care Med.* 2011; 39 (4): 818–826. DOI: 10.1097/CCM.0b013e31820a856b. PMID: 21263315.
11. Konietzke P., Steentoft H.H., Wagner W.L., Albers J., Dullin C., Skornitzke S., Stiller W., et al. Consolidated lung on contrast-enhanced chest CT: the use of spectral-detector computed tomography parameters in differentiating atelectasis and pneumonia. *Heliyon.* 2021; 7 (5): e07066. DOI: 10.1016/j.heliyon.2021.e07066. PMID: 34113729.
12. Namiki H., Kobayashi T. Lung ultrasound for initial diagnosis and subsequent monitoring of aspiration pneumonia in elderly in home medical care setting. *Gerontol Geriatr Med.* 2019; 5: 2333721419858441. DOI: 10.1177/2333721419858441. PMID: 31259205.
13. Yamanaka H., Maita H., Kobayashi T., Akimoto T., Osawa H., Kato H. Diagnostic accuracy of pocket-sized ultrasound for aspiration pneumonia in elderly patients without heart failure: a prospective observational study. *Geriatr Gerontol Int.* 2021; 21 (12): 1118–1124. DOI: 10.1111/ggi.14293. PMID: 34647413.
14. Buonsenso D., De Rose C., Morello R., Lazzareschi I., Valentini P. Aspiration pneumonia in children with neurological disorders: a new indication for lung ultrasound? A case series. *J Ultrasound.* 2022; 25 (2): 325–331. DOI: 10.1007/s40477-020-00520-4. PMID: 32757145.
15. Щепарев И.С., Теплых Б.А., Киреева Г.С., Проценко Д.Н., Коцюбинский Д.В., Броннов О.Ю., Баланык Э.А. Эволюция методики и новые протоколы ультразвукового исследования легких при COVID-19 пневмониях. *Общая реаниматология.* 2023; 19 (6): 39–47. Shcheparev I.S., Teplykh B.A., Kireeva G.S., Protsenko D.N., Kotsyubinsky D.V., Bronov O.Yu., Balanyuk E.A. Evolution of the techniques and new protocols for lung ultrasound examination in COVID-19 pneumonia patients. *General Reanimatology = Obshchaya Reanimatologiya.* 2023; 19 (6): 39–47. (in Russ.&Eng.). DOI: 10.15360/1813-9779-2023-6-39-47
16. Magnusson L., Spahn D.R. New concepts of atelectasis during general anaesthesia. *Br J Anaesth.* 2003; 91 (1): 61–72. DOI: 10.1093/bja/aeg085. PMID: 12821566.
17. Miskovic A., Lumb A.B. Postoperative pulmonary complications. *Br J Anaesth.* 2017; 118 (3): 317–334. DOI: 10.1093/bja/aex002. PMID: 28186222.
18. Writing Committee for the PROBESE Collaborative Group of the PROtective VEntilation Net-

- work (PROVENet) for the Clinical Trial Network of the European Society of Anaesthesiology; Bluth T, Serpa Neto A, Schultz M.J., Pelosi P, Gama de Abreu M.; PROBESE Collaborative Group; Bluth T, Bobek I, Canet J.C., Cinnella G., de Baerdemaeker L., Gama de Abreu M., Gregoretti C., et al. Effect of intraoperative high Ppositive end-expiratory pressure (PEEP) with recruitment maneuvers vs low PEEP on postoperative pulmonary complications in obese patients: a randomized clinical trial. *JAMA*. 2019; 321 (23): 2292–2305. DOI: 10.1001/jama.2019.7505. PMID: 31157366.
19. Warner M.A., Warner M.E., Weber J.G. Clinical significance of pulmonary aspiration during the perioperative period. *Anesthesiology*. 1993; 78 (1): 56–62. DOI: 10.1097/00000542-199301000-00010. PMID: 8424572.
  20. Kluger M.T., Short T.G. Aspiration during anaesthesia: a review of 133 cases from the Australian Anaesthetic Incident Monitoring Study (AIMS). *Anaesthesia*. 1999; 54 (1): 19–26. DOI: 10.1046/j.1365-2044.1999.00642.x. PMID: 10209365.
  21. Cook T.M., Woodall N., Frerk C.; Fourth National Audit Project. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 1: anaesthesia. *Br J Anaesth*. 2011; 106 (5): 617–631. DOI: 10.1093/bja/aer058. PMID: 21447488.
  22. Boussier J., Lemasle A., Hantala N., Scatton O., Vaillant J.C., Paye F., Langeron O., et al. Lung ultrasound score on postoperative day 1 Is predictive of the occurrence of pulmonary complications after major abdominal surgery: a multicenter prospective observational study. *Anesthesiology*. 2024; 140 (3): 417–429. DOI: 10.1097/ALN.0000000000004855. PMID: 38064713.
  23. Szabó M., Bozó A., Darvas K., Soós S., Özse M., Iványi Z.D. The role of ultrasonographic lung aeration score in the prediction of postoperative pulmonary complications: an observational study. *BMC Anesthesiol*. 2021; 21 (1): 19. DOI: 10.1186/s12871-021-01236-6. PMID: 33446103.
  24. Light R.W. Clinical practice. Pleural effusion. *N Engl J Med*. 2002; 346 (25): 1971–7. DOI: 10.1056/NEJMcp010731. PMID: 12075059.
  25. Лакхин Р.Е., Жирнова Е.А., Щеголев А.В., Железняк И.С., Чирский В.С., Пнаминский Д.Ю. Сопоставление ультразвуковых признаков, данных компьютерной томографии и морфологического исследования легких у пациентов с коронавирусной инфекцией: post hoc анализ. *Вестник интенсивной терапии им. А. И. Салтанова*. 2023; 3: 82–96. Lakhin R.E., Zhirnova E.A., Shchegolev A.V., Zheleznyak I.S., Chirskiy V.S., Pluminskiy D.Y. Comparison of ultrasound signs, computed tomography data, and morphological examination of the lungs in patients with coronavirus infection: a post hoc analysis. *Ann Crit Care = Vestnik Intensivnoy Terapii im A.I. Saltanova*. 2023; 3: 82–96. (in Russ.). DOI: 10.21320/1818-474X-2023-3-82-96.
  26. Muscedere J., Rewa O., McKechnie K., Jiang X., Laporta D., Heyland D.K. Subglottic secretion drainage for the prevention of ventilator-associated pneumonia: a systematic review and meta-analysis. *Crit Care Med*. 2011; 39 (8): 1985–91. DOI: 10.1097/CCM.0b013e318218a4d9. PMID: 21478738.

Received 18.03.2026

Accepted 08.07.2026

# Effect of Octenidine Dihydrochloride on Gingival Inflammation, Dental Plaque, and Xerostomia in Patients Receiving Respiratory Support

Irina A. Ruslyakova\*, Ekaterina A. Zakharova, Yulia A. Mironova, Ilja S. Chertsov, Elvina Z. Shamsutdinova, Alexey V. Silin

I. I. Mechnikov North-Western State Medical University, Ministry of Health of Russia, 47 Piskarevskii prospect, 195067 St. Petersburg, Russia

**For citation:** Irina A. Ruslyakova, Ekaterina A. Zakharova, Yulia A. Mironova, Ilja S. Chertsov, Elvina Z. Shamsutdinova, Alexey V. Silin. Effect of Octenidine Dihydrochloride on Gingival Inflammation, Dental Plaque, and Xerostomia in Patients Receiving Respiratory Support. *Obshchaya Reanimatologiya = General Reanimatology*. 2026; 22 (4): 28–37. <https://doi.org/10.15360/1813-9779-2026-4-2650> [In Russ. and Engl.]

\*✉ Irina A. Ruslyakova, [ruslyakova777dok@gmail.com](mailto:ruslyakova777dok@gmail.com)

## Summary

Maintaining oral hygiene in patients receiving respiratory support is critically important for preventing healthcare-associated infections.

**The aim of the study** was to evaluate the clinical effect of octenidine dihydrochloride mouthwash added to local oral hygiene care protocol for patients receiving respiratory support.

**Materials and Methods.** This prospective cohort study included 299 patients receiving respiratory support in the ICU setting during 2023–2026 years; after propensity score matching (PSM), 208 (104 pairs) patients were included in the final analysis. Oral hygiene protocol included twice-daily tooth brushing and oral rinsing at a frequency determined by the Intensive Care Oral Care Frequency Assessment Scale (ICOCFAS). Octenidine dihydrochloride 0.1% solution was used as the rinse in the study group, and distilled water — in the control group. A dentist assessed oral health using the Challacombe Scale of Clinical Oral Dryness (CSCOD), Plaque Index (PI), and Modified Gingival Index (MGI) at predefined time points.

**Results.** During days 1–3, the study group showed a decrease in the median MGI and PI values compared with the control group ( $p < 0.001$ ). By day 7, the favorable changes in the MGI and PI in the study group had boosted, and between-group differences remained significant ( $p < 0.001$ ). The effect of the intervention did not depend on the clinical outcome: the «group × outcome» interaction was not statistically significant for  $\Delta\text{MGI}_{1-3}$  and  $\Delta\text{MGI}_{1-7}$  ( $p = 0.269$  and  $p = 0.141$ , respectively). Changes in xerostomia (CSCOD) did not differ significantly between the groups ( $p = 0.119$ ).

**Conclusion.** The use of 0.1% octenidine dihydrochloride mouthwash as a part of the oral hygiene protocol in patients receiving respiratory support results in rapid resolution of gingival inflammation (MGI) and effective removal of dental plaque (PI). However, the persisting rigidity of xerostomia (CSCOD) regardless of the hygiene care protocol warrants searching for additional correction strategies.

**Keywords:** octenidine dihydrochloride; gingival inflammation; dental plaque; xerostomia; modified gingival index; oral hygiene; respiratory support

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

## Информация об авторах / Information about the authors:

Руслякова Ирина Анатольевна / Irina A. Ruslyakova, <https://orcid.org/0000-0003-1507-833X>; SPIN: 3417-8804; ResearcherID: KFA-3047-2024

Захарова Екатерина Александровна / Ekaterina A. Zakharova, <https://orcid.org/0000-0001-9545-9807>

Миронова Юлия Александровна / Yulia A. Mironova, <https://orcid.org/0009-0000-3308-7251>

Черцов Илья Сергеевич / Ilja S. Chertsov, <https://orcid.org/0009-0005-7864-8012>

Шамсутдинова Эльвина Зинуровна / Elvina Z. Shamsutdinova, <https://orcid.org/0009-0003-5800-8697>

Силин Алексей Викторович / Alexey V. Silin, <https://orcid.org/0000-0001-9785-7243>

## Introduction

Oral hygiene is a cornerstone of the prevention of healthcare-associated infections [1–3]. In critically ill patients receiving respiratory support, the risk of developing and progressing plaque-induced gingivitis increases substantially because of reduced salivary flow, insufficient scope of hygiene measures, and the prolonged persistence of opportunistic microflora within the biofilm. Each type of respiratory support adds its own risk factors. For example, with mechanical ventilation (MV), additional threats include traumatic injury to the mucosa from the endotracheal

tube and nasogastric tube [4, 5], as well as increased accumulation of plaque on the chewing surfaces of the molars. In noninvasive ventilation (NIV), mask design interferes with thorough oral cavity care [5]. In contrast, high-flow oxygen therapy (HFOT) has a dual effect: in nasal breathing adequate humidification and warming of the gas provide protection of the mucosa, whereas high flow in mouth breathing promotes xerostomia and damage to the epithelial barrier. In addition, in all patients receiving respiratory support, regardless of the modality, prosthodontic appliances (fixed and removable dentures) play an

important role by creating additional retention sites for microbial colonization [6].

Mechanical removal of dental plaque and irrigation (rinsing) are well established basic methods of maintaining oral hygiene [7]. Various solutions are used for oral irrigation in the ICU: povidone-iodine, sodium bicarbonate, tap water, chlorhexidine, herbal extracts, and antibiotics in toothpaste formulations [8–10]. According to Amrita et al., octenidine dihydrochloride is superior to 0.2% chlorhexidine solution in antimicrobial activity, effectiveness in reducing periodontal inflammation, and plaque control [11]. In a study by Sabantseva et al., it was shown that a seven-day course of a mouth rinsing with 0.1% octenidine dihydrochloride solution associated not only with a reduction in pathogenic and atypical oral microorganisms, but also with a lower incidence or less severity of oral dysbiosis [12].

In clinical practice, there remains considerable variability in approaches to oral assessment and heterogeneity in the protocols used, which is associated with the lack of consensus among professional organizations [13, 14]. Scales used in ICU oral hygiene protocols, such as the Beck Oral Assessment Score (BOAS) and the Intensive Care Oral Care Frequency Assessment Scale (ICOCFAS), regulate the frequency of oral care [15, 16]. To quantitatively assess the effectiveness of hygiene interventions in clinical practice, validated dental indices are used: Lobene or Modified Gingival Index (MGI), Gingival Bleeding Index (GBI), Papillary Bleeding Index (PIBI/Mazza PIBI), Plaque Index (PI), Mucosal-Plaque Score (MPS), Turesky Quigley-Hein plaque index (TQHPi), as well as the Challacombe Scale of Clinical Oral Dryness (CSCOD) [17–20].

Thus, to date, there are no data on the clinical efficacy of including a 0.1% octenidine dihydrochloride solution in a local oral hygiene care protocol for patients receiving respiratory support. In addition, the available literature does not describe any objective assessment of the outcomes of such interventions using validated dental indices.

Study objective: to evaluate the clinical effect of adding octenidine dihydrochloride solution to the local oral hygiene care protocol in patients receiving respiratory support.

## Materials and Methods

A single-center prospective cohort study with propensity score matching (PSM) for the control group was conducted in the therapeutic intensive care unit (ICU) of the I.I. Mechnikov North-Western State Medical University (NWSMU) from October 5, 2023, to May 20, 2026. Approval was obtained from the local ethics committee of NWSMU (Protocol No. 2, dated February 12, 2020). Upon admission to the hospital, all patients signed informed consent for medical intervention and processing of personal data. All study participants

signed informed consent, disclosing that they may receive the investigational drug.

The inclusion criteria for the study were as follows: age 18 to 95 years inclusive; presence of hypoxemia ( $\text{SpO}_2 < 90\%$  or  $\text{PaO}_2 < 60$  mm Hg) while on low-flow oxygen therapy, requiring escalation to respiratory support (high-flow oxygen therapy, noninvasive ventilation, or invasive ventilation); presence of dental plaque ( $\text{PI} \geq 1.0$ ) and gingival inflammation ( $\text{MGI} \geq 1.0$ ); and periodontal pocket depth  $< 5$  mm.

The exclusion criteria were as follows: refusal to participate in the study; impaired consciousness that prevented the patient from signing the informed consent form; the presence of a hospital-acquired infection at the time of study enrollment (lower respiratory tract infection, catheter-associated urinary tract infection, catheter-associated bloodstream infection); a history of allergic reactions to octenidine dihydrochloride; the presence of severe periodontitis (periodontal pockets  $> 6$  mm) or acute ulceronecrotic gingival lesions; and the presence of severe xerostomic syndrome ( $\text{CSCOD} > 7$  scores) at screening.

The study primary endpoint was change from baseline in the modified gingival index (MGI). Secondary endpoints included changes in the plaque index (PI) and in the xerostomia score assessed by CSCOD, as well as the incidence of lower respiratory tract infection (LRTI).

The sample size was planned based on the primary endpoint (change in MGI between days 1 and 3 of follow-up). According to the pilot analysis, the expected between-group difference in  $\Delta\text{MGI}_{1-3}$  was approximately 0.3 scores, with a standard deviation of about 0.4 scores. With a two-sided significance level of  $\alpha = 0.05$ , 80% power, and a 1:1 group allocation ratio, the minimum required sample size was 29 patients per group. Taking into account the nonrandomized study design, the need for subsequent PSM, and possible missing data, an expanded initial sample was assembled. The final dataset included 299 patients, 63 of whom had an adverse outcome (death).

The following baseline covariates, recorded on day 1, were included in the PSM model: age, scores on the ICOCFAS, MGI, PI, and CSCOD scales, the Charlson Comorbidity Index (CCI), and the presence of orthodontic appliances (prostheses). The patient flow and covariate balance are shown in the Appendix (Tables 1 and 2).

The probability of group assignment was estimated using logistic regression. Patients were matched using nearest-neighbor matching at a 1:1 ratio without replacement of control-group patients. To limit the allowable distance between matched patients, a caliper equal to 0.30 of the standard deviation of the logit of the estimated probability was used. The actual caliper value was 0.155. Matching quality was assessed using standardized mean differences (SMDs).

An SMD of  $<0.10$  was considered optimal balance. The SOFA (Sequential Organ Failure Assessment) score was not included in the main matching model because of the large number of missing values; after matching, balance for SOFA was additionally assessed among patients with available data (SMD 0.008). To compare changes in the overall matched sample, the Wilcoxon signed-rank test for paired samples was used, since after PSM patients were paired. After matching, 104 patient pairs were enrolled in the intervention and control groups. In the intervention group ( $n=104$ ), patients received standard care, including supervised tooth brushing with toothpaste twice daily for 2 minutes, and a mouth rinse with 15 mL of 0.1% octenidine dihydrochloride solution for 30 seconds. In the control group ( $n=104$ ), patients received the same standard care and mouth rinse with 15 mL of distilled water for 30 seconds.

The study scheme is presented in Fig. 1.

The frequency of oral rinsing was determined using the ICOCFAS scale, which takes into account the condition of the oral mucosa, age, and the type of respiratory and nutritional support [16]. For all patients, oral hygiene procedures were performed using an oral care kit containing a foam swab, suction tube, toothbrush, and vacuum connector. The introduction of the local oral hygiene protocol into routine clinical practice was accompanied by quarterly training workshops held jointly with epidemiologists under the supervision of a dentist.

A dentist assessed the condition of the oral cavity and monitored the effectiveness of oral hygiene measures on days 1, 3, and 7 of intensive care using the following indices and scales: the plaque index (PI), the gingivitis index (MGI), and the clinical xerostomia assessment scale (CSCOD).

The severity of gingivitis was evaluated using the modified gingivitis index (MGI, Lobene, 1986). An abbreviated examination protocol was used, assessing the condition of the gingiva in the area of all present molars, incisors, and canines in the upper and lower jaws (excluding premolars). The index was calculated as the arithmetic mean of the scores obtained for each patient.

Analyzed parameters: age (years), gender, primary and concomitant diseases, CCI (scores), duration of respiratory support (days), presence of dental prostheses (yes/no), ICU length of stay (days), ICOCFAS (score), MGI (score), PI (score), and CSCOD (score) (Appendix, Table 3).

The data were statistically processed using Jamovi 2.6.26, as well as the Python programming language for additional analysis and visualization.

Quantitative variables were presented as the median ( $Me$ ) and interquartile range ( $Q_1-Q_3$ ). Categorical variables were described using absolute frequencies and percentages —  $n$  (%). Quantitative measures in two independent groups were compared using the nonparametric Mann–Whitney  $U$  test. Pearson's chi-square test was used to analyze contingency tables; when the expected frequency in any cell was less than 5, Fisher's exact test was applied. To assess whether the magnitude of the intervention effect depended on the clinical outcome, an interaction analysis of «group  $\times$  outcome» was performed (reference category: unfavorable outcome). The coefficient for the «group» variable reflects the difference in the change in MGI between the intervention and control groups in patients with an unfavorable outcome, whereas the interaction coefficient indicates whether this effect changes in patients with a favorable outcome.

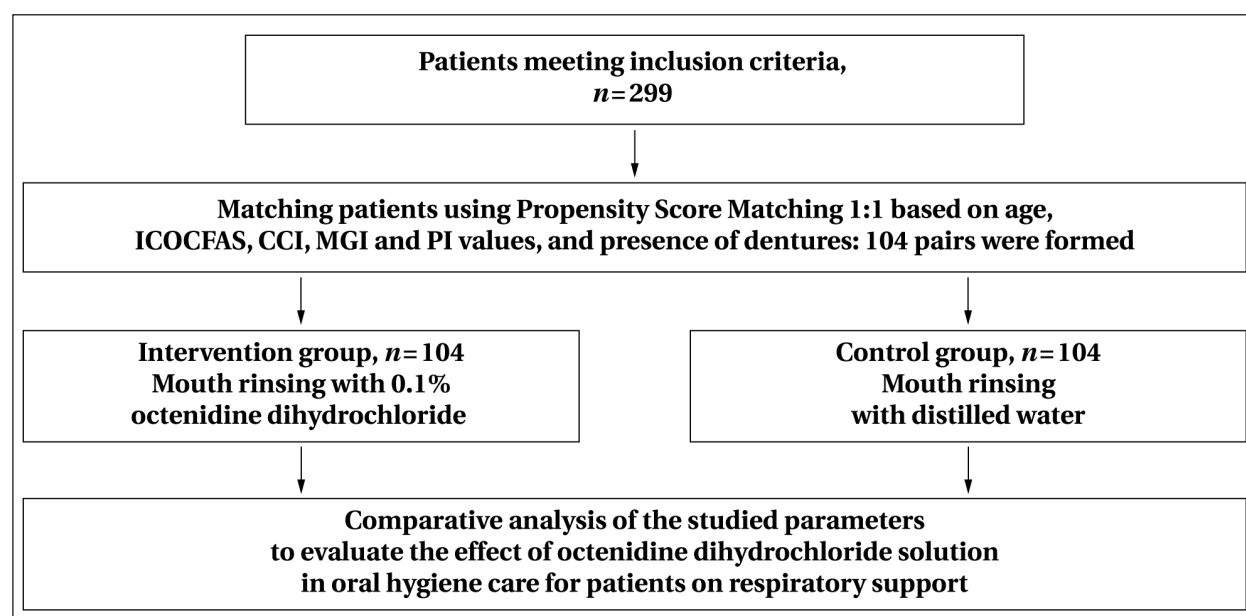


Fig. 1. Study scheme.

**Table 1. General characteristics of the groups after PSM.**

| Parameters                        | Parameter values in the groups |                         | <i>p</i> |
|-----------------------------------|--------------------------------|-------------------------|----------|
|                                   | Intervention, <i>n</i> = 104   | Control, <i>n</i> = 104 |          |
| Age, years, <i>Me</i> (Q1; Q3)    | 71 (60.75; 80)                 | 72 (63.75; 80.25)       | 0.813    |
| Gender, <i>f n</i> (%)            | 60 (57.7)                      | 56 (53.8)               | 0.577    |
| SOFA, score, <i>Me</i> (Q1; Q3)   | 8 (6; 10)                      | 8 (6; 12)               | 0.969    |
| CCI, score, <i>Me</i> (Q1; Q3)    | 7 (6; 8)                       | 7 (5.75; 8)             | 0.788    |
| ADHF, <i>n</i> (%)                | 89 (85.6)                      | 85 (81.7)               | 0.453    |
| DM, <i>n</i> (%)                  | 38 (36.5)                      | 42 (40.4)               | 0.569    |
| ECLD, <i>n</i> (%)                | 20 (19.2)                      | 20 (19.2)               | 1.0      |
| SCAP, <i>n</i> (%)                | 30 (28.8)                      | 27 (26)                 | 0.641    |
| GCS, <i>n</i> (%)                 | 22 (21.2)                      | 26 (25)                 | 0.51     |
| ABT, <i>n</i> (%)                 | 78 (75)                        | 76 (73.1)               | 0.752    |
| Anemia, <i>n</i> (%)              | 58 (55.8)                      | 60 (57.7)               | 0.78     |
| Dentures, <i>n</i> (%)            | 53 (51)                        | 55 (52.9)               | 0.781    |
| ICOCFAS, балл, <i>Me</i> (Q1; Q3) | 30 (26; 32)                    | 30 (27.75; 32)          | 0.862    |
| MGI, <i>Me</i> (Q1; Q3)           | 2.1 (1.8; 2.5)                 | 2.1 (1.8; 2.42)         | 0.824    |
| PI, <i>Me</i> (Q1; Q3)            | 2 (1.8; 2.12)                  | 2 (1.68; 2.2)           | 0.888    |
| CSCOD, <i>Me</i> (Q1; Q3)         | 6 (6; 7)                       | 6 (6; 7)                | 0.998    |

**Note.** SOFA — the Sequential Organ Failure Assessment score; CCI — Charlson Comorbidity Index; ADHF — acute decompensated heart failure; ECLD — exacerbation of chronic lung disease; SCAP — severe community-acquired pneumonia; DM — decompensated diabetes mellitus; GCS — glucocorticosteroids; ABT — antibacterial therapy. For Tables 1 and 4: ICOCFAS — Intensive Care Oral Care Frequency Assessment Scale. For Tables 1, 2, 4, and 5: MGI — Modified Gingival Index, Lobene; PI — Plaque Index; CSCOD — The Challacombe Scale of Clinical Oral Dryness.

**Table 2. Comparison of index changes across the study groups.**

| Parameters | Parameter values in the groups |                        | <i>p</i> $\Delta_{1-3}$ | Parameter values in the groups |                        | <i>p</i> $\Delta_{1-7}$ |
|------------|--------------------------------|------------------------|-------------------------|--------------------------------|------------------------|-------------------------|
|            | Intervention $\Delta_{1-3}$    | Control $\Delta_{1-3}$ |                         | Intervention $\Delta_{1-7}$    | Control $\Delta_{1-7}$ |                         |
| MGI        | -0.25 (-0.4; -0.2)             | 0 (-0.1; 0)            | <0.001                  | -0.4 (-0.75; -0.3)             | -0.1 (-0.1; 0.1)       | <0.001                  |
| PI         | -0.3 (-0.5; -0.1)              | -0.1 (-0.1; 0)         | <0.001                  | -0.5 (-0.8; -0.3)              | -0.1 (-0.2; 0)         | <0.001                  |
| CSCOD      | 0 (-1; 0)                      | 0 (-1; 0)              | 0.094                   | -1 (-2; 0)                     | -0.5 (-1; 0)           | 0.119                   |

**Note.** For Tables 2 and 3:  $\Delta_{1-3}$  and  $\Delta_{1-7}$  — indicate the change in the parameter between days in the ICU.

Pairwise correlations between the ICOCFAS scale and dental indices (MGI, PI, CSCOD) over time (on days 1, 3, and 7) were assessed using repeated-measures correlation (*rmcorr*). This approach made it possible to analyze within-subject associations over time while excluding the effect of between-subject variability. Results were presented as the repeated-measures correlation coefficient (*r<sub>rm</sub>*) and the two-tailed significance level (*p*). The strength of the correlation was interpreted as follows: *r<sub>rm</sub>* < 0.10 — essentially no association; 0.10–0.29 — weak; 0.30–0.49 — moderate; 0.50–0.69 — noticeable; 0.70–0.89 — high;  $\geq 0.90$  — very high. The direction of the association was determined by the sign of the coefficient. Differences and correlations were considered statistically significant at *p* < 0.05.

## Results

After PSM, the intervention and control groups were well balanced in terms of baseline clinical and dental characteristics: all key standardized mean differences were < 0.10. In addition, between-group differences in the analyzed parameters did not reach statistical significance (Table 1).

An analysis of changes in the indicators over the interval from day 1 to day 3 ( $\Delta_{1-3}$ ) demonstrated statistically significant between-group differences (Table 2). In the intervention group, a more pronounced reduction in the MGI and PI indices was observed (by 0.25 scores and 0.3 scores, respectively)

compared with the control group (*p* < 0.001). No statistically significant between-group differences were found in CSCOD dynamics over the  $\Delta_{1-3}$  interval. The median value in both groups remained at zero: 0 [0; 0] score in the intervention group and 0 [-1; 0] score in the control group (*p* = 0.094). By day 7 ( $\Delta_{1-7}$ ), the positive changes in the MGI and PI indices in the intervention group became more evident, and the differences between the compared groups remained highly significant (*p* < 0.001). Over the  $\Delta_{1-7}$  interval, changes in the CSCOD scale were relatively modest: the decrease of 1 score was documented in the intervention group versus 0.5 scores in the control group; however, no statistically significant between-group differences were observed (*p* = 0.119).

Fig. 2 shows the dynamics of the MGI index in the compared groups.

To assess whether the intervention effect depended on clinical outcome, we conducted an interaction analysis of «group × outcome», with unfavorable outcome serving as the reference category. In this model, the coefficient for the «group» variable characterizes the difference in MGI dynamics between groups specifically among patients with an unfavorable outcome. The interaction coefficient, in turn, shows how much this effect is amplified or attenuated in the case of a favorable outcome.

For the  $\Delta\text{MGI}_{1-3}$  measure, the group effect was statistically significant ( $\beta$  = -0.204; *p* = 0.005),

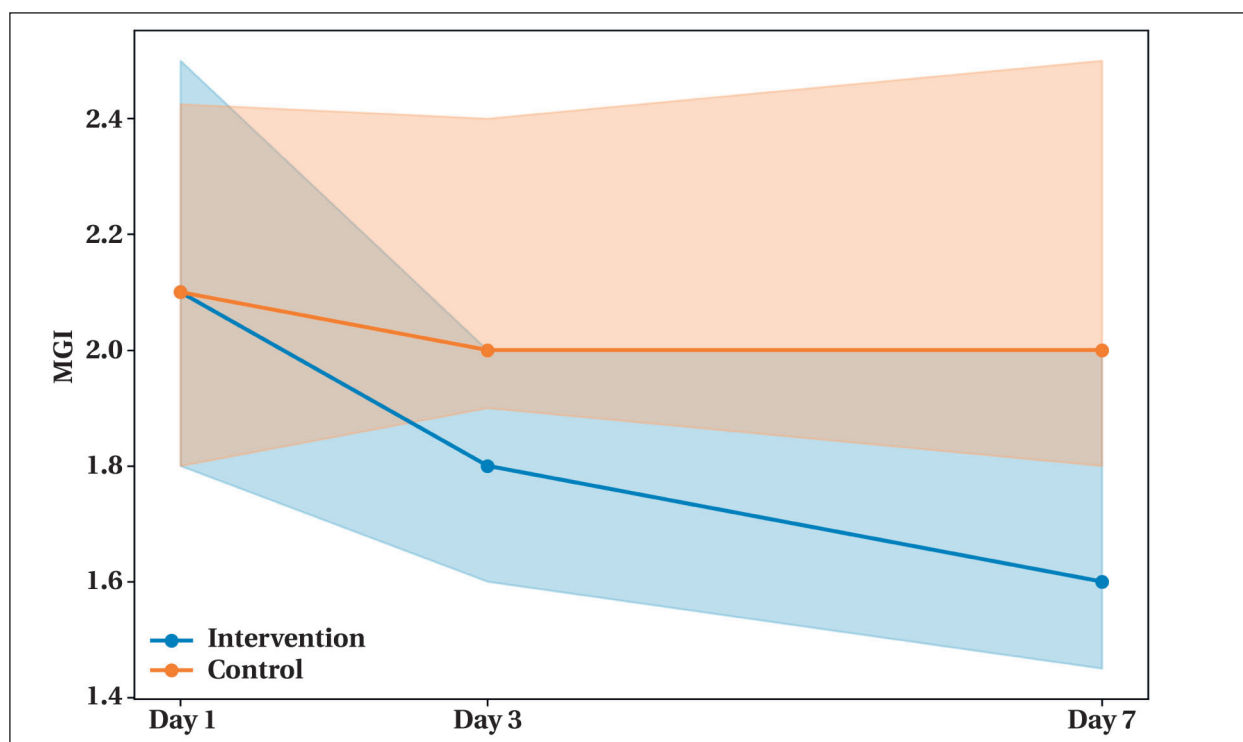


Fig. 2. Changes in the modified gingival index (MGI) in the study groups.

Table 3. Analysis of the interaction «group × vital outcome».

| End point                | <i>n</i> | $\beta$<br>of the group | <i>p</i><br>of the group | $\beta$ of interaction<br>«group × favorable outcome» | <i>p</i><br>of interaction |
|--------------------------|----------|-------------------------|--------------------------|-------------------------------------------------------|----------------------------|
| $\Delta\text{MGI}_{1-3}$ | 208      | -0.204                  | 0.005                    | -0.090                                                | 0.269                      |
| $\Delta\text{MGI}_{1-7}$ | 97       | -0.313                  | 0.012                    | -0.221                                                | 0.141                      |

Table 4. Assessment of correlation between indices and scales.

| Relationship between metrics | <i>r<sub>rm</sub></i> | 95% CI      | <i>p</i> | <i>df</i> | Observations, <i>n</i> | Patients, <i>n</i> | Interpretation |
|------------------------------|-----------------------|-------------|----------|-----------|------------------------|--------------------|----------------|
| ICOCFAS ~ MGI                | 0.613                 | 0.537–0.678 | < 0.001  | 304       | 513                    | 208                | Noticeable     |
| ICOCFAS ~ PI                 | 0.593                 | 0.514–0.661 | < 0.001  | 304       | 513                    | 208                | Noticeable     |
| ICOCFAS ~ CSCOD              | 0.548                 | 0.464–0.622 | < 0.001  | 303       | 511                    | 207                | Noticeable     |
| MGI ~ PI                     | 0.806                 | 0.763–0.842 | < 0.001  | 304       | 513                    | 208                | High           |
| MGI ~ CSCOD                  | 0.530                 | 0.444–0.606 | < 0.001  | 303       | 511                    | 207                | Noticeable     |
| PI ~ CSCOD                   | 0.515                 | 0.427–0.593 | < 0.001  | 303       | 511                    | 207                | Noticeable     |

Note. *r<sub>rm</sub>* — is the repeated-measures correlation coefficient; *df* — is the number of degrees of freedom.

which by day 3 was reflected in a more substantial reduction in the MGI index in the intervention group compared with the control group (Fig. 2). For the  $\Delta\text{MGI}_{1-7}$  measure, the group effect also persisted ( $\beta = -0.313$ ;  $p = 0.012$ ). No statistically significant «group × clinical outcome» interaction was identified, indicating that the intervention effect did not depend on the clinical outcome (Table 3).

All pairwise correlations between the MGI and PI indices and the ICOCFAS and CSCOD scales were statistically significant ( $p < 0.001$ ). The strongest association was found between MGI and PI ( $r_{rm} = 0.806$ ), while the remaining correlations were noticeable ( $r_{rm}$  ranging from 0.515 to 0.613) (Table 4).

No statistically significant inter-group differences were found for any of the analyzed complications or outcomes (Table 5). Severe xerostomia

syndrome (CSCOD  $\geq 6$  points) as a complication was recorded in 35% of patients. The incidence of LRTI was 1.9% in the intervention group and 5.8% in the control group ( $p = 0.279$ ).

All patients in the intervention group showed good tolerability of the 0.1% octenidine dihydrochloride solution; no allergic reactions or mucosal irritation were reported with the use of the mouthwash. No adverse events, such as burning, itching, or altered taste, were also observed.

## Discussion

The patient group under study lends particular importance to this issue: in elderly patients, age-related changes, comorbidity, and polypharmacy create a unique background for dental complications. The median age in the study groups was 72 (62; 80) years, and the median Charlson Comorbidity Index

**Table 5. Complications and clinical outcomes in patients with plaque-induced gingivitis.**

| Parameters                                           | Parameter values in the group |                         | <i>p</i> |
|------------------------------------------------------|-------------------------------|-------------------------|----------|
|                                                      | Intervention, <i>n</i> = 104  | Control, <i>n</i> = 104 |          |
| Complications                                        |                               |                         |          |
| Oral candidosis, <i>n</i> (%)                        | 13 (12.5)                     | 16 (15.4)               | 0.548    |
| Severe xerostomia syndrome (CSCOD I 6), <i>n</i> (%) | 36 (34.6)                     | 34 (32.7)               | 0.769    |
| LRTI, <i>n</i> (%)                                   | 2 (1.9)                       | 6 (5.8)                 | 0.279    |
| Outcomes                                             |                               |                         |          |
| Days on RS, <i>Me</i> (Q1; Q3)                       | 5 (3; 7)                      | 3 (3; 6)                | 0.114    |
| BD in ICU, <i>Me</i> (Q1; Q3)                        | 6 (4; 8)                      | 6 (4; 11)               | 0.13     |
| Lethal outcome, <i>n</i> (%)                         | 24 (23.1)                     | 22 (21.2)               | 0.738    |

**Note.** LRTI — lower respiratory tract infection; RS — respiratory support; BD — bed-day.

was 7 (6; 8) scores. Acute decompensation of chronic heart failure (ADCHF), which required the prescription of xerogenic medications (angiotensin-converting enzyme inhibitors/ARBs, diuretics, etc.), was identified in 174 (83.6%) patients; diabetes mellitus was present in 80 (38.4%). In this patient cohort, the use of xerogenic medications and glucocorticosteroids, poor oral hygiene, and the presence of prosthetic appliances all contribute to microbial colonization [21, 22].

According to a recent study conducted in Flanders, poor level of hygiene for removable dentures was documented in 68.5% of older adults living in nursing homes, with xerostomia being the leading complaint (32.8%) [23]. In the present study, prosthodontic dental appliances were present in 108 patients (51.9%), of whom 23 (21.2%) used removable appliances.

Xerostomia and immunosuppression further increase susceptibility to bacterial and fungal infections [21]. Microtrauma to the mucosal lining, triggered by changes in ventilation settings and alterations in the flow of the respiratory gas mixture, facilitates bacterial adhesion [24]. As a result, oral hygiene is difficult to maintain in critically ill elderly patients, which is accompanied by reduced microbial alpha diversity and an increase in pathogenic bacteria [25].

In a study by A. Gómez et al., among ICU patients, gingivitis was found in 54.5% of cases, ulcerative lesions in 45.4%, and xerostomia, caries, and periodontitis were observed in equal proportions (36.4%) [7]. In another study conducted among residents of nursing homes older than 80 years, the mean MGI score was  $1.8 \pm 1.2$ , with the score reaching 2.1 in 41% of cases [23].

Teeth brushing and the use of mouth rinses are basic hygiene procedures for patients receiving respiratory support [26]. In a study by Yao et al., twice-daily tooth brushing helped reduce the PI score [27], while in a study by Marino et al., a similar procedure was associated with lower GI and PI values [28]. At the same time, tooth brushing leads to a significant increase in the number of bacteria in saliva, so rinsing the oral cavity afterwards is mandatory [29].

The choice of a 0.1% octenidine dihydrochloride solution as a rinse was driven by its broad biocidal

activity, high clinical efficacy [11, 12], and favorable safety profile [30, 31]. The presence of multiple comorbidities in patients receiving respiratory support places stringent safety requirements on antiseptics. All patients reported good tolerance of the 0.1% octenidine dihydrochloride solution; no allergic reactions or signs of mucosal irritation (itching, burning, swelling) were observed, which is consistent with data from earlier studies [30, 31].

The frequency of oral mucosa irrigation was calculated according to the ICOCFAS scale [16]. The correlation analysis performed showed (Table 4) that the severity of the overall condition and the frequency of irrigations according to the ICOCFAS scale significantly correlated with the severity of gingivitis (MGI:  $r_{rm}=0.613$ ), dental plaque (PI:  $r_{rm}=0.593$ ), and xerostomia (CSCOD:  $r_{rm}=0.548$ ). As expected, the strongest association was found between dental plaque and gingival inflammation ( $r_{rm}=0.806$ ), which confirms the pathogenetic role of biofilm in the development of gingivitis, supports the use of octenidine, due to its strong anti-plaque effect, and is consistent with studies demonstrating its advantages over other antiseptics in reducing dental plaque and gingival inflammation [11, 30, 31]. In the present study, we showed that a 0.1% octenidine dihydrochloride solution provides a statistically significant reduction in the MGI and PI scores as early as on day 3 (Table 2), with a further increase in effect by day 7 ( $p < 0.001$ ). At the same time, the effect of octenidine (Table 3) on MGI did not depend on the clinical outcome ( $p=0.269$  for  $\Delta MGI_{1-3}$  and  $p=0.141$  for  $\Delta MGI_{1-7}$ ).

The reduction in the MGI and PI scores in the intervention group compared with the control group (Fig. 2) confirmed the advantage of the local protocol using a 0.1% octenidine dihydrochloride solution for eliminating hospital-acquired biofilm. These changes are critically important for preventing nosocomial infections, including lower respiratory tract infections, in patients on ventilatory support, because a compromised epithelial barrier serves as a potential portal of entry for microorganisms [32].

On day 7, plaque-induced gingivitis (MGI > 2.1 scores) was identified in 40% of patients receiving

respiratory support (40.4% in the intervention group versus 41.3% in the control group;  $p=0.88$ ). This finding does not contradict the statistically significant reduction in  $\Delta\text{MGI}_{1-7}$  observed in the intervention group described above, since it reflects not the dynamics of the process but the absolute prevalence of residual inflammatory signs.

At the same time, no statistically significant differences in the incidence of LRTI were found between the groups (Table 5): 1.9% in the intervention group vs. 5.8% in the control group ( $p=0.279$ ). The observed threefold trend toward a reduction in LRTI underscores the need for further multicenter studies with sample size calculations based on infectious outcomes.

The development of severe xerostomia syndrome in patients receiving respiratory support is due to a combination of factors: the use of pressurized oxygen-air mixtures, administration of xerogenic medications, and reduced salivary secretion in the setting of endotoxemia. Analysis of the data obtained showed that irrigation of the oral mucosa with a 0.1% octenidine dihydrochloride solution had no significant effect on the severity of xerostomia syndrome. Xerostomia (CSCOD) showed a weaker correlation with the MGI and PI values ( $r_{rm}=0.515-0.548$ ), indicating the stochastic nature of its association with the local inflammatory process (Table 4). The median CSCOD score during the first three days remained zero (Table 2) in both groups ( $p=0.094$ ), and by day 7 the reduction was minimal (1 score in the intervention group vs. 0.5 scores in the control group;  $p=0.119$ ). The persistence of xerostomia despite treatment in patients receiving respiratory support confirms the hypothesis that systemic (organ-related or pharmacological) factors play the dominant role in hyposalivation. A promising approach to correcting xerostomia may be the use of mucoadhesive moisturizing gels and/or moisturizing toothpaste that resist being washed away by saliva and provide prolonged protection of the epithelium [33].

## Supplement

**Table 1. Patient flow.**

| Stage                              | Total | Main group | Control group |
|------------------------------------|-------|------------|---------------|
| Initial analytical base            | 299   | 152        | 147           |
| Covariates available. PSM          | 276   | 137        | 139           |
| After PSM 1:1                      | 208   | 104        | 104           |
| Available $\Delta\text{MGI}_{1-3}$ | 208   | 104        | 104           |
| Available $\Delta\text{MGI}_{1-7}$ | 97    | 47         | 50            |

**Table 2. Covariate Balance.**

| Variable      | SMD  before PSM | SMD  after PSM |
|---------------|-----------------|----------------|
| ICOCFAS day 1 | 0,168           | 0,035          |
| Age           | 0,093           | 0,024          |
| CCI           | 0,025           | 0,006          |
| MGI day 1     | 0,046           | 0,029          |
| PI day 1      | 0,047           | 0,003          |
| SOFA          | 0,069           | 0,008          |
| Dentures      | 0,367           | 0,038          |
| CSCOD day 1   | 0,253           | 0,049          |

**Study limitations.** This study has several methodological limitations. First, the single-center design limits external validity, although it did help ensure consistency of protocols. Second, no comparative analysis by type of respiratory support was performed because NIPPV and HFOT were used in combination, and the subgroups receiving monotherapy were not sufficiently representative; any attempt at stratification would have created an unacceptable risk of false-negative results. Third, the limited sample size did not allow for a detailed assessment of infectious complications, and the short follow-up period (7 days) may not have captured long-term outcomes. Finally, despite the use of PSM, the prospective cohort design does not fully exclude residual confounding. Nevertheless, we believe that the internal validity of the study remains high, and the limitations listed above should be viewed as an impetus for larger multicenter studies.

## Conclusion

The identified strong correlation between changes in the dental plaque index and gingival inflammation ( $r_{rm}=0.806$ ) confirms that, in elderly ICU patients, the main etiopathogenetic factor in gingivitis is the microbial biofilm. This provides a pathophysiological rationale for the routine clinical use of antiseptics with targeted anti-plaque activity.

The use of a 0.1% octenidine dihydrochloride solution as part of an oral hygiene protocol in patients receiving respiratory support provides rapid reduction of gingival inflammation (decrease in MGI score) and effective removal of dental plaque (decrease in PI score) as early as day 3, with a greater effect by day 7.

The severity of xerostomia in patients receiving respiratory support persists regardless of the oral hygiene protocol, which calls for additional methods to manage it, including the use of mucoadhesive moisturizing gels and moisturizing toothpaste.

Table 3. Indices and Scales.

| № | Index/sale                                                                                                    | References                                                                                                                                                                                                                                                       |
|---|---------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | Modified Gingival Index — MGI                                                                                 | Lobene R. R., Weatherford T., Ross N. M., Lamm R. A., Menaker L. A modified gingival index for use in clinical trials // <i>Clinical Preventive Dentistry</i> . 1986. Vol. 8, No. 1. P. 3–6.                                                                     |
| 2 | Plaque Index — PI, Silness-Loe, 1964                                                                          | Löe H. The Gingival Index, the Plaque Index and the Retention Index Systems. <i>J Periodontol</i> . 1967; 38 (6): Suppl: 610-6. doi: 10.1902/jop.1967.38.6.610. PMID: 5237684.                                                                                   |
| 3 | Xerostomia severity scale — Challacombe Scale of Clinical Oral Dryness — CSCOD, Challacombe S.J. et al., 2008 | Osailan S.M., Pramanik R., Shirlaw P., Proctor G.B., Challacombe S.J. Clinical assessment of oral dryness: development of a scoring system related to salivary flow and mucosal wetness. <i>Oral Surg Oral Med Oral Pathol Oral Radiol</i> . 2012; 114: 597–603. |
| 4 | Intensive Care Oral Care Frequency Assessment Scale, ICOCFAS, 2022                                            | Doğu Kökcü Ö., Terzi B. Development of an intensive care oral care frequency assessment scale. <i>Nursing in critical care</i> . 2022; 27 (5): 667–675. DOI: 10.1111/nicc.12529. PMID: 32633044.                                                                 |

## References

- Candel F.J., Salavert M., Estella A., Ferrer M., Ferrer R., et al. Ten Issues to Update in Nosocomial or Hospital-Acquired Pneumonia: An Expert Review. *Journal of clinical medicine*. 2023; 12 (20): 6526. DOI: 10.3390/jcm12206526. PMID: 37892664.
- Кузовлев А.Н., Мороз В.В. Нозокомиальная пневмония — принципы ранней диагностики и профилактики. *Вестник интенсивной терапии имени А.И. Салтанова*. 2019; 2: 40–47. Kuzovlev A.N., Moroz V.V. Nosocomial pneumonia — principles of early diagnosis and prevention. *Annals of Critical Care*. 2019; (2): 40–47. (in Russ.). DOI: 10.21320/1818-474X-2019-2-40-47.
- Satheeshkumar P.S., Papatheodorou S., Sonis S. Enhanced oral hygiene interventions as a risk mitigation strategy for the prevention of non-ventilator-associated pneumonia: a systematic review and meta-analysis. *Br Dent J*. 2020; 228 (8): 615–622. DOI: 10.1038/s41415-020-1452-7. PMID: 32332964.
- Jun M.K., Ku J.K., Kim I.H., Park S.Y., Hong J., et al. Hospital Dentistry for Intensive Care Unit Patients: A Comprehensive Review. *J Clin Med*. 2021; 10 (16): 3681. DOI: 10.3390/jcm10163681. PMID: 34441976.
- Kitsios G.D., Sayed K., Fitch A., Yang H., Britton N., et al. Prognostic Insights from Longitudinal Multicompartment Study of Host-Microbiota Interactions in Critically Ill Patients. *medRxiv [Preprint]*. 2023; 26. DOI: 10.1101/2023.09.25.23296086. PMID: 37808745; PMCID: PMC10557814.
- Бизязев А.А., Коннов В.В., Поспелов А.Н., Кречетов С.А., Маслеников Д.Н., Прошин А.Г. Особенности гигиенического ухода за съемными протезами из термопластов. *Актуальные проблемы медицины*, 2024; 47 (1): 64–71. DOI: 10.52575/2687-0940-2024-47-1-64-71. Bizyayev A.A., Konnov V.V., Pospelov A.N., Krechetov S.A., Maslennikov D.N., Proshin A.G. Features of hygienic care of removable dentures made of thermoplasts. *Current Issues in Medicine*. 2024; 47 (1): 64–71. (in Russ.). DOI: 10.52575/2687-0940-2024-47-1-64-71.
- Aranda Gómez M.P., Chaparro Torres E., Hernández Abahunza N.D., Vargas Carreño A.C., Herrera Sandoval L.V., Castellanos Domínguez Y.Z. Oral findings of patients in the intensive care unit: a systematic review. *Rev Cuid*. 2025; 27: 16 (1): e3959. DOI: 10.15649/cuidarte.3959. PMID: 40529943.
- Байкулова М.Д., Разумова С.Н., Браго А.С., Утц Н.В., Баракат Х.Б., Разумов Н.М., Мяндиев М.С. Методы гигиены полости рта тяжелобольных пациентов в условиях реанимации и интенсивной терапии. Обзор литературы. *Российский стоматологический журнал*. 2024; 28 (4): 420–431. Baykulovala M.D., Razumova S.N., Brago A.S., Utz N.V., Barakat H.B., Razumov N.M., Myandiev M.S. Oral hygiene for severe care: a literature review. *Russian Journal of Dentistry*. 2024; 28 (4): 420–431. (in Russ.). DOI: 10.17816/dent633055.
- Rezaei S., Rezaei K., Mahboubi M., Jarahzadeh M.H., Momeni E., et al. Comparison the efficacy of herbal mouthwash with chlorhexidine on gingival index of intubated patients in Intensive Care Unit. *J Indian Soc Periodontol*. 2016; 20 (4): 404–408. DOI: 10.4103/0972-124X.194269. PMID: 28298822.
- Al-Maweri S.A., Nassani M.Z., Alaizari N., Kalakonda B., Al-Shamiri H.M., et al. Efficacy of aloe vera mouthwash versus chlorhexidine on plaque and gingivitis: A systematic review. *Int J Dent Hyg*. 2020; 18 (1): 44–51. DOI: 10.1111/idh.12393. PMID: 30829440.
- Amrita A., Agarwal P., Agarwal M.C., Agarwal A., Garg J., et al. Comparative Evaluation of Oc-tenidine with Chlorhexidine Mouthwash in Gingivitis and Periodontitis Patients: A Randomized Clinical Trial. *Journal of pharmacy & bioallied sciences*. 2024; 16 (Suppl 1): S789–S791.

- DOI: 10.4103/jpbs.jpbs\_1011\_23.  
PMID: 38595450.
12. Сабанцева Е.Г., Дмитриева Н.А., Авраменко Е.А., Иванова Е.В., Ежова Е.Г., Почивалин В.П. Оценка эффективности применения ополаскивателя, содержащего антисептик октенидина дигидрохлорид. *Стоматология*. 2021; 100 (2): 32–39. Sabanceva E.G., Dmitrieva N.A., Avramenko E.A., Ivanova E.V., Ezhova E.G., Pochivalin V.P. Evaluation of effectiveness of a mouthwash containing antiseptic octenidine dihydrochloride. *Stomatology*. 2021; 100 (2): 32–39. (In Russ.) DOI: 10.17116/stomat202110002132. PMID: 33874658.
  13. Kelly N., Blackwood B., Credland N., Stayt L., Causey C., et al. Oral health care in adult intensive care units: A national point prevalence study. *Nurs Crit Care*. 2023; 28 (5): 773–780. DOI: 10.1111/nicc.12919. PMID: 37125669.
  14. Jun M.K., Ku J.K., Kim I.H., Park S.Y., Hong J., et al. Hospital Dentistry for Intensive Care Unit Patients: A Comprehensive Review. *J Clin Med*. 2021; 10 (16): 3681. DOI: 10.3390/jcm10163681. PMID: 34441976.
  15. Ames N.J., Sulima P., Yates J.M., McCullagh L., Gollins S.L., Soeken K., Wallen G.R. Effects of systematic oral care in critically ill patients: a multicenter study. *American journal of critical care: an official publication. American Association of Critical-Care Nurses*. 2011; 20 (5): e103–14. DOI: 10.4037/ajcc2011359. PMID: 21885453.
  16. Dođu Kökcü Ö., Terzi B. Development of an intensive care oral care frequency assessment scale. *Nursing in critical care*. 2022; 27 (5): 667–675. DOI: 10.1111/nicc.12529. PMID: 32633044.
  17. He T, Qu L, Chang J, Wang J. Gingivitis Models — Relevant Approaches to Assess Oral Hygiene Products. *J Clin Dent*. 2018; 29 (2): 45–51. PMID: 30211990.
  18. Turesky S., Gilmore N.D., Glickman I. Reduced plaque formation by the chloromethyl analogue of vitamin C. *J Periodontol*. 1970; 41 (1): 41–43. DOI: 10.1902/jop.1970.41.41.41. PMID: 5264376.
  19. Henriksen B.M., Ambjørnsen E., Axéll T.E. Evaluation of a mucosal-plaque index (MPS) designed to assess oral care in groups of elderly. *Spec Care Dentist*. 1999; 19 (4): 154–157. DOI: 10.1111/j.1754-4505.1999.tb01378.x. PMID: 10765880.
  20. Бабина К.С., Боровский Е.В., Макеева И.М. Выбор метода индексной оценки гигиенического состояния полости рта. *Сеченовский вестник*. 2013; 1 (11): 10–14. Babina, K.S., Borovsky, E.V., Makeeva, I.M. Choice of a method for index assessment of the hygienic state of the oral cavity. *Sechenov Medical Journal*. 2013; 1 (11): 10–14. (in Russ.).
  21. Петрова Т.Г., Обухова Л.Д., Герасименко О.Н., Зверева Т.В., Рагимова Т.М. Клиническая оценка проявлений ксеростомического синдрома у лиц пожилого и старческого возраста. *Пародонтология*. 2023; 28 (4): 380–388. Petrova T.G., Obukhova L.D., Gerasimenko O.N., Zvereva T.V., Ragimova T.M. Clinical evaluation of xerostomia manifestations in young-old and middle-old age. *Parodontologiya*. 2023; 28 (4): 380–388 (in Russ.). DOI: 10.33925/1683-3759-2023-834
  22. Gonsalves, W. C., Wrightson, A. S., Henry, R. G. Common oral conditions in older persons. *American family physician*. 2008; 78 (7): 845–852. PMID: 18841733.
  23. Vandenbulcke P.A.I., de Almeida Mello J., Schoebrechts E., De Lepeleire J., Declercq A., Declerck D., Duyck J. Oral health of nursing home residents in Flanders, Belgium, and its associated factors. *Sci Rep*. 2025; 14: 15 (1): 5463. DOI: 10.1038/s41598-025-89910-4. PMID: 39953136; PMCID: PMC11829024.
  24. Luo F, Shi W, Fan X, Zhou M, Shen F, Zhu H, Zhu J, et al. Impact of non-invasive ventilation on microbial colonisation patterns in preterm infants: a single-centre study. *BMJ Paediatr Open*. 2024; 8 (1): e002783. DOI: 10.1136/bmjpo-2024-002783. PMID: 39489525.
  25. Rathbun K.P., Sole M.L., Yooseph S., Xie R., Borgault A.M., et al. Oral Microbiome Changes During Hospitalization in Older Adults Not Receiving Mechanical Ventilation. *Am J Crit Care*. 2025; 34 (3): 208–217. DOI: 10.4037/ajcc2025470. PMID: 40307181.
  26. Collins T, Plowright C., Gibson V, Stayt L., Clarke S., et al. British Association of Critical Care Nurses: Evidence-based consensus paper for oral care within adult critical care units. *Nursing in critical care*. 2021; 26 (4): 224–233. DOI: 10.1111/nicc.12570. PMID: 33124119.
  27. Yao L.Y., Chang C.K., Maa S.H., Wang C., Chen C.C. Brushing teeth with purified water to reduce ventilator-associated pneumonia. *J Nurs Res*. 2011; 19 (4): 289–297. DOI: 10.1097/JNR.0b013e318236d05f. PMID: 22089654.
  28. Marino P.J., Hannigan A., Haywood S., Cole J.M., Palmer N., et al. Comparison of foam swabs and toothbrushes as oral hygiene interventions in mechanically ventilated patients: a randomised split mouth study. *BMJ Open Respir Res*. 2016; 3 (1): e000150. DOI: 10.1136/bmjresp-2016-000150. PMID: 27843549.
  29. Funahara M., Yamaguchi R., Honda H., Matsuo M., Fujii W, et al. Factors affecting the number of bacteria in saliva and oral care methods for the recovery of bacteria in contaminated

- saliva after brushing: a randomized controlled trial. *BMC Oral Health*. 2023; 23 (1): 917. DOI: 10.1186/s12903-023-03676-7. PMID: 38001433.
30. Köck R., Denkel L., Feßler A.T., Eicker R., Mellmann, A., et al. Clinical Evidence for the Use of Octenidine Dihydrochloride to Prevent Healthcare-Associated Infections and Decrease *Staphylococcus aureus* Carriage or Transmission — *Pathogens* 2023; 12 (4): 612. DOI: 10.3390/pathogens12040612. PMID: 37111498. PMCID: PMC10145019.
  31. Jockel-Schneider Y., Schlagenhauf U., Petsos H., Rüttermann S., et al. Impact of 0.1% octenidine mouthwash on plaque re-growth in healthy adults: a multi-center phase 3 randomized clinical trial. *Clinical oral investigations*. 2021; 25 (7): 4681–4689. DOI: 10.1007/s00784-021-03781-3. PMID: 33483868.
  32. Zhao T., Wu X., Zhang Q., Li C., Worthington H.V., et al. Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia. *Cochrane Database Syst Rev*. 2020; 12 (12): CD008367. DOI: 10.1002/14651858.CD008367.pub4. PMID: 33368159.
  33. Руслякова И.А., Хромова Е.А., Захарова Е.А., Кулик И.В., Глуценко В.А., Силин А.В. Случай эффективного лечения орального мукозита, ассоциированного с противоопухолевой терапией, у пациента в критическом состоянии. *Вестник Северо-Западного государственного медицинского университета им. И.И. Мечникова*. 2025; 17 (4): 89–98. DOI: 10.17816/mechnikov676905. Ruslyakova I.A., Khromova E.A., Zakharova E.A., Kulik I.V., Glushchenko V.A., Silin A.V. A case of effective treatment of oral mucositis associated with antitumor therapy in a critically ill patient. *HERALD of North-Western State Medical University named after I.I. Mechnikov*. 2025; 17 (4): 89–98. DOI: 10.17816/mechnikov676905

Received 06.05.2026

Accepted 08.07.2026

# Effect of Hypothermia on the Expression of Brain Injury Marker Proteins in the Presence of Interleukin-6 and Anoxia *in vitro*

Artem A. Ivkin<sup>1\*</sup>, Elena D. Khilazheva<sup>1</sup>, Evgeniy V. Grigoriev<sup>2</sup>, Angelina I. Mosyagina<sup>2</sup>

<sup>1</sup> Research Institute of Complex Problems of Cardiovascular Disease, Ministry of Education and Science of the Russian Federation, 6 Academician L. S. Barbarash Boulevard, 650002 Kemerovo, Russia

<sup>2</sup> Prof. V. F. Voyno-Yasenetsky Krasnoyarsk State Medical University, Ministry of Health of Russia, 1 Partizana Zheleznyaka Str., 660022 Krasnoyarsk, Krasnoyarsk area, Russia

**For citation:** Artem A. Ivkin<sup>1</sup>, Elena D. Khilazheva, Evgeniy V. Grigoriev, Angelina I. Mosyagina. Effect of Hypothermia on the Expression of Brain Injury Marker Proteins in the Presence of Interleukin-6 and Anoxia *in vitro*. *Obshchaya Reanimatologiya = General Reanimatology*. 2026; 22 (4): 38–46. <https://doi.org/10.15360/1813-9779-2026-4-2695> [In Russ. and Engl.]

\*✉ Artem A. Ivkin, [ivkiaa@kemcardio.ru](mailto:ivkiaa@kemcardio.ru)

## Summary

Hypothermia has long been used in cardiac surgery for neuroprotection; however, its effectiveness is not clear-cut.

**Objective of the study:** to investigate the neuroprotective potential of hypothermia under conditions of hypoxia and interleukin-6, which simulates systemic inflammation *in vitro*.

**Materials and methods.** We established an *in vitro* model of a neurovascular unit (NVU) consisting of neurons, astrocytes, and endothelial cells. The NVU was cultured under anoxic conditions with the addition of serum containing either the maximum or minimum concentration of interleukin-6 (IL-6). Serum samples were obtained from a collection of serum samples from 78 pediatric patients aged 1 month to 6.5 years (13 [9–23] months) with body weights ranging from 3.3 to 21.5 kg (8.7 [6.9–11.0] kg), who underwent surgical correction of congenital septal heart defects under cardiopulmonary bypass. An intact NVU model was used as the control group. Cells were incubated for 15 minutes at different temperatures (20, 24, 28, and 37°C), followed by immunocytochemical assessment of the following NVU damage markers expression: claudin-5, occludin-1, and receptors for interleukin-1 (IL-1) and IL-6.

**Results.** We found that, during incubation under anoxic conditions, a decrease in the fluorescence intensity of claudin-5 occurred at all temperature conditions, and hypothermia had no protective effect. For occludin-1, a temperature of 24°C counteracted the effect of anoxia only when exposed to serum with the minimum IL-6 concentration ( $p=0.442$ ). Exposure to serum with the maximum IL-6 concentration resulted in a significant decrease in the fluorescence intensity of this marker compared to the control group ( $p=0.092$ ). Hypothermia at 20°C did not restore the expression levels of IL-1 receptors to those of the control group; however, it had a protective effect on the expression of IL-6 receptors and neutralized the effects of anoxia ( $p=0.044$ ), but only in the absence of serum.

**Conclusion.** Exposure to serum containing varying concentrations of IL-6 results in a more pronounced effect on the expression of NVU damage markers than hypoxia. Hypothermia within the temperature range studied generally did not provide the expected protective effect: the expression of claudin-5, IL-1 and IL-6 receptors was not comparable to that of the control group, even without the addition of serum.

**Keywords:** hypothermia; cerebral injury; interleukin-6; anoxia; occludin-1; claudin-5; interleukin-1 receptors; neurovascular unit; NVU; septal congenital heart defects in children

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

## Информация об авторах / Information about the authors:

Ивкин Артем Александрович / Artem A. Ivkin, <https://orcid.org/0000-0002-3899-1642>

Григорьев Евгений Валерьевич / Evgeniy V. Grigoriev, <https://orcid.org/0000-0001-8370-3083>

Хилажева Елена Дмитриевна / Elena D. Khilazheva, <https://orcid.org/0000-0002-9718-1260>

Мосягина Ангелина Ивановна / Angelina I. Mosyagina, <https://orcid.org/0000-0002-7344-7925>

## Introduction

The role of hypothermia in organ protection was first described by W.G. Bigelow et al. in 1950, following an experimental study in dogs: the authors induced cardiac arrest in the animals while cooling them to 20°C for 15 minutes, followed by the restoration of vital functions [1]. In cardiac surgery, hypothermia was first used by F.J. Lewis to correct an atrial septal defect in a child [2]. Thus, hypothermia has been used for organ protection in cardiac surgery for many years, but to date, its efficacy and safety

remain largely under-researched, especially with regard to its neuroprotective effects.

The effects of hypothermia on the neurovascular unit (NVU) — composed of neurons, astrocytes, and endothelial cells — are versatile and include the following:

- Decreased cerebral metabolism: Brain metabolic activity decreases by 5–7% for every 1°C drop in temperature. This leads to a reduction in oxygen and glucose consumption, the conservation of high-energy phosphates (ATP, ADP), and the maintenance

of ion gradients, which allows for an extension of the period during which the brain can tolerate complete ischemia without irreversible damage [3].

- **Suppression of excitotoxicity:** hypothermia directly inhibits the presynaptic release of excitatory neurotransmitters (glutamate, aspartate) and prevents calcium ion overload in neurons via NMDA receptors — a key link in the ischemic cascade — while also modulating postsynaptic receptors, thereby reducing the subsequent activation of lipases and endonucleases [4].

- **Modulation of apoptosis:** Hypothermia affects intrinsic apoptotic pathways by inhibiting caspase activation, the release of cytochrome C from mitochondria, and the expression of pro-apoptotic proteins, while simultaneously stimulating the synthesis of anti-apoptotic factors [5].

- **Suppression of the inflammatory response:** Hypothermia inhibits microglial activation and the release of pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6) as well as chemokines, thereby limiting neuroinflammation and damage to the blood-brain barrier (BBB) [6].

- **Reduction of reactive oxygen species (ROS) formation:** massive ROS formation occurs during reperfusion. Hypothermia reduces ROS generation and modulates the activity of antioxidant enzymes, such as superoxide dismutase, thereby reducing oxidative stress [7].

- **In astrocytes,** hypothermia reduces the activity of the astroglial glutamate transporter EAAT2, preventing its reverse transport and thereby inhibiting further glutamate release under excitotoxic conditions [8].

- **Hypothermia stabilizes the BBB** by reducing the expression of adhesion molecules on endothelial cells and inhibiting the activity of matrix metalloproteinases to limit leukocyte infiltration and cerebral edema [5].

**Clinical and experimental studies on the efficacy of hypothermia.** Studies have shown that deep hypothermia (18°C) significantly preserves high-energy phosphates and intracellular pH, delaying the onset of ischemic damage to the cerebral cortex, basal ganglia, and hippocampus compared to normothermia [9]. According to a systematic review with a meta-analysis, hypothermia not only preserves energy status but also significantly improves functional neurological outcomes and reduces the histopathological extent of brain damage following ischemia [10].

A separate issue is the effect of hypothermia on systemic inflammation. Given its significant role in cerebral injury, it is worth noting a clinical study involving pediatric patients, which found that the use of hypothermia at 27°C initially reduced the concentration of L-selectin, but after 30 minutes, its concentration was comparable to that in the group of subjects undergoing hypothermia at 33°C [11].

In one of the largest and longest-running randomized controlled trials, the Boston Circulatory Arrest Study, strategies involving deep hypothermia with circulatory arrest were compared with deep hypothermia with continuous cardiopulmonary bypass in children undergoing correction of transposition of the great arteries. The results showed that although the circulatory arrest strategy was technically much more convenient for the surgeon, it was associated with a higher risk of postoperative seizures and poorer long-term outcomes in terms of motor development and speech function compared with continuous low-volume perfusion [12]. This suggests that circulatory arrest itself, even under conditions of deep hypothermia, carries significant risks.

Current clinical practices have shifted away from elective hypothermic cardiopulmonary bypass in favor of continuous cerebral perfusion under conditions of moderate (25–32°C) or deep hypothermia. This approach has been shown to be associated with better neurological outcomes, a reduced incidence of postoperative seizures, and lower rates of postoperative cognitive dysfunction [13].

Some researchers even advocate abandoning hypothermia in favor of normothermia with continuous cerebral perfusion. For example, in a study by Caputo M. et al. [14], a comparison was conducted between two groups of children—one undergoing CPB under normothermic conditions and the other under hypothermia at 28°C — and it was found that the groups were comparable in terms of the severity of brain NVU injury, as well as the duration of their subsequent stay in the intensive care unit.

Another study with a similar design showed, however, that the hypothermia group had a significantly higher need for transfusions, as well as longer durations of mechanical ventilation and ICU stay [15].

Researchers at Texas Children's Hospital suggested that moderate hypothermia may be just as effective for neuroprotection during certain types of surgery, and with fewer side effects associated with deep hypothermia [16]. It demonstrates that the optimal temperature range remains a subject of debate.

The aim of this study was to investigate the neuroprotective potential of hypothermia under conditions of hypoxia and interleukin-6, which simulates systemic inflammation *in vitro*.

## Materials and Methods

The clinical part of the study and the collection of patient serum samples were conducted at the Research Institute for Complex Problems of Cardiovascular Diseases (RI CPCD, Kemerovo, Russia) from 2018 to 2023. The experimental part of the study was conducted at the Krasnoyarsk State Medical University named after Professor V. F. Voino-Yasenetsky, Ministry of Health of Russia (KrasSMU). The study

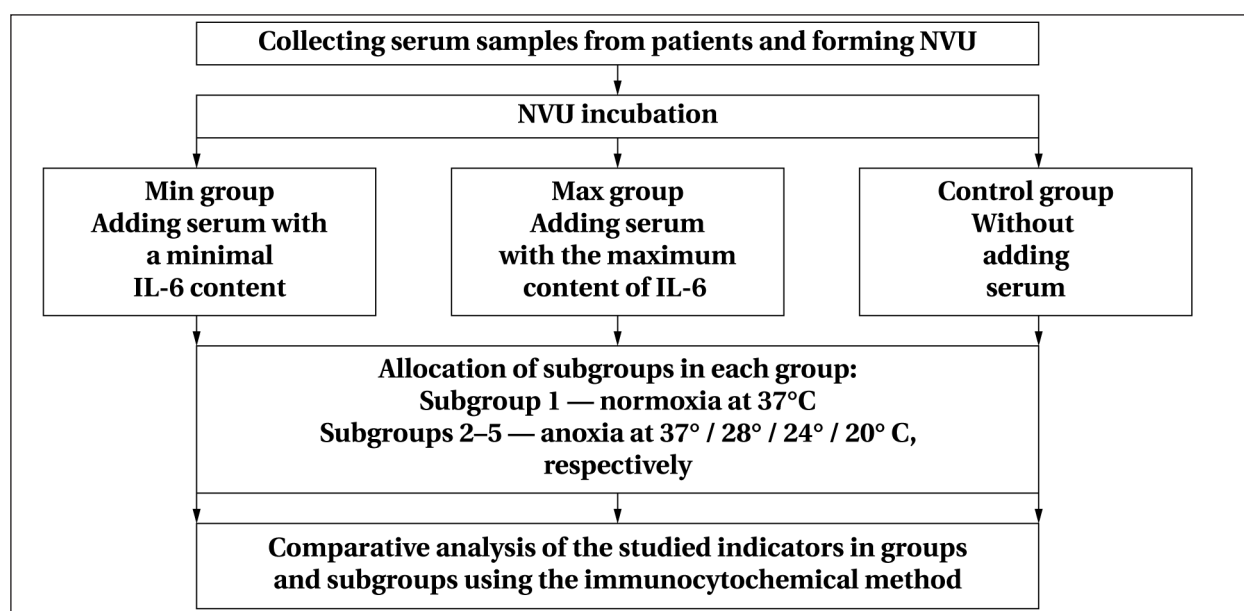


Fig. 1. Study scheme.

was approved by the local ethics committee of the RI CPCD (Protocol No. 20 dated November 20, 2018). The study design is presented in Fig. 1.

**A cellular model of the neurovascular unit.** A Transwell cellular model of the NVU was used, containing a semipermeable membrane insert 10  $\mu\text{m}$  thick. The insert forms two chambers: an outer upper (luminal) chamber and an inner lower (ablu-minal) chamber, located between the insert and the bottom of the well. This design mimics the lumen of a blood vessel and allows for the study of the mechanisms of blood-brain barrier (BBB) permeability [17, 18]. The inner chamber contains cells that mimic brain tissue — astrocytes and neurons — which are located on the underside of the membrane and at the bottom of the well. A schematic representation of the Transwell model is shown in Fig. 2.

The establishment of the NVU cellular model involved four steps:

1. Isolation of cerebral endothelial cells.
2. Isolation and cultivation of neurospheres.
3. Isolation of astrocytes and neurons from the obtained neurospheres via directed differentiation into astrocytes and neurons.
4. Forming of the NVU model. To do this, a mixture of endothelial cells and neurons was placed at the bottom of the wells of a culture plate, followed by the insertion of culture inserts (Corning-Costar, USA), onto which astrocytes were placed. The cell mixture was cultured a medium consisting of DMEM with FBS, glutamine, and a mixture of antibiotics at 37°C with 5%  $\text{CO}_2$ .

**Isolation of primary brain cell cultures.** We used primary cultures of brain endothelial cells, astrocytes, and neurons isolated from Wistar rats. The animals were housed in cages with free access

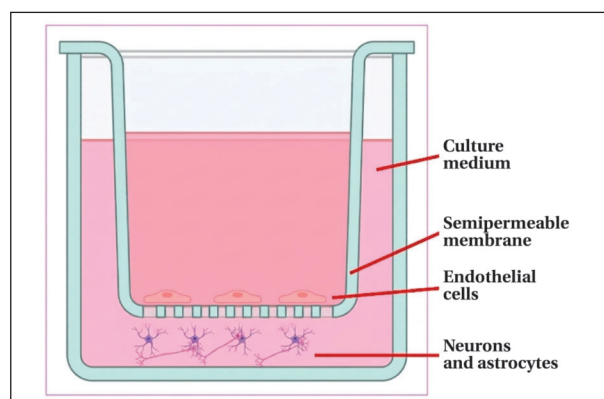


Fig. 2. Cellular model of the neurovascular unit (figure by the authors).

to food and water. The temperature was maintained at a constant  $21 \pm 1^\circ\text{C}$ . The light-dark cycle was 12 hours light/12 hours dark. Animal experiments were conducted in accordance with the principles of animal welfare set forth in the European Union Directive (2010/63/EU) [19]. The total number of animals was  $n = 10$ .

At the Krasnoyarsk State Medical University laboratory, a model of brain injury during cardiac surgery was developed based on the NVU cell model; this model can be cultured under various conditions that mimic factors of the intraoperative period.

**Serum samples.** The authors have a collection of serum samples from 78 pediatric patients — ranging in age from 1 month to 6.5 years (13 [9–23] months) with body weights ranging from 3.3 to 21.5 kg (8.7 [6.9–11.0] kg), who underwent surgical correction of congenital septal heart defects under cardiopulmonary bypass (CPB) at the RI CPCD.

The inclusion criteria for patients in the study were as follows: elective surgery for correction of a congenital heart defect (atrial or ventricular septal defect) under CPB, the presence of informed consent for participation in the study signed by the child's legal representative, and the child's age ranging from 1 month to 7 years; body weight ranging from 3 to 25 kg (the «Serum Samples» subsection provides actual data on the patients included in the study).

**Exclusion criteria:** emergency and urgent surgical procedures; the presence of clinically significant anemia, hypothermic CPB, or episodes of desaturation during the perioperative period; the presence of congenital heart defects other than atrial or ventricular septal defects, as well as combinations thereof; a history of central nervous system disorders; an implanted pacemaker; hemodynamic instability requiring preoperative pharmacological and/or mechanical support; any history of cerebrovascular events or such events in the perioperative period; the presence of severe comorbidities that impair mental and physical status; acute infection or exacerbation of a chronic infection in the perioperative period; concomitant autoimmune diseases; presence of malignant neoplasms; and surgical complications in the postoperative period.

The concentration of interleukin-6 (IL-6), one of the main markers of the systemic inflammatory response (SIR), was evaluated in each serum sample [20].

For the *in vitro* study, three serum samples each with the highest and lowest IL-6 concentrations were selected from the available collection, as they reflected the highest and lowest levels of SIR, respectively. The frozen serum was transported to KrasSMU under controlled temperature conditions.

**Study groups.** To determine the effects of IL-6 on the cellular model of NVU, serum mixed from three samples with the lowest IL-6 concentration or mixed from three samples with the highest IL-6 concentration was added to the culture medium.

Groups were formed based on the concentration of IL-6 in the serum.

1. «Control» group — intact NVU model.
2. «Minimum» (Min) group — addition of a mixture of serum samples with the lowest IL-6 content to the culture.
3. «Maximum» (Max) group — addition of a mixture of serum samples with the highest IL-6 content to the culture.

To determine the effects of hypothermia under anoxic conditions, the following subgroups were formed for each group:

1. Normoxia 37°: standard culture conditions, N<sub>2</sub> 75%, O<sub>2</sub> 20%, CO<sub>2</sub> 5%, t = 37°C.
2. Anoxia 37°: N<sub>2</sub> 95%, O<sub>2</sub> 0%, CO<sub>2</sub> 5%, t = 37°C.
3. Anoxia 28°: N<sub>2</sub> 95%, O<sub>2</sub> 0%, CO<sub>2</sub> 5%, t = 28°C.
4. Anoxia 24°: N<sub>2</sub> 95%, O<sub>2</sub> 0%, CO<sub>2</sub> 5%, t = 24°C.
5. Anoxia 20°: N<sub>2</sub> 95%, O<sub>2</sub> 0%, CO<sub>2</sub> 5%, t = 20°C.

Anoxia and hypothermia conditions were established in the HypoxyLab hypoxic chamber (Oxford Optronix, UK). Plates containing cell cultures were placed in the chamber, which had been preset to specific temperature and oxygen levels. The duration of exposure to anoxia and hypothermia was 15 minutes. Immediately after exposure, the cells were fixed with a 4% formaldehyde solution and subsequently analyzed by immunocytochemistry for marker molecules. The number of observations per group was 5 wells per group. At least 5 fields of view were analyzed in each well.

**Immunocytochemical studies.** To detect target marker molecules, we used a double indirect immunocytochemical staining method in accordance with the antibody manufacturer's protocol. Cells were fixed with 4% formaldehyde solution in PBS for 15 minutes. Permeabilization was performed with a 0.25% solution of Triton X-100 in PBS for 5 minutes at room temperature. Blocking of non-specific binding was performed in a 10% solution of BSA in PBS for 30 minutes at 37°C. Primary antibodies used included those against GFAP (ab4648, Abcam), NeuN (ABN78, Merck Millipore), VWF (LS-B4034, LSBio), Claudin-5 (AF0130, Affinity Biosciences), ZO1 (AF5145, Affinity Biosciences), Interleukin-1 Receptor Type I (PAA066Ra01, Cloud-Clone Corp), Interleukin-6 Receptor (DF2530, Affinity Biosciences), TNF Receptor I (AF0282, Affinity Biosciences), and TNF Receptor II (AF0364, Affinity Biosciences). The primary antibodies were used at a working dilution of 1:200. The incubation time with the primary antibodies was 18 hours at 4°C. FITC-labeled secondary antibodies (SAA544Rb58, Cloud-Clone Corp.) were used at a dilution of 1:400, with an incubation time of 2 hours at 37°C.

Cell microscopy was performed using a ZOE fluorescence microscope (Bio-Rad, USA). The fluorescence intensity of the markers under study was quantified using ImageJ software.

**Statistical analysis.** Data were analyzed statistically using BioStat Pro 5.9.8. Data in the text and tables are presented as the median (*Me*), lower (*Q1*), and upper (*Q3*) quartiles, since most of the data followed a distribution other than normal (Shapiro-Wilk test,  $p < 0.05$ ). Quantitative variables were compared using the two-sided Mann-Whitney *U* test. Differences were considered statistically significant at  $p < 0.05$ . The Kruskal-Wallis test was used to identify significant differences among multiple independent groups. The Bonferroni correction was applied when comparing multiple groups or subgroups. The effect of different IL-6 concentrations on NVU — in two groups with serum added and the first control group without serum added — showed a *p*-value of 0.017. The effect of NVU incubation temperature for each group was assessed in four subgroups with anoxia and one subgroup with normoxia; the significance of the differences was 0.0125.

## Results

**Claudin-5 expression (Table 1).** In the Control and Min groups under anoxic conditions, there was a statistically significant decrease in claudin-5 expression in all subgroups compared to normoxia ( $p=0.003$ ). At temperatures below 37°C, a trend toward stabilization and an increase in claudin-5 expression was observed in these groups. However, the values did not reach those observed under normoxia ( $p=0.011$ ).

In the Max group, temperature and oxygen concentration did not affect claudin-5 expression ( $p=0.130$ ).

The decrease in claudin-5 expression compared to the control was more pronounced in the Max group than in the Min group, both under normoxia and anoxia ( $p=0.011$ ). Thus, under normoxic conditions, the presence of serum in the culture medium led to a decrease in claudin-5 expression compared to the control: 2.5-fold in the Min group ( $p=0.011$ ) and 9.6-fold in the Max group ( $p=0.011$ ).

**Occludin-1 Expression (Table 2).** The second protein under investigation, which plays a role in maintaining the functional activity of the blood-

brain barrier, was the tight junction protein occludin-1. In the control group and the Max group, following anoxia exposure at all temperature conditions, no statistically significant change in occludin-1 expression was detected compared with normoxia ( $p>0.0125$ ). Under normoxia, occludin-1 expression in the Min group decreased by a factor of 2.05 ( $p=0.011$ ), and in the Max group by a factor of 6.6 ( $p=0.011$ ). However, in the Min group, starting with hypothermia at 24°C, no statistically significant difference was observed between the normoxia and anoxia conditions ( $p=0.442$ ).

**Expression of interleukin-1 receptors (IL-1R) (Table 3).** It was found that, in the control group, incubating cells under anoxic conditions at 37°C led to a statistically significant increase in IL-1R fluorescence intensity from 9.85 to 21.20 RU ( $p=0.011$ ). As the temperature decreased, a trend toward a reduction in the negative effect of anoxia was observed. Starting at 24°C, this reduction was statistically significant ( $p=0.011$ ).

Nevertheless, even at 20°C, the fluorescence intensity of IL-1R expression differed statistically significantly from that of the control group ( $p=0.011$ ).

**Table 1. Fluorescence intensity of claudin-5 expression.**

| Groups                | Indicator values in subgroups |                     |                     |                        |                        | <i>p</i>                                 |            |            |            |            |
|-----------------------|-------------------------------|---------------------|---------------------|------------------------|------------------------|------------------------------------------|------------|------------|------------|------------|
|                       | Normoxia<br>37°C              | Anoxia              |                     |                        |                        | Normoxia vs Anoxia                       |            |            |            |            |
|                       |                               | 37°C                | 28°C                | 24°C                   | 20°C                   | vs 37°C<br>vs 28°C<br>vs 24°C<br>vs 20°C | vs<br>37°C | vs<br>28°C | vs<br>24°C | vs<br>20°C |
| Control               | 34.25<br>[30.90–36.88]        | 9.20<br>[8.23–9.80] | 9.20<br>[8.43–9.75] | 11.20<br>[10.28–11.93] | 17.55<br>[16.75–18.23] | 0.003                                    | 0.011      | 0.011      | 0.011      | 0.011      |
| Min                   | 13.50<br>[11.18–15.80]        | 4.15<br>[3.95–4.58] | 4.95<br>[4.68–5.45] | 6.35<br>[5.68–7.10]    | 7.40<br>[7.20–7.75]    | 0.003                                    | 0.011      | 0.011      | 0.011      | 0.011      |
| Max                   | 3.55<br>[3.28–3.83]           | 2.30<br>[2.18–2.33] | 2.15<br>[2.08–2.53] | 2.25<br>[1.98–2.78]    | 2.50<br>[2.25–2.80]    | 0.130                                    | —          | —          | —          | —          |
| Control vs Min vs Max | 0.007                         | 0.007               | 0.007               | 0.007                  | 0.007                  |                                          |            |            |            |            |
| Control vs Min        | 0.011                         | 0.011               | 0.011               | 0.011                  | 0.011                  |                                          |            |            |            |            |
| Control vs Max        | 0.011                         | 0.011               | 0.011               | 0.011                  | 0.011                  |                                          |            |            |            |            |
| Min vs Max            | 0.011                         | 0.011               | 0.011               | 0.011                  | 0.011                  |                                          |            |            |            |            |

**Note.** For Tables 1–4: All values are expressed in relative units (RU) of fluorescence; the significance level for differences within groups is 0.017; for the normoxia vs. anoxia subgroups, it is 0.0125.

**Table 2. Fluorescence intensity of occludin-1 expression.**

| Groups                | Indicator values in subgroups |                        |                        |                        |                        | <i>p</i>                                 |            |            |            |            |
|-----------------------|-------------------------------|------------------------|------------------------|------------------------|------------------------|------------------------------------------|------------|------------|------------|------------|
|                       | Normoxia<br>37°C              | Anoxia                 |                        |                        |                        | Normoxia vs Anoxia                       |            |            |            |            |
|                       |                               | 37°C                   | 28°C                   | 24°C                   | 20°C                   | vs 37°C<br>vs 28°C<br>vs 24°C<br>vs 20°C | vs<br>37°C | vs<br>28°C | vs<br>24°C | vs<br>20°C |
| Control               | 53.75<br>[51.60–56.85]        | 43.90<br>[40.98–48.38] | 43.35<br>[42.98–45.05] | 57.40<br>[56.70–58.38] | 62.0<br>[59.28–64.48]  | 0.003                                    | 0.042      | 0.022      | 0.124      | 0.042      |
| Min                   | 26.25<br>[25.0–28.10]         | 16.65<br>[15.43–17.70] | 18.05<br>[16.95–18.88] | 26.90<br>[25.68–27.68] | 29.15<br>[27.35–30.65] | 0.007                                    | 0.011      | 0.011      | 0.442      | 0.193      |
| Max                   | 8.15<br>[7.83–8.58]           | 8.40<br>[7.98–8.83]    | 8.30<br>[8.13–8.78]    | 10.05<br>[9.28–10.83]  | 12.0<br>[11.68–12.58]  | 0.092                                    | —          | —          | —          | —          |
| Control vs Min vs Max | 0.007                         | 0.018                  | 0.018                  | 0.018                  | 0.018                  |                                          |            |            |            |            |
| Control vs Min        | 0.011                         | 0.011                  | 0.011                  | 0.011                  | 0.011                  |                                          |            |            |            |            |
| Control vs Max        | 0.011                         | 0.011                  | 0.011                  | 0.011                  | 0.011                  |                                          |            |            |            |            |
| Min vs Max            | 0.011                         | 0.011                  | 0.011                  | 0.011                  | 0.011                  |                                          |            |            |            |            |

**Table 3. Fluorescence intensity of interleukin-1 receptor expression.**

| Groups                | Indicator values in subgroups |                        |                        |                        |                        | <i>p</i>                                 |            |            |            |            |
|-----------------------|-------------------------------|------------------------|------------------------|------------------------|------------------------|------------------------------------------|------------|------------|------------|------------|
|                       | Normoxia<br>37°C              | Anoxia                 |                        |                        |                        | Normoxia vs Anoxia                       |            |            |            |            |
|                       |                               | 37°C                   | 28°C                   | 24°C                   | 20°C                   | vs 37°C<br>vs 28°C<br>vs 24°C<br>vs 20°C | vs<br>37°C | vs<br>28°C | vs<br>24°C | vs<br>20°C |
| Control               | 9.85<br>[9.78–10.05]          | 21.20<br>[19.98–22.58] | 18.25<br>[16.05–21.00] | 15.70<br>[14.55–16.68] | 13.95<br>[13.30–14.90] | 0.004                                    | 0.011      | 0.011      | 0.011      | 0.011      |
| Min                   | 22.65<br>[21.65–23.68]        | 43.25<br>[42.20–44.33] | 40.80<br>[38.45–43.18] | 33.30<br>[38.45–43.18] | 31.25<br>[29.60–33.73] | 0.003                                    | 0.011      | 0.011      | 0.011      | 0.011      |
| Max                   | 27.55<br>[49.35–50.25]        | 49.35<br>[48.15–50.25] | 44.25<br>[41.80–47.50] | 40.70<br>[39.45–42.48] | 38.65<br>[35.25–40.60] | 0.006                                    | 0.011      | 0.011      | 0.011      | 0.022      |
| Control vs Min vs Max | 0.010                         | 0.007                  | 0.017                  | 0.018                  | 0.018                  |                                          |            |            |            |            |
| Control vs Min        | 0.011                         | 0.011                  | 0.011                  | 0.011                  | 0.011                  |                                          |            |            |            |            |
| Control vs Max        | 0.011                         | 0.011                  | 0.011                  | 0.011                  | 0.011                  |                                          |            |            |            |            |
| Min vs Max            | 0.022                         | 0.011                  | 0.095                  | 0.011                  | 0.124                  |                                          |            |            |            |            |

**Table 3. Fluorescence intensity of interleukin-1 receptor expression.**

| Groups                | Indicator values in subgroups |                        |                        |                        |                        | <i>p</i>                                 |            |            |            |            |
|-----------------------|-------------------------------|------------------------|------------------------|------------------------|------------------------|------------------------------------------|------------|------------|------------|------------|
|                       | Normoxia<br>37°C              | Anoxia                 |                        |                        |                        | Normoxia vs Anoxia                       |            |            |            |            |
|                       |                               | 37°C                   | 28°C                   | 24°C                   | 20°C                   | vs 37°C<br>vs 28°C<br>vs 24°C<br>vs 20°C | vs<br>37°C | vs<br>28°C | vs<br>24°C | vs<br>20°C |
| Control               | 8.55<br>[7.85–8.98]           | 22.90<br>[22.33–24.68] | 22.70<br>[20.68–24.15] | 15.20<br>[13.98–16.75] | 8.35<br>[7.33–9.15]    | 0.003                                    | 0.011      | 0.011      | 0.011      | 0.044      |
| Min                   | 8.80<br>[8.20–9.40]           | 30.85<br>[28.93–32.78] | 33.95<br>[30.95–36.13] | 27.15<br>[26.13–28.53] | 20.85<br>[19.05–22.55] | 0.003                                    | 0.011      | 0.011      | 0.011      | 0.011      |
| Max                   | 8.90<br>[8.25–10.10]          | 49.45<br>[45.55–51.78] | 43.40<br>[41.63–46.00] | 39.15<br>[36.05–41.65] | 34.25<br>[32.60–35.63] | 0.005                                    | 0.011      | 0.011      | 0.011      | 0.011      |
| Control vs Min vs Max | 0.668                         | 0.013                  | 0.007                  | 0.010                  | 0.007                  |                                          |            |            |            |            |
| Control vs Min        | —                             | 0.042                  | 0.011                  | 0.011                  | 0.011                  |                                          |            |            |            |            |
| Control vs Max        | —                             | 0.011                  | 0.011                  | 0.011                  | 0.011                  |                                          |            |            |            |            |
| Min vs Max            | —                             | 0.011                  | 0.011                  | 0.022                  | 0.011                  |                                          |            |            |            |            |

We also found that under normoxic conditions, the presence of blood serum in the culture medium led to a statistically significant increase in IL-1R expression ( $p=0.011$ ), regardless of the concentration of IL-6 in the serum. Under hypothermic conditions at 20°C in the Max group, the differences in IL-1R expression between normoxic and hypoxic conditions were negated ( $p=0.022$ ).

**Expression of interleukin-6 receptors (IL-6R) (Table 4).** It was found that in the Control group, under anoxic conditions at 37°C, 28°C, and 24°C, there was a significant increase in IL-6R expression compared with normoxia ( $p=0.011$ ). At the same time, a trend toward decreased expression was observed as the temperature decreased. At 20°C, IL-6R expression did not differ from that under normoxia ( $p=0.044$ ).

In the Min and Max groups under anoxic conditions, IL-6R expression was higher than under normoxia in all subgroups (37°C, 28°C, 24°C, and 20°C;  $p=0.011$ ). Lowering the temperature to 20°C in both groups did not restore IL-6R expression levels to those observed under normoxic conditions ( $p=0.011$ ).

Under normoxic conditions, the Control, Min, and Max groups did not differ significantly in terms of IL-6R expression levels ( $p=0.668$ ). However, under

anoxic conditions, a statistically significant increase in IL-6R expression was observed compared to the Control group: in the Min group — starting at 28°C ( $p=0.011$ ), and in the Max group — starting at 37°C ( $p=0.011$ ). Starting at 28°C and below, the increase in IL-6R expression compared to normoxia was more pronounced in the Min and Max groups than in the Control group ( $p\leq 0.010$ ).

## Discussion

The observed decrease in the expression of claudin-5 and occludin-1 under anoxic conditions is fully consistent with existing data indicating that ischemia/hypoxia is a potent destabilizing factor for BBB integrity. It has been shown that, within just a few minutes after middle cerebral artery occlusion in rodents, there is a rapid decrease in the expression and redistribution of tight-junction proteins, leading to increased BBB permeability [21,22]. Similar findings have been obtained *in vitro*: oxygen-glucose deprivation in cultures of brain endothelial cells leads to the dissociation of occludin-1 and claudin-5 complexes from the cytoskeleton and their internalization [23]. Our results, demonstrating a decrease in the expression of these proteins during anoxia in the serum-free group and in the group with low IL-6 levels, confirm this widely ac-

cepted pathophysiological concept. It appears that, even despite the possible protective effects of hypothermia on stabilizing the BBB, these effects are insufficient to preserve it. However, this requires further study in more complex NVU models that simulate blood flow.

Of particular interest are the findings regarding the effect of patient serum on the NVU model. It was found that even serum with minimal IL-6 concentrations significantly reduced the expression of claudin-5 and occludin-1, while serum with high IL-6 levels had the most damaging effect, virtually eliminating the difference between the effects of anoxia and normoxia. This indicates that systemic inflammation, mediated by humoral factors in the blood, is an independent and potent damaging agent for the blood-brain barrier. This conclusion is supported by studies demonstrating that pro-inflammatory cytokines, such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6, are capable of directly modulating the expression and organization of tight junction proteins. In particular, it has been shown that IL-6 can activate the JAK-STAT signaling pathway, leading to the suppression of claudin-5 gene transcription [24].

As our data show, the neuroprotective effect of hypothermia depends to a large extent on concomitant factors, in particular, the presence of concomitant systemic inflammation. The most pronounced protective effect of hypothermia in the experiment was observed in groups without added serum or with serum containing low levels of IL-6. An increase in claudin-5 expression was observed when the temperature was lowered to 20°C compared to anoxia at 37°C, but it was statistically significantly lower than the values in the control group; consequently, the effects of hypothermia proved insufficient for neuroprotection. With regard to IL-1R, hypothermia also demonstrated an insufficient protective effect, failing to reduce their anoxia-induced overexpression. Hypothermia significantly reduced IL-6R expression only at a temperature of 20°C.

However, a key limitation to the effectiveness of hypothermia, identified within the temperature range studied, is its inability to fully counteract the damaging effects of high concentrations of pro-inflammatory factors in serum. In the Max group, based on IL-6 levels, hypothermia had no significant effect on either claudin-5 expression or IL-6R expression. This suggests that the signaling cascades triggered by high cytokine concentrations (e. g., JAK-STAT, NF- $\kappa$ B) are highly resistant to the modulatory effects of temperature reduction. Overcoming this resistance may require deeper or longer-lasting hypothermia, or combination therapy that includes, in addition to hypothermia, pharmacological inhibitors of pro-inflammatory pathways.

**The limitations of the study** are primarily related to the NVU model itself, which does not simulate blood flow. In addition, the limited level of hypothermia (20°C) may not have been sufficient to produce protective effects. However, in cardiac surgery practice, it is rare to cool a patient to lower temperatures [25, 26]. Furthermore, it is important to note that to simulate the effects of SIR, the researchers used not IL-6 itself, but blood serum from patients with known IL-6 levels. This may skew the results, as serum also contains many other factors that trigger systemic inflammation.

## Conclusion

Exposure to serum containing various concentrations of IL-6 had a more pronounced effect on the expression of NVU damage markers than anoxia.

Hypothermia within the temperature range studied did not provide the expected protective effect: the expression levels of claudin-5 and receptors for IL-1 and IL-6 were not comparable to that of the control group, even without the addition of serum.

## References

1. Bigelow W.G., Lindsay W.K., Greenwood W.F. Hypothermia: its possible role in cardiac surgery: an investigation of factors governing survival in dogs at low body temperatures. *Ann Surg.* 1950; 132: 849–866. DOI: 10.1097/00000658-195011000-00001. PMID: 14771796.
2. Lewis F.J., Taufic M. Closure of atrial septal defects with the aid of hypothermia; experimental accomplishments and the report of one successful case. *Surgery.* 1953; 33: 52–59. PMID: 13015312.
3. Flickinger K.L., Weissman A., Elmer J., Coppler P.J., Guyette F.X., Repine M.J., Dezfulian C., et al. Metabolic manipulation and therapeutic hypothermia. *Ther Hypothermia Temp Manag.* 2024; 14 (1): 46–51. DOI: 10.1089/ther.2023.0010. PMID: 37405749.
4. Campos F, Pérez-Mato M., Agulla J., Blanco M., Barral D., Almeida A., Brea D., et al. Glutamate excitotoxicity is the key molecular mechanism which is influenced by body temperature during the acute phase of brain stroke. *PLoS One.* 2012; 7 (8): e44191. DOI: 10.1371/journal.pone.0044191. PMID: 22952923.
5. Xu L., Yenari M.A., Steinberg G.K., Giffard R.G. Mild hypothermia reduces apoptosis of mouse neurons *in vitro* early in the cascade. *J Cereb Blood Flow Metab.* 2002; 22 (1): 21–28. DOI: 10.1097/00004647-200201000-00003. PMID: 11807390.
6. Sun H., Cai J., Shen S., Ren X. Hypothermia treatment ameliorated cyclin-dependent kinase 5-mediated inflammation in ischemic stroke and improved outcomes in ischemic stroke patients. *Clinics (Sao Paulo).* 2019; 74: e938. DOI: 10.6061/clinics/2019/e938. PMID: 31644666.
7. Gong P, Li C.S., Hua R., Zhao H., Tang Z.R., Mei X, Zhang M.Y., et al. Mild hypothermia attenuates mitochondrial oxidative stress by protecting respiratory enzymes and upregulating MnSOD in a pig model of cardiac arrest. *PLoS One.* 2012; 7 (4): e35313. DOI: 10.1371/journal.pone.0035313. PMID: 22532848.
8. Nishi H., Nakatsuka T., Takeda D., Miyazaki N., Sakanaka J., Yamada H., Yoshida M. Hypothermia suppresses excitatory synaptic transmission and neuronal death induced by experimental ischemia in spinal ventral horn neurons. *Spine (Phila Pa 1976).* 2007; 32 (25): E741–747. DOI: 10.1097/BRS.0b013e31815b654b. PMID: 18245989.
9. Greeley W.J., Kern F.H., Ungerleider R.M., Boyd 3<sup>rd</sup> J.L., Quill T., Smith L.R., Baldwin B., et al. The effect of hypothermic cardiopulmonary bypass and total circulatory arrest on cerebral metabolism in neonates, infants, and children. *J Thorac Cardiovasc Surg.* 1991; 101 (5): 783–794. PMID: 2023435.
10. van der Worp H.B., Sena E.S., Donnan G.A., Howells D.W., Macleod M.R. Hypothermia in animal models of acute ischaemic stroke: a systematic review and meta-analysis. *Brain.* 2007; 130 (Pt 12): 3063–3074. DOI: 10.1093/brain/awm083. PMID: 17478443.
11. Deist F.L., Menasché P., Kucharski C., Bel A., Piwniwa A., Bloch G. Hypothermia during cardiopulmonary bypass delays but does not prevent neutrophil-endothelial cell adhesion. A clinical study. *Circulation.* 1995; 92 (9 Suppl): 354–358. DOI: 10.1161/01.cir.92.9.354. PMID: 7586437.
12. Newburger J.W., Jonas R.A., Wernovsky G., Wypij D., Hickey P.R., Kuban K.C., Farrell D.M., et al. A comparison of the perioperative neurologic effects of hypothermic circulatory arrest versus low-flow cardiopulmonary bypass in infant heart surgery. *N Engl J Med.* 1993; 329 (15): 1057–1064. DOI: 10.1056/NEJM199310073291501. PMID: 8371727.
13. Algra S.O., Jansen N.J., van der Tweel I., Schouten A.N.J., Groenendaal F., Toet M., van Oeveren W., et al. Neurological injury after neonatal cardiac surgery: a randomized, controlled trial of 2 perfusion techniques. *Circulation.* 2014; 129 (2): 224–233. DOI: 10.1161/CIRCULATIONAHA.113.003312. PMID: 24141323.
14. Caputo M., Pike K., Baos S., Sheehan K., Selway K., Ellis L., Stoica S., et al. Normothermic versus hypothermic cardiopulmonary bypass in low-risk paediatric heart surgery: a randomised controlled trial. *Heart.* 2019; 105 (6): 455–464. DOI: 10.1136/heartjnl-2018-313567. PMID: 30322847.
15. Corno A.F., Bostock C., Chiles S.D., Wright J., Tala M.-T. Jn, Mimic B., Cvekovic M. Comparison of early outcomes for normothermic and hypothermic cardiopulmonary bypass in children undergoing congenital heart surgery. *Front Pediatr.* 2018; 6: 219. DOI: 10.3389/fped.2018.00219. PMID: 30175089.
16. Andropoulos D.B., Hunter J.V., Nelson D.P., Stayer S.A., Stark A.R., McKenzie E.D., Heinle J.S., et al. Brain immaturity is associated with brain injury before and after neonatal cardiac surgery with high-flow bypass and cerebral oxygenation monitoring. *J Thorac Cardiovasc Surg.* 2010; 139 (3): 543–556. DOI: 10.1016/j.jtcvs.2009.08.022. PMID: 19909994.

17. Cenini G., Hebisch M., Iefremova V., Flitsch L.J., Breitzkreuz Y., Tanzi R.E., Kim D.Y., et al. Dissecting Alzheimer's disease pathogenesis in human 2D and 3D models. *Mol Cell Neurosci*. 2021; 110: 103568. DOI: 10.1016/j.mcn.2020.103568. PMID: 33068718.
18. Nakagawa S., Deli M.A., Kawaguchi H., Shimizudani T., Shimono T., Kittel A., Tanaka K., et al. A new blood-brain barrier model using primary rat brain endothelial cells, pericytes and astrocytes. *Neurochem Int*. 2009; 54 (3–4): 253–263. DOI: 10.1016/j.neuint.2008.12.002. PMID: 21240470.
19. Hartung T. Comparative analysis of the revised Directive 2010/63/EU for the protection of laboratory animals with its predecessor 86/609/EEC — a t4 report. *ALTEX*. 2010; 27 (4): 285–303. DOI: 10.14573/altex.2010.4.285. PMID: 21240470.
20. Jekarl D.W., Lee S.Y., Lee J., Park Y.J., Kim Y., Park J.H., Wee J.H., et al. Procalcitonin as a diagnostic marker and IL-6 as a prognostic marker for sepsis. *Diagn Microbiol Infect Dis*. 2013; 75 (4): 342–347. DOI: 10.1016/j.diagmicrobio.2012.12.011. PMID: 23391607.
21. Zhao Y., Gan L., Ren L., Lin Y., Ma C., Lin X. Factors influencing the blood-brain barrier permeability. *Brain Res*. 2022; 1788: 147937. DOI: 10.1016/j.brainres.2022.147937. PMID: 35568085.
22. Li L., Welser J.V., Dore-Duffy P., del Zoppo G.J., Lamanna J.C., Milner R. In the hypoxic central nervous system, endothelial cell proliferation is followed by astrocyte activation, proliferation, and increased expression of the alpha 6 beta 4 integrin and dystroglycan. *Glia*. 2010; 58 (10): 1157–1167. DOI: 10.1002/glia.20995. PMID: 20544851.
23. Haile W.B., Gavegnano C., Tao S., Jiang Y., Schinazi R.F., Tyor W.R. The Janus kinase inhibitor ruxolitinib reduces HIV replication in human macrophages and ameliorates HIV encephalitis in a murine model. *Neurobiol Dis*. 2016; 92 (Pt B): 137–143. DOI: 10.1016/j.nbd.2016.02.007. PMID: 26851503.
24. Yeung Y.T., Aziz F., Guerrero-Castilla A., Arguelles S. Signaling pathways in inflammation and anti-inflammatory therapies. *Curr Pharm Des*. 2018; 24 (14): 1449 1484. DOI: 10.2174/1381612824666180327165604. PMID: 29589535.
25. Muehlschlegel G., Kubicki R., Jacobs-LeVan J., Kroll J., Klemm E., Humburger F., Stiller B., et al. Neurological impact of slower rewarming during bypass surgery in infants. *Thorac Cardiovasc Surg*. 2024; 72 (S 03): e7-e15. DOI: 10.1055/s-0044-1787650. PMID: 38909608.
26. Bhalala U.S., Appachi E., Mumtaz M.A. Neurologic injury associated with rewarming from hypothermia: is mild hypothermia on bypass better than deep hypothermic circulatory arrest?. *Front Pediatr*. 2016; 4: 104. DOI: 10.3389/fped.2016.00104. PMID: 27734011.

**Received 16.03.2026**  
**Accepted 08.07.2026**

## Concept of Infectious Perioperative Risk (Analytical Review)

Ekaterina I. Glushko<sup>1,2\*</sup>, Nikita V. Trembach<sup>1,2</sup>,  
Alexey A. Noskov<sup>1,2</sup>, Igor B. Zabolotskikh<sup>1,2,3</sup>

<sup>1</sup> Kuban State Medical University, Ministry of Health of the Russian Federation,  
4 Mitrofana Sedina Str., 350063 Krasnodar, Russia

<sup>2</sup> Regional Clinical Hospital No. 2, Ministry of Health of the Krasnodar Area,  
6 Krasnykh Partizan Str., bldg 2, 350012 Krasnodar, Krasnodar Area, Russia

<sup>3</sup> Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology, Ministry of Education and Science of Russia,  
25 Petrovka Str., Bldg. 2, 107031 Moscow, Russia

**For citation:** Ekaterina I. Glushko, Nikita V. Trembach, Alexey A. Noskov, Igor B. Zabolotskikh. Concept of Infectious Perioperative Risk (Analytical Review). *Obshchaya Reanimatologiya = General Reanimatology*. 2026; 22 (4): 47–61. <https://doi.org/10.15360/1813-9779-2026-4-2663> [In Russ. and Engl.]

\*✉ Ekaterina I. Glushko, egadzieva2@gmail.com

### Summary

**Objective.** To substantiate the concept of perioperative infectious risk by analyzing current approaches to classifying complications, methods for predicting them, and the key factors influencing surgical outcomes.

**Materials and Methods.** We conducted an analytical review based on expert judgement and a systematic search of publications from the preceding 10 years in PubMed and Lens.org. The analysis included data on the epidemiology of infectious complications, classification systems (CDC, Clavien-Dindo, Accordion), prognostic scores (ASA, SOFA, ACS-NSQIP, SORT), laboratory markers (CRP, IL-6, procalcitonin, neutrophil-to-lymphocyte ratio), and machine learning models (PERISCOPE AI, Random Forest, SVM, ensemble methods).

**Results.** The risk of infectious complications was shown to be determined by the cumulative effect of modifiable and nonmodifiable factors related to both the patient and the healthcare facility. Laboratory markers demonstrated high prognostic value: IL-6 levels above 432 pg/mL and CRP >150 mg/L on postoperative day 3 were statistically significantly associated with adverse outcomes. Advanced prognostic tools provided high accuracy: the AUROC for ACS-NSQIP reached 0.80, and for PERISCOPE AI, 0.82–0.91. The use of scoring systems and machine learning made it possible to identify high-risk patients before clinical symptoms appeared.

**Conclusion.** Risk of perioperative infections is multifactorial and requires an integrated approach to risk stratification, incorporating clinical data, risk assessment scales, laboratory markers, and AI models. The use of structured prognostic tools enables early identification of complications, optimize prevention, and reduce mortality.

**Keywords:** *perioperative risk; infectious complications; postoperative infection; sepsis; septic shock; risk prediction; abdominal surgery; risk factors.*

**Conflict of interest.** I. B. Zabolotskikh is Vice President of the All-Russian Public Organization «Federation of Anesthesiologists and Reanimatologists» (FAR). The General Reanimatology journal is affiliated with the FAR, which does not change the editorial standards for reviewing this article. The review process and the decision to publish were made according to established procedure. The other authors declare no conflict of interest.

**Funding information.** This work was carried out as part of the project «Calculator of High Perioperative Risk in Elective Abdominal Surgery» using funds from the subsidy under Agreement No. 075-15-2025-108, dated March 29, 2025, within the framework of the Strategic Academic Leadership Program «Priority 2030».

### Информация об авторах / Information about the authors:

Глушко Екатерина Игоревна / Ekaterina I. Glushko, <https://orcid.org/0000-0001-7869-9331>

Трембач Никита Владимирович / Nikita V. Trembach, <https://orcid.org/0000-0002-0061-0496>

Носков Алексей Андреевич / Alexey A. Noskov, <https://orcid.org/0000-0002-0662-9358>

Заболотских Игорь Борисович / Igor B. Zabolotskikh, <https://orcid.org/0000-0002-3623-2546>

### Introduction

Perioperative risk of infectious complications is the probability of developing an infection associated with surgical intervention during any phase of the perioperative period (preoperative, intraoperative, and postoperative periods) [1]. Infectious complications arising during abdominal surgery lead to a significant prolongation of in-hospital treatment, potential emergence of antibiotic resistance, significant increase in the cost of medical care. Moreover, these complications remain one of the leading causes of

mortality in surgical hospitals. Their incidence ranges from 1% (urinary tract infections, UTIs) to 22.6% (sepsis), and the mortality rate from septic shock reaches 67.8% [2–6]. Alternative methods are increasingly being used to study and assess this problem, including various calculators based on machine learning, artificial intelligence, and other techniques

**Purpose of the review.** To substantiate the concept of perioperative infection risk, systematize definitions, classifications, and risk factors for infectious complications, and analyze prognostic

scales, laboratory markers, and machine learning methods.

## Materials and Methods

The evidence reviewed in this study combines the author's expert opinion with a comprehensive search of several English-language databases (which are also indexed by Russian-language sources) and a subsequent analysis of the relevant publications. The search in the PubMed database was supplemented by a search on Lens.org, which included articles not listed in PubMed, provided they had a DOI and at least one citation. The search covered a 10-year period. Types of included studies: guidelines, meta-analyses, large cohort studies, and reviews. The following main keywords were used for the literature search: infectious complications, intra-abdominal infections, septic complications, and postoperative infectious complications. The logical framework and structural approach of the narrative review by I. B. Zabolotskikh (2024), which proposes a systematic model for describing perioperative risk, served as the conceptual basis for this review and were used in shaping its structure [7].

**Epidemiology of infectious and septic complications.** Postoperative infections rank second in prevalence in the Russian Federation, accounting for 23.6% of the 42% of all cases of healthcare-associated infections (HAIs) in surgical hospitals [8]. In particular, the incidence of superficial wound infections reaches 14.9% [9], while deeper infections (organ/space) occur less frequently (5.9%), and deep wound infections — even less frequently (0.9%) [10].

One of the most serious postoperative complications is anastomotic failure. Its incidence ranges from 2.8% to 8.8% [3], but the mortality rate remains consistently high — about 16–18% [9, 11] — making this localized problem one of the most dangerous.

As for mortality, there is a direct correlation with the severity and systemic nature of the infection. The lowest risk is associated with superficial wound infections (mortality rate of 0.3–3.6%) [12, 13]. As the infection spreads to deeper levels, the risk increases significantly: deep wound infection is associated with a mortality rate of 7.5%, while organ or space infection has a mortality rate of 21.7% [13].

Generalized systemic infections pose the greatest threat to a patient's life. Sepsis with estimated in various studies incidence ranging from 1.84% to 22.6% [14, 15], is characterized by a wide range of mortality rates— ranging from 4.4% to 27.8% [2]. Its progression to septic shock is a critical condition with an extremely high mortality rate of 67.8% [2]. Similar mortality rates are reported for bacteremia (29.7%) [2] and infections with no clearly identified source (30–35%) [16], underscoring the importance of early diagnosis and control of infection spread.

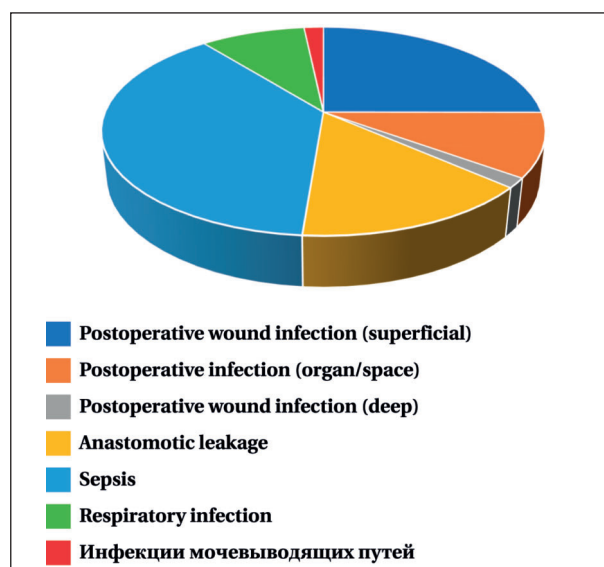


Fig. Incidence of infectious complications.

Respiratory infections (most commonly pneumonia), occurring at a rate of approximately 3.8–5.4% [9], also pose a significant threat, and their outcome depends heavily on the type of surgery. The overall mortality rate from postoperative pneumonia is 19.5%, but in emergency procedures, this figure rises to 27.3%, which is more than three times higher than the mortality rate for elective surgeries (8.1%) [17]. Despite their relatively low incidence (about 1%) [18], UTIs are characterized by an extremely wide range of mortality rates — from 5% to 50% — which is likely related to the patient's general condition and comorbidities [19, 20].

The distribution of each type of complication within the total number of all recorded postoperative infections is clearly illustrated in Figure.

The data in Table 1 demonstrate the pattern, prevalence, and severity of major septic complications in abdominal surgery, with references to the sources of the information.

**Perioperative risks of infectious complications: key aspects and comments.** For systemic inflammatory response syndrome (SIRS), two or more of the following signs are pathognomonic: a change in body temperature (either an increase to over 38°C or a decrease to below 36°C), increased heart rate (more than 90 beats per minute) and respiratory rate (more than 20 breaths per minute), and changes in white blood cell count (less than  $4 \times 10^9$  or more than  $12 \times 10^9$  cells per liter of blood, or more than 10% immature forms) [21, 22].

Infectious-septic complications are a progressive pathological process initiated by an infectious agent, with underlying inadequate systemic inflammatory response by the body, characterized by the development of SIRS, sepsis, multiple organ dysfunction, and (in the most severe cases) septic shock [21, 22].

**Table 1. Incidence and mortality rates of septic complications in abdominal surgery.**

| Complication                                | Incidence, %             | Mortality, %                                                                                                                         |
|---------------------------------------------|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| Respiratory infection                       | 5.4% [20]<br>3.8% [9]    | Overall mortality rate<br>for postoperative pneumonia: 19.5%<br>For emergency surgeries: 27.3%<br>For elective procedures: 8.1% [17] |
| Anastomotic failure                         | 8.8% [3]<br>2.8% [9]     | 18% [11]<br>16.4% [9]                                                                                                                |
| Infection of unknown origin                 | —                        | 30–35% [16]                                                                                                                          |
| Laboratory-confirmed bacteremia             | —                        | 29.7% [2]                                                                                                                            |
| Postoperative wound infection (superficial) | 14.9% [9]<br>11.8% [12]  | 3.6% [12,13]                                                                                                                         |
| Postoperative wound infection (deep)        | 0.9% [10]                | 7.5% [13]                                                                                                                            |
| Postoperative infection(organ/space)        | 5.9% [10]                | 21.7% [13]                                                                                                                           |
| Urinary tract infections                    | 1% [18]                  | 5–50% [19]                                                                                                                           |
| Sepsis                                      | 1.84% [14]<br>22.6% [15] | 4.4–27.8% [2]                                                                                                                        |
| Septic shock                                | —                        | 67.8% [2]                                                                                                                            |

**Table 2. Comparative characteristics of postoperative complications included in the American and European classifications [7].**

| №                               | List of complications                       | ACS-NSQIP | ESA-ESICM |
|---------------------------------|---------------------------------------------|-----------|-----------|
| <b>Infectious complications</b> |                                             |           |           |
| 1.                              | Infection                                   | ×         |           |
| 2.                              | Infection of unknown origin                 |           | ×         |
| 3.                              | Urinary tract infections                    |           | ×         |
| 4.                              | Postoperative infection (organ/space).      |           | ×         |
| 5.                              | Postoperative wound infection (deep).       |           | ×         |
| 6.                              | Postoperative wound infection (superficial) |           | ×         |
| 7.                              | Respiratory infection                       |           | ×         |
| 8.                              | Laboratory-confirmed bacteremia .           |           | ×         |
| 9.                              | Sepsis/septic shock                         | ×         |           |

The American or European classification systems are most commonly used to classify complications.

The Clavien-Dindo classification (European) was developed in Switzerland (2004, with revisions in 2009) and, thanks to its simplicity and objectivity, has become the most widely used worldwide, including in the United States and Europe. It ranks complications by severity based on the treatment required for correction of complications.

The Accordion classification (American) was developed in the United States. It is less rigidly structured than the Clavien-Dindo classification. It utilizes the concept of «interventions» to grade severity. The Accordion classification is frequently employed in major American databases (e. g., NSQIP — National Surgical Quality Improvement Program). The essence of the classification is that complications are categorized by severity (from «Mild» to «Death») based on the resources expended on their treatment.

Table 2 presents the most common classifications of postoperative complications.

Infectious perioperative complications are described in more detail below.

Infectious perioperative complications, which represent a serious public health problem, occur either at the incision site (superficial or deep) or in any organ or body cavity. This problem is associated

with prolonged hospital stays, high likelihood of readmission, and a low quality of life.

Postoperative infectious complications included in the American and European classifications include: infection of unknown origin, urinary tract infection, postoperative infection (organ/space), postoperative wound infection (deep), postoperative wound infection (superficial), respiratory infection, laboratory-confirmed bacteremia, sepsis/septic shock.

**An infection of unknown origin** is identified by the presence of clinical signs suggestive of infection without confirmation of one of several clinically suspected sources, provided that two or more of the following criteria are met (body temperature  $< 36^{\circ}\text{C}$  or  $> 38^{\circ}\text{C}$ ; white blood cell count  $> 12 \times 10^9/\text{L}$  or  $< 4 \times 10^9/\text{L}$ ; RR  $> 20/\text{min}$  or  $\text{PaCO}_2 < 35 \text{ mm Hg}$ ; HR  $> 90/\text{min}$ ) [20].

**Urinary tract infection.** Criteria for a UTI: a positive urine culture — a titer of  $\geq 10^5/\text{mL}$  for no more than two types of microorganisms — as well as the presence of other symptoms indicative of an inflammatory process [20].

**Postoperative infection (organ/space)** is an infection that occurs in any anatomical area exposed or manipulated during surgery, excluding the incision (wound) itself [20].

**Postoperative wound infection (superficial)** is an infection that occurs within 30 days after surgery and affects only the skin and subcutaneous

fat in the incision area. Deeper tissues (fascia, muscles) are not involved. The site of infection is located above the muscular fascia [20].

**Postoperative wound infection (deep)** is an infection that occurs within 30 days after surgery (or within 1 year if an implant was placed) and affects deep soft tissues: muscle fascia and muscles. The infection is localized below the muscular fascia but does not spread to anatomical cavities or organs [19].

**Laboratory-confirmed bacteremia** is a condition in which live bacteria are detected in human blood — which is normally sterile — as confirmed by microbiological methods (culture isolation) [20].

**Sepsis, septic shock [21, 22].** Sepsis is a life-threatening organ dysfunction caused by a dysregulation of the host's response to infection. Clinically, organ dysfunction manifests as an increase of 2 scores or more by the Sepsis-Associated Organ Failure (SOFA) scoring system, and is associated with an in-hospital mortality rate exceeding 10%. Septic shock is a subset of sepsis in which particularly severe disturbances in circulation, cellular processes, and metabolism are associated with a higher risk of death than in sepsis. Patients with septic shock can be clinically identified by their need for vasopressors to maintain a mean arterial pressure of 65 mmHg or higher and by a serum lactate concentration above 2 mmol/L, in the absence of hypovolemia. This combination is associated with a mortality rate exceeding 40%.

**Respiratory complications [23]** are among the most common and dangerous consequences of abdominal surgery, significantly increasing mortality and length of hospital stay.

Infectious manifestations of respiratory complications include purulent tracheobronchitis, aspiration pneumonitis, including pneumonia, etc.

Criteria:

1. Clinical: fever  $>38^{\circ}\text{C}$  + new infiltrates on the X-ray
2. Laboratory: leukocytosis  $>10 \times 10^9/\text{L}$  or leukopenia  $<4 \times 10^9/\text{L}$
3. Microbiological:  $\geq 10^3$  CFU/mL in bronchoalveolar lavage (BAL)

In addition to the criteria listed above, the CPIS (Clinical Pulmonary Infection Score) scale can also be used for diagnosis. It is used for the clinical assessment of pulmonary infections and was developed to diagnose nosocomial pneumonia (NP).

The scale consists of a score-based assessment of 7 clinical, laboratory, and radiological parameters [24]. Some indicators and their corresponding scores are as follows:

1. Temperature: 0 scores —  $\geq 36.5^{\circ}\text{C}$  or  $\leq 38.4^{\circ}\text{C}$ , 1 score —  $\geq 38.5^{\circ}\text{C}$  or  $\leq 38.9^{\circ}\text{C}$ , 2 scores —  $\geq 39.0^{\circ}\text{C}$  or  $\leq 36.0^{\circ}\text{C}$ .
2. White blood cell count: 0 scores —  $\geq 4,000$  or  $\leq 11,000$ , 1 score —  $< 4,000$  or  $> 11,000$ ; 1 score is added if «immature» forms account for  $\geq 50\%$ .

3. Tracheal secretions: 0 scores — absent, 1 score — nonpurulent secretions present, 2 scores — purulent secretions present.

4. Oxygenation ( $\text{PaO}_2/\text{FiO}_2$ ): 0 scores —  $\geq 240$  mm Hg, 2 scores —  $\leq 240$  mm Hg

5. Chest X-ray: 0 scores — absence of infiltrates, 1 score — diffuse infiltrates, 2 scores — focal infiltrate or progression of radiographic changes.

**Approaches to assessing perioperative infectious complications.** Risk factors during the perioperative period can be divided into the following groups [25, 26]:

1. Modifiable/non-modifiable;
2. Dependent on medical staff, the healthcare facility/patient-oriented.

Table 3 presents the most common perioperative risks of infectious complications based on data from sources [27–43], which have been grouped according to modifiability — a factor important for assessing the consequences of surgical interventions.

Table 4 lists the most common perioperative risks of infectious complications based on data from sources [9, 12, 21, 26–50], dividing them into two broad groups: those dependent on healthcare personnel and those patient-related.

Analysis of the data in Tables 3 and 4 leads to the conclusion that risk factors are interrelated and intertwined at all stages of surgical intervention, forming stable cause-and-effect relationships, knowledge and understanding of which are critically important.

**Approaches to assessing perioperative infectious complications: assessment scales.** Perioperative risk scales are widely used to predict complications and mortality; however, their predictive value regarding infectious outcomes varies. Some tools (ASA, ACS-NSQIP, SORT) assess overall surgical risk, while others (SIRS, qSOFA, SOFA, SOFA2) focus on sepsis and organ dysfunction. For a comprehensive assessment of infection risk, it is crucial to identify the components of these scales that directly correlate with infectious complications. It is important to emphasize that most currently used scales lack specialized parameters for predicting infections, which naturally reduces their predictive ability in this regard.

**The ASA scale** assesses patient's overall health, ranging from healthy (ASA I) to terminally ill, e. g., severe, life-threatening, fatal conditions (A IV–V; and AVI — are brain-dead organ donors) and is traditionally used for a general assessment of anesthetic and surgical risk. According to large cohort studies, a high ASA category is associated with an increased incidence of postoperative complications, including infections, and higher 30-day mortality. However, the subjective nature of the assessment and the lack of a direct focus on infectious factors limit its standalone role in predicting infectious complica-

**Table 3. Perioperative risks of infectious complications: modifiable/non-modifiable.**

| Perioperative risks of infectious complications                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                              |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Modifiable                                                                                                                                                                                                                                                                                                                                                            | Non-modifiable                                                                                                                                                                                                               |
| Nutritional status: Severe malnutrition, obesity [26–28].                                                                                                                                                                                                                                                                                                             | Age: Advanced age (decreased physiological reserves, immunosenescence) [29–32].                                                                                                                                              |
| Smoking and alcohol abuse [11,29].                                                                                                                                                                                                                                                                                                                                    | Comorbidities [9, 29, 31]:<br>• Diabetes mellitus (especially in the decompensated stage)<br>• Chronic kidney disease (CKD)<br>• Cirrhosis of the liver<br>• Heart failure<br>• COPD (Chronic Obstructive Pulmonary Disease) |
| Decompensation of comorbid conditions [9, 30]:<br>• High levels of glycated hemoglobin (HbA1c) in people with diabetes.<br>• Decompensation of cardiac, hepatic or renal failure                                                                                                                                                                                      | Immunosuppression [21]:<br>• Congenital immunodeficiencies<br>• Cancer (especially during chemotherapy)<br>• Autoimmune diseases (e.g., rheumatoid arthritis, IBD)                                                           |
| Use of immunosuppressive drugs [26]:<br>• Corticosteroids<br>• Biologicals (e.g., TNF inhibitors; adjust the dose before elective surgery if possible)                                                                                                                                                                                                                | High risk of contamination [34–36, 44]:<br>• Surgery for peritonitis<br>• Perforation of a hollow organ<br>• Presence of an infected foreign body                                                                            |
| Intraoperative factors [29, 32, 34, 39]:<br>• Maintenance of normothermia (prevention of intraoperative hypothermia).<br>• Monitoring blood glucose levels during surgery.<br>• Adequate tissue oxygenation and perfusion.<br>• Proper surgical technique (minimizing trauma, hemostasis, choice of suture material).<br>• Drainage (appropriate use and proper care) | Complexity and extent of the surgery [26, 31, 33, 36–38]:<br>• Duration of surgery (> 3–4 hours)<br>• Extensive tissue trauma<br>• Anastomosis<br>• Reoperations on abdominal organs                                         |
| Postoperative care [32, 33, 40–43]:<br>• Timely removal of urinary and vascular catheters.<br>• Adequate pain management (allows for early mobilization and breathing exercises).<br>• Early mobilization and breathing exercises (to prevent pneumonia).<br>• Rational antibiotic therapy (avoiding unnecessary use)                                                 | Wound classification according to Altemeier [44]:<br>• Contaminated (Class III) and dirty (Class IV) wounds                                                                                                                  |

tions, which justifies the use of the ASA classification as part of integrated models rather than as a stand-alone tool [51, 52].

Most recently, in 2020, the ASA published an updated version of the physical status assessment, which takes into account the physical status of adults, children, and pregnant women [51]. The scale demonstrated good predictive value: for the occurrence of complications — AUROC = 0.714; for mortality — AUROC = 0.82 [52].

Main areas of application [53, 54]:

- Preoperative risk assessment.
- Surgical risk stratification.
- Assessment of disease severity

**The SOFA scale** is a scoring system that evaluates the function of six key organ systems (respiratory, cardiovascular, hepatic, renal, coagulation, and neurological status) and is used for dynamic monitoring of the severity of organ dysfunction. Developed in 1994 (Vincent et al.) as a modification of the MODS scale [55], the SOFA scale assesses six above mentioned organ systems, and an increase in its score is closely associated with in-hospital mortality. However, SOFA reflects the severity of organ dysfunction that has already developed and is poorly suited for preoperative prediction of infectious complications, which limits the scale's role to that of a tool for the early detection of sepsis in the postoperative period.

Main areas of application [56]:

- Diagnosis of sepsis (SOFA  $\geq 2$  scores + infection).
- Assessment of severity in septic shock, sepsis of any etiology, and multiple organ failure.
- Mortality prognosis:
- SOFA  $\geq 11 \rightarrow$  mortality  $> 90\%$ .
- SOFA  $\leq 6 \rightarrow$  survival rate  $> 80\%$ .

According to various sources, this scale is prognostically reliable for predicting postoperative mortality — AUROC 0.753, AUROC 0.74 [57, 58].

Despite the high prognostic significance of this scale, it has limitations when used in elective surgery. Based on data from numerous sources [55–58], it can be concluded that, unfortunately, SOFA describes the patient's current, already existing condition. It answers the question: «How severe are the existing organ dysfunctions?» rather than «Will they develop in the future?» Consequently, a patient in stable condition undergoing elective surgery (for example, for gallstone disease or a hernia) will have normal SOFA scores (0). The scale cannot help differentiate this patient's risk from that of a similar patient, even though their individual characteristics (age, comorbidities, extent of surgery) may differ drastically [21, 55, 59].

**SOFA-2** is an updated organ failure assessment scale developed by experts from the European Society of Intensive Care Medicine.

**Table 4. Perioperative risks of infectious complications: those related to healthcare personnel and healthcare facilities, and those related to the patient.**

| Risk factors                                                                                            |                                                                 |                                                                                                  |
|---------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Preoperative                                                                                            | Intraoperative                                                  | Postoperative                                                                                    |
|                                                                                                         | <b>Related to healthcare personnel or the facility</b>          |                                                                                                  |
| Emergency surgery                                                                                       | Infected/poorly prepared surgical site [43]                     | Drains for > 3 days [39]                                                                         |
| Prior radiation therapy [45]                                                                            | Intraoperative low SpO <sub>2</sub> [34]                        | Presence of an invasive device (central venous, urethral catheter, endotracheal tube, etc.) [32] |
| Prolonged preoperative hospital stay [33, 35]                                                           | Surgery duration > 2 hours [31]                                 | Lack of adequate wound care [43]                                                                 |
| Prophylactic antibiotics [32, 40–42]                                                                    | Hypothermia [34]                                                | Prolonged course of antibiotics without medical indication (development of resistant flora) [33] |
| Shortage of qualified personnel [46]                                                                    | More than one surgical procedure within a short period [36, 38] | Shortage of qualified personnel [47]                                                             |
|                                                                                                         | Duration of anesthesia [47]                                     | High rate of nosocomial infections [33]                                                          |
|                                                                                                         | Extent of surgical intervention [35]                            |                                                                                                  |
|                                                                                                         | Wound contamination [34, 44]                                    |                                                                                                  |
|                                                                                                         | Shortage of qualified personnel [46]                            |                                                                                                  |
| <b>Patient-related</b>                                                                                  |                                                                 |                                                                                                  |
| Presence of systemic diseases (cardiovascular, endocrine, RenF, HepF, hemostatic disorders) [9, 29, 31] |                                                                 |                                                                                                  |
| Physiological and anthropometric factors (age, weight, general physical condition) [29–32]              |                                                                 |                                                                                                  |
| Harmful habits (alcoholism, drug addiction, smoking) [12, 29]                                           |                                                                 |                                                                                                  |
| Dietary and nutritional status (malnutrition) [26]                                                      |                                                                 |                                                                                                  |
| Vitamin deficiencies [27, 28]                                                                           |                                                                 |                                                                                                  |
| Autoimmune diseases [33]                                                                                |                                                                 |                                                                                                  |
| Geographic region [34]                                                                                  |                                                                 |                                                                                                  |
| Immune status (GCS use, cancer, HIV, etc.) [26]                                                         |                                                                 |                                                                                                  |
| Cognitive impairments (dementia, delirium) [29, 48]                                                     |                                                                 |                                                                                                  |
| Immune status (GCS use, cancer, HIV, etc.) [28]                                                         |                                                                 |                                                                                                  |
| Parenteral nutrition [49]                                                                               |                                                                 |                                                                                                  |
| Infection colonization at the time of surgery [26, 33, 45]                                              |                                                                 |                                                                                                  |
| Intraoperative hemodynamic instability [29]                                                             |                                                                 |                                                                                                  |
| Volume of blood loss [50]                                                                               |                                                                 |                                                                                                  |
| Presence of a chronic site of infection [37]                                                            |                                                                 |                                                                                                  |
| Quantity of blood components transfused intraoperatively [34, 50]                                       |                                                                 |                                                                                                  |

**Note.** CVC — central venous catheter; CVD — cardiovascular disease; RenF — renal failure; HepF — hepatic failure; GCS — glucocorticosteroids; HIV — human immunodeficiency virus.

The redistribution of scores across key systems improves its content validity and enhances interpretability in line with current clinical practice, addressing the two priorities underlying the SOFA update.

The updated SOFA-2 scale, which incorporates modern methods of organ support therapy and new threshold values, describes organ dysfunction in a large, geographically and socioeconomically diverse population of critically ill adult patients and has good prognostic validity. The AUROC for predicting mortality is 0.79.

**Prognostic calculator ACS-NSQIP** is based on a large number of preoperative and intraoperative variables and allows for the assessment of the 30-day mortality risk and a number of complications, including surgical infections. Studies have demonstrated the model's good discriminatory ability (an AUC of approximately 0.8 for adverse outcomes); however, the accuracy of predicting specific infectious complications varies depending on the type of procedure, and the model itself requires local calibration [60–62].

The sensitivity of the ACS-NSQIP calculator for predicting the risk of a serious infection (including

surgical site infections, pneumonia, and urinary tract infections) is approximately 65–85%, depending on the study population and the type of infection. For an isolated prediction, sensitivity typically ranges from 70–80% [63].

For the combined outcome of serious postoperative infectious complications, the AUC was 0.807. Specifically for a complication such as surgical site infections, the AUC was 0.802 [62].

Based on the information presented above, it can be concluded that this calculator is a reliable and clinically useful tool that effectively identifies a significant proportion of at-risk patients.

**SORT (Surgical Outcome Risk Tool)** is a validated tool developed to predict 30-day mortality following elective non-cardiac surgery (Table 5). Its main advantages are ease of use and high accuracy. The assessment procedure takes little time, as it uses only 6 easily assessed factors [52, 63–69]. Although it directly predicts mortality, patients with a high SORT score are automatically classified as being at risk for all serious complications, including sepsis, pneumonia, and other infections. All variables in the SORT system are known predictors of an adverse postoperative outcome. This scale has high

**Table 5. Interpretation of SORT scale results.**

| SORT score | Risk of 30-day mortality | Clinical risk category |
|------------|--------------------------|------------------------|
| 0–1        | ~ 0.1–0.2%               | Very low               |
| 2–3        | ~ 0.3–0.7%               | Low                    |
| 4–5        | ~ 0.9–1.8%               | Intermediate           |
| 6–8        | ~ 2.7–5.4%               | High                   |
| ≥9         | ≥8.9%                    | Very high              |

**Table 6. Advantages and disadvantages of the scales reviewed.**

| Scale/calculator | Advantages                                                                                                                                                                                                | Disadvantages                                                                                                                                                                                                                                                                                                        |
|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ASA              | Quick assessment (subjective).                                                                                                                                                                            | No precise numerical criteria.                                                                                                                                                                                                                                                                                       |
| SIRS/SOFA        | Optimal for sepsis                                                                                                                                                                                        | Does not account for surgical factors.                                                                                                                                                                                                                                                                               |
| ACS-NSQIP        | — Calculates a personalized prognosis for a specific patient based on their age, comorbidities, and type of surgery.<br>— Versatility: Covers a wide range of surgical specialties and types of surgeries | — Issues with calibration: may inaccurately predict risks for individual hospitals or patients with extremely high or low risk.<br>— It takes time and data: to use it, you need to collect and enter about 20 variables, which takes time                                                                           |
| SORT             | — High accuracy for target outcome<br>— Simplicity and speed in use                                                                                                                                       | — Does not include key of infection: BMI, diabetes, smoking, wound class, duration of surgery<br>— Not for emergency surgery:<br>Originally was developed for elective non-cardiac surgery. Its use in emergency surgery, cardiac surgery, neurosurgery, and pediatrics has been less studied and may be inaccurate. |

**Note.** ASA — American Society of Anesthesiologists; SOFA — a scoring system for assessing organ function used for dynamic monitoring of the severity of organ dysfunction; ACS-NSQIP — a calculator used to assess the risk of postoperative complications; SORT — Surgical Outcome Risk Scale.

**Таблица 7. Влияние концентрации СРБ на послеоперационный исход.**

| CRP concentration (mg/L)              | CRP ≤ 85                     | CRP > 85–140 | CRP > 140–200 | CRP > 200–587 |
|---------------------------------------|------------------------------|--------------|---------------|---------------|
|                                       | <b>Key outcomes, %</b>       |              |               |               |
| Disability up to 90 days or mortality | 10.8                         | 13.2         | 18.2          | 25.6          |
|                                       | <b>Secondary outcomes, %</b> |              |               |               |
| 12-month mortality                    | 4.4                          | 5.2          | 7.7           | 9.0           |
| Unplanned admission to the ICU        | 5.9                          | 8.4          | 11.1%         | 16.0          |
| Rehospitalization within 12 months    | 36.9                         | 42.9         | 46.3          | 54.5          |

accuracy in predicting outcomes, with an AUROC of 0.738 for the occurrence of complications and an AUROC of 0.823 for mortality. The extent of surgical intervention significantly influences the risk of postoperative mortality [63,64,66–70].

Table 6 lists the advantages and disadvantages of the scales under consideration [71–74].

**Approaches to assessing perioperative infectious complications: laboratory parameters.** In addition to assessment scales, the main diagnostic criteria are laboratory parameters, the levels of which largely depend on the severity of the septic process. Based on available lab parameters, it is possible to predict the outcome of an infectious complication and take timely action to resolve it.

**C-reactive protein (CRP)** concentration typically rises during the acute phase; it is produced by the liver and other cells, such as alveolar macrophages. A bacterial infection is a strong stimulus that causes a marked short-term increase in CRP; changes in its levels can aid in diagnosing infection and predicting the outcome [75].

CRP levels also statistically significantly reflect the extent of surgical injury. Numerous systematic reviews of retrospective analyses in surgery have shown that high postoperative CRP is associated

with increased mortality and the frequency of readmissions [76–78] (Table 7).

**Interleukin-6 (IL-6)** is an early mediator of the inflammatory response and following major abdominal surgery, it rises earlier than CRP. Studies in colorectal surgery have shown that high IL-6 concentrations on the first day after surgery are associated with the subsequent development of severe complications, including anastomotic failure and sepsis. Proposed cutoff values vary considerably, but overall, IL-6 demonstrates higher sensitivity to early complications compared to CRP, making it a promising component of multifactorial models of infection risk (Table 8) [79–81].

**Procalcitonin (PCT)** is a precursor of calcitonin consisting of 116 amino acids. Its concentration rises in the first few hours after the onset of sepsis and peaks after 24–48 hours. PCT secretion is particularly enhanced in systemic bacterial infections, which allows for a minimal differentiation between bacterial and viral infections [82].

According to various sources, this marker is not equally informative for all organs and systems, nor for all clinical situations. For example, there is compelling evidence regarding the prediction of the severity of bacterial infections in the following

**Table 8. Incidence of complications at different IL-6 concentrations on day 1.**

| Complication          | High IL-6<br>( <i>n</i> = 52), <i>n</i> (%) | Low IL-6<br>( <i>n</i> = 80), <i>n</i> (%) | <i>p</i> |
|-----------------------|---------------------------------------------|--------------------------------------------|----------|
| Sepsis                | 11 (21.2)                                   | 4 (5.0)                                    | 0.004    |
| Reoperation           | 9 (17.3)                                    | 4 (5.0)                                    | 0.020    |
| Anastomotic failure   | 9 (17.3)                                    | 2 (2.5)                                    | 0.007    |
| Atrial fibrillation   | 9 (17.3)                                    | 5 (6.3)                                    | 0.216    |
| Respiratory failure   | 7 (13.5)                                    | 3 (3.8)                                    | 0.006    |
| Pneumonia             | 5 (9.6)                                     | 3 (3.8)                                    | 0.263    |
| Wound infection       | 6 (11.5)                                    | 3 (3.8)                                    | 0.154    |
| Heart failure         | 4 (7.7)                                     | 3 (3.8)                                    | 0.433    |
| Myocardial infarction | 0                                           | 0                                          | —        |
| Mortality             | 3 (5.8)                                     | 0 (0.0)                                    | 0.059    |
| Any complication      | 23 (44.2)                                   | 13 (16.3)                                  | < 0.001  |

**Note.** IL-6 measurements on Day 1 were unavailable for 3 patients. One patient may have had more than one complication. High IL-6: > 432 pg/mL. Low IL-6: ≤ 432 pg/mL.

conditions: meningitis, pneumonia, upper respiratory tract infections, sepsis, and septic shock. This marker is less reliable in cases of arthritis, endocarditis, neutropenia, etc. [83].

PCT is a reliable marker for the early diagnosis of infectious complications in the perioperative period, especially when used for dynamic monitoring. A positive correlation has been identified between PCT concentration and mortality: higher values are associated with an increased risk of death (Table 9).

The results of this biomarker analysis also help the physician determine the appropriate duration and regimen of antibiotic therapy. Studies show that if the PCT concentration has decreased by 80% from its peak or has fallen below 0.5 ng/mL, antibiotics can be safely discontinued, thereby mitigating the risks associated with the overuse of antimicrobial agents [85, 86]. To improve decision-making accuracy, it is recommended to combine the interpretation of this indicator with clinical assessment and diagnostic tests.

**The neutrophil-to-lymphocyte ratio (NLR)** is a simple indicator of the severity of the inflammatory response, calculated from a standard clinical blood test. Systematic reviews have shown that an elevated preoperative NLR is associated with an increased risk of postoperative infectious complications and adverse oncological outcomes, while a rise in the NLR in the early postoperative period may signal a developing infection. Although optimal NLR cutoff values vary across studies, this parameter is attractive as a low-cost and readily available marker that can be incorporated into combined scales and machine learning models for stratifying infection risk [87].

Reference ranges: normal values are most commonly in the range of 1.0–2.0. However, reference ranges may vary slightly depending on the laboratory, population, and patients' age. A value > 3.0 is generally considered elevated. A value > 5.0–10.0 is often considered high/significant (especially in the context of prognosis for severe diseases).

NLR has fairly good accuracy. The AUC for this indicator was 0.84, and the sensitivity was 0.77 [88].

**Table. № 9. Example of the relationship between mortality and PCT concentration [84].**

| PCT concentration (ng/mL) | Mortality (%) |
|---------------------------|---------------|
| < 0,5                     | < 5%          |
| 0,5–2                     | 10–15%        |
| 2–5                       | 20–30%        |
| 5–10                      | 40–50%        |
| > 10                      | > 60%         |

**Machine learning and artificial intelligence methods in the assessment of perioperative risk of infectious complications.** A machine learning model is a mathematical or computational construct (algorithm) that, during the training process, adjusts its internal parameters to identify relationships between input and output data. Classical machine learning models are most commonly used for prediction. These models require prior feature selection and perform well on structured data (e. g., data from electronic health records, EHRs).

**PERISCOPE AI** is one of the most advanced models for predicting the risk of postoperative infections. It uses gradient boosting algorithms (XG-Boost) and is capable of predicting the risk of infectious complications on the 7<sup>th</sup> and 30<sup>th</sup> days after surgery with high accuracy by analyzing EHR data. The model has been validated at several centers, shows excellent ROC-AUC results, and demonstrates value for clinical practice. A key feature of this approach is the adaptation and recalibration of local models to specific clinics, which significantly enhances clinical applicability. The AUROC for the hospitals included in the study ranged from 0.82 to 0.91 for 30-day predictions on validation datasets (2022–2023) [89].

**The Random Forest model** is a machine learning algorithm used for classification and regression tasks. It is effective for analyzing multifactorial clinical data and allows for the modeling of complex nonlinear relationships. Random Forest is a powerful and versatile algorithm that is often used as a «baseline» for comparison with more complex models. It is widely used to predict the occurrence of infectious complications in abdominal surgery and demonstrates good sensitivity, with an AUROC of 0.8–0.89 [89, 90].

**Table 10. Accuracy and completeness metrics for models predicting infection in the surgical site.**

| Model               | AUROC |             | AUPRC |             |
|---------------------|-------|-------------|-------|-------------|
|                     | Mean  | 95% CI      | Mean  | 95% CI      |
| Logistic regression | 0.677 | 0.669–0.685 | 0.194 | 0.189–0.199 |
| Random forest       | 0.764 | 0.756–0.772 | 0.484 | 0.476–0.492 |
| Gradient boosting   | 0.766 | 0.759–0.774 | 0.483 | 0.475–0.491 |
| Neural network      | 0.770 | 0.763–0.778 | 0.488 | 0.480–0.496 |

**Note.** Surgical site infection (SSI) is defined as a superficial, deep, or organ/cavity infection. AUROC — Area under the ROC curve (the «sensitivity-specificity» curve); AUPRC — Area under the Precision-Recall curve («precision-recall» curve).

**The Support Vector Machine (SVM)** is a powerful machine learning algorithm used for classification and regression tasks. Its key idea is to find the optimal separating hyperplane in feature space that maximizes the margin between classes. In the article by Yuan JH, Jin YM, Xiang JY, et al., 2025 [91], ROC curve analysis showed that the Support Vector Machine model, when applied to the training cohort, demonstrated an AUC of 0.985 (95% CI: 0.970–0.999) with a specificity of 0.944 and a perfect sensitivity of 1.000 when assessing the risk of postoperative mortality in patients who underwent abdominal surgery.

**Ensemble machine learning models** are an approach in which several base models (e. g., random forests, linear regressions, or SVMs) are combined to improve the accuracy and robustness of predictions. The main idea is to combine weak or diverse models to create a stronger and more reliable algorithm. According to various studies, ensemble methods are the most accurate in predicting events, with a sensitivity of up to 85% six hours prior to clinical diagnosis [90].

Table 10, based on data from Chen KA et al. 2023 [10], presents a comparison of the performance characteristics of various machine learning methods in predicting the onset of infection at the surgical site.

**The AISE (Artificial Intelligence Scoring Engine)** system is a specific commercial system for predicting sepsis and other complications, developed by PeraHealth. It is one of the few AI tools to have been widely implemented in hospitals.

The model is highly effective (AUROC 0.85) and can predict the onset of sepsis 4 hours before it develops, based on medical history, clinical, and laboratory data [92].

**The microbiological aspect of perioperative infection risk and antibiotic resistance.** The perioperative risk of infection is undoubtedly determined not only by patient-related risk factors and the type of surgery, but also by the likely spectrum of pathogens, as well as the local situation regarding antibiotic resistance in the ward and the hospital [34, 93–96]. *Staphylococcus aureus* and coagulase-negative staphylococci are the most common pathogens for superficial and deep surgical site infections, whereas *Escherichia coli* and anaerobes, including

*Bacteroides* spp., are more typical for infections of internal organs and abdominal surgery [34, 96]. In community-acquired intra-abdominal infections these are the *Enterobacterales* (*E. coli*, *Klebsiella* spp.), streptococci, and anaerobic flora; in postoperative peritonitis, the spectrum of pathogens often expands to include *Enterococcus* spp., multidrug-resistant (MDR) Gram-negative bacteria, and, in some patients, fungal flora [96].

The choice of antimicrobial therapy should be based on the source of infection, the severity of the condition, the patient's immune status, risk factors for antibiotic resistance, and local antibiotic susceptibility testing data [96–98]. High-risk factors for infection with resistant Gram-negative microorganisms include recent hospitalization, prior therapy with broad-spectrum antibiotics, colonization with MDR pathogens, repeat surgeries, and prolonged hospital stays [96–98]. In patients in this group, it is necessary to collect specimens for microbiological testing, as the results of culture and susceptibility testing are important not only for tailoring treatment but also for understanding local microbiological epidemiology [96–98].

Current guidelines for perioperative antibiotic prophylaxis indicate the need to administer an antibiotic before the surgical incision: within 120 minutes according to WHO recommendations [95] and, as a rule, within 60 minutes according to SHEA/IDSA/APIC and ASHP [93, 94]; for vancomycin and fluoroquinolones, an interval of up to 120 minutes is permitted [93, 94]. It should be noted that for prolonged procedures, repeat administration of the drug is required [93, 94]. Extending prophylaxis beyond the end of surgery — including in cases where drains are in place — is not recommended, as it does not reduce the incidence of surgical site infection and increases the risk of adverse effects, including the selection of resistant microorganisms [34, 93–95, 99]. For elective colorectal surgery, the combination of oral and parenteral antibiotic prophylaxis has been shown to be effective [93, 94].

## Conclusion

Risk factors for infectious complications in the perioperative period can be divided into the following groups: modifiable/non-modifiable,

healthcare personnel-related, healthcare facility-related, or patient-related.

This review helps to substantiate the concept of perioperative risk of infectious complications based on an analysis of current approaches to the definition, classification, and prediction of adverse outcomes.

The information presented underscores the importance of a multidisciplinary approach to reducing the risk of infection during the perioperative period. Optimizing the use of prognostic scales and

laboratory markers can significantly improve outcomes.

Infectious complications following abdominal surgery remain one of the key causes of postoperative mortality, prolonged hospital stays, and financial costs. Their incidence ranges from 1% (surgical site infection) to 22.6% (sepsis), and the mortality rate for septic shock reaches 67.8%.

Based on current knowledge, preventive measures must be implemented to reduce the incidence of perioperative infectious complications.

## References

1. Kehlet H., Lobo D.N. Exploring the need for reconsideration of trial design in perioperative outcomes research: a narrative review. *EClinicalMedicine*. 2024; 70: 102510. DOI: 10.1016/j.eclinm.2024.102510. PMID: 38444430.
2. Sartelli M, Barie P, Agnoletti V, Al-Hasan MN, Ansaloni L, Biffi W, Buonomo L, et al. Intra-abdominal infections survival guide: a position statement by the Global Alliance For Infections In Surgery. *World J Emerg Surg*. 2024; 19 (1): 22. DOI: 10.1186/s13017-024-00552-9. PMID: 38851700.
3. Riché F.C., Dray X., Laisné M.J., Matéo J., Raskine L., Sanson-Le Pors M.J., Payen D., et al. Factors associated with septic shock and mortality in generalized peritonitis: comparison between community-acquired and postoperative peritonitis. *Crit Care*. 2009; 13 (3): R99. DOI: 10.1186/cc7931. PMID: 19552799.
4. Zimlichman E., Henderson D., Tamir O., Franz C., Song P., Yamin C.K., Keohane C., et al. Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. *JAMA Intern Med*. 2013; 173 (22): 2039–2046. DOI: 10.1001/jamainternmed.2013.9763. PMID: 23999949.
5. Kirkland K.B., Briggs J.P., Trivette S.L., Wilkinson W.E., Sexton D.J. The impact of surgical-site infections in the 1990s: attributable mortality, excess length of hospitalization, and extra costs. *Infect Control Hosp Epidemiol*. 1999; 20 (11): 725–730. DOI: 10.1086/501572. PMID: 10580621.
6. de Lissovoy G., Fraeman K., Hutchins V., Murphy D., Song D., Vaughn B.B. Surgical site infection: incidence and impact on hospital utilization and treatment costs. *Am J Infect Control*. 2009; 37 (5): 387–397. DOI: 10.1016/j.ajic.2008.12.010. PMID: 19398246.
7. Заболотских И.Б. Концепция периоперационного риска: обзор литературы. *Вестник интенсивной терапии имени А.И. Салтанова*. 2024; (4): 40–57. Zabolotskikh I.B. The concept of perioperative risk: a literature review. *Ann Crit Care = Vestnik Intensivnoy Terapii im A.I. Saltanova* 2024; (4): 40–57. (in Russ.). DOI: 10.21320/1818-474X-2024-4-40-57.
8. Денисюк Н.Б. Эпидемиологические особенности инфекций, связанных с оказанием медицинской помощи, в Оренбургской области. *Эпидемиология и инфекционные болезни. Актуальные вопросы*. 2021; 11 (1): 37–42. Denisyuk N.B. Epidemiological features of healthcare-associated infections in the Orenburg Region. *Epidemiology and Infectious Diseases. Current Items = Epidemiologiya i Infektsionnye Bolezni. Aktualnye Voprosy*. 2021; 11 (1): 37–42. DOI: 10.18565/epidem.2021.11.1.37-42.
9. Wong J.K.L., Ke Y., Ong Y.J., Li H., Wong T.H., Abdullah H.R. The impact of preoperative glycated hemoglobin (HbA1c) on postoperative complications after elective major abdominal surgery: a meta-analysis. *Korean J Anesthesiol*. 2022; 75 (1): 47–60. DOI: 10.4097/kja.21295. PMID: 34619855.
10. Chen K.A., Joisa C.U., Stem J.M., Guillem J.G., Gomez S.M., Kapadia M.R. Improved prediction of surgical-site infection after colorectal surgery using machine learning. *Dis Colon Rectum*. 2023; 66 (3): 458–466. DOI: 10.1097/DCR.0000000000002559. PMID: 36538699.
11. Okui J., Ueno R., Matsui H., Uegami W., Hayashi H., Miyajima T., Kusanagi H. Early prediction model of organ/space surgical site infection after elective gastrointestinal or hepatopancreatobiliary cancer surgery. *J Infect Chemother*. 2020; 26 (9): 916–922. DOI: 10.1016/j.jiac.2020.04.009. PMID: 32360091.
12. Shakir A., Abate D., Tebeje F., Weledegebreel F. Magnitude of surgical site infections, bacterial etiologies, associated factors and antimicrobial susceptibility patterns of isolates among post-operative patients in Harari Region public hospitals, Harar, Eastern Ethiopia. *Infect Drug Resist*. 2021; 14: 4629–4639. DOI: 10.2147/IDR.S329721. PMID: 34764659.
13. Erdem H., Ankarali H., Al-Tawfiq J.A., Angamuthu K., Piljic D., Umihanic A., Dayyab F., et al; ID-IRI Study Group. Mortality associated with surgical site infections following cardiac surgery: insights from the International ID-IRI Study. *IJID Reg*. 2025; 14: 100566. DOI: 10.1016/j.ijregi.2025.100566. PMID: 39931188.
14. Plaeke P., De Man J.G., Coenen S., Jorens P.G., De Winter B.Y., Hubens G. Clinical- and surgery-specific risk factors for post-operative sepsis: a systematic review and meta-analysis of over 30 million patients. *Surg Today*. 2020; 50 (5): 427–439. DOI: 10.1007/s00595-019-01827-4. PMID: 31172283.
15. Xu X., Dong H.C., Yao Z., Zhao Y.Z. Risk factors for postoperative sepsis in patients with gastrointestinal perforation. *World J Clin Cases*. 2020; 8 (4): 670–678. DOI: 10.12998/wjcc.v8.i4.670. PMID: 32149051.
16. Seymour C.W., Gesten E., Prescott H.C., Friedrich M.E., Iwashyna T.J., Phillips G.S., Lemeshow S., et al. Time to treatment and mortality during mandated emergency care for sepsis. *N Engl J Med*. 2017; 376 (23): 2235–2244. DOI: 10.1056/NEJMoa1703058. PMID: 28528569.
17. Canet J., Gallart L., Gomar C., Paluzie G., Vallès J., Castillo J., Sabate S., et al; ARISCAT Group. Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology*. 2010; 113 (6): 1338–1350. DOI: 10.1097/ALN.0b013e3181fc6e0a. PMID: 21045639.
18. Plat V.D., Voeten D.M., Daams F., van der Peet D.L., Straatman J. C-reactive protein after major abdominal surgery in daily practice. *Surgery*. 2021; 170 (4): 1131–1139. DOI: 10.1016/j.surg.2021.04.025. PMID: 34024474.
19. Napolitano L.M. Intra-abdominal infections. *Semin Respir Crit Care Med*. 2022; 43 (1): 10–27. DOI: 10.1055/s-0041-1741053. PMID: 35172355.
20. Horan T.C., Andrus M., Dudeck M.A. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control*. 2008; 36 (5): 309–332. DOI: 10.1016/j.ajic.2008.03.002. PMID: 18538699.
21. Киров М.Ю., Кузьков В.В., Проценко Д.Н., Щеголев А.В., Бабаев М.А., Белоцерковский Б.З., Быков А.О., и соавт. Септический шок у взрослых: клинические рекомендации Общероссийской общественной организации «Федерация анестезиологов и реаниматологов». *Вестник интенсивной терапии им. А.И. Салтанова*. 2023;

- 4: 7–42. Kirov M.Yu., Kuzkov V.V., Protsenko D.N., Shchegolev A.V., Babaev M.A., Belotserkovsky B.Z., Bykov A.O., et al. Septic shock in adults: guidelines of the All-Russian public organization «Federation of Anesthesiologists and Reanimatologists». *Ann Crit Care = Vestnik Intensivnoy Terapii im A.I. Saltanova*. 2023; 4: 7–42. (in Russ.). DOI: 10.21320/1818-474X-2023-4-7-4.
22. Singer M., Deutschman C.S., Seymour C.W., Shankar-Hari M., Annane D., Bauer M., Bellomo R., et al. The Third International Consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016; 315 (8): 801–810. DOI: 10.1001/jama.2016.0287. PMID: 26903338.
23. Torres A., Niederman M.S., Chastre J., Ewig S., Fernandez-Vandellos P., Hanberger H., Kollef M., et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT). *Eur Respir J*. 2017; 50 (3): 1700582. DOI: 10.1183/13993003.00582-2017. PMID: 28890434.
24. Pugin J., Auckenthaler R., Mili N., Janssens J.P., Lew P.D., Suter P.M. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic «blind» bronchoalveolar lavage fluid. *Am Rev Respir Dis*. 1991; 143 (5 Pt 1): 1121–1129. DOI: 10.1164/ajrccm/143.5\_Pt\_1.1121. PMID: 2024824.
25. Xu Z., Qu H., Gong Z., Kanani G., Zhang F., Ren Y., Shao S., et al. Risk factors for surgical site infection in patients undergoing colorectal surgery: a meta-analysis of observational studies. *PLoS One*. 2021; 16 (10): e0259107. DOI: 10.1371/journal.pone.0259107. PMID: 34710197.
26. Allegranzi B., Bischoff P., de Jonge S., Kubilay N.Z., Zayed B., Gomes S.M., Abbas M., et al; WHO Guidelines Development Group. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis*. 2016; 16 (12): e276–e287. DOI: 10.1016/S1473-3099(16)30398-X. PMID: 27816413.
27. Balci B., Kilinc G., Calik B., Aydin C. The association between preoperative 25-OH vitamin D levels and postoperative complications in patients undergoing colorectal cancer surgery. *BMC Surg*. 2021; 21 (1): 369. DOI: 10.1186/s12893-021-01369-y. PMID: 34666739.
28. Washko P.W., Wang Y., Levine M. Ascorbic acid recycling in human neutrophils. *J Biol Chem*. 1993; 268 (21): 15531–15535. PMID: 8340380.
29. Pichler A., Kurz A., Eichlseder M., Graf A., Eichinger M., Taschner A., Kabon B., et al; INSIGHT Study Group. Perioperative inflammatory reSponse assessment In hiGH-risk patienTs undergoing non-cardiac surgery (INSIGHT): study protocol of a prospective non-interventional observational study. *BMJ Open*. 2023; 13 (7): e065469. DOI: 10.1136/bmjopen-2022-065469. PMID: 37474184.
30. Tian Y., Li R., Wang G., Xu K., Li H., He L. Prediction of postoperative infectious complications in elderly patients with colorectal cancer: a study based on improved machine learning. *BMC Med Inform Decis Mak*. 2024; 24 (1): 11. DOI: 10.1186/s12911-023-02411-0. PMID: 38184556.
31. Bislenghi G., Vanhaverbeke A., Fieuws S., de Buck van Overstraeten A., D'Hoore A., Schuermans A., Wolt-huis A.M. Risk factors for surgical site infection after colorectal resection: a prospective single centre study. *Acta Chir Belg*. 2021; 121 (2): 86–93. DOI: 10.1080/00015458.2019.1675969. PMID: 31577178.
32. Eder M., Sommerstein R., Szelecsenyi A., Schweiger A., Schlegel M., Atkinson A., Kuster S.P., et al. Association between the introduction of a national targeted intervention program and the incidence of surgical site infections in Swiss acute care hospitals. *Antimicrob Resist Infect Control*. 2023; 12 (1): 134. DOI: 10.1186/s13756-023-01336-7. PMID: 37996935.
33. Vincent J.L., Rello J., Marshall J., Silva E., Anzueto A., Martin C.D., Moreno R., et al; EPIC II Group. International study of the prevalence and outcomes of infection in intensive care units. *JAMA*. 2009; 302 (21): 2323–2329. DOI: 10.1001/jama.2009.1754. PMID: 19952319.
34. Berríos-Torres S.I., Umscheid C.A., Bratzler D.W., Leas B., Stone E.C., Kelz R.R., Reinke C.E., et al. Centers for Disease Control and Prevention guideline for the prevention of surgical site infection, 2017. *JAMA Surg*. 2017; 152 (8): 784–791. DOI: 10.1001/jamasurg.2017.0904. PMID: 28467526.
35. Hou Y., Collinsworth A., Hasa F., Griffin L. Incidence and impact of surgical site complications on length of stay and cost of care for patients undergoing open procedures. *Surg Open Sci*. 2023; 14: 31–45. DOI: 10.1016/j.sopen.2023.05.004. PMID: 37599673.
36. Verberk J.D.M., Meijs A.P., Vos M.C., Schreurs L.M.A., Geerlings S.E., de Greeff S.C., Koek M.B.G. Contribution of prior, multiple-, and repetitive surgeries to the risk of surgical site infections in the Netherlands. *Infect Control Hosp Epidemiol*. 2017; 38 (11): 1298–1305. DOI: 10.1017/ice.2017.195. PMID: 28918773.
37. Moreno R.P., Metnitz B., Adler L., Hoecht A., Bauer P., Metnitz P.G.; SAPS 3 Investigators. Sepsis mortality prediction based on predisposition, infection and response. *Intensive Care Med*. 2008; 34 (3): 496–504. DOI: 10.1007/s00134-007-0943-1. PMID: 18060541.
38. van Ramshorst G.H., Nieuwenhuizen J., Hop W.C., Arends P., Boom J., Jeekel J., Lange J.F. Abdominal wound dehiscence in adults: development and validation of a risk model. *World J Surg*. 2010; 34 (1): 20–27. DOI: 10.1007/s00268-009-0277-y. PMID: 19898894.
39. Mujagic E., Zeindler J., Coslovsky M., Hoffmann H., Soysal S.D., Mechera R., von Strauss M., et al. The association of surgical drains with surgical site infections: a prospective observational study. *Am J Surg*. 2019; 217 (1): 17–23. DOI: 10.1016/j.amjsurg.2018.06.015. PMID: 29935905.
40. Stavropoulou E., Atkinson A., Eisenring M.C., Fux C.A., Marschall J., Senn L., Troillet N. Association of antimicrobial perioperative prophylaxis with cefuroxime

- plus metronidazole or amoxicillin/clavulanic acid and surgical site infections in colorectal surgery. *Antimicrob Resist Infect Control*. 2023; 12 (1): 105. DOI: 10.1186/s13756-023-01307-y. PMID: 37726838.
41. Paasch C., Schildberg C., Lünse S., Heisler S., Meyer J., Kirbach J., Kobelt E., et al. Optimal timing for antimicrobial prophylaxis to reduce surgical site infections: a retrospective analysis of 531 patients. *Sci Rep*. 2023; 13 (1): 9405. DOI: 10.1038/s41598-023-36588-1. PMID: 37296185.
  42. Sommerstein R., Atkinson A., Kuster S.P., Vuichard-Gysin D., Harbarth S., Troillet N., Widmer A.F.; Swiss-noso Network. Association between antimicrobial prophylaxis with double-dose cefuroxime and surgical site infections in patients weighing 80 kg or more. *JAMA Netw Open*. 2021; 4 (12): e2138926. DOI: 10.1001/jamanetworkopen.2021.38926. PMID: 34910149.
  43. Menzenbach J., Layer Y.C., Layer Y.L., Mayr A., Coburn M., Wittmann M., Hilbert T. The level of postoperative care influences mortality prediction by the POSPOM score: a retrospective cohort analysis. *PLoS One*. 2021; 16 (9): e0257829. DOI: 10.1371/journal.pone.0257829. PMID: 34587207.
  44. Jahangir F., Haghdooost A., Moameri H., Okhovati M. Incidence and risk factors of surgical site infection in abdominal surgeries: a scoping review of cohort and case-control studies. *Iran J Med Sci*. 2024; 49 (7): 402–412. DOI: 10.30476/ijms.2024.100819.3338. PMID: 39114633.
  45. Chapman B.C., Hosokawa P., Henderson W., Paniccia A., Overbey D.M., Messersmith W., Lieu C., et al. Impact of neoadjuvant chemoradiation on perioperative outcomes in patients with rectal cancer. *J Surg Oncol*. 2017; 115 (8): 1033–1044. DOI: 10.1002/jso.24613. PMID: 28334436.
  46. Janes G., Mills T., Budworth L., Johnson J., Lawton R. The association between health care staff engagement and patient safety outcomes: a systematic review and meta-analysis. *J Patient Saf*. 2021; 17 (3): 207–216. DOI: 10.1097/PTS.0000000000000807. PMID: 33427792.
  47. Bain C.R., Myles P.S., Martin C., Wallace S., Shulman M.A., Corcoran T., Bellomo R., et al; RELIEF Trial Investigators. Postoperative systemic inflammation after major abdominal surgery: patient-centered outcomes. *Anaesthesia*. 2023; 78 (11): 1365–1375. DOI: 10.1111/anae.16104. PMID: 37531295.
  48. Zhu Y., Xu H., Liu W., Qi W., Yang X., Ye L., Cao Q., et al. Glasgow prognostic score is a practical predictive index for postoperative intra-abdominal septic complications after bowel resection in Crohn's disease patients. *Int J Colorectal Dis*. 2018; 33 (7): 947–953. DOI: 10.1007/s00384-018-3035-5. PMID: 29687374.
  49. Weimann A., Braga M., Harsanyi L., Laviano A., Ljungqvist O., Soeters P., DGEM (German Society for Nutritional Medicine); Jauch K.W., et al. ESPEN guidelines on enteral nutrition: surgery including organ transplantation. *Clin Nutr*. 2006; 25 (2): 224–244. DOI: 10.1016/j.clnu.2006.01.015. PMID: 16698152.
  50. Puértolas N., Osorio J., Jericó C., Miranda C., Santamaría M., Artigau E., Galofre G., et al. Effect of perioperative blood transfusions and infectious complications on inflammatory activation and long-term survival following gastric cancer resection. *Cancers (Basel)*. 2022; 15 (1): 144. DOI: 10.3390/cancers15010144. PMID: 36612141.
  51. Owens W.D., Felts J.A., Spitznagel E.L. Jr. ASA physical status classifications: a study of consistency of ratings. *Anesthesiology*. 1978; 49 (4): 239–243. DOI: 10.1097/00000542-197810000-00003. PMID: 697077.
  52. Заболотских И.Б., Трембач Н.В., Мусаева Т.С., Дуниц П.В., Голубцов В.В., Григорьев Е.В., Грищан А.И., с соавт. Национальное многоцентровое проспективное обсервационное исследование «Роль сопутствующих заболеваний в стратификации риска послеоперационных осложнений» — STOPRISK: протокол исследования. *Вестник интенсивной терапии им. А.И. Салтанова*. 2022; 4: 24–35. Zabolotskikh I.B., Trembach N.V., Musaeva T.S., Dunts P.V., Golubtsov V.V., Grigoriev E.V., Gritsan A.I., et al. National multicenter prospective observational study «The role of concomitant diseases in the poSTOPerative complications RISK stratification» — STOPRISK: study protocol. *Ann Crit Care = Vestnik Intensivnoy Terapii im A.I. Saltanova*. 2022; 4: 24–35. (in Russ.). DOI: 10.21320/1818-474X-2022-4-24-35.
  53. Grigorescu B.L., Săplăcan I., Petrișor M., Bordea I.R., Fodor R., Lazăr A. Perioperative risk stratification: a need for an improved assessment in surgery and anesthesia — a pilot study. *Medicina (Kaunas)*. 2021; 57 (10): 1132. DOI: 10.3390/medicina57101132. PMID: 34684169.
  54. Заболотских И.Б., Трембач Н.В. Пациенты высокого периоперационного риска: два подхода к стратификации. *Вестник интенсивной терапии имени А.И. Салтанова*. 2019; (4): 34–46. Zabolotskikh I.B., Trembach N.V. High perioperative risk patients: two approaches to stratification. Review. *Ann Crit Care = Vestnik Intensivnoy Terapii im A.I. Saltanova*. 2019; (4): 34–46. (in Russ.). DOI: 10.21320/1818-474X-2019-4-34-46.
  55. Vincent J.L., de Mendonça A., Cantraine F., Moreno R., Takala J., Suter P.M., Sprung C.L., et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. *Crit Care Med*. 1998; 26 (11): 1793–1800. DOI: 10.1097/00003246-199811000-00016. PMID: 9824069.
  56. Evans L., Rhodes A., Alhazzani W., Antonelli M., Coopersmith C.M., French C., Machado E.R. et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med*. 2021; 47 (11): 1181–1247. DOI: 10.1007/s00134-021-06506-y. PMID: 34599691.
  57. Seymour C.W., Liu V.X., Iwashyna T.J., Brunkhorst F.M., Rea T.D., Scherag A., Rubenfeld G., et al. Assessment of clinical criteria for sepsis: for the Third International Consensus Definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016; 315 (8): 762–774. DOI: 10.1001/jama.2016.0288. PMID: 26903335.
  58. Raith E.P., Udy A.A., Bailey M., McGloughlin S., MacIsaac C., Bellomo R., Pilcher D.V. Prognostic accuracy of the SOFA score, SIRS criteria, and qSOFA score for in-hospital mortality among adults with suspected

- infection admitted to the ICU. *JAMA*. 2017; 317 (3): 290–300. DOI: 10.1001/jama.2016.20328. PMID: 28114553.
59. Vincent J.L., Moreno R., Takala J., Willatts S., De Mendonça A., Bruining H., Reinhart C.K., et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med*. 1996; 22 (7): 707–710. DOI: 10.1007/BF01709751. PMID: 8844239.
  60. McMillan M.T., Allegrini V., Asbun H.J., Ball C.G., Bassi C., Beane J.D., Behrman S.W., et al. Incorporation of procedure-specific risk into the ACS-NSQIP Surgical Risk Calculator improves the prediction of morbidity and mortality after pancreateoduodenectomy. *Ann Surg*. 2017; 265 (5): 978–986. DOI: 10.1097/SLA.0000000000001796. PMID: 27232260.
  61. van Walraven C., Musselman R. The Surgical Site Infection Risk Score (SSIRS): a model to predict the risk of surgical site infections. *PLoS One*. 2013; 8 (6): e67167. DOI: 10.1371/journal.pone.0067167. PMID: 23826224.
  62. Bilimoria K.Y., Liu Y., Paruch J.L., Zhou L., Kniecik T.E., Ko C.Y., Cohen M.E. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. *J Am Coll Surg*. 2013; 217 (5): 833–842.e1-3. DOI: 10.1016/j.jamcollsurg.2013.07.385. PMID: 24055383.
  63. Copeland G.P., Jones D., Walters M. POSSUM: a scoring system for surgical audit. *Br J Surg*. 1991; 78 (3): 355–360. DOI: 10.1002/bjs.1800780327. PMID: 2021856.
  64. Protopapa K.L., Simpson J.C., Smith N.C., Moonesinghe S.R. Development and validation of the Surgical Outcome Risk Tool (SORT). *Br J Surg*. 2014; 101 (13): 1774–1783. DOI: 10.1002/bjs.9638. PMID: 25388883.
  65. Sellers M.M., Merkow R.P., Halverson A., Hinami K., Kelz R.R., Bentrem D.J., Bilimoria K.Y. Validation of new readmission data in the American College of Surgeons National Surgical Quality Improvement Program. *J Am Coll Surg*. 2013; 216 (3): 420–427. DOI: 10.1016/j.jamcollsurg.2012.11.013. PMID: 23332220.
  66. Lee T.H., Marcantonio E.R., Mangione C.M., Thomas E.J., Polanczyk C.A., Cook E.F., Sugarbaker D.J., et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999; 100 (10): 1043–1049. DOI: 10.1161/01.CIR.100.10.1043. PMID: 10477528.
  67. Gajdos C., Kile D., Hawn M.T., Finlayson E., Henderson W.G., Robinson T.N. Advancing age and 30-day adverse outcomes after nonemergent general surgeries. *J Am Geriatr Soc*. 2013; 61 (9): 1608–1614. DOI: 10.1111/jgs.12401. PMID: 23927841.
  68. Wolters U., Wolf T., Stützer H., Schröder T. ASA classification and perioperative variables as predictors of postoperative outcome. *Br J Anaesth*. 1996; 77 (2): 217–222. DOI: 10.1093/bja/77.2.217. PMID: 8881629.
  69. Morris E.J., Taylor E.F., Thomas J.D., Quirke P., Finan P.J., Coleman M.P., Rachet B., et al. Thirty-day postoperative mortality after colorectal cancer surgery in England. *Gut*. 2011; 60 (6): 806–813. DOI: 10.1136/gut.2010.232181. PMID: 21486939.
  70. Pearse R.M., Harrison D.A., James P., Watson D., Hinds C., Rhodes A., Grounds R.M., et al. Identification and characterisation of the high-risk surgical population in the United Kingdom. *Crit Care*. 2006; 10 (3): R81. DOI: 10.1186/cc4928. PMID: 16749940.
  71. Prytherch D.R., Whiteley M.S., Higgins B., Weaver P.C., Prout W.G., Powell S.J. POSSUM and Portsmouth POSSUM for predicting mortality. *Br J Surg*. 1998; 85 (9): 1217–1220. DOI: 10.1046/j.1365-2168.1998.00840.x. PMID: 9752863.
  72. Oduncu A.F., Kyyan G.S., Yalçınly S. Comparison of qSOFA, SIRS, and NEWS scoring systems for diagnosis, mortality, and morbidity of sepsis in emergency department. *Am J Emerg Med*. 2021; 48: 54–59. DOI: 10.1016/j.ajem.2021.04.006. PMID: 33839632.
  73. Bagateliya Z.A., Grekov D.N., Komarova A.G., Kulshhev V.M., Sokolov N.Y., Kuts I.N., Lebedko M.S. Integral scales in assessing the risk of postoperative morbidity and mortality. *Khirurgiya (Mosk)*. 2023; (11): 25–33. DOI: 10.17116/hirurgia202311125. PMID: 38010015.
  74. Vather R., Zargar-Shoshtari K., Adegbola S., Hill A.G. Comparison of the POSSUM, P-POSSUM and Cr-POSSUM scoring systems as predictors of postoperative mortality in patients undergoing major colorectal surgery. *ANZ J Surg*. 2006; 76 (9): 812–816. DOI: 10.1111/j.1445-2197.2006.03875.x. PMID: 16922904.
  75. Witczak A., Jurałowicz P., Modzelewski B., Gawlik M. C-reactive protein as a marker of postoperative septic complications. *Pol Przegl Chir*. 2012; 84 (2): 93–98. DOI: 10.2478/v10035-012-0015-2. PMID: 22487742.
  76. Ge X., Cao Y., Wang H., Ding C., Tian H., Zhang X., Gong J., et al. Diagnostic accuracy of the postoperative ratio of C-reactive protein to albumin for complications after colorectal surgery. *World J Surg Oncol*. 2017; 15 (1): 15. DOI: 10.1186/s12957-016-1092-1. PMID: 28069031.
  77. Straatman J., Harmsen A.M., Cuesta M.A., Berkhof J., Jansma E.P., van der Peet D.L. Predictive value of C-reactive protein for major complications after major abdominal surgery: a systematic review and pooled-analysis. *PLoS One*. 2015; 10 (7): e0132995. DOI: 10.1371/journal.pone.0132995. PMID: 26177542.
  78. Gans S.L., Atema J.J., van Dieren S., Koerkamp B.G., Boermeester M.A. Diagnostic value of C-reactive protein to rule out infectious complications after major abdominal surgery: a systematic review and meta-analysis. *Int J Colorectal Dis*. 2015; 30 (7): 861–873. DOI: 10.1007/s00384-015-2205-y. PMID: 25935447.
  79. Tanaka T., Narazaki M., Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol*. 2014; 6 (10): a016295. DOI: 10.1101/cshperspect.a016295. PMID: 25190079.
  80. Procházka V., Lacina L., Smetana K. Jr, Svoboda M., Skřivanová K., Beňovská M., Jarkovský J., et al. Serum concentrations of proinflammatory biomarker interleukin-6 (IL-6) as a predictor of postoperative complications after elective colorectal surgery. *World J Surg Oncol*. 2023; 21 (1): 384. DOI: 10.1186/s12957-023-03270-9. PMID: 38098074.

81. Rettig T.C., Verwijmeren L., Dijkstra I.M., Boerma D., van de Garde E.M., Noordzij P.G. Postoperative interleukin-6 level and early detection of complications after elective major abdominal surgery. *Ann Surg*. 2016; 263 (6): 1207–1212. DOI: 10.1097/SLA.0000000000001342. PMID: 26135695.
82. Basodan N., Al Mehmadi A-z.E., Al Mehmadi A-h.E., Aldawood S.M., Hawsawi A., Fatini F., Mulla Z.M., et al. Septic shock: management and outcomes. *Cureus*. 2022; 14 (12): e32158. DOI: 10.7759/cureus.32158. PMID: 36601152.
83. Sager R., Kutz A., Mueller B., Schuetz P. Procalcitonin-guided diagnosis and antibiotic stewardship revisited. *BMC Med*. 2017; 15 (1): 15. DOI: 10.1186/s12916-017-0795-7. PMID: 28114931.
84. Wacker C., Prkno A., Brunkhorst F.M., Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013; 13 (5): 426–435. DOI: 10.1016/S1473-3099(12)70323-7. PMID: 23375419.
85. Huang T.S., Huang S.S., Shyu Y.C., Lee C.H., Jwo S.C., Chen P.J., Chen H.Y. A procalcitonin-based algorithm to guide antibiotic therapy in secondary peritonitis following emergency surgery: a prospective study with propensity score matching analysis. *PLoS One*. 2014; 9 (3): e90539. DOI: 10.1371/journal.pone.0090539. PMID: 24594916.
86. Chomba R.N., Moeng M.S., Lowman W. Procalcitonin-guided antibiotic therapy for suspected and confirmed sepsis of patients in a surgical trauma ICU: a prospective, two period cross-over, interventional study. *S Afr J Surg*. 2020; 5 (3): 143–149. PMID: 33231007.
87. Tur-Martínez J., Osorio J., Pérez-Romero N., Puértolas-Rico N., Pera M., Delgado S., Rodríguez-Santiago J. Preoperative neutrophil-to-lymphocyte ratio behaves as an independent prognostic factor even in patients with postoperative complications after curative resection for gastric cancer. *Langenbecks Arch Surg*. 2022; 407 (3): 1017–1026. DOI: 10.1007/s00423-022-02432-9. PMID: 34999967.
88. Qian B., Zheng Y., Jia H., Zheng X., Gao R., Li W. Neutrophil-lymphocyte ratio as a predictive marker for postoperative infectious complications: a systematic review and meta-analysis. *Heliyon*. 2023; 9 (5): e15586. DOI: 10.1016/j.heliyon.2023.e15586. PMID: 37159687.
89. van der Meijden S.L., van Boekel A.M., Schinkelshoek L.J., van Goor H., Steyerberg E.W., Nellissen R.G.H.H., Mesotten D., et al; PERISCOPE Group. Development and validation of artificial intelligence models for early detection of postoperative infections (PERISCOPE): a multicentre study using electronic health record data. *Lancet Reg Health Eur*. 2024; 49: 101163. DOI: 10.1016/j.lanepe.2024.101163. PMID: 39720095.
90. Lin T.H., Chung H.Y., Jian M.J., Chang C.K., Lin H.H., Yen C.T., Tang S.H., et al. AI-driven innovations for early sepsis detection by combining predictive accuracy with blood count analysis in an emergency setting: retrospective study. *J Med Internet Res*. 2025; 27: e56155. DOI: 10.2196/56155. PMID: 39854695.
91. Yuan J.H., Jin Y.M., Xiang J.Y., Li S.S., Zhong Y.X., Zhang S.L., Zhao B. Machine learning-based prediction of postoperative mortality risk after abdominal surgery. *World J Gastrointest Surg*. 2025; 17 (4): 103696. DOI: 10.4240/wjgs.v17.i4.103696. PMID: 40291872.
92. Nemati S., Holder A., Razmi F., Stanley M.D., Clifford G.D., Buchman T.G. An interpretable machine learning model for accurate prediction of sepsis in the ICU. *Crit Care Med*. 2018; 46 (4): 547–553. DOI: 10.1097/CCM.0000000000002936. PMID: 29286945.
93. Calderwood M.S., Anderson D.J., Bratzler D.W., Dellinger E.P., Garcia-Houchins S., Maragakis L.L., Nyquist A.-C., et al. Strategies to prevent surgical-site infections in acute-care hospitals: 2022 update. *Infect Control Hosp Epidemiol*. 2023; 44 (5): 695–720. DOI: 10.1017/ice.2023.67. PMID: 37137483.
94. Bratzler D.W., Dellinger E.P., Olsen K.M., Perl T.M., Auwaerter P.G., Bolon M.K., Fish D.N., et al.; American Society of Health-System Pharmacists; Infectious Disease Society of America; Surgical Infection Society; Society for Healthcare Epidemiology of America. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm*. 2013; 70 (3): 195–283. DOI: 10.2146/ajhp120568. PMID: 23327981.
95. World Health Organization. Global Guidelines for the Prevention of Surgical Site Infection. 2<sup>nd</sup> ed. World Health Organization; 2018.
96. Huston J.M., Barie P.S., Dellinger E.P., Forrester J.D., Duane T.M., Tessier J.M., Sawyer R.G., et al.; Therapeutics and Guidelines Committee. The Surgical Infection Society guidelines on the management of intra-abdominal infection: 2024 update. *Surg Infect (Larchmt)*. 2024; 25 (6): 419–435. DOI: 10.1089/sur.2024.137. PMID: 38990709.
97. Righi E., Mutters N.T., Guirao X., Del Toro M.D., Eckamm C., Friedrich A.W., Giannella M., et al. ESCMID/EUCIC clinical practice guidelines on perioperative antibiotic prophylaxis in patients colonized by multidrug-resistant Gram-negative bacteria before surgery. *Clin Microbiol Infect*. 2023; 29 (4): 463–479. DOI: 10.1016/j.cmi.2022.12.012. PMID: 36566836.
98. Righi E., Mutters N.T., Guirao X., Del Toro M.D., Eckamm C., Friedrich A.W., Giannella M., et al. European Society of Clinical Microbiology and Infectious Diseases/European Committee on Infection Control clinical practice guidelines on pre-operative decolonization and targeted prophylaxis in patients colonized by multidrug-resistant Gram-positive bacteria before surgery. *Clin Microbiol Infect*. 2024; 30 (12): 1537–1550. DOI: 10.1016/j.cmi.2024.07.012. PMID: 39154859.
99. de Jonge S.W., Boldingh Q.J.J., Solomkin J.S., Dellinger E.P., Egger M., Salanti G., Allegranzi B., et al. Effect of postoperative continuation of antibiotic prophylaxis on the incidence of surgical site infection: a systematic review and meta-analysis. *Lancet Infect Dis*. 2020; 20 (10): 1182–1192. DOI: 10.1016/S1473-3099(20)30084-0. PMID: 32470329.

Received 19.01.2026  
Accepted 08.07.2026

# Impact of Frailty on Outcomes and Management of Older and Very Old Patients in the Intensive Care Unit (Review)

Ainagul Zh. Bayalieva<sup>1,2</sup>, Veronica R. Davydova<sup>1,2\*</sup>

<sup>1</sup> Kazan State Medical University, Ministry of Health of Russia,  
49 Butlerova Str., 420012 Kazan, Russia

<sup>2</sup> Republican Clinical Hospital, Ministry of Health of the Republic of Tatarstan,  
138 Orenburgsky Trakt, 420064 Kazan, Russia

**For citation:** Ainagul Zh. Bayalieva, Veronica R. Davydova. Impact of Frailty on Outcomes and Management of Older and Very Old Patients in the Intensive Care Unit (Review). *Obshchaya Reanimatologiya = General Reanimatology*. 2026; 22 (4): 62–74. <https://doi.org/10.15360/1813-9779-2026-4-2611> [In Russ. and Engl.]

\*✉ Veronica R. Davydova, [veronika.dawyd@yandex.ru](mailto:veronika.dawyd@yandex.ru)

## Summary

**The aim of this review** is to assess the impact of frailty on outcomes in critical illness among older and very old patients, and to summarize current approaches to their management in the intensive care unit (ICU).

**Materials and Methods.** The review included 66 publications from PubMed, Google Scholar, the Cochrane Library, and eLIBRARY.RU. The search was conducted using the keywords «frailty», «older patient in intensive care», «treatment of elderly and senescent patients», «critical conditions in older age», «immunosenescence», «cognitive impairment», and «sarcopenia».

**Results.** We reviewed the processes encompassed by the concept of frailty or «senile asthenia» (SA); tools for assessing SA severity; identified the factors of physiological aging that affect the course of the underlying disease in elderly and senile patients in the ICU; and highlighted the specific features of their treatment approach.

**Conclusion.** A number of physiological aging factors significantly influence the management strategy for the studied ICU patient cohort, including changes in hormonal regulation, immunosenescence, sarcopenia, and altered cognitive function. Comorbidities, medication use patterns, and mobility status should also be taken into account. Frailty leads to higher mortality among older and very old ICU patients compared with patients without SA. For management of frail patients a unified approach is recommended combining a multidisciplinary team and family caregivers to maintain patient's motivation and adherence to the prescribed treatment.

**Keywords:** *frailty; older and very old patients; senescence; intensive care; mortality; comorbidity; sarcopenia; cognitive deficit; immunosenescence*

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

## Информация об авторах / Information about the authors:

Баялиева Айнагуль Жолдошевна / Ainagul Zh. Bayalieva, <https://orcid.org/0000-0001-7577-3284>

Давыдова Вероника Рустэмовна / Veronica R. Davydova, <https://orcid.org/0000-0003-4718-5076>

## Introduction

**Mortality rate among elderly and very old patients in intensive care units (ICUs).** At present, the average age of critically ill patients is approaching 65 years in many countries, and the proportion of critically ill patients aged 80 years and older is expected to grow faster than any other group in the ICU [1]. The mortality rate of elderly and very old patients in the ICU. Currently, the average age of critically ill patients is approaching 65 years in many countries, and the proportion of critically ill patients aged 80 years and older will increase faster than any other group in the ICU [1].

A meta-analysis of 129 studies examining outcomes in patients over 75 years of age admitted to the ICU found that ICU mortality ranged from 1% to 51% across the studies, in-hospital mortality ranged from 10% to 76%, 6-month mortality ranged from 21% to 58%, and 1-year mortality ranged from 33% to 72% [2].

According to a multicenter prospective cohort study by R. Bruno et al., ICU mortality among pa-

tients over 80 years of age was 19.8%, while 30-day mortality reached 34% [3]. According to the study by Jung et al., among patients aged 70 years and older who had COVID-19, the 30-day mortality rate was as high as 59% [4]. The use of ICU resources for such patients places a substantial burden on health-care systems [5, 6]. According to a Canadian study, the average cost of ICU stay for patients aged 80 years and older was USD 31,679 [7].

Undoubtedly, caring for elderly patients often presents ethical and practical challenges both before and during admission to the ICU. This growing trend requires a thorough understanding of the aging process and its impact on outcomes in critically ill patients [8]. Frailty in older adults may contribute to higher mortality rates in this age group, greater severity of illness, and increased healthcare costs.

The purpose of this review is to assess the impact of frailty on outcomes in critically ill geriatric — elderly and very old — patients and to summarize current approaches to their management in the ICU.

## Materials and Methods

The literature search was conducted using international and Russian scientific publication databases, including PubMed, Google Scholar, the Cochrane Library, and eLIBRARY.RU. The search queries included combinations of the following keywords: «old and senile age,» «intensive care of old patient,» «mortality,» «frailty,» «comorbidity,» «sarcopenia,» «cognitive deficit,» and «immuno-aging,» as well as additional terms reflecting age-related changes in elderly and very old patients, including «cardiovascular changes in old patient,» «pulmonary changes in old patient,» «renal changes in old patient,» and «age-specific syndromes».

The inclusion criteria were as follows: clinical studies conducted on large patient cohorts; meta-analyses; and topics focused on the study and specific assessment of frailty, the impact of physiological aging processes on the course of critical illnesses, and the evaluation of ICU admission rates among elderly and very old patients.

Studies with weak evidence and low informational value were excluded.

The review involved 66 sources published between 2015 and 2025, including 12 review articles, 6 systematic reviews and meta-analyses, data from the Cochrane Library database, 42 articles reporting the results of observational studies, 3 articles presenting the results of interventional studies, and 2 publications containing recommendations for patient management. The analyzed sources examined in particular patients older than 65 years, and the Clinical Frailty Scale (CFS) was used.

**Frailty in older adults and its contribution to outcomes in ICU patients.** The concept of frailty has evolved considerably over the past 25 years. The impact of frailty on the body is mediated through age-related changes in the functional state of the endocrine system; the central nervous system, primarily cognitive function, as well as the muscular and immune systems [9–13]. Thus, frailty is understood as an age-related condition characterized by the loss of physical and cognitive reserves, reduced compensatory mechanisms in response to stress, and increased susceptibility to a wide range of adverse outcomes (death, ICU admission, risk of falls, and hospitalization).

Frailty may or may not present obvious symptoms in everyday life, is not considered a diagnosis or classified as a separate clinical entity, yet it has its own pathophysiology and, consequently, affects treatment outcomes, especially in the ICU [14].

In the multicenter cohort study by J. Hewitt et al., which included 2,279 patients, frailty upon ICU admission was identified in 9% of patients aged 60–69 years, in 25% of those aged 70–79 years, and in 45% of patients older than 80 years. The 90-day mortality rate among patients with confirmed frailty

was 19%, compared with 3.6% among patients without frailty. Similar findings were observed for 30-day mortality, which was five times higher in the group of patients with confirmed frailty. Their average length of stay in the ICU increased from 3 to 5 days [15].

The VIP1 study evaluated 3,869 patients over the age of 80 who were admitted to the ICU with sepsis or other acute conditions over the course of one year. Clinical frailty, confirmed using the Clinical Frailty Scale, was present in 51.1% of patients with sepsis and in 46.4% of patients with other acute conditions. ICU mortality among frail patients with sepsis was 31.2%, while 30-day mortality reached 44.6%. Among frail patients with other conditions, the corresponding rates were 27.2% and 40.2%, respectively. The most significant independent predictors of 30-day mortality were age, the presence of clinical frailty, and a high SOFA score, rather than the type of condition that led to ICU admission [16].

The prospective cohort study VIP2 included patients aged 80 years and older who were admitted to 242 intensive care units across 22 countries over a six-month period. Frailty and cognitive impairment were evaluated as potential prognostic factors for 30-day survival. The average length of stay in the ICU was 3.88 days, while ICU survival and 30-day survival rates were 72.5% and 61.2%, respectively. The Clinical Frailty Scale (CFS) score was identified as an independent predictor of 30-day survival following ICU treatment [17].

Table 1 presents data from the main studies evaluating mortality and survival rates among elderly and very old patients with frailty (senile asthenia, SA).

**The processes of physiological aging that significantly affect the severity of conditions in elderly and very old patients.** Concurrency of reduced bodily functions with the development of severe illness among elderly patients in the ICU is the most likely cause of increased short-term and long-term mortality [18]. Comorbidities significantly contribute to aging processes therefore significantly affecting the severity of conditions in geriatric patients include the influence of [19], changes in the endocrine system, alterations in the central nervous system, sarcopenia, and immunosenescence [20]. The main physiological aging processes that significantly affect the severity of conditions in elderly patients include the influence of comorbidities [19], changes in the endocrine system, alterations in the central nervous system, sarcopenia, and immunosenescence [20].

**The role of comorbidities.** The proportion of patients with comorbidities and the number of comorbidities per patient increase with age. The average number of comorbidities per patient aged 65–84 years is  $2.6 \pm 2.2$ , and for those aged 85 and older, it is  $3.6 \pm 2.3$  [21]. The most common comor-

bidities include arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease, heart failure, cancer, and cognitive disorders. Comorbidities are associated with increased mortality, loss of physical independence, and a higher frequency of hospitalizations [22].

To predict mortality in critically ill patients, the Charlson Comorbidity Index (CCI) is used [23]. This index includes 19 disease entities, categorized according to their impact on prognosis. Each condition is assigned a weighted score ranging from 1 to 6 points (see Table 2). The higher the score, the greater is the likelihood of mortality for that patient. A score of 0 indicates a minimal risk and highest 10-year survival (98%); 1–2 scores indicate a low risk

(and 90–96% survival); 3–4 scores indicate a moderate risk (77–87% survival); and  $\geq 5$  scores indicate a high risk (less than 53% survival). The CCI is utilized to forecast both short-term (30-day) and long-term (1-year) mortality following a critical illness.

The study by N M Rehatta et al., which examined the impact of comorbidities in patients over 60 years old upon admission to the ICU with a primary diagnosis of COVID-19, found that the 30-day mortality rate was 38.6%. The five most common comorbidities were hypertension (21.1%), diabetes (16.2%), moderate to severe kidney disease (10.6%), congestive heart failure (9.2%), and cerebrovascular diseases (9.1%). Among patients with a CCI greater than 5, the mortality rate was 66%. Patients with

**Table 1. Parameters studied in elderly and very old patients with senile asthenia.**

| Sources                                                              | Patients |            | Frailty assessment tool | Parameter values presented in the studies                                                                                                                                                                                                                                                                    |
|----------------------------------------------------------------------|----------|------------|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                      | n        | Age, years |                         |                                                                                                                                                                                                                                                                                                              |
| H. Vallet, et al., 2021, systematic review [2]                       | 278      | > 75       | CFS                     | Mortality:<br>ICU — from 1% to 51%,<br>hospital — from 10% to 76%<br>6-months — from 21% to 58%,<br>1-year — from 33% to 72%                                                                                                                                                                                 |
| R. R. Bruno, et al., 2020 multicenter prospective cohort study [3]   | 415      | > 80       | CFS                     | ICU mortality — 19.8%,<br>30-day mortality — 34%                                                                                                                                                                                                                                                             |
| C. Jung, et al., 2021, prospective observational study [4]           | 2625     | > 70       | CFS                     | Mortality:<br>30-day - 59%                                                                                                                                                                                                                                                                                   |
| J. Hewitt, et. al., 2019, multicenter cohort study [10]              | 2279     | > 65       | CFS                     | ICU rates of confirmed frailty/SA :<br>60–69 years — 9%<br>70–79 years — 25%<br>> 80 years — 45%<br>Mortality among patients with SA vs without SA:<br>90-days — 19% vs 3.6%<br>30-days — 5 times higher in patients with SA vs without SA<br>Average length of ICU stay, days:<br>5 with SA vs 3 without SA |
| D. K. Singh, et. al., 2025, prospective one-center cohort study [11] | 317      | > 70       | CFS                     | Incidence of confirmed SA in ICU: 24.6%<br>ICU mortality, hospital mortality,<br>30-day mortality: with SA > without SA:<br>Vasopressor support: c CA > без CA<br>Nosocomial infections:<br>with SA > without SA<br>Duration of hospital stay:<br>with SA > without SA                                       |
| I. Margalit, et. al., 2024, multicenter cohort study [13]            | 563      | $\geq 75$  | N/A                     | Mortality: 28-day — 50%<br>The age itself was not associated with death of functionally independent patients.                                                                                                                                                                                                |
| M. Ehrlington, et. al., 2024 [14]                                    | 1840     | $\geq 65$  | CFS                     | Mortality: with SA > without SA:<br>7-day — 2.6% vs 0.2%<br>30-day — 7.9% vs 0.9%<br>90-day — 15.5% vs 2.4%                                                                                                                                                                                                  |
| M. Ibarz, et. al. 2020, cohort study [15]                            | 3869     | > 80       | CSF                     | Confirmed SA incidence:<br>(1) in patients with sepsis — 51.1%<br>(2) in patients with other acute conditions — 46.4%<br>Mortality (1) vs (2):<br>ICU — 31.2% vs 27.2%<br>30-day — 44.6% vs 40.2%                                                                                                            |
| B. Guidet, et. al, 2020, prospective cohort study [16]               | 3920     | > 80       | CSF                     | Average length of ICU stay: 3.88 days<br>Survival:<br>In the ICU — 72.5%<br>30-day — 61.2%                                                                                                                                                                                                                   |

comorbidities and COVID-19 had a shorter lifespan than those without these conditions. It was established that the greater was the number of comorbidities in geriatric ICU patients, the higher was the likelihood of death within 30 days ( $p < 0.005$ , correlation coefficient  $R 0.22$ ). Comorbidities such as COPD and heart failure in elderly patients with COVID-19 increase the length of hospital stay as well as in-hospital mortality. Saad Alsaad et al. emphasize the clinical significance of comorbidities among the geriatric population [25].

In an observational study of 523 patients with aortic aneurysm (AA), Yu-Fei Zhan et al. found that those readmitted to the ICU had a higher CCI. An independent nonlinear relationship was identified between the Charlson Index and the likelihood of readmission to the ICU. Age, renal failure, chronic pulmonary diseases, and dementia were important components of the CCI in predicting readmission to the ICU [26].

**The role of age-related changes in organs using the heart and kidneys as examples.** Changes in the cardiovascular system include, among other factors, degeneration of the cells in the pacemaker system and conduction pathways, leading to a slowing of the heart rate in response to stress, which increases the risk of arrhythmias. Cardiac valves become stiff and calcified, thereby increasing afterload, turbulence of blood flow, and the risk of valve insufficiency [21]. Both hypertrophy of myocytes and an increase in the fibrin matrix reduce the plasticity of the myocardium and, consequently, its response to stress. Changes of the cardiac shape, such as in septal hypertrophy and ventricular hypertrophy, can decrease the efficiency of cardiac output. Vascular changes primarily affect the intima and media, increasing their thickness, which ultimately leads to decreased elasticity of the vascular wall [27].

Aging of the kidneys is a complex and not fully understood process that involves changes in their structure, function, and metabolism. There is a gradual decrease in the size and number of nephrons, as well as changes in the tubules and thickening of the glomerular basement membrane with age. Additionally, there is progressive glomerulosclerosis, often referred to as nephrosclerosis. Besides these macroscopic structural changes, there's also an age-related gradual decline in glomerular filtration rate. The decrease in glomerular filtration can range from 0.4 ml / 1.73 m<sup>2</sup> to nearly 4 ml / 1.73 m<sup>2</sup> [2, 24]. There is also a reduction in tubular function, which affects sodium reabsorption and potassium excretion, leading to a decreased concentrating ability of the kidneys. Age-related changes in the renal vessels are accompanied by an increase in intrarenal blood shunting. Renal blood flow (600 ml/min) remains virtually unchanged until the fourth decade of life and then decreases by about 10% per decade [28].

**The role of changes in the endocrine system.** The hypothalamic-pituitary system plays a significant role in regulating the aging processes. A deficiency in the secretion of glucocorticoid hormones, insulin-like growth factor (IGF) secretion, and androgen production is associated with both, SA and normal aging [29].

Changes in thyroid function during the aging process have a considerable impact on bodily functions. Several population studies have shown that normal aging is accompanied by an increase in serum thyroid-stimulating hormone (TSH) levels, except in individuals with thyroid diseases and those with positive antithyroid antibodies. However, changes in TSH concentration also depend on the region of residence and may not always reflect the physiological aging process. The concentration of free thyroxine remains stable with increasing age,

**Table 2. Charlson Comorbidity Index scores.**

| Comorbidities                | Parameters                                  | Scores |
|------------------------------|---------------------------------------------|--------|
| Diabetes mellitus            | Not complicated                             | 1      |
|                              | With damage to target organs.               | 2      |
| Age                          | 50–59 years                                 | 1      |
|                              | 60–69 years                                 | 2      |
|                              | 70–79 years                                 | 3      |
|                              | ≥80 years                                   | 4      |
|                              |                                             |        |
| Liver diseases               | Mild                                        | 1      |
|                              | Moderate/severe                             | 3      |
| Malignant neoplasms          | Any type of leukemia, solid tumor, lymphoma | 2      |
|                              | Metastatic solid tumor                      | 6      |
| HIV infection                |                                             | 6      |
| Kidney disease               | Mild, moderate, severe                      | 2      |
| Congestive heart failure     |                                             | 1      |
| Myocardial infarction        |                                             | 1      |
| Chronic lung diseases        |                                             | 1      |
| Peripheral vascular diseases |                                             | 1      |
| Cerebrovascular diseases     |                                             | 1      |
| Dementia                     |                                             | 1      |
| Hemiplegia                   |                                             | 2      |
| Connective tissue diseases   |                                             | 1      |
| Gastric ulcer                |                                             | 1      |

while the concentration of free triiodothyronine (T3) generally decreases over the course of life [30, 31].

The intensity and nature of changes in thyroid function during the aging process vary significantly among different individuals. For instance, some people experience increased levels of TSH and free T4, while others exhibit a rise in TSH alongside a decrease in free T4 levels [32]. Finally, the increased prevalence of autoimmune thyroid disease and autonomous nodules with age may lead to changes in thyroid hormone concentrations.

Glucocorticoids affect a number of metabolically active tissues that are important for the development of particular asthenia phenotype, including skeletal muscles, bones, and the cardiovascular system. Persistently high concentrations of cortisol are associated with increased catabolism overall and skeletal muscles in particular. This significantly contributes to the development of age-related sarcopenia, as well as to the decline in muscle mass during various critical conditions [33].

A normal level of testosterone is crucial for the synthesis of skeletal muscle. The decline in testosterone levels that occurs with age contributes to the development of sarcopenia. The decrease in growth hormone secretion with age, often referred to as somatopause, leads to reduced synthesis of insulin-like growth factor 1 (IGF-1) in the liver. Recent findings have shown that IGF-1 is independently associated with asthenia in older adults. Yang Wang et al. evaluated age-related changes in IGF-1 expression across various human organs. The most significant increase in IGF-1 levels with age was found in the skin [34, 35].

**The role of changes in the central nervous system.** With age, there is a continuous loss of neurons in the brain, although they are preserved in most cortical areas. Changes often affect highly metabolically active neurons found in the hippocampus. It has been found that the hippocampal region is responsible for the development of cognitive function and dementia. Additionally, the hippocampus provides negative feedback to the hypothalamus, thereby indirectly contributing to the endocrine changes described above. Furthermore, it has been found that microglial cells (resident macrophage cells in the CNS) undergo structural and functional changes with aging [36, 37].

The maintenance of cognitive abilities and the development of SA are influenced by vitamin D levels. A study involving 509 adults aged 64 to 92 with and without cognitive impairments (Alzheimer's disease and mixed dementia) found a significant association between vitamin D levels and the results of the Mini Mental State Examination. Patients with mild cognitive impairment had higher vitamin D levels compared to other groups. Those with Alzheimer's disease and moderate dementia ex-

hibited the lowest levels of vitamin D. Notably, the most significant deficiency was observed in patients with moderate dementia, those over 65 years old, and individuals with cognitive and functional impairments [38].

Almost one third of patients admitted to the ICU develop delirium, and these patients are at an increased risk of death in the hospital, longer hospital stays, and cognitive impairments after discharge [39].

In a retrospective cohort study, Zheng and colleagues analyzed data from 11,740 patients aged  $\geq 65$  years with sepsis admitted to the ICU. They assessed frailty (SA) using the Clinical Frailty Scale (CFS) and delirium using the Confusion Assessment Method for the ICU (CAM-ICU). Among the entire cohort, frail patients showed a trend towards longer ICU stays, higher severity scores, and potentially worse clinical outcomes. The study revealed a significant positive association between the severity of frailty and the risk of developing delirium (confidence interval, CI: 1.09–1.17,  $p < 0.001$ ). Furthermore, frail patients had a higher risk of developing sepsis-associated delirium compared to those without frailty (CI: 1.20–1.43,  $p < 0.001$ ). The CAM-ICU assessment can be used for the early detection of delirium in adult patients hospitalized in the ICU, including those on mechanical ventilation, provided that the CAM-ICU test is conducted by properly trained healthcare staff. This test is most useful for ruling out delirium [41].

**The role of immunosenescence.** Immunosenescence is the gradual decline of immune system function caused by the natural aging process. It is primarily characterized by a higher secretion of pro-inflammatory cytokines compared to younger ages. As a result, there is a reduced ability to induce an effective immune response to antigens, which increases the risk and severity of infections [42].

The available data suggest that inflammation plays a significant role in the pathophysiology of SA, manifesting as an abnormal, subdued inflammatory response that persists for an extended period after the removal of the initial inflammatory stimulus. Macrophages exhibit a reduced ability to phagocytose and an increased production of cytokines. There is a decrease in B cell production, but their lifespan is prolonged. As a consequence, there is a change in the antigen-recognizing pool of B cells and an increase in the production of pro-inflammatory cytokines [9, 10].

The number of young CD8 and CD4 T cells decreases (due to thymic involution), while the number of «immunological memory» CD8 and CD4 T cells increases. Additionally, the pool of T cell receptors, which determines antigenic diversity, is limited. The number of neutrophils does not change with age, but their functions do: chemotaxis, phagocytosis, and cellular production of free radicals de-

cline. NK cells show reduced cytotoxicity and IL-2 production [43].

In the study by J. Palmer et al., 100 elderly patients with injuries were included. The average age was  $77.1 \pm 9.8$  years, with women making up 34% of the participants. Sarcopenia was recorded in 39% of the patients. Frail patients exhibited higher levels of TNF- $\alpha$  ( $p=0.01$ ), IL-1 $\beta$  ( $p=0.01$ ), and IL-6 ( $p=0.01$ ) compared to patients without frailty, but lower levels of growth hormone ( $p=0.03$ ) and insulin-like growth factor-1 ( $p<0.04$ ). No differences in IL-2R $\alpha$  levels were found ( $p=0.25$ ). Regression analysis revealed that sarcopenia positively correlates with the levels of pro-inflammatory biomarkers TNF- $\alpha$ , IL-1 $\beta$ , and IL-6, and negatively with endocrine biomarkers [44].

When analyzing the clinical manifestations, severity of the disease, and outcomes in groups of elderly patients with and without immunodeficiency hospitalized for community-acquired pneumonia, it was found that immunosuppression was significantly associated with a higher risk of 30-day mortality [45].

The decrease in immune response is likely a factor explaining the well-known fact that sepsis occurs much more frequently in patients with SA than in younger individuals, causing higher mortality [46].

**The Role of sarcopenia.** Sarcopenia is a complex syndrome associated with the loss of muscle mass either alone or in combination with an increase in fat mass. The causes of sarcopenia are multifactorial and include: physical inactivity and changes in endocrine function, particularly a decrease in the synthesis of testosterone, insulin-like growth factor, and alterations in corticosteroid secretion, as discussed above [47]. Additionally, chronic diseases, inflammation, insulin resistance, and nutrient deficiencies also contribute to the development of sarcopenia. While cachexia may be a component of sarcopenia, these two conditions are not the same.

In a retrospective observational study conducted in the ICU of Australia, sarcopenia was identified in 68% of patients. It was associated with older age (68 vs 55 years,  $p<0.001$ ), lower body mass index (27 vs 32 kg/m<sup>2</sup>,  $p<0.001$ ), and longer hospital stays (279 vs 223 hours,  $p=0.043$ ) [48].

Assessment of sarcopenia among hospitalized patients in central India revealed that sarcopenia is more commonly associated with severe stages of SA, along with an increased demand for MV and increased mortality specifically in this group of patients [47].

In a study conducted in a surgical ICU, Yun Ji et al. analyzed data of 236 patients after emergency surgery who had sepsis caused by intra-abdominal infection. Sarcopenia, visceral obesity, and sarcopenic obesity were assessed using computed tomography. Multivariate analysis revealed that sarcopenic obesity

was associated with an increased risk of 30-day mortality. Patients with sarcopenia were older than those without sarcopenia. The risk of 30-day mortality significantly increased in patients with sarcopenia, both those aged  $\leq 70$  and those  $> 70$  years old [49].

Nutritional deficiency or malnutrition is one of the reasons for development of sarcopenia. In a study examining the impact of SA, malnutrition, and endocrine changes on outcomes after aortic valve replacement, the prevalence of SA varied from 6.4% to 65.7%, while the prevalence of malnutrition syndrome ranged from 5.9% to 10.5%, depending on the assessment tool used. Both parameters were associated with higher concentrations of cortisol and parathyroid hormone, as well as lower levels of IGF-1, testosterone, and C-reactive protein. The 30-day mortality rate was increased in patients with SA and malnutrition [50].

Insufficient nutrition in severely ill elderly patients with COVID-19 is associated with a 35% increased risk of developing delirium and a longer duration of ICU compared to patients with adequate nutrition [51].

**Methods of assessing sarcopenia.** One method of assessing sarcopenia is the Fried Criteria, which is based on evaluating gate speed and grip strength. Clinical diagnostic criteria for sarcopenia are primarily assessed by gate speed test measured over a 4-meter course. Patients with a usual walking speed of  $< 1.0$  m/s should be considered for quantitative assessment of body composition using dual-energy X-ray absorptiometry (DXA). Muscle strength is measured using a hand dynamometer [52].

The SARC-F scale is used to assess the severity of sarcopenia. This 5-item questionnaire assesses strength, assistance with walking, rising from a chair, climbing stairs, and falls.

Using the SARC-CalF questionnaire, the risk of sarcopenia was assessed in 653 critically ill patients over the age of 60. The combined assessment of sarcopenia and frailty enhances the accuracy of predicting mortality in elderly patients in critical condition and may therefore be useful in the clinical decision-making process [53].

Ultrasound is a reliable and valid diagnostic method for quantitatively assessing limb muscle mass in sarcopenia among older adults. The thickness and cross-sectional area of the rectus femoris muscle (RF) or gluteus maximus muscle (GM) are considered suitable ultrasound parameters for predicting muscle mass in sarcopenia [54,55].

C. R. Hernández-Socorro et al. [56] proposed a protocol for the ultrasonographic assessment of the quadriceps muscle (QM) in real-time using B-mode, color Doppler, and M-mode, as well as for evaluating the thickness of the central tendon of the QM, the cross-sectional area, and the muscle thickness in B-mode. It was shown that the area

and thickness of the muscle (QRF) significantly decreased ( $p \leq 0.001$ ), while the thickness of the central tendon significantly increased ( $p = 0.047$ ) in the ICU patient group compared to the control group of healthy volunteers. QRF muscle echogenicity and the angiogenic activity of fasciculations, subcutaneous edema, and intramuscular fluid also significantly differed between the two groups ( $p < 0.001$ ).

However, a standardized procedure for assessing sarcopenia in patients with catabolic syndrome who are undergoing prolonged inpatient treatment has not been developed.

**Medications in elderly patients.** The specifics of medication use also affect the course of the underlying disease [19].

The issue of medication adherence and bioavailability in elderly patients has been extensively documented since 1980. Polypharmacy, including the inappropriate prescribing of medications to geriatric patients, arises in part due to treatment discoordination (the inconsistent prescribing of medications by different specialists); and after emergency hospitalizations, when a patient after discharge continues on medications used to manage acute critical condition alongside with regular pharmacotherapy for chronic illnesses.

For example, antipsychotics used to treat delirium are the most common group of medications, and their use often continues even after discharge from the ICU and the hospital [57]. In the phase 3 study of MIND-USA, which was conducted across 16 hospitals in the United States, the impact of antipsychotic medications on cognitive functions, quality of life, and psychological and functional outcomes after delirium was examined in different age groups. The results indicated that antipsychotics should not be routinely used to treat delirium in critically ill adult patients. Often, the continuation of these medications is unjustified and does not lead to improvements in cognitive function or overall treatment outcomes [58, 59]. A common complication of critical conditions is the exacerbation of psychological symptoms, sleep cycle disturbances, delirium, and cognitive impairments, which is associated with an increased prescription of specific medications such as antipsychotics or benzodiazepines [60].

**Overall assessment of baseline functional status of geriatric patients upon admission to the ICU.** Several scales for assessing functional independence are distinguished, such as the «Activities of Daily Living» scale and the «Instrumental Activities of Daily Living» (IADL) scale [61].

In clinical practice, a simplified version of the IADL scale is used. In 2008, a user-friendly scale for clinical assessment of frailty (CFS — Clinical Frailty Scale) was proposed, ranking patients into 9 groups from «very fit» to «terminally ill». This scale is

included in National clinical guidelines and is applied in both inpatient and outpatient settings.

The applicability of the Clinical Frailty Scale (CFS) was studied by D Javadzadeh et al. in a retrospective, single-center, observational study involving severely ill geriatric patients aged  $\geq 70$  years [62]. The CFS score was independently associated with overall short-term, medium-term, and long-term mortality. Frail patients exhibited nearly double the risk of death. This information is clinically significant, as the risk of death over various time frames should be considered in the individual treatment and care planning for geriatric patients.

The CRS and the Frailty Index (FI) based on Comprehensive Geriatric Assessment (CGA) were used in the multicenter prospective cohort study FORECAST involving patients aged  $\geq 50$  years who received life support for more than 24 hours [63]. Frailty severity was assessed over time: upon admission to the ICU, at hospital discharge, and six months post-discharge. A predetermined scoring range was established as an indicator of frailty severity: CFS  $\geq 5$  or FI  $\geq 0.2$ . The use of the FI based on CGA may provide advantages in identifying deficits and potential intervention targets compared to clinical assessment of frailty using CFS.

**Principles of managing patients of elderly and very old age in intensive care settings.** The heterogeneity of elderly and very old patients, along with the prevalence of complex geriatric syndromes, poses significant challenges in managing these patients in critical conditions.

The European Society of Intensive Care Medicine (ESICM) initiated a Delphic study to transform the empirical knowledge of experts in the field into consensus-based recommendations for clinical practice.

A multinational group of experts in intensive care, emergency medicine, and geriatric medicine provided insights on management of geriatric patients in critical conditions. Resulting consensus includes 48 recommendations and 2 checklists. The recommendations were developed based on the goals and key principles of treatment in the ICU, as well as the structure of post-discharge care [64]. The main recommendations for managing geriatric patients in the ICU are presented in Table 3.

The recommendations of the European Geriatric Society regulate the management of geriatric patients in the emergency department. The guidelines from the European Society of Intensive Care Medicine pertain to the emergency department and directly to the ICU.

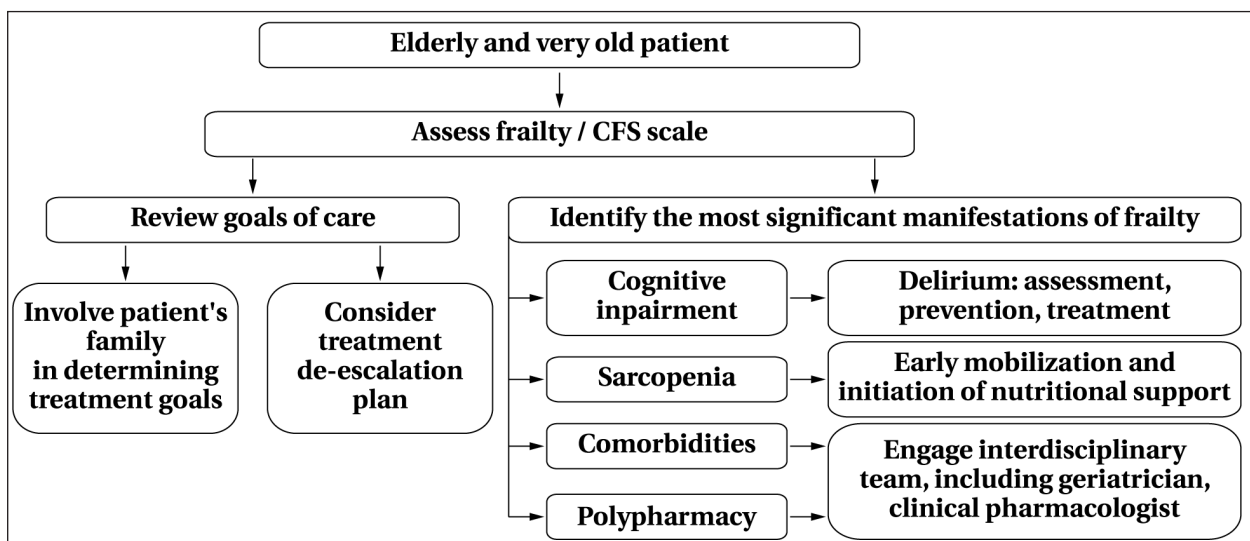
Based on this data, the following step-by-step algorithm can be proposed for geriatric patients upon admission to emergency department or ICU (see figure).

Although a comprehensive geriatric assessment (CGA) based on the recommendations of the Euro-

**Table 3. Key recommendations for managing elderly and very old patients in intensive care, ranked by level of agreement among research groups.**

| Recommendations                                                                                                                                                                                                                                                       | Delphic study       |                                                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|-------------------------------------------------------|
|                                                                                                                                                                                                                                                                       | Rounds,<br><i>n</i> | Agreement<br>between ICS,<br>EMS, and GS<br>groups, % |
| <b>High level of evidentiary support for the recommendation</b>                                                                                                                                                                                                       |                     |                                                       |
| The treatment plan and goals, as well as any potential intensification or reduction of therapy, should be reviewed at regular intervals in the ICU                                                                                                                    | 1                   | 99,0                                                  |
| It is recommended to involve the patient's family, if possible, to determine the level of care that is appropriate for the specific patient                                                                                                                           | 1                   | 97,5                                                  |
| The early mobilization should begin in the ICU                                                                                                                                                                                                                        | 1                   | 97,5                                                  |
| When taking a patient's medical history from the patient or their relatives, it's important to find out whether there are any pre-existing vision or hearing problems and whether glasses or hearing aids can be provided                                             | 2                   | 95,7                                                  |
| Noninvasive ventilation or high-flow nasal oxygen therapy may be considered a minimally invasive treatment option for respiratory failure, depending on the patient's baseline functional status                                                                      | 1                   | 95,6                                                  |
| Decisions to limit life-sustaining treatment should be made when aggressive interventions are unlikely to achieve an acceptable quality of life, as judged by the patient or their family                                                                             | 1                   | 95,5                                                  |
| Patient's age-related characteristics should be taken into account when MV is considered                                                                                                                                                                              | 2                   | 94,6                                                  |
| Recommendations for preventing pressure ulcers and other skin conditions need to be developed                                                                                                                                                                         | 1                   | 94,1                                                  |
| A separate guideline on the prevention, recognition, and treatment of delirium in the ICU is required                                                                                                                                                                 | 1                   | 93,5                                                  |
| When sedating geriatric patients, age-related aspects should be taken into account                                                                                                                                                                                    | 1                   | 89,7                                                  |
| <b>Low level of evidentiary support for the recommendation</b>                                                                                                                                                                                                        |                     |                                                       |
| Cardiovascular support (restoring fluid balance, vasopressor/inotropic support, and optimizing cardiac output) in geriatric patients should account for age-related changes                                                                                           | 2                   | 93,8                                                  |
| Medication reviews should be conducted by an appropriate healthcare professional, such as a clinical pharmacist, geriatrician, or another specialist experienced in caring for elderly and very old patients, in order to minimize preventable adverse drug reactions | 2                   | 90,1                                                  |
| When planning meals for very old patients, their age-related characteristics should be taken into account                                                                                                                                                             | 2                   | 89,1                                                  |

**Note.** Research groups: ICS — Intensive Care Society; EMS — Emergency Medicine Society; GS — Geriatrics Society.

**Figure.** Management algorithm for geriatric patients in the intensive care unit.

pean Geriatric Medicine Society and the European Society of Intensive Care Medicine often cannot be fully implemented [64, 65], a synthesis of these recommendations makes it possible to identify the key factors that determine the specific approach to managing elderly and very old patients in the ICU. These include:

- regular review of the treatment plan;
- family involvement in determining the level of care, collecting medical history, and making decisions about limiting life-sustaining treatment;
- early ambulation of the patient in the ICU;
- consideration of age-related characteristics and functional status when providing mechanical

ventilation, noninvasive ventilation, or high-flow nasal oxygen therapy, as well as during sedation;

- prevention, identification, and treatment of delirium, pressure ulcers, and other skin conditions (Table 3).

Recommendations regarding the above parameters are supported by a high level of evidence and a strong degree of consensus among research groups from intensive care, emergency medicine, and geriatric societies (99–89.7%; Table 3).

As shown, these recommendations place special emphasis on involving the family in the treatment of elderly and very old patients. In addition, they highlight the need to take into account the patient's own wishes regarding whether to receive or refuse treatment [64].

Comprehensive frailty (SA) assessment is also recommended in the emergency department. It can be used to triage patients according to the severity of frailty. Frailty and delirium independently increase the risk of in-hospital mortality and prolonged hospital stay [66].

Recommendations for cardiovascular and nutritional support were supported by a low level of evidence, apparently due to the heterogeneity of the study groups.

A recommendation to review medication therapy in collaboration with a clinical pharmacist, geriatrician, or another specialist experienced in caring for elderly patients had a low level of evidence despite a high degree of consensus among the research groups (90.1%). However, 91.4% of intensive care physicians subsequently agreed that medication therapy review should be conducted upon transfer from the ICU in order to achieve a more significant long-term impact on patient outcomes. Therefore, it is important to develop treatment strategies jointly with physicians from other specialties who will par-

ticipate in the care of elderly and very old patients, thereby ensuring a multidisciplinary approach.

When assessing vital signs, it is recommended to consider blood pressure, body temperature, and heart rate, as these may be associated with mortality [65].

## Conclusion

Factors associated with physiological aging — such as changes in hormonal regulation, immunosenescence, sarcopenia, and cognitive decline — have a significant impact on the management strategies for elderly and very old patients in the ICU. Comorbidities, medication use, and mobility status in this patient population should also be taken into account.

Most of the studies analyzed showed that the presence of frailty is associated with higher mortality rates among elderly and very old ICU patients compared with patients without frailty, as well as with younger patients.

Assessing frailty syndrome upon admission of elderly and very old patients to the ICU is necessary to optimize treatment strategies for this age group. Age, the presence of frailty syndrome, and a high SOFA score were identified as the most significant independent predictors of 30-day mortality. An independent predictor of 30-day survival after ICU treatment was the score obtained using the Clinical Frailty Scale (CFS). Frailty syndrome and cognitive impairment were also evaluated as potential prognostic factors for 30-day survival.

When treating patients in the analyzed cohort, a multidisciplinary approach is recommended, with particular attention given to the role of the family in the treatment process, as well as to supporting the patient's motivation and adherence to the prescribed treatment.

## References

1. Perrella A., Geen O., Ahuja M., Scott S., Kaushik R., Ferrante L.E., Brummel N.E., et al. Exploring the impact of age, frailty, and multimorbidity on the effect of ICU interventions: a systematic review of randomized controlled trials. *Crit Care Med.* 2024; 52 (9): e463–e472. DOI: 10.1097/CCM.0000000000006315. PMID: 38661459.
2. Vallet H., Schwarz G.L., Flaatten H., de Lange D.W., Guidet B., Dechartres A. Mortality of older patients admitted to an ICU: a systematic review. *Crit. Care Med.* 2021; 49 (2): 324–334. DOI: 10.1097/CCM.0000000000004772. PMID: 33332816.
3. Bruno R.R., Wernly B., Beil M., Muessig J.M., Rahmel T., Graf T., Meybohm P., et al. Therapy limitation in octogenarians in German intensive care units is associated with a longer length of stay and increased 30 days mortality: A prospective multicenter study. *J Crit Care.* 2020; 60: 58–63. DOI: 10.1016/j.jcrc.2020.07.024. PMID: 32769006.
4. Jung C., Fjølner J., Bruno R.R., Wernly B., Artigas A., Pinto B.B., Schefold J.C., et al. Differences in mortality in critically ill elderly patients during the second COVID-19 surge in Europe. *Crit Care.* 2021; 25 (1): 344. DOI: 10.1186/s13054-021-03739-7. PMID: 34556171.
5. Beard J.R., Jotheeswaran A.T., Cesari M., de Carvalho A.I. The structure and predictive value of intrinsic capacity in a longitudinal study of ageing. *BMJ Open.* 2019; 9 (11): e026119. DOI: 10.1136/bmjopen-2018-026119. PMID: 31678933.
6. Chin-Yee N., D'Egidio G., Thavorn K., Heyland D., Kyeremanteng K. Cost analysis of the very elderly admitted to intensive care units. *Crit Care.* 2017; 21 (1): 109. DOI: 10.1186/s13054-017-1689-y. PMID: 28506243.
7. Nguyen Q.D., Moodie E.M., Forget M.F., Desmarais P., Keezer M.R., Wolfson C. Health heterogeneity in older adults: exploration in the Canadian longitudinal study on aging. *J Am Geriatr Soc.* 2021; 69 (3): 678–687. DOI: 10.1111/jgs.16919. PMID: 33155270.
8. Forget M.F., Wang H.T., Carignan R., Dessureault A., Gravel M., Bienvenue J., Boucharde M., et al. Critically ill older adults representation in intervention trials: a systematic review. *Crit Care Explor.* 2024; 6 (7): e1107. DOI: 10.1097/CCE.0000000000001107. PMID: 38919511.
9. Singh D.K., Ganesh V., Sahni N., Kannamani B., Saini V., Yaddanapudi L. Prevalence of frailty and its effect on requirement of organ support and clinical outcomes in critically ill patients: a prospective observational single center study. *BMC Anesthesiol.* 2025; 25 (1): 215. DOI: 10.1186/s12871-025-03096-w. PMID: 40287615.
10. Bruno B.W., Wernly B., Bagshaw S.M., van den Boogaard M., Darvall J.N., Geer L.D., RuizMiguelena P.R.de G., et al. The Clinical Frailty Scale for mortality prediction of old acutely admitted intensive care patients: a meta-analysis of individual patient-level data. *Ann Intensive Care.* 2023; 13 (1): 37. DOI: 10.1186/s13613-023-01132-x. PMID: 37133796.
11. Margalit I., Yahav D., Hoffman T., Tabah A., Ruckly S., Barbier F., Singer P., et al. Presentation, management, and outcomes of older compared to younger adults with hospital-acquired bloodstream infections in the intensive care unit: a multicenter cohort study. *Infection.* 2024; 52 (6): 2435–2443. DOI: 10.1007/s15010-024-02304-y. PMID: 38869773.
12. Ehrlington S., M., Hörlin E., John R.T., Wretborn J., Wilhelms D. Frailty is associated with 30-day mortality: a multicentre study of Swedish emergency departments. *Emerg Med J.* 2024; 41 (9): 514–519. DOI: 10.1136/emered-2023-213444. PMID: 39053972.
13. Pillatt A.O., Da Silva B., Franz L.B.B., Berlezi E.M., Schneider R.H. Muscle, endocrine, and immunological markers of frailty in older people. *Exp Gerontol.* 2021; 151: 111405. DOI: 10.1016/j.exger.2021.111405. PMID: 34015373.
14. А. М. Кузьминов, А. В. Полев, Е. В. Хаммад, Т. Л. Петрище Синдром старческой астении как гетерогенное клиническое состояние. *Клиническая геронтология.* 2019; 7 (25): 25–32. Kuzminov A.M., Polev A.V., Khammad E.V., Petrishche T.L. Frail as a heterogeneous clinical condition. *Clinical Gerontology= Klinicheskaya Gerontologiya.* 2019; 7 (25): 25-32. (in Russ.). DOI: 10.26347/1607-2499201907-08025-032.
15. Hewitt J., Carter B., McCarthy K., Pearce L., Law J., Wilson F.V., Tay H.S., et al. Frailty predicts mortality in all emergency surgical admissions regardless of age. an observational study. *Age Ageing.* 2019; 48 (3): 388–394. DOI: 10.1093/ageing/afy217. PMID: 30778528.
16. Ibarz M., Boumendil A., Haas L.E.M., Irazabal M., Flaaten H., de Lange D.W., Morandi A., et al. Sepsis at ICU admission does not decrease 30-day survival in very old patients: a post-hoc analysis of the VIP1 multinational cohort study. *Ann Intensive Care.* 2020; 10 (1): 56. DOI: 10.1186/s13613-020-00672-w. PMID: 32406016.
17. Guidet B., de Lange D.W., Boumendil A., Leaver S., Watson X., Boulanger C., Szczeklik W., et al. The

- contribution of frailty, cognition, activity of daily life and comorbidities on outcome in acutely admitted patients over 80 years in European ICUs: the VIP2 study. *Intensive Care Med.* 2020; 46 (1): 57–69.  
DOI: 10.1007/s00134-019-05853-1.  
PMID: 31784798.
18. Guidet B., Vallet H., Flaatten H., Joynt G., Bagshaw S.M., Leaver S.K., Beil M., et al. The trajectory of very old critically ill patients. *Intensive Care Med.* 2024; 50 (2): 181–194.  
DOI: 10.1007/s00134-023-07298-z.  
PMID: 38236292.
  19. Kaushik R., Ferrante L.E. Long-term recovery after critical illness in older adults. *Curr Opin Crit Care.* 2022; 28 (5): 572–580.  
DOI: 10.1097/MCC.0000000000000981.  
PMID: 35950731.
  20. Flaatten H., Beil M., Guidet B. Elderly patients in the intensive care unit. *Semin Respir Crit Care Med.* 2021; 42 (1): 10–19.  
DOI: 10.1055/s-0040-1710571. PMID: 32772353.
  21. Rodríguez-García R., González-Lamuño L., Santullano M., Martín-Carro B., Fernández-Martín J.L., Basanta M.D.C.C., Forcelledo L., et al. Clinical features and disease progression of elderly patients at the ICU setting. *Med Intensiva (Engl Ed).* 2024; 48 (5): 254–262.  
DOI: 10.1016/j.medine.2024.02.009.  
PMID: 38519374.
  22. Cuenca S.L., López L.O., Martín N.L., Jaimes M.M.I., Villamayor M.I., Artigas A., Balanz J.A.L. Frailty in patients over 65 years of age admitted to Intensive Care Units (FRAIL-ICU). *Med Intensiva (Engl Ed).* 2019; 43 (7): 395–401.  
DOI: 10.1016/j.medin.2019.01.010.  
PMID: 30905473.
  23. Stavem K., Hoel H., Skjaker S.A., Haagensen R. Charlson comorbidity index derived from chart review or administrative data: agreement and prediction of mortality in intensive care patients. *Clin Epidemiol.* 2017; 9: 311–320.  
DOI: 10.2147/CLEPS133624. PMID: 28652813.
  24. Rehatta N.M., Chandra S., Sari D., Lestari M.I., Senapathi T.G.A., Nurdin H., Wirabuan B., et al. Comorbidities and COVID-19 status influence the survival rate of geriatric patients in intensive care units: a prospective cohort study from the Indonesian Society of Anaesthesiology and Intensive Therapy. *BMC Geriatr.* 2022; 22 (1): 523.  
DOI: 10.1186/s12877-022-03227-9.  
PMID: 35752756.
  25. Alsaad S., Addweesh A., Beyari M., Alkhateb M., Alswat A., Alshabnan A., Alsaad A., et al. Comorbidities associated with risk of ICU admission in elderly patients with COVID-19: *Medicine (Baltimore)*. 2022; 101 (39): e30799.  
DOI: 10.1097/MD.00000000000030799.  
PMID: 36181092.
  26. Zhan Y.-F., Li F., Wu L.-C., Chen L., Zhu C.-Y., Han M.-S., Ma G.-F., et al. Role of Charlson comorbidity index in predicting intensive care unit readmission in patients with aortic aneurysm. *Medicine (Baltimore)*. 2024 1; 103 (44): e40033.  
DOI: 10.1097/MD.00000000000040033.  
PMID: 39496060.
  27. Borri M., Jacobs M.E., Carmeliet P., Rabelink T.J., Dumas S.J. Endothelial dysfunction in the aging kidney. *Am J Physiol Renal Physiol.* 2025; 328 (4): F542–F562.  
DOI: 10.1152/ajprenal.00287.2024.  
PMID: 39933752.
  28. Doi T., Makizako H., Tsutsumimoto K., Hotta R., Nakakubo S., Makino K., Suzuki T., et al. Association between insulin-like growth Factor-1 and frailty among older adults. *J Nutr Health Aging.* 2018; 22 (1): 68–72.  
DOI: 10.1007/s12603-017-0916-1.  
PMID: 29300424.
  39. Strich D., Karavani G., Edri S., Gillis D. TSH enhancement of FT4 to FT3 conversion is age dependent. *Eur J Endocrinol.* 2016; 175: 49–54.  
DOI: 10.1530/EJE-16-0007. PMID: 27150496.
  30. Chaker L., Korevaar T.I., Medici M., Uitterlinded A., Hofman A., Dehghan A., Franco O.H., et al. Thyroid function characteristics and determinants: the Rotterdam Study. *Thyroid.* 2016; 26 (9): 1195–204.  
DOI: 10.1089/thy.2016.0133. PMID: 27484151.
  31. Mammen J.S., McGready J., Ladenson P.W., Simonsick E.M. Unstable thyroid function in older adults is caused by alterations in both thyroid and pituitary physiology and is associated with increased mortality. *Thyroid.* 2017; 27: 1370–1377.  
DOI: 10.1089/thy.2017.0211. PMID: 28854871.
  32. Fiocco S., Walther A., Ehlert U. Steroid secretion in healthy aging. *Psychoneuroendocrinology.* 2019; 105: 64–78.  
DOI: 10.1016/j.psyneuen.2018.09.035.  
PMID: 30314729.
  33. Alemany M. The roles of androgens in humans: biology, metabolic regulation and health. *Int J Mol Sci.* 2022; 23 (19): 11952.  
DOI: 10.3390/ijms23191195. PMID: 36233256.
  34. Wang Y., Yang J., Luo Y., Zhao Z., Yuan Y., Li J., Liu Y., et al. Targeting IGF1-induced cellular senescence to rejuvenate hair follicle aging. *Aging Cell.* 2025; 24 (7): e70053.  
DOI: 10.1111/ace.70053. PMID: 40159808.
  35. Cosarderelioglu C., Nidadavolu L.S., George C.J., Oh E.S., Bennett D.A., Walston J.D., Abadir P.M. Brain renin-angiotensin system at the intersect of physical and cognitive frailty. *Front Neurosci.* 2020; 14: 586314 DOI: 10.3389/fnins.2020.586314.  
PMID: 33117127.
  36. Fischer N., Chacko L.J., Glueckert R., Schrott-Fischer A. Age-dependent changes in the cochlea.

- Gerontology*. 2020; 66 (1): 33–39.  
DOI: 10.1159/000499582. PMID: 31117093.
37. Arosio B., Rossi P.D., Ferri E., Cesari M., Vitale G. Characterization of vitamin D status in older persons with cognitive impairment. *Nutrients*. 2022; 14 (6): 1142. DOI: 10.3390/nu14061142. PMID: 35334800.
  38. Salluh J.I.F., Wang H., Schneider E.B., Nagaraja N., Yenokyan G., Damluji A., Serafim R.B., et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. *BMJ*. 2015; 350: h2538. DOI: 10.1136/bmj.h2538. PMID: 26041151.
  39. Zheng G., Yan J., Li W., Chen Z. Frailty as an independent risk factor for sepsis-associated delirium: a cohort study of 11,740 older adult ICU patients. *Aging Clin Exp Res*. 2025; 37 (1): 52. DOI: 10.1007/s40520-025-02956-2. PMID: 40011361.
  40. Miranda F., Gonzalez F., Plana M.N., Zamora J., Quinn T.J., Seron P. Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) for the diagnosis of delirium in adults in critical care settings. *Cochrane Database Syst Rev*. 2023; 11 (11): CD013126. DOI: 10.1002/14651858.CD013126.pub2. PMID: 37987526.
  41. Martín S., Pérez A., Aldecoa C. Sepsis and immunosenescence in the elderly patient: a review. *Front Med*. 2017; 4: 20. DOI: 10.3389/fmed.2017.00020. PMID: 28293557.
  42. Garley M., Omeljaniuk W.J., Motkowski R., Ratajczak-Wrona W., Jabłońska E., Filipkowski D., Charkiewicz A.E. Immunoaging — the effect of age on serum levels of NET biomarkers in men: a pilot study. *Int J Occup Med Environ Health*. 2023; 36 (3): 333–348. DOI: 10.13075/ijom.1896.02125. PMID: 37681423.
  43. Palmer J., Pandit V., Zeeshan M., Kulvatunyou N., Hamidi M., Hanna K., Fain M., et al. The acute inflammatory response after trauma is heightened by frailty: a prospective evaluation of inflammatory and endocrine system alterations in frailty. *J Trauma Acute Care Surg*. 2019; 87 (1): 54–60. DOI: 10.1097/TA.0000000000002229. PMID: 30768559.
  44. Huang L., Weng B., Wang Y., Wang M., Mei Y., Chen W., Ma M., et al. The effect of immunosuppression on outcomes in elderly patients with community-acquired pneumonia. *Respir Res*. 2025; 26 (1): 30. DOI: 10.1186/s12931-024-03080-x. PMID: 39844256.
  45. Li X., Tang Y., Deng X., Zhou F., Huang X., Bai Z., Liang X., et al. Modified frailty index effectively predicts adverse outcomes in sepsis patients in the intensive care unit. *Intensive Crit Care Nurs*. 2024; 84: 103749. DOI: 10.1016/j.iccn.2024.103749. PMID: 38896964.
  46. Bhurchandi S., Kumar S., Agrawal S., Acharya S., Jain S., Talwar D., Lomte S. Correlation of sarcopenia with modified frailty index as a predictor of outcome in critically ill elderly patients: a cross-sectional study. *Cureus*. 2021; 13 (10): e19065. DOI: 10.7759/cureus.19065. PMID: 34849305.
  47. Joyce P.R., O'Dempsey R., Kirby G., Anstey C. A retrospective observational study of sarcopenia and outcomes in critically ill patients. *Anaesth Intensive Care*. 2020; 48 (3): 229–235. DOI: 10.1177/0310057X20922234. PMID: 32486830.
  48. Ji Y., Cheng B., Xu Z., Ye H., Lu W., Luo X., Fu S., et al. Impact of sarcopenic obesity on 30-day mortality in critically ill patients with intra-abdominal sepsis. *J Crit Care*. 2018; 46: 50–54. DOI: 10.1016/j.jcrc.2018.03.019. PMID: 29677586.
  49. Al-Kassou B., Shamekhi J., Weber M., Germeroth J., Gillrath J., Feldmann K., Sedaghat A., et al. Frailty, malnutrition, and the endocrine system impact outcome in patients undergoing aortic valve replacement. *Catheter Cardiovasc Interv*. 2022; 99 (1): 145–157. DOI: 10.1002/ccd.29821. PMID: 34143555.
  50. Gholi Z., Rezaei M., Shariatpanahi Z.V., Momen R., Shaidaei M.F.B., Gholami M., Aghaee S., et al. Malnutrition elevates delirium and ICU stay among critically ill older adult COVID-19 patients. *Front Med (Lausanne)*. 2024; 11: 1259320. DOI: 10.3389/fmed.2024.1259320. PMID: 38799151.
  51. Kamwa V., Welch C., Hassan-Smith Z.-K. The endocrinology of sarcopenia and frailty. *Minerva Endocrinol (Torino)*. 2021; 46 (4): 453–468. DOI: 10.23736/S2724-6507.20.03198-3. PMID: 33331737.
  52. Bai W., Ge H., Han H., Xu J., Qin L. Association of frailty and sarcopenia with short-term mortality in older critically ill patients. *J Nutr Health Aging*. 2024; 28 (8): 100321. DOI: 10.1016/j.jnha.2024.100321. PMID: 39033576.
  53. Zhao R., Li X., Jiang Y., Su N., Li J., Kang L., Zhang Y., et al. Evaluation of appendicular muscle mass in sarcopenia in older adults using ultrasonography: a systematic review and meta-analysis. *Gerontology*. 2022; 68 (10): 1174–1198. DOI: 10.1159/000525758. PMID: 35878591.
  54. Siniscalchi C., Nouvenne A., Cerundolo N., Mescchi T., Ticinesi A. Diaphragm ultrasound in different clinical scenarios: a review with a focus on older patients. *Geriatrics (Basel)*. 2024; 9 (3): 70. DOI: 10.3390/geriatrics9030070. PMID: 38920426.

55. Hernández-Socorro C.-R., Saavedra P., López-Fernández J.C., Ruiz-Santana S. Assessment of muscle wasting in long-stay ICU patients using a new ultrasound protocol. *Nutrients*. 2018; 10 (12): 1849. DOI: 10.3390/nu10121849. PMID: 30513718.
56. Scales D.C., Fischer H.D., Li P., Bierman A.S., Fernandes O., Mamdani M., Rochon P., et al. Unintentional continuation of medications intended for acute illness after hospital discharge: a population-based cohort study. *J Gen Intern Med*. 2016; 31 (2): 196–202. DOI: 10.1007/s11606-015-3501-5. PMID: 26369941.
57. Mart M.F., Boehm L.M., Kiehl A.L., Gong M.N., Malhotra A., Owens R.L., Khan B.A., et al. Long-term outcomes after treatment of delirium during critical illness with antipsychotics (MIND-USA): a randomised, placebo controlled, phase 3 trial. *Lancet Respir Med*. 2024; 12 (8): 599–607. DOI: 10.1016/S2213-2600 (24)00077-8. PMID: 38701817.
58. Tomich J.E., Stollings J.L., Pandharipande P.P., Chandrasekhar R., Ely E.W., Girard T.D. Antipsychotic prescribing patterns during and after critical illness: a prospective cohort study. *Crit Care*. 2016; 20 (1): 378. DOI: 10.1186/s13054-016-1557-1. PMID: 27881149.
59. Charlton K., Sinclair D.R., Hanratty B., Burrow E., Stow D. Measuring frailty and its association with key outcomes in the ambulance setting: a cross sectional observational study. *BMC Geriatr*. 2022; 22 (1): 935. DOI: 10.1186/s12877-022-03633-z. PMID: 36471316.
60. Kojima G. Quick and simple FRAIL scale predicts incident activities of daily living (ADL) and instrumental ADL (IADL) disabilities: a systematic review and meta-analysis. *J Am Med Dir Assoc*. 2018; 19 (12): 1063–1068. DOI: 10.1016/j.jamda.2018.07.019. PMID: 30206033.
61. Javadzadeh D., Karlson B.W., Alfredsson J., Ekerstad E., Hellberg J., Herlitz J., Ekerstad N. Clinical Frailty Scale score is a predictor of short-, mid- and long-term mortality in critically ill older adults ( $\geq 70$  years) admitted to the emergency department: an observational study. *BMC Geriatr*. 2024; 24 (1): 852. DOI: 10.1186/s12877-024-05463-7. PMID: 39434029.
62. Muscedere J., Bagshaw S.M., Kho M., Mehta S., Cook D.J., Boyd J.G., Sibley S., et al. Frailty, Outcomes, Recovery and Care Steps of Critically Ill Patients (FORECAST): a prospective, multi-centre, cohort study. *Intensive Care Med*. 2024; 50 (7): 1064–1074. DOI: 10.1007/s00134-024-07404-9. PMID: 38748266.
63. Beil M., Alberto L., Bourne R.S., Brummel N.E., de Groot B., de Lange D.W., Elbers P., et al. ESICM consensus-based recommendations for the management of very old patients in intensive care. *Intensive Care Med*. 2025; 51 (2): 287–301. DOI: 10.1007/s00134-025-07794-4. PMID: 39961851.
64. Lucke J.A., Mooijaart S.P., Heeren P., Singler K., McNamara R., Gilbert T., Nickel C.H., et al. Providing care for older adults in the Emergency Department: expert clinical recommendations from the European Task Force on Geriatric Emergency Medicine. *Eur Geriatr Med*. 2022; 13 (2): 309–317. DOI: 10.1007/s41999-021-00578-1. PMID: 34738224.
65. Sahle B.W., Pilcher D., Litton E., Ofori-Asenso R., Peter K., McFadyen J., Tracey Bucknall T. Association between frailty, delirium, and mortality in older critically ill patients: a binational registry study. *Ann Intensive Care*. 2022; 12 (1): 108. DOI: 10.1186/s13613-022-01080-y. PMID: 36394660.

Received 19.08.2025

Accepted 08.07.2026

## К юбилею доктора медицинских наук Ивана Федоровича Острейкова

18 августа 2026 г. исполняется 85 лет доктору медицинских наук Ивану Федоровичу Острейкову.

Иван Федорович Острейков родился 18 августа 1941 г. в деревне Серковка Смоленской области.

В 1966 г. окончил лечебный факультет Смоленского медицинского института. С 1966 по 1968 гг. обучался в клинической ординатуре по анестезиологии и реаниматологии в Первом Московском медицинском институте им. И. М. Сеченова (в наст. время Первый Московский государственный медицинский университет им. И. М. Сеченова). С 1968 по 1986 гг. работал во 2-ом Московском ордена Ленина государственном медицинском институте им. Н. И. Пирогова (в наст. время Российский национальный исследовательский медицинский университет им. Н. И. Пирогова) в должностях младшего, старшего научного сотрудника, ассистента кафедры детской хирургии.

В 1971 г. защитил диссертацию на соискание ученой степени кандидата медицинских наук на тему «Изменения дыхания в ближайшем послеоперационном периоде у детей младшего возраста», после чего продолжал интенсивно заниматься научно-исследовательской и преподавательской работой.

В 1984 г. защитил диссертацию на соискание ученой степени доктора медицинских наук по теме «Анестезиологическая защита организма ребенка и оценка ее эффективности». В ноябре 1986 г. был избран на должность заведующего кафедрой анестезиологии и реаниматологии детского возраста.

В 1990 г. Иван Федорович был избран председателем Общества анестезиологов и реаниматологов г. Москвы и Московской области, в этой должности проработал 4 года.



В 2011 г. был избран Главным детским анестезиологом города Москвы. В данной должности проработал до 2021 г.

Иван Федорович внес существенный вклад в развитие научно-образовательных аспектов детской анестезиологии-реаниматологии, являясь одним из организаторов детской анестезиолого-реанимационной помощи в Российской Федерации. Под его руководством защищено 32 кандидатских и 5 докторских диссертаций. В соавторстве издано 5 монографий и более 250 научных статей.

Острейков И. Ф. — Почетный заведующий кафедрой анестезиологии, реаниматологии и токсикологии детского возраста Российской медицинской академии непрерывного профессионального образования (РМАНПО) Минздрава России, награжден почетными грамотами Правительства Москвы и РМАНПО, премией Правительства Москвы, медалью «За заслуги перед отечественным здравоохранением», золотой медалью Вроцлавского Университета.

В настоящее время Иван Федорович продолжает педагогическую, учебно-методическую и лечебную работу, занимается научными исследованиями в области анестезиологии и реаниматологии у детей.

## К юбилею доктора медицинских наук Игоря Владимировича Молчанова

27 июня 2026 г. исполнилось 80 лет Игорю Владимировичу Молчанову, главному научному сотруднику НИИ общей реаниматологии им. В.А. Неговского Федерального научно-клинического центра реаниматологии и реабилитации (ФНКЦ РР).

И. В. Молчанов родился 27 июня 1946 г. в городе Москве в семье служащего. В 1964 г. поступил на дневное отделение лечебного факультета Первого Московского медицинского института им. И. М. Сеченова (в наст. время Первый Московский государственный медицинский университет им. И. М. Сеченова). С 1967 г. учебу в институте совмещал с работой в отделении реанимации Городской клинической больницы им. С. П. Боткина в должности медицинского брата. В 1970 г., после окончания института, поступил в клиническую ординатуру по реаниматологии в Лабораторию экспериментальной физиологии по оживлению организма АМН СССР академика В.А. Неговского. С 1975 г. работал врачом-реаниматологом в реанимационном отделении гипербарической оксигенации Городской клинической больницы (ГКБ) им. С. П. Боткина (в наст. время Московский многопрофильный научно-клинический центр им. С. П. Боткина), а с 1978 г. был переведен на должность заведующего отделением нейрораннимации той же больницы. В 1979 г. поступил в очную аспирантуру на кафедру анестезиологии и реаниматологии Центрального института усовершенствования врачей. В 1983 г. защитил диссертацию на соискание ученой степени кандидата медицинских наук.

В 1997 г. И. В. Молчанов назначен главным специалистом комитета здравоохранения Правительства г. Москвы по анестезиологии и реаниматологии. С 1998 г. в ГКБ им. С. П. Боткина совмещал должность заместителя главного врача с руководителем анестезиолого-реанимационного центра. В 1998 г. защитил диссертацию на соискание ученой степени доктора медицинских наук, избран на должность заведующего кафедрой анестезиологии и реаниматологии Российской медицинской академии последипломного образования (РМАПО; в наст. время Российская медицинская академия непрерывного профес-



сионального образования, РМАНПО). С 1998 по 2000 гг. был президентом Федерации анестезиологов и реаниматологов России. В 2000 г. избран в состав законодательной комиссии Всемирной федерации анестезиологов.

В 2001 г. И. В. Молчанов назначен на должность главного специалиста Минздрава России по анестезиологии и реаниматологии. В этой должности И. В. Молчанов выступил в качестве одного из организаторов анестезиолого-реаниматологической помощи в Российской Федерации и создателя профессионального стандарта «врач — анестезиолог-реаниматолог».

В 2017 по 2020 гг. руководил НИИ общей реаниматологии им. В.А. Неговского ФНКЦ РР. В эти годы был создан уникальный Симуляционный центр ФНКЦ РР и лаборатория экспериментальных исследований, оснащенные передовым научным оборудованием.

И. В. Молчанов исполнял обязанности вице-президента ФАР, профессора и заведующего кафедрой анестезиологии и реаниматологии РМАНПО Минздрава России, был председателем подкомиссии по анестезиологии и реаниматологии Центральной аттестационной комиссии Минздрава России, председателем профильной комиссии по специальности «Анестезиология — реаниматология» Минздрава России, экспертом Росздравнадзора, главным редактором журнала «Анестезиология и реаниматология». И. В. Молчановым опубликовано более 380 печатных работ, он является соавтором 9 патентов и изобретений, 6 монографий, под его руководством выполнено и успешно защищено 9 кандидатских диссертаций.

**К юбилею  
доктора медицинских наук,  
профессора  
Геннадия Андреевича  
Бояринова**

25 августа 2026 г. исполняется 80 лет со дня рождения и 57 лет врачебной, научной и педагогической деятельности Геннадия Андреевича Бояринова — заслуженного врача Российской Федерации, полковника медицинской службы, доктора медицинских наук, профессора, Почетного члена ФАР, Нижегородского и Мордовского научных обществ анестезиологов и реаниматологов, Лауреата премии Нижнего Новгорода в области медицины, действительного члена Российской академии медико-технических наук, почетного президента Азиатско-Европейского союза озонотерапевтов и производителей медицинского оборудования.

Бояринов Геннадий Андреевич родился 25 августа г. 1946 г. в селе Ужово Починковского района Горьковской области. В 1969 г. окончил Горьковский государственный медицинский институт им. С. М. Кирова и начал трудовую деятельность младшим научным сотрудником Горьковского НИИ Травматологии и Ортопедии в отделение термических поражений. В разные годы работал в Центральной Научно-исследовательской Лаборатории Горьковского медицинского института, руководил кафедрами анестезиологии и реаниматологии в Нижегородской ГМА и Военно-медицинском институте. В настоящее время работает в должности профессора кафедры анестезиологии, реаниматологии и трансфузиологии Приволжского исследовательского медицинского университета (ПИМУ). Является почетным профессором ПИМУ.

Геннадий Андреевич Бояринов — известный и уважаемый в России и за рубежом ученый и педагог в области патофизиологии, анестезио-



логии-реаниматологии и озонотерапии. Под его руководством выполнено 16 докторских и 45 кандидатских диссертаций. Он автор и соавтор более 700 научных работ, 6 монографий, 40 изобретений и 65 рационализаторских предложений. Научные доклады профессора Бояринова были представлены на международных конгрессах (Германия, Польша, Англия, Франция, Япония, Куба, США, Украина, Грузия).

Профессор А. Г. Бояринов — пионер российской озонотерапии. Его научные исследования внесли большой вклад в обоснование различных механизмов лечебного действия медицинского озона и расширили сферы его применения в различных областях медицины.

Геннадий Андреевич Бояринов не только известный ученый, врач, педагог, но и отличный семьянин — любящий муж и заботливый отец. Геннадий Андреевич замечательный, отзывчивый, честный и порядочный человек, которого любят и уважают не только в Нижнем Новгороде, но и далеко за его пределами.

*Друзья и товарищи, сотрудники, коллеги  
и редакция журнала «Общая реаниматология»  
сердечно поздравляют юбиляров, желают им доброго здоровья,  
активного долголетия, счастья, успехов и благополучия!*



XXVIII Всероссийская конференция  
с международным участием

# ЖИЗНЕОБЕСПЕЧЕНИЕ ПРИ КРИТИЧЕСКИХ СОСТОЯНИЯХ

16-17 октября 2026 г. | Москва



## ТЕМАТИКИ КОНФЕРЕНЦИИ

- Доказательная медицина критических состояний
- Дыхательная недостаточность и респираторная поддержка
- Иммунология и генетика критических состояний
- Искусственный интеллект и цифровая трансформация в реаниматологии
- Критические состояния в акушерстве
- Критические состояния в педиатрии
- Метаболизм и нутритивная поддержка при критических состояниях
- Мониторинг микроциркуляции при критических состояниях
- Нейроанестезиология, нейрореаниматология
- Неотложная кардиология и неврология
- Общая патология хронических критических состояний
- Организация медицинской помощи в экстремальных условиях удаленных промышленных объектов
- Органопротекция при критических состояниях
- Остановка кровообращения и сердечно-легочная реанимация
- Персонализация в медицине критических состояний
- Ранняя нейрореабилитация пациентов в критических состояниях
- Сепсис
- Сестринское дело в анестезиологии-реаниматологии
- Экспериментальные исследования в реаниматологии
- Экстракорпоральная мембранная оксигенация



## ФОРМАТ И МЕСТО ПРОВЕДЕНИЯ

Очно — Международный мультимедийный пресс-центр  
«РИА Новости», г. Москва, Зубовский бульвар, 4

CRITICALCONF.RU

Тел.: +7 (499) 390 34 38

E-mail: criticalconf@confreg.org

