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ОБЩАЯ РЕАНИМАТОЛОГИЯ

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ERRATUM

Obshchaya Reanimatologiya = General Reanimatology. 2024; 20 (5): 55.

Correction to the article: «Procedural Complications of Central Venous Catheter Placement in Pediatric Oncology Practice (a Clinical Case Series)» DOI: https://doi.org/10.15360/1813-9779-2024-5-55-69.

The editor pointed out a misspelled patronymic of one of the authors in the author line of the Russian version of the article in the print edition. Instead of E. S. Spiridonova, the correct version [In Russ.] is: Е. А. Спиридонова.

ОПЕЧАТКА

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Post-Discharge Cardiovascular Complications in Noncardiac Surgery: Incidence and Prediction

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Summary

The aim of this study was to assess the incidence of cardiovascular complications (CVC) within 12 months after vascular surgery and to analyze inpatient perioperative examination data to identify potential predictors.

Materials and Methods. A prospective cohort study included 103 patients aged 66 years [61–70] who underwent vascular surgery. Clinical outcomes within 12 months after surgery, including CVC and/or other cardiac events (composite outcome) and cardiac death, were assessed by telephone interviews with patients or their relatives. Patient physiological parameters, comorbidities, cardiac risk indices (CRI), platelet-lymphocyte ratio (PLR), concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP), and other parameters were obtained and analyzed from medical records. Logistic regression and ROC analysis were used to assess the predictive power of the investigated indicators.

Results. The composite outcome was recorded in 33 % of cases and cardiac death occurred in 6.8 %. The risk of the composite outcome was associated with ASA class (OR 2.7413; 95 % CI 1.1126–6.7541), whereas the risk of perioperative myocardial infarction or cardiac arrest was associated with CRI (OR 1. 6051; 95 % CI 0.6645–2.0215), American University of Beirut (AUB) CRI (OR 2.1106; 95 % CI 1.0260–4.3414), PLR (1.0120; 95 % CI 1.0018–1.0222), and NT-proBNP concentration during hospitalization. Concurrent congestive heart failure (OR 5.0658; 95 % CI 1.2400–20.6956), revised CRI (OR 2.1024; 95 % CI 1.0572–4.1813), Khoronenko CRI (OR 103.76; 95 % CI 1.8752–5796.55), AUB CRI (OR 3.1902; 95 % CI 1.1040–9.2181), and NT-proBNP concentration all increased the risk of cardiac death. Predischarge NT-proBNP levels > 179 pg/mL (OR 1.0071; 95 % CI 1.0038–1.0104; AUC 0.795) and maximum postoperative NT-proBNP levels were reliable predictors of the composite outcome. The most effective predictor of postoperative mortality was a maximum NT-proBNP concentration > 303 pg/mL after surgery (OR 1.0039; 95 % CI 1.0015–1.0063; AUC 0.836).

Conclusion. CVC developed in 33 % of patients within 12 months after vascular surgery, with cardiac death occurring in 6.8 % of cases. An NT-proBNP concentration > 179 pg/mL before hospital discharge or a maximum NT-proBNP concentration > 248 pg/mL in the postoperative period predicted CVC within one year. Postoperative NT-proBNP concentration > 303 pg/mL was a strong predictor of one-year cardiac mortality. Other factors associated with the risk of postoperative CVC did not provide an accurate prognosis.

Keywords: prognosis of post-discharge complications; cardiovascular complications; non-cardiac surgery; predictors of cardiac complications; cardiac risk indices; natriuretic peptides; NT-proBNP; perioperative complications

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

Introduction

Long-term post-discharge cardiovascular complications (CVCs) after non-cardiac surgery are gaining attention among clinicians worldwide [1–4]. Researchers emphasize their medical and public importance [5, 6] while investigating the structure [3] and pathophysiological mechanisms [2, 3, 7] of these complications. Evidence-based analyses have led to the development of national and international guidelines to reduce the risk of CVCs in noncardiac surgical settings [8–13]. Despite these efforts, post-discharge CVCs remain common and are associated with high mortality rates [3, 14].

Current research focuses on improving the prediction of CVCs using modern diagnostic tools [1] and laboratory tests [4, 15–17]. Attempts have also been made to use cardiac risk indices (CRIs) for this purpose [15]. However, methods for predicting post-hospital CVCs need to be refined to improve prognostic accuracy.

In Russia, clinicians have extensively studied perioperative CVCs [18–24], but there are few publications on post-discharge complications. For example, the multicenter STOPRISK study found that the overall incidence of various CVCs within 30 days after abdominal surgery was about 1.4%, which is

comparable to the rate of intestinal paresis but higher than the prevalence of infectious complications [25, 26]. Our previous study found that in a mixed population of patients with vascular disease and cancer, various cardiac events were observed in 27.7% of cases within 12 months of surgery, of which 2.1% were fatal [27]. However, the prevalence and accurate prediction of post-discharge CVCs in vascular surgery remain poorly understood.

Objective: to assess the incidence of CVCs within 12 months after vascular surgery and to investigate the feasibility of predicting these complications using perioperative inpatient data.

Materials and Methods

A prospective cohort study was conducted at the Yaroslavl Regional Clinical Hospital, including patients who underwent surgery in the Department of Vascular Surgery between May 1 and November 1, 2021 (approved by the local ethics committee of Yaroslavl State Medical University, protocol No. 50-2021). The sample size was calculated under the assumption of regression analysis using the formula $N > 50 + 8m$, where m represents the number of independent variables [28].

Inclusion criteria:

— Discharge from hospital after elective open vascular surgery performed under general anesthesia.

— Age between 45 and 85 years.

— Written informed consent to participate in the study.

— Availability of a contact telephone number.

— Presence of perioperative cardiac biomarker results documented in the medical record.

Exclusion criteria:

— Documented major surgical complications and/or reoperations during hospitalization.

— Presence of clinically significant valvular heart disease and/or left ventricular ejection fraction (LVEF) < 40%.

— Class III obesity with body mass index (BMI) > 40 kg/m².

— Preoperative elevated serum creatinin (> 120 μmol/L).

— Inability to contact the patient by telephone.

— Patient refusal to participate in the study.

— Lack of information about the patient from available contacts.

The study initially included 146 patients discharged from the hospital. Seventeen patients were excluded for the following reasons: five due to surgical complications, four requiring reoperation, two with aortic stenosis, one with a left ventricular ejection fraction (LVEF) of 37 %, two with a body mass index (BMI) of 41 and 44 kg/m², and three with preoperative hypercreatininemia.

Between May 10 and November 10, 2022, telephone interviews were conducted with 129 potential respondents. However, 21 telephone numbers were unreachable and five individuals declined to participate. Finally, data from 103 respondents (patients or their relatives) were included in the study.

The interviews used a specially designed questionnaire (Table 1) to assess the occurrence of cardiovascular complications and/or other cardiac events within 12 months of surgery. Major adverse cardiovascular and cerebrovascular events (MACCE) were defined as cardiac mortality, myocardial infarction, stroke, or a combination thereof [29, 30]. The presence of one or more cardiovascular complications identified by the questionnaire was classified as a composite outcome.

The primary endpoints of the study were the composite outcome and cardiac mortality.

The following patient data were collected from medical records: sex, age at the time of surgery, functional status according to the American Society of Anesthesiologists (ASA) classification, presence of cardiovascular comorbidities, type of surgical procedure, calculated cardiac risk indices (CRIs), and blood indices. The CRIs analyzed included the Revised Cardiac Risk Index (RCRI) [31], the American College of Surgeons Risk Calculator for Perioperative Myocardial Infarction or Cardiac Arrest (MICA CRI) [32], the CRI developed by V. E. Khoronenko et al. (Khoronenko CRI) [33], and the American University of Beirut Cardiovascular Risk Index (AUB-HAS2 CRI) [34]. Increased cardiovascular risk was defined as RCRI > 2 points, MICA CRI > 1%, Khoronenko CRI > 0.3 units, and AUB-HAS2 CRI > 1 point.

Preoperative complete blood counts were used to calculate platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR).

Table 1. Questionnaire used in the study.

№	Question	Answer	Note
1.	Has the patient survived?	yes/no	If not, what was the cause of death
2.	Did the patient have any cardiovascular disease?	yes/no	If yes, which ones
3.	Was there any progression of cardiovascular disease after surgery?	yes/no	If yes, which ones
4.	Did the patient have a myocardial infarction, development or decompensation of heart failure, stroke, arrhythmia within the last 12 months?	yes/no	If yes, specify
5.	Is the patient taking cardiovascular medications?	yes/no	If yes, which ones
6.	Was dosage adjustment of cardiovascular medications required postoperatively?	yes/no	If yes, which drugs
7.	Were there any hospitalizations for heart disease during the year?	yes/no	If yes, specify the cause of hospitalization
8.	Were there any hospitalizations for cardiac surgery performed during the year?	yes/no	If yes, which ones

The serum concentration of cardiac-specific troponin I (cTnI) was measured using the «Troponin I – ELISA – BEST» reagent kit (AO Vector-Best, Russia) on a Lazurit automated immunoassay analyzer (Dynex Technologies, USA). A value > 0.2 ng/mL was considered to be significantly above the upper limit of the reference range based on the laboratory standards. The concentration of the inactive fragment of the B-type natriuretic peptide precursor (NT-proBNP) in serum was determined by solid-phase enzyme immunoassay using the NT-proBNP ELISA-BEST reagent kit (AO Vector-Best, Russia) on the same analyzer. The upper reference limit for NT-proBNP was set at 200 pg/mL.

Biomarkers were assessed at three time points: preoperatively ($cTnI_1$, $NT\text{-}proBNP_1$), 24 hours postoperatively ($cTnI_2$, $NT\text{-}proBNP_2$), and on postoperative days 5–7 before discharge ($cTnI_3$, $NT\text{-}proBNP_3$). Peak (maximum) postoperative biomarker levels were recorded as $cTnI_{peak}$ and $NT\text{-}proBNP_{peak}$.

The study included 71 male and 32 female participants aged 47–83 years (median age 66 [61–70] years). Of the participants, 55 (53.4%) were over 65 years of age at the time of surgery. During hospitalization, their physical status and anesthesiological risk level were consistent with ASA class III–IV (median score 3.0 [3.0–4.0]). Cohort characteristics, including comorbidities, surgical procedures, and other relevant parameters, are detailed in Table 2.

Data were processed using the MedCalc statistical software package (version 15.2). The Kolmogorov–Smirnov test was used to assess the data distribution. Results were reported as medians *(Me)* with interquartile ranges *(LQ–UQ)*. Logistic regression was used to assess the effect of independent variables (predictors) on dependent variables (outcomes). The effect was binary encoded. Odds ratios *(OR)*, 95% confidence intervals *(CIs)*, and *P*-values were calculated. Potential predictors included demographic and clinical parameters, cardiac risk indices (CRIs), blood indices, and cardiac biomarkers. Composite outcomes and cardiac mortality were analyzed as dependent variables. Receiver operating characteristic (ROC) analysis was performed to evaluate the discriminative ability of the predictors identified by logistic regression. ROC curve characteristics were assessed by calculating area under the curve (AUC), 95% CI, and *P*-values. Model quality was categorized as follows:

AUC ⩾ 0.9: Excellent
0.89–0.8: Very good
0.79–0.7: Good
0.69–0.6: Moderate
< 0.6: Poor.

Thresholds (cut-offs) for variables were determined based on the Youden index, prioritizing the highest sum of sensitivity and specificity. Additional criteria included sensitivity/specificity approaching 80% and balance of sensitivity and specificity (minimizing the difference). The cut-off that best met these criteria was selected, with 95% CIs calculated for the sensitivity and specificity of the cut-off. Statistical significance was set at $P < 0.05$ using a two-tailed significance level.

Table 2. Characteristics of the patient cohort.

Parameter	Value
Comorbidities, frequency, *N* (%)	
Hypertension	96 (93.2)
Coronary heart disease	43 (41.8)
Congestive heart failure	23 (22.3)
History of ACVA	29 (28.2)
Type 2 DM	24 (23.3)
Surgeries with various cardiac risks, frequency, *N* (%)	
Low (on vertebral arteries)	6 (5.8)
Moderate (on carotid arteries)	77 (74.8)
High (on aorta)	20 (19.4)
Cardiovascular complications, frequency, *N* (%)	
Perioperative	12 (11.6)
Cardiac risk assessment tools and blood indices	
RCRI, points	1–5 (2.0 [1.0–3.0])
MICA CRI, %	0.5–6.5 [0.73 [0.65–1.45])
Khoronenko CRI, units	0.02–0.62 (0.02 [0.02–0.05])
AUB-HAS2 CRI, points	1–3 (1.0 [1.0–2.0])
Preoperative NLR, units	0.51–4.6 (1.8 [1.5–2.6])
Preoperative PLR, units	49.2–254.1 (101.9 [74.9–136.6])
Cardiac biomarkers	
$cTnI_1$, ng/mL	0.01–0.025 (0.029 [0.02–0.05])
$cTnI_2$, ng/mL	0.01–3.7 (0.04 [0.02–0.12])
$cTnI_3$, ng/mL	0.01–0.79 (0.03 [0.02–0.06])
$cTnI_{peak}$, ng/mL	0.01–3.7 (0.05 [0.03–0.16])
Postoperative troponin elevation, frequency, *N* (%)	20 (19.4)
$NT\text{-}proBNP_1$, pg/mL	23.9–774.3 (53.0 [42.0–185.3])
$NT\text{-}proBNP_2$, pg/mL	37.6–1035.0 (135.6 [59.2–258.1])
$NT\text{-}proBNP_3$, pg/mL	37.2–1013.3 (77.3 [48.2–269.4])
$NT\text{-}proBNP_{peak}$, pg/mL	37.6–1035.0 (189.1 [64.6–327.3]

Note. For Tables 2, 4, 5: ACVA — acute cerebrovascular accident; DM — diabetes mellitus. The calculated cardiac risk scores, blood parameters and biomarkers are presented as min–max (*Me [LQ–HQ]*).

Results and Discussion

Survey results. There were 54 positive responses from 34 respondents (33%), including 27 operated patients and 7 relatives of non-survivors. Of the 27 patients, 12 (44.5%) provided one positive response, 10 (37.0%) provided two, and 5 (18.5%) provided three. The remaining 69 respondents (67%) answered all questions negatively. The most commonly reported post-discharge CVCs included worsening CV symptoms and major adverse cardiovascular and cerebrovascular events (MACCE) (Table 3).

Clinical and comorbidity parameters as predictors of post-discharge cardiovascular complications. Sex, age, elevated cardiac risk index associated with surgery, and the presence of perioperative hospital complications and comorbidities were not associated with the composite outcome (Table 4). The only significant predictor was the American Society of Anesthesiologists (ASA) class. The dis-

Table 3. CVCs within 12 months after vascular surgery identified from a questionnaire survey of 103 respondents.

Post-discharge CVCs	*N* (%)
Cardiac mortality	7 (6.8)
Myocardial infarction	2 (2.1)
ACVE	6 (5.8)
Significant arrhythmias	5 (4.8)
Progression of cardiovascular disease	27 (26.2)
Hospitalization for cardiac indications	7 (6.8)
MACCE	16 (15.5)
Composite outcome	34 (33.0)

Note. ACVE — acute cerebrovascular event; MACCE — major adverse cardiovascular and cerebrovascular events.

criminative power of ASA was characterized by a model of moderate quality (AUC 0.600; 95% CI, 0.500–0.695; P = 0.035). An ASA class > 3 did not provide adequate sensitivity, which was only 38.9% (95% CI, 23.1–56.5%) with a specificity of 81.2% (95% CI, 69.9–89.6%).

Comorbid congestive heart failure (CHF) was identified as a predictor of one-year cardiac mortality (Table 4). The discriminatory power of CHF as a predictor was characterized by a model of moderate quality (AUC 0.679; 95% CI, 0.581–0.767; P = 0.047), with a sensitivity of 55.6% (95% CI, 21.2–86.3%) and a specificity of 80.2% (95% CI, 70.8–87.6%). Other common clinical indicators and comorbidities were not associated with mortality risk.

Cardiac risk indices (CRI) and blood indices as predictors of post-discharge cardiovascular complications. Several parameters were associated with the composite outcome: MICA CRI, AUB-HAS2 CRI, and platelet to lymphocyte ratio (PLR) (Table 5). The discriminatory power of MICA CRI (AUC 0.593; 95% CI 0.493–0.688; P = 0.151) and AUB-HAS2 CRI (AUC 0.507; 95% CI 0.408–0.606; P = 0.921) was not sufficient. The model based on PLR was of moderate quality (AUC 0.643; 95% CI, 0.535–0.740; P = 0.028). The optimal threshold for PLR > 132.0 discriminated the composite outcome with a sensitivity of 50.0% (95% CI, 31.3–68.7%) and specificity of 85.25% (95% CI, 73.8–93.0%). Other parameters were not associated with the composite outcome.

The RCRI, Khoronenko CRI, and AUB-HAS2 CRI were found to be predictors of one-year cardiac mortality (Table 5). ROC analysis showed that RCRI did not provide a statistically significant model (AUC 0.679; 95% CI, 0.581–0.767; P = 0.105). The discriminatory power of the Khoronenko CRI was characterized by a good quality model (AUC 0.726; 95% CI, 0.630-0.808; P = 0.022), with a threshold of > 0.14 providing the best prediction of mortality, achieving a sensitivity of 55.6% (95% CI 21.2–86.3%) and a specificity of 90.6% (95% CI, 82.9–95.6%). The AUB-HAS2 CRI also provided a good quality model (AUC 0.689; 95% CI, 0.591–0.775; P = 0.035). A threshold of > 1 for AUB-HAS2 CRI discriminated fatal outcomes with balanced sensitivity and specificity of 66.7% (95% CI, 29.9–92.5%) and 69.8% (95% CI, 59.6–78.7%), respectively. Neither MICA CRI nor blood indices were associated with the risk of one-year mortality.

Cardiac biomarkers as predictors of post-discharge cardiovascular complications. Perioperative

Table 4. Association of clinical parameters and comorbidity with composite outcome and one-year cardiac mortality.

Parameter	OR	95% CI	P-value
Association with composite outcome			
Sex	0.9148	0.3784–2.2115	0.843
Age	1.0116	0.9527–1.0742	0.705
Age over 65 years	1.3039	0.5713–2.9761	0.528
ASA class	2.7413	1.1126–6.7541	0.028
High cardiac risk surgery	0.8768	0.3682–2.0880	0.766
Perioperative hospital CVCs	1.4286	0.4192–4.8678	0.568
Comorbidities			
Hypertension	1.3827	0.6035–3.1679	0.444
Coronary heart disease	1.4143	0.5406–3.6998	0.480
Congestive heart failure	1.2500	0.2298–6.8004	0.796
ACVE	1.0965	0.4425–2.7168	0.842
DM	2.0602	0.8062–5.2650	0.131
Association with one-year cardiac mortality			
Sex	0.5771	0.1214–2.7439	0.490
Age	1.0475	0.9366–1.1715	0.417
Age over 65 years	2.5000	0.4622–13.5210	0.287
ASA class	1.2000	0.2184–6.5931	0.834
High cardiac risk surgery	0.6458	0.1361–3.0648	0.582
Perioperative hospital CVCs	0.9659	0.1101–8.4733	0.975
Comorbidities			
Coronary heart disease	3.8158	0.7040–20.6817	0.120
Congestive heart failure	5.0658	1.2400–20.6956	0.024
Hypertension	0.4000	0.0412–3.8819	0.429
ACVE	1.0222	0.1869–5.5909	0.980
DM	2.6786	0.5555–12.9167	0.220

Table 5. Association of CRIs and blood indices with composite outcome and one-year cardiac mortality

Parameter	OR	95% CI	*P*-value
Association with composite outcome			
RCRI, points	1.1047	0.7145–1.7080	0.654
MICA CRI, %	1.6051	1.0899–2.3638	0.017
Khoronenko CRI, units	2.6700	0.0893–79.7995	0.571
AUB-HAS2 CRI, points	2.1106	1.0260–4.3414	0.042
Preoperative NLR, units	0.8959	0.4643–1.7288	0.743
Preoperative PLR, units	1.0120	1.0018–1.0222	0.021
Association with one-year cardiac mortality			
RCRI, points	2.1024	1.0572–4.1813	0.034
MICA CRI, %	1.1590	0.6645–2.0215	0.603
Khoronenko CRI, units	103.76	1.8752–5796.55	0.024
AUB-HAS2 CRI, points	3.1902	1.1040–9.2181	0.032
Preoperative NLR, units	1.5539	0.6057–3.9866	0.359
Preoperative PLR, units	1.0058	0.9891–1.0228	0.499

Table 6. Association of cardiac biomarkers with composite outcome and one-year cardiac mortality.

Parameter	OR	95% CI	*P*-value
Association with composite outcome			
$cTnI_1$	778.3	0.1251–8415.6	0.135
$cTnI_2$	2.1576	0.5111–9.1087	0.295
$cTnI_3$	0.538	0.0012–10.2985	0.342
$cTnI_{peak}$	1.6283	0.5450–4.8647	0.383
$NT\text{-}proBNP_1$	1.0047	1.0015–1.0079	0.004
$NT\text{-}proBNP_2$	1.0033	1.0010–1.0055	0.004
$NT\text{-}proBNP_3$	1.0071	1.0038–1.0104	<0.0001
$NT\text{-}proBNP_{peak}$	1.0046	1.0023–1.0069	0.0001
Association with one-year cardiac mortality			
$cTnI_1$	1.3667	0.1427–13.0900	0.786
$cTnI_2$	0.8197	0.0639–10.5074	0.879
$cTnI_3$	0.0310	0.0000–9669.3941	0.590
$cTnI_{peak}$	0.4178	0.0049–35.3554	0.699
$NT\text{-}proBNP_1$	1.0039	1.0003–1.0076	0.035
$NT\text{-}proBNP_2$	1.0040	1.0014–1.0066	0.002
$NT\text{-}proBNP_3$	1.0034	1.0008–1.0060	0.011
$NT\text{-}proBNP_{peak}$	1.0039	1.0015–1.0063	0.001

cardiac troponin I (cTnI) levels were not associated with the composite outcome or one-year mortality (Table 6). Cardiac troponin elevation in the post-operative period also did not predict the composite outcome (OR 1.3571; 95% CI, 0.4980–3.6982; $P = 0.551$) or one-year cardiac mortality (OR 1.2381; 95% CI, 0.2371–6.4660; $P = 0.801$).

NT-proBNP levels at all perioperative stages as well as $NT\text{-}proBNP_{peak}$ levels were associated with the composite outcome (Table 6). The discriminatory power of NT-proBNP1 for the composite outcome was characterized by a model of moderate quality, whereas the remaining NT-proBNP measurements showed models of good quality (Table 7, Fig. *a*). Sensitivity and specificity for $NT\text{-}proBNP_3$ and $NT\text{-}proBNP_{peak}$ exceeded 70% and were well balanced. The cut-off value for $NT\text{-}proBNP_3$ was found to be close to the upper limit of normal, while the $NT\text{-}proBNP_{peak}$ levels were above it.

All levels of NT-proBNP were associated with one-year cardiac mortality (Table 6). In the ROC analysis (Table 7), the prognostic model quality (Fig. *b*) was good for $NT\text{-}proBNP_1$ and $NT\text{-}proBNP_2$ and very good for $NT\text{-}proBNP_3$ and $NT\text{-}proBNP_{peak}$. Thresholds for $NT\text{-}proBNP_3$ and $NT\text{-}proBNP_{peak}$ effectively discriminated patients at risk for 1-year mortality, with sensitivity and specificity greater than 70%.

The observed incidence of specific CVCs in the year following vascular surgery was very close to previously published data on the occurrence of various post-discharge CVCs in non-cardiac surgery patients [3, 4, 14]. For example, myocardial infarction was reported to occur in up to 1.6% of cases, major adverse cardiovascular and cerebrovascular events (MACCE) ranged from 8.8% to 20.6%, and cardiac mortality within 12 months was reported to range from 3.7% to 4.2% [3,4].

It is important to note that comparing data from different authors on the prevalence of long-term post-discharge CVCs is challenging. Published studies differ in design, patient categories, follow-up periods, and other characteristics, including terminology. In this study, we considered the presence of all cardiovascular complications and events as a composite outcome. A similar approach was proposed by S. S. Murashko et al. [22], who emphasized the clinical significance and economic feasibility

Table 7. Discriminatory power of perioperative NT-proBNP values in relation to composite outcome and one-year cardiac mortality.

Parameters	AUC	95% CI	*P*-value	Cut-off value, pg/mL	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Discriminatory power for composite outcome						
NT-roBNP$_1$	0.691	0.592–0.779	0.0006	> 54.6	64.7 (46.5–80.3)	60.3 (47.7–72.0)
NT-roBNP$_2$	0.712	0.614–0.797	0.0001	> 151.1	68.6 (50.7–83.1)	62.7 (50.0–74.2)
NT-roBNP$_3$	0.795	0.702–0.869	< 0.0001	> 179.3	70.6 (52.5–84.9)	81.8 (70.4–90.2)
NT-proBNP$_{peak}$	0.779	0.688–0.854	< 0.0001	> 248.5	72.2 (54.8–85.8)	75.4 (63.5–84.9)
Discriminatory power for one-year cardiac mortality						
NT-proBNP$_1$	0.761	0.666–0.840	0.0004	> 142.1	66.7 (29.9–92.5)	73.1 (62.9–81.8)
NT-proBNP$_2$	0.786	0.693–0.861	0.0004	> 289.3	66.7 (29.9–92.5)	83.8 (74.8–90.7)
NT-proBNP$_3$	0.833	0.745–0.900	< 0.0001	> 269.4	77.8 (40.0–97.2)	79.1 (69.3–86.9)
NT-proBNP$_{peak}$	0.836	0.751–0.901	< 0.0001	> 302.7	88.9 (51.8–99.7)	75.0 (65.1–83.3)

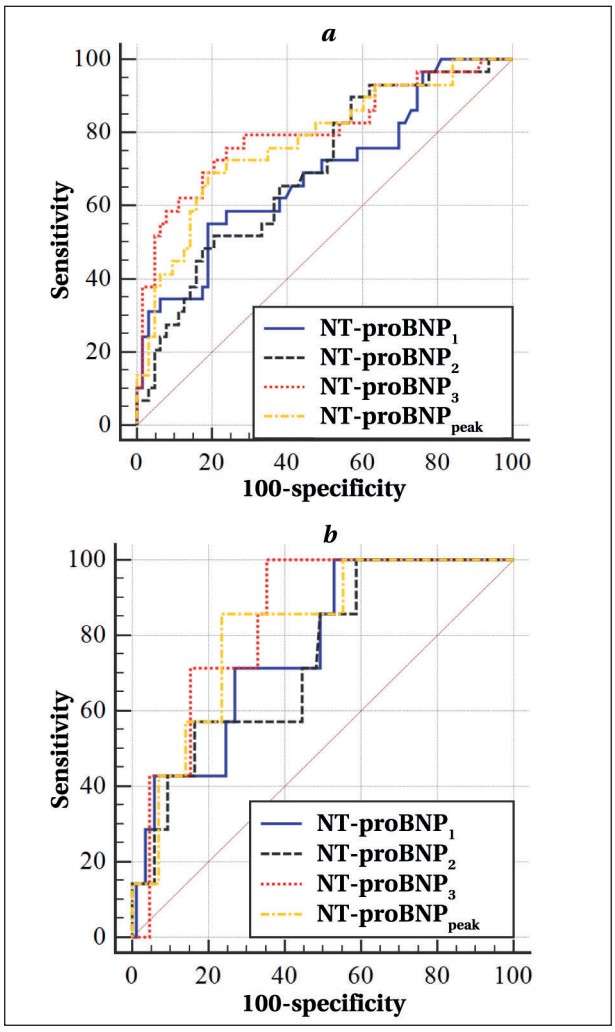

Fig. ROC curves showing the sensitivity and specificity of perioperative NT-proBNP levels in relation to the composite outcome (*a*) and the risk of one-year cardiac mortality (*b*).

of considering any abnormality in the cardiovascular system during the postoperative period (any cardiovascular events, ACVE). According to these researchers, the incidence of ACVE after non-cardiac surgery can be as high as 54.7%. While such an approach has not been applied to vascular surgery within 12 months of surgery, previous attempts have been made to expand the concept of long-term CVCs by identifying four etiological and pathogenetic variants of postoperative myocardial injury [3]. Despite the particularities of the studies conducted, clinicians are unanimous in emphasizing the wide prevalence of post-discharge CVCs in non-cardiac surgery and their highly adverse prognostic significance [1, 3, 4, 6, 14].

In our study, ASA class > 3 was identified as a predictor of CVCs within the first year after vascular surgery. The multicenter STOPRISK study also found that preoperative physical status was a significant risk factor for postoperative complications [25]. In a previous study in a mixed population of noncardiac surgery patients, we found an association between ASA class and post-discharge CVCs [27]. However, due to its very low sensitivity, ASA class > 3 cannot be recommended as an accurate predictor of various cardiac events after vascular surgery [35].

Patients with chronic heart failure (CHF) had a higher risk of cardiac death within one year after vascular surgery. Some investigators have previously suggested that CHF may double the risk of one-year cardiac mortality in patients undergoing vascular surgery [14]. A similar pattern was found in the mixed surgical population [27]. However, the sensitivity of the predictor indicated a high risk of false-positive predictions. Other predictors of post-discharge cardiovascular complications and cardiac mortality were not identified in the study patients. We did not see the correlation between delayed mortality and early perioperative complications reported by other authors [36, 37].

Although developed and validated primarily to predict in-hospital cardiovascular events [31–34], cardiac risk indices have been evaluated as predictors of 1-year cardiac mortality [15]. We have shown that, although MICA CRI and AUB-HAS2 CRI were associated with an increased risk of cardiovascular complications, they did not show sufficient discriminatory power for composite outcomes. However, AUB-HAS2 CRI proved to be a significant predictor of 1-year cardiac mortality, consistent with previous findings highlighting its advantages over the Revised Cardiac Risk Index (RCRI) [38]. Notably,

the RCRI failed to achieve significant discriminatory power for post-discharge mortality in our study. The predictive ability of the AUB-HAS2, although statistically significant, was unreliable as its 95% confidence intervals for sensitivity indicated inadequate effectiveness [35]. Similarly, the Khoronenko CRI showed inadequate sensitivity despite good model quality, indicating a high likelihood of false-positive predictions.

The risk of composite outcomes was also associated with the preoperative platelet to lymphocyte ratio (PLR). The relationship between PLR and the likelihood of early postoperative cardiovascular complications in non-cardiac surgery has been investigated in several focused studies [39, 40]. In addition, PLR has been associated with outcomes in certain cardiovascular diseases [41]. This association highlights the potential role of this blood index as marker for postoperative cardiovascular complications. However, the low sensitivity of PLR as a predictor limits its utility for widespread clinical application.

In the studied patient cohort, neither cardiac troponin I (cTnI) levels nor the presence of elevated serum troponin were identified as predictors of composite outcomes or one-year cardiovascular mortality. This finding contrasts with the prevailing consensus on the importance of cardiac troponins (cTn) in assessing the risk of post-discharge cardiovascular complications [4, 16, 42]. Previous studies have demonstrated the prognostic significance of both preoperative [43, 44] and postoperative [44, 45] cTn levels. However, the lack of predictive significance in this study may be due to several factors:

1. Differential predictive value of cTn isoforms: In certain clinical scenarios, cTnI may be less accurate than cTnT in predicting postoperative complications [46].

2. Analytical variability: The characteristics of the reagents and the specific equipment used in immunoassays can influence cTn measurements. Methodological variability and lack of standardization in cTn assays remain significant challenges, as highlighted by leading experts [47, 48].

Thus, despite these findings, it would be premature to exclude cTnI or cTnT as candidate predictors of postoperative major adverse cardiac events (MACE) or cardiovascular complications in general. Further studies are needed to refine the role of cTn monitoring in risk stratification and to validate national laboratory techniques for cTn analysis.

Preoperative levels of NT-proBNP and/or active B-type natriuretic peptide (BNP) are widely recognized as highly informative predictors of perioperative cardiovascular complications [11–13, 42]. Meanwhile, the utility of assessing postoperative NT-proBNP/BNP levels remains controversial. Some researchers argue that there is insufficient evidence to confirm their prognostic value [42]. However, several studies and meta-analyses suggest otherwise. They have shown that postoperative NT-proBNP/BNP levels outperform other predictors in predicting cardiovascular complications 6 and 12 months after surgery as well as one-year mortality [15, 17, 49].

Of all the predictors examined, only postoperative NT-proBNP levels reliably predicted the risk of CVCs and one-year cardiac mortality. NT-proBNP levels at discharge and peak levels during the postoperative period were found to be effective predictors of composite outcomes [35]. One-year cardiac mortality was reliably predicted only by the NT-proBNP$_{peak}$ values. Specifically, NT-proBNP cut-off levels associated with composite outcomes were near the upper end of the reference range, which is consistent with previous research on the predictive value of the biomarker for in-hospital CVCs [50]. NT-proBNP$_{peak}$ levels 1.5 times above normal were reliable predictors of one-year mortality. This evidence supports the use of serial NT-proBNP measurements in the postoperative period to identify levels associated with poor surgical outcomes. This approach has been used successfully in cardiac surgery patients [51] and our findings support its use in non-cardiac surgery.

It can be concluded that more than 30% of patients undergoing vascular surgery experience various CVCs within the first year after surgery. Although general clinical parameters, cardiac risk indices, and platelet to lymphocyte ratio (PLR) have been associated with the risk of post-discharge CVCs and cardiac mortality, their efficacy as predictors in clinical practice remains limited. Prediction of one-year CVCs and mortality was reliably achieved by assessment of NT-proBNP levels in the postoperative period. However, the predictive value of troponins requires further investigation to clarify its clinical applicability.

Study limitation. The study protocol was not registered in advance.

Conclusion

Within 12 months after vascular surgery, 33% of patients develop cardiovascular complications, including cardiac death in 6.8% of cases. These complications are reliably predicted by discharge NT-proBNP levels greater than 179 pg/mL and postoperative NT-proBNP$_{peak}$ levels greater than 248 pg/mL. Postoperative NT-proBNP levels greater than 303 pg/mL predict cardiac mortality within one year. Other variables associated with the risk of post-discharge CVCs do not show sufficient predictive power to be considered useful in clinical practice.

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Caspase-9 and p53 Protein Levels in Cancer Patients after Different Anesthesia Techniques

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Summary

The aim of this study was to investigate the changes in caspase-9 and p53 levels as biomarkers of pro- and anti-apoptotic pathways in the early postoperative period in patients who underwent lung surgery for malignant tumors under different types of multimodal or inhalation-intravenous anesthesia.

Material and Methods. A single-center prospective study of 22 patients aged 45–64 years was conducted at the Omsk Clinical Oncology Early Treatment and Prevention Center from January to April 2020. The participants were divided into two groups. Group 1 patients received multimodal anesthesia, which included sympathetic nerve block and prolonged epidural analgesia in the postoperative period. Group 2 patients received inhalational and intravenous anesthesia followed by systemic morphine analgesia. Serum caspase-9 and p53 protein levels were measured at four time points: before anesthesia, one, twelve, and twenty-four hours after surgery. Statistical hypotheses were tested using nonparametric (rank) analysis methods. Friedman's ANOVA was used to compare multiple time points, while the Wilcoxon test was used to compare variables between two time points in dependent samples. The Mann-Whitney test was used to assess differences between groups in independent samples. *P*-values < 0.05 were considered statistically significant. Results are expressed as median ± half interquartile range *(Me ± (LQ – UQ) / 2)*.

Results. At time point 2, caspase-9 levels were significantly higher in group 2 patients than in group 1 ($P = 0.045$). There were no significant differences between the groups at any other time points.

Conclusion. The lack of a significant difference in serum levels of caspase-9 and p53 protein at most time points between the groups demonstrates the efficacy of the anesthesia and analgesia methods used. Meanwhile, a significantly higher level of caspase-9 one hour after surgery demonstrates a greater susceptibility of patients without sympathetic blockade to activation of the apoptotic cell death program.

Keywords: inflammation; caspase-9; protein p53; multimodal anesthesia; combined inhalation and intravenous anesthesia

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

Introduction

Several critical factors affecting the human body typically cause damage by inflammation [1, 2]. Inflammationrepresents a common pathological process that is essential for the post-injury survival strategy of the body leading either to the restoration of homeostasis, i.e., recovery, or death. The latter is associated with the activation of so-called cell suicide programs. Cell death has been studied extensively over the past 25 years. In 2005, the Nomenclature Committee on Cell Death issued its first recommendations, identifying three types of cell death: necrosis, apoptosis, and autophagy. The committee's 2018 recommendations identify twelve types.

This situation can be explained by the fact that the original recommendations focused solely on the morphological changes in cells during the execution of suicidal cell programs, whereas the more recent guidelines focus on the processes that occur within the cell during death. Clearly, the identification of new types of programmed cell death could be an endless process, inextricably linked to the development of new research methods. Should modern anesthesiologists and intensivists be concerned about the complexity of cell suicide programs? Probably not. However, given the vast amount of information available on this topic, here are a few key points to remember:

- Modern oncologic surgery is highly traumatic, and similar injuries to an organism in the «wild» would always be fatal.
- Anesthesia, analgesia, and intensive care are all options for treating severe injuries.
- The primary goal of these methods is to reduce the metabolic response to injury rather than to provide «anti-stress protection».
- Metabolic responses to injury include not only hormonal changes (e. g., elevated cortisol and

catecholamine levels), but also immunological changes such as activation of cytokine cascades, expression of acute phase proteins, caspases, and pro- and anti-apoptotic proteins.

- The duration and intensity of the metabolic response to injury may affect the outcome of surgery.

Anesthesiologists should distinguish between immunogenic and non-immunogenic cell death [3]. In contrast to the elimination of dying cells by specific suicide programs (e. g., apoptosis), which does not lead to subsequent inflammatory response [4], immunogenic cell death can have negative consequences, such as widespread inflammation and overexpression of various cytokines in the early stages. While apoptosis can cause inflammation in some cases [5], the release of DAMPs (damage-associated molecular patterns) is the primary immunogenic factor that controls the balance between immunity and its absence. Furthermore, the receptors for endogenous DAMPs (heat shock proteins, histones, transcription factor A, DNA, RNA, extracellular ATP, etc.) will be the same PRRs (pattern recognition receptors) as for MAMPs [6-8]. However, various types of cell death will naturally differ in their DAMP expression profiles in response to different stimuli [6]. In any case, there will undoubtedly be a universal «signal 0» that causes local inflammation.

In the case of minor injury, activation of the cytokine cascade in the form of a balanced increase in the concentration of pro- and anti-inflammatory cytokines will trigger a local response that will lead to restoration of anatomical and functional integrity, i. e. recovery.

When an endocrine (generalized) inflammatory response develops, the bloodstream will contain large amounts of cytokines, especially if natural limiting agents (such as cortisol and adrenocorticotropic hormone) are deficient. Such a situation can act as a powerful proapoptotic signal, activating a cell suicide program.

In the best-studied form of programmed cell death, apoptosis, the induction of pro-apoptotic signals occurs via two primary pathways, extrinsic and intrinsic, and using combination of both. The apoptotic process begins with the interaction of a specific «extracellular domain and ligand» pair. An example of extrinsic pathway activation is the interaction of TNFα with specialized receptors, in particular the transmembrane receptors TNFR1 and TNFR2 [9], FAS [4], UNS5B, DCC [10] and others.

The intrinsic pathway is mediated by mitochondria-related mechanisms. A specific sequence of events leads to mitochondrial outer membrane permeabilization (MOMP), resulting in loss of functional membrane integrity, followed by release of mitochondrial proteins (DIABLO, HTRA2, cytochrome c) into the cytosol [11]. Mitochondrial membrane permeability is controlled by proteins of the Bcl-2 family, whose pro- or anti-apoptotic role is determined by the number and type of BH domains [12]. The levels of Bcl-2 family proteins are in turn regulated by the product of the tumor suppressor gene TP53, the p53 protein [1,13].

The programmed cell death (PCD) pathway is obviously executed according to one scenario. Tetramers are formed to activate initiation caspases, which in turn activate effector caspases [14]. Despite differences in the pathways leading to the pro-apoptotic signal, the process converges at a single point: the activation of initiation caspases followed by the activation of effector caspases [15]. Caspases 8, 9, 10, and 12 belong to initiators, whereas caspases 3, 6, 7, and 14 are effectors [16].

Direct p53-induced apoptosis is likely to be the first rapid phase of the inflammatory response to extensive damage. Some studies have found that in radiosensitive tissues (such as thymus or spleen), p53 translocation to mitochondria and activation of the effector caspase-3 occur very rapidly (within 30 minutes), even before sufficient p53-regulated gene products are produced. The next wave of apoptosis induction occurs 6 to 7 hours later and is associated with p53 transcriptional activity in the nucleus [17].

It appears that p53 acts at multiple levels, using different mechanisms to induce both a «rapid» inflammatory response to stressors and a «slower» but highly effective apoptotic program for damaged cells [18]. Our study considered changes in serum levels of p53 and the initiator caspase-9 as markers of potential activation of the most well-studied cell death program, apoptosis, without specifying the activation pathway, whether via specialized receptors or the mitochondrial pathway [19].

We have previously described changes in other inflammatory response markers in patients with the similar profile [20].

The next step in this research is to investigate changes in caspase-9 and p53 levels as potential indicators of inflammation in patients who have undergone lung resection for malignant neoplasms under different multimodal or balanced (inhalation and intravenous) anesthesia during the early postoperative period.

Materials and Methods

We conducted a single-center prospective study of 22 patients, aged 47–68 years, who underwent lobectomy for lung malignancies at the Omsk Regional Cancer Center from January to April 2020.

The collection of material for the study did not affect anesthesia and analgesia techniques or protocols. Patients signed the informed consent form. The local ethics committee of the Omsk State Medical University approved the use of the collected data for publication (protocol No. 4, dated 14.09.2022).

A double-blind method was used (both anesthesia and intensive care staff and laboratory staff were blinded to the group assignments).

All patients were weaned from mechanical ventilation in the operating room within 4±2 minutes after surgery. Patients were divided into two groups: the main (group 1, *N*=11) and the control (group 2, *N*=11). Random allocation of patients to the groups was performed from the general flow of patients in the ICU of the center using a random number table, ensuring the absence of selection bias.

Fig. 1 shows the study flow chart, while Table 1 details the characteristics of patients in groups 1 and 2.

Patients in group 1 received multimodal anesthesia and analgesia along with neuromuscular block and mechanical ventilation. An epidural catheter was inserted at the Th5–Th6 level to administer a three-component mixture of 0.2% ropivacaine, fentanyl, and adrenaline.

Patients in group 2 received inhalational and intravenous anesthesia based on sevoflurane and fentanyl under muscle paralysis and lung ventilation.

In the postoperative period, patients in group 1 continued to receive a three-component mixture into the epidural space for analgesia. Patients in group 2 received morphine 30 mg/day by titration.

All patients also received intravenous administration of acetaminophen, 3 grams/day. Pain intensity in all patients did not exceed 2–3 points on the VAS, and the duration of surgery and anesthesia was 90±20 minutes. Comorbidities in the groups included controlled hypertension, COPD GOLD1. The ASA class of anesthesia did not exceed III (see Table 1).

Patients with comorbidities such as diabetes mellitus, postobstructive pneumonia, ischemic heart disease with II and greater class, and those taking beta-blockers or with intraoperative blood loss greater than 500 mL were excluded from the study.

Four study time points were identified: before induction of anesthesia, and at 1, 12, and 24 hours postoperatively. At these time points, serum levels of caspase-9 and p53 protein were measured.

Serum concentrations of caspase-9 and p53 protein were analyzed by the sandwich enzyme-linked immunosorbent assay (ELISA) method using test kits on the Multiscan Fc Immunological Analyzer (Thermo Fisher Scientific Corporation, USA). The caspase-9 ELISA kit used was from Cloud-Clone Corp., USA (Lot L 190226123), and the p53 (TP53) ELISA kit was also from Cloud-Clone Corp., USA (Lot L 190226138).

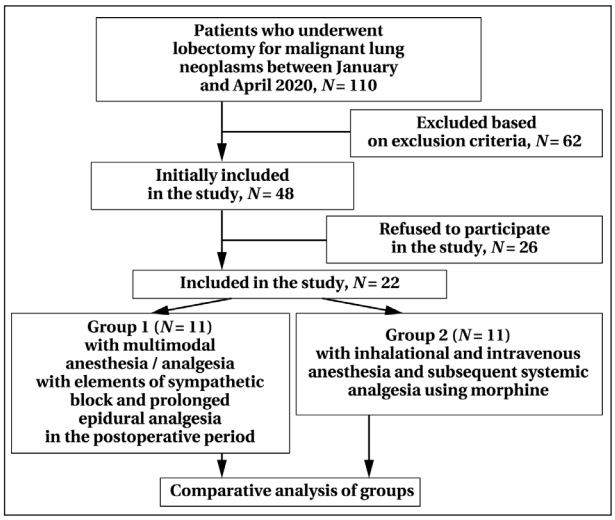

Fig. Study flowchart.

The study did not use standard checklists such as CONSORT or STROBE, as decided by the research team, which is permissible for studies with small sample sizes. The study was limited by the lack of an a priori sample size calculation and did not have a registered protocol.

Statistical analysis included tests of distribution of variables (Kolmogorov–Smirnov and Shapiro–Wilk tests) in the study groups, as well as variance values. Given the small sample size (*N*=11), non-normal distributions and unequal variances, robust non-parametric (rank-based) statistical methods were used. Statistical hypothesis testing was performed using the Wilcoxon signed-rank test (two-sample nonparametric test) for paired comparisons between two points, and Friedman's ANOVA for comparisons between four points. Differences between independent groups 1 and 2 at identical time points were assessed using the Mann–Whitney *U* test. The null hypothesis was rejected for paired comparisons between the two groups when $P < 0.05$

Table 1. Patient characteristics.

Parameter	Values in groups		*P*-value
	Group 1, *N* = 11	Group 2, *N* = 11	
Male sex, *N* (%)	8 (72.7)	9 (81.8)	0.62
Female sex, *N* (%)	3 (27.3)	2 (18.2)	
Age, years (min–max)	52–68	47–68	0.29
Comorbidities, *N* (%) (controlled hypertension, COPD GOLD1)	6 (54.5)	7 (63.6)	0.67
ASA score, points	3	3	1.0
Pain intensity on VAS, points	2–3	2–3	1.0
Duration of surgery, min	90±20	90±20	1.0

Note. Data are expressed as *Me* ± *(LQ – UQ)* / 2. No significant differences were found between groups; $P > 0.05$ (χ^2, Fisher, Mann–Whitney tests).

(using a two-tailed P value), and for multiple comparisons of study points with correction for the number of paired comparisons when $P < 0.013$ (using the Bonferroni correction). Data are presented as *Me* ± *(LQ — UQ)* / 2, i. e. the median ± half of the interquartile range. Statistical analyses were performed with STATISTICA, StatSoft, Inc. (2007), version 8.0.

Results

Results are shown in Table 2.

The analysis of the data obtained showed the following results. At the first time point (before induction of anesthesia), there was a high degree of similarity in the changes of the studied variables, indicating that the patients in both groups were comparable. The inclusion criteria used for the groups showed that none of the patients had values for the studied parameters that exceeded the upper reference limits. It is important to note that the study was performed before the first case of COVID-19 was registered in the region.

At the second time point (one hour postoperatively), significant differences between the groups were observed. Patients in the second group, who received inhalational and intravenous anesthesia with sevoflurane and systemic morphine-based analgesia, showed a significant difference in one of the parameters (caspase-9) compared to patients in the first group. However, p53 protein levels in all patients at this time point were comparable to normal and did not exceed the reference limit of 0.78 pg/mL.

At the third time point (12 hours postoperatively), patients in both groups showed statistically significant similarity in the two variables studied. None of the values in the 22 cases exceeded the reference limits.

At the fourth time point (24 hours postoperatively), no significant differences were observed between the first and second groups. All measured parameters remained within their respective reference ranges.

Discussion

The lack of difference in p53 protein levels between the groups of operated patients can be interpreted in two ways. First, it could mean that both types of anesthesia/analgesia provided adequate protection to the organism. Alternatively, it could indicate the absence of DNA damage capable of causing cell cycle arrest at any of the time points tested. As a result, there was no «need» for p53 overexpression to maintain genome stability.

Another possible explanation is discussed below. It is well known that p53 is a short-lived protein [21], with elevated levels lasting only 5 to 20 minutes, depending on the cell type. A larger number of sampling time points could have captured transient periods of p53 overexpression, potentially revealing significant differences between groups. However, the time points used in this study were previously defined and justified in our previous research [20–23].

The short lifespan of p53 has been attributed to a negative autocrine feedback loop involving the MDM2 protein, a key ubiquitin ligase responsible for p53 degradation [21]. This feedback mechanism is activated in response to stress, ensuring that the organism's «protective strategy» remains within physiological limits. However, during stress, protein kinases phosphorylate serine residues, disrupting the interaction between p53 and MDM2 [24]. This disruption causes p53 to accumulate intracellularly, allowing the coordination of multiple signaling pathways in response to cellular damage [21, 25]. Unfortunately, the ELISA method used in this study measures serum p53 levels but does not provide information on its functional activity [26].

In mammals, both major apoptotic pathways — extrinsic (receptor-induced) and intrinsic (mitochondrial) — use a caspase cascade [27]. The key feature of this cascade is its stepwise activation: pro-caspases are cleaved to active inducer caspases (such as caspase-9), which then activate effector caspases. Effector caspases are responsible for the

Table 2. Changes in serum concentrations of caspase-9 and p-53 in patients of groups 1 and 2, *Me (LQ – UQ)* / 2.

Study time point	Values in groups		*P*-value
	Group 1, *N* = 11	Group 2, *N* = 11	
Caspase-9 (reference range: 0–0.312 pg/mL)			
1	0.22 (0.13–0.25)	0.13 (0.10–0.23)	0.14
2	0.21 (0.17–0.25)	0.14 (0.11–0.22)	0.045*
3	0.14 (0.11–0.18)	0.15 (0.14–0.17)	0.38
4	0.16 (0.11–0.19)	0.14 (0.10–0.17)	0.22
ANOVA	χ^2 (d_f = 3) = 6.82; P = 0.077	χ^2 (d_f = 3) = 2.28; P = 0.52	—
p53 (reference range: 0–78 pg/mL)			
1	52.60 (45.40–61.70)	51.30 (43.50–70.60)	0.82
2	58.40 (50.20–68.10)	47.80 (45.00–69.70)	0.41
3	47.80 (44.50–61.70)	55.90 (34.00–66.30)	0.72
4	50.00 (43.10–65.00)	56.10 (45.80–77.60)	0.72
ANOVA	χ^2 (d_f = 3) = 6.69; P = 0.083	χ^2 (d_f = 3) = 1.15; P = 0.77	—

Note. * — statistically significant difference between groups (Mann–Whitney test) at $P < 0.05$. ANOVA — one-way Friedman analysis of variance for dependent samples (used for dynamic observation across time points).

physical disassembly of cell structures. Caspase-9, as a direct activator of effector caspases, is critical in translating the death signal into the first proteolytic event, making its regulation diagnostically relevant [27].

Furthermore, there is evidence that caspase-9 influences both programmed cell death and survival strategies such as autophagy [28, 29].

Practical limitations prevent the real-time study of various components of host defense mechanisms in response to tissue injury. Most of these methods involve sequential processes that take a certain amount of time. However, the identification of patterns in the early postoperative period using different anesthesia/analgesia methods, based on previous results, has the potential to improve surgical outcomes. One study found that the analgesic methods used were both effective and safe from a pathophysiologic standpoint for patients undergoing lung resection surgery [20]. Our previous research has shown that epidural analgesia provides strong antinociceptive protection, but may also induce an endocrine response that manifests as a widespread inflammation [22, 23].

Conclusion

Elevated levels of the initiator of caspase-9 one hour after lung resection surgery suggest an increased inflammatory response to tissue injury in patients without sympathetic blockade. The lack of significant differences in serum caspase-9 and p53 levels 12 and 24 hours after surgery demonstrates both the effectiveness of the anesthesia and analgesia methods used and the localized nature of the inflammatory response, which remained paracrine and limited to the site of tissue injury.

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Linking Cerebral Oximetry to Outcomes of Reperfusion Therapy in Ischemic Stroke: a *Post-Hoc* Analysis of a Randomized Controlled Trial

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Summary

Aim. To evaluate the predictive value of cerebral oximetry for functional recovery in patients undergoing reperfusion therapy for ischemic stroke.

Materials and Methods. A post hoc analysis was performed using data from a single-center, open-label, randomized controlled trial. The study included 45 patients with ischemic stroke who received systemic thrombolysis. Primary outcomes included functional recovery as assessed by modified Rankin Scale and mortality. Serial cerebral oximetry was performed within the first 24 hours after thrombolysis. The interhemispheric difference (IHD) in cerebral oximetry was used to determine a cutoff point for predicting functional recovery using ROC curve analysis. Associations between IHD and outcomes were analyzed using univariate and multivariate logistic regression models.

Results. The IHD in cerebral oxygenation between the unaffected and affected hemispheres was 4% (3–5%) before thrombolysis and dropped to 3% (1–4%) 24 hours after thrombolysis ($P = 0.024$). An IHD of less than 4% was identified as an independent predictor of favorable functional outcome with an adjusted odds ratio of 12 (95% CI: 1.6–93.7; $P = 0.017$). However, IHD less than 4% was not predictive of mortality ($P = 0.301$).

Conclusion. Systemic thrombolysis in ischemic stroke is associated with improved cerebral oxygenation. An IHD in cerebral oxygenation of less than 4% serves as an independent predictor of favorable functional recovery in ischemic stroke patients but does not correlate with reduced mortality.

Keywords: ischemic stroke, systemic thrombolysis, cerebral oximetry, functional outcome

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

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Introduction

Ischemic stroke (IS) is a common debilitating condition with a high mortality rate and a significant economic burden on healthcare systems [1–3]. Treatment during the hyperacute phase of IS focuses on rapid recanalization of the occluded artery and restoration of cerebral blood flow [4, 5]. Both pharmacological and mechanical methods of reperfusion are used. Pharmacological approaches include systemic and local thrombolytic therapy (TLT), while mechanical methods include thrombectomy and thrombus aspiration [4, 6]. Advances in neuroimaging techniques, such as magnetic resonance imaging (MRI) and perfusion studies, have facilitated the extension of therapeutic windows for reperfusion interventions [7–9].

In recent years, the potential benefits of additional monitoring methods during the hyperacute phase of IS have been widely discussed in the scientific literature. Cerebral oximetry is one such method that offers a non-invasive, user-friendly method to assess local brain oxygenation with sufficient accuracy [10, 11]. Currently, cerebral oximetry is used as an adjunctive monitoring tool in various cardiovascular surgeries and critical illness [10, 12, 13].

Cerebral oximetry has shown utility in the diagnosis of secondary hypoperfusion, oligemia caused by intracranial hypertension, and cerebral vasospasm. It can also assess cerebral blood flow and autoregulatory integrity and help individualize hemodynamic parameters in patients with aneurysmal subarachnoid hemorrhage [10]. In addition, cerebral oximetry has been shown to accurately detect intracerebral hematomas larger than 3.5 mL located within 2.5 cm of the cortical surface of the brain [14].

The use of cerebral oximetry in intensive care for patients with focal brain injury, such as ischemic stroke or hypertensive intracerebral hemorrhage, is controversial due to potential discrepancies between the site of cerebral saturation measurement (rSO_2) and the location of the brain lesion. However, this monitoring method is particularly promising for ischemic stroke patients for several reasons.

First, cerebral oximetry may aid in the early detection of large vessel occlusion in the prehospital setting, thereby improving triage. It allows determination of appropriate patient routing — either to a center equipped with endovascular reperfusion techniques or to the nearest facility capable of administering systemic thrombolysis [15]. Second, this method can be used to comprehensively monitor the recanalization status during mechanical thrombectomy (MT) under general anesthesia [16]. Third, cerebral oximetry has the potential to predict functional and social recovery in patients undergoing reperfusion therapy for ischemic stroke [17, 18].

In addition, preliminary evidence suggests that cerebral oximetry is useful in assessing the safety of early mobilization in stroke patients [19].

All of the applications of rSO_2 monitoring discussed are in patients with large intracranial vessel occlusions and subsequent use of MT for recanalization. However, the scientific literature lacks data on the extent to which rSO_2 measurements can predict functional recovery in patients who have undergone TLT alone or in mixed groups receiving both TLT and MT.

Therefore, the aim of our study is to evaluate the predictive ability of cerebral oximetry for functional recovery in patients after reperfusion interventions for ischemic stroke.

Materials and Methods

A post hoc analysis was performed using data from a single-center, open-label, randomized controlled trial (RCT) conducted at the Department of Anesthesiology and Intensive Care of the Regional Vascular Center (RVC) of the First City Clinical Hospital named after E. E. Volosevich in Arkhangelsk, Russia.

The RCT protocol was approved by the Ethics Committee of the Northern State Medical University (Arkhangelsk) on January 26, 2022 (Protocol No. 01/01-22) and registered at ClinicalTrials.gov (NCT05517109). Written informed consent was obtained from all participants. For patients who were unable to provide informed consent, a medical consilium was convened to determine the feasibility of enrolling them in the study.

Patients over 18 years of age diagnosed with IS and scheduled for TLT or MT were included in the study. All enrolled participants were required to have a systolic blood pressure (SBP) of at least 140 mmHg at enrollment. For post hoc analysis, only patients with IS in the anterior cerebral circulation and rSO_2 measurements taken within the first 24 hours after TLT were included.

Randomization was performed using a sealed envelope method. Upon admission to the ICU of the RVC, patients were randomized into two groups: the control group with a target SBP of 161–185 mmHg during the first 24 hours and the intensive hypotensive therapy group with a target SBP of < 160 mmHg. Randomized SBP targets were maintained during reperfusion and for the first 24 hours after TLT. If SBP exceeded the target range, TLT was stopped temporarily for SBP correction; once target SBP was achieved, reperfusion was resumed.

Exclusion criteria were as follows:

- Lack of informed consent or a medical consilium decision.
- Patient refusal to participate in the study.
- Pregnancy.
- Participation in another clinical trial within the previous 90 days.
- Off-label use of TLT, except in cases where patient selection was based on DWI/FLAIR mismatch assessment using brain MRI.
- Failure to achieve target SBP within 20 minutes prior to initiation of TLT.
- SBP above target range for more than 60 minutes during the first 24 hours after TLT.
- SBP less than 100 mmHg for more than 60 minutes after reperfusion therapy.

Hemodynamic parameters were monitored with GE PROCARE B40 (USA) or Comen WQ-002 (China) devices. Blood pressure was controlled according to the randomization protocol with intravenous azamethonium bromide and urapidil as needed.

Thrombolytic therapy was administered with alteplase at a dose of 0.9 mg/kg. For patients over 80 years of age, the attending intensivist could reduce the dose to 0.6 mg/kg. Ten percent of the dose was given as an intravenous bolus, with the remainder infused continuously over the next hour using a syringe pump.

For all patients, biometric parameters, primary and comorbid conditions, IS subtype according to the TOAST classification [20], and stroke severity according to the National Institutes of Health Stroke Scale (NIHSS) [21] were recorded.

Cerebral oxygen saturation (rSO_2) was monitored using the Masimo Root device (USA). Two sensors were placed in standard positions on the forehead, right and left of the midline. Data from both sensors were collected, reflecting rSO_2 values for the intact and affected hemispheres during the first 24 hours post-TLT. Studies suggest that the ratio of arterial to venous blood oxygenation in the cerebral cortex is highly individual, which can significantly influence absolute rSO_2 values and define an individual normal range [22]. With this in mind, the degree of damage to the affected hemisphere was assessed by calculating the difference in rSO_2 values between the intact and affected hemispheres ($\triangle rSO_2$).

The primary endpoints were 90-day mortality and functional recovery as assessed by the modified Rankin Scale (mRS) at 90 days after stroke onset [23]. Data were collected via telephone interviews with

the patient or their next of kin. Functional recovery was categorized as favorable (mRS score 0–2) or unfavorable (mRS score 3–5) [24].

Statistical data analysis. Continuous data were presented according to their distribution, either as mean *(M)* ± standard deviation *(SD)* or as median *(Me)* with interquartile range *(IQR: Q1; Q3)*. Categorical data were described as absolute numbers *(N)* and percentages (%). Normality of distribution was assessed using the Shapiro–Wilk test.

For comparisons of continuous variables between groups, independent samples were analyzed using either the Student's t-test (for normally distributed data) or the Mann–Whitney *U* test (for non-normally distributed data). For paired samples, the Wilcoxon signed-rank test was used. Comparisons of categorical variables were made using Fisher's exact test.

The cutoff point for predicting favorable functional recovery based on $\triangle rSO_2$ values was determined using receiver operating characteristic (ROC) curve analysis, which evaluates the proportion of correctly classified values. The association between rSO_2 measurements and functional recovery was evaluated using univariate and multivariate logistic regression models.

For multivariate logistic regression models, confounders significant in published studies (such as age and NIHSS score on admission) were selected and simultaneously included in the model. Statistical analyses were performed with STATA 14 MP software (StataCorp, USA).

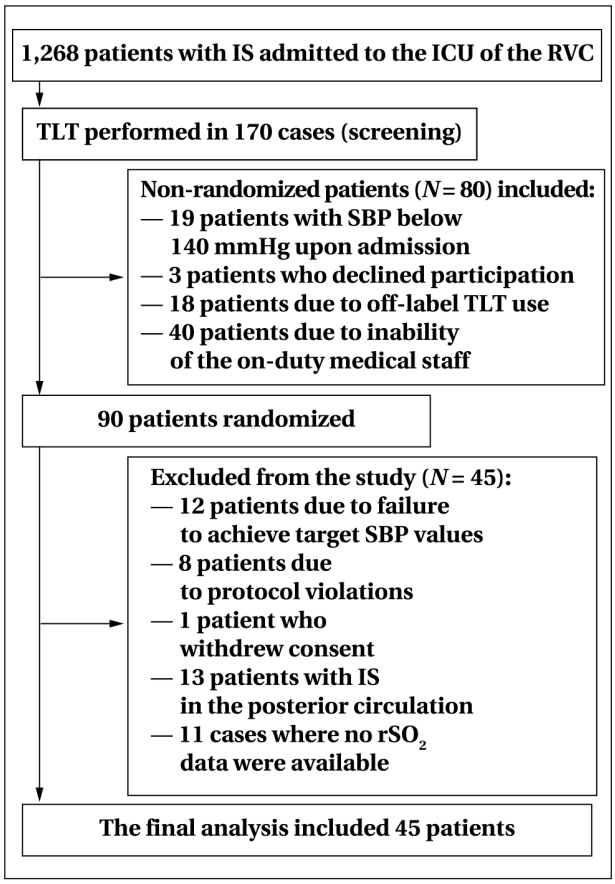

Fig. 1. Study flowchart.
Note. IS — ischemic stroke; TLT — thrombolytic therapy; SBP — systolic blood pressure.

Results and Discussion

During the study period, 1,268 patients with IS were admitted to the ICU of the RVC. Screening was performed in 170 patients who underwent TLT, of whom 90 were randomized. The final analysis included 45 patients with carotid territory strokes and recorded rSO_2 measurements (Fig. 1).

Of the participants, 27 (60%) were men with a mean age of 70.9±10.9 years and a median NIHSS score of 9 (IQR: 6; 16) (Table 1). The distribution of IS subtypes was as follows:

- Atherothrombotic stroke: 17 patients (37.8%)
- Cardioembolic stroke: 14 patients (31.1%)
- Lacunar stroke: 3 patients (6.7%)
- Cryptogenic stroke: 11 patients (24.4%).

The $\triangle rSO_2$ before TLT was 4 (3; 5). Twenty-four hours after TLT, $\triangle rSO_2 24$ was 3 (1; 4), which was significantly different ($P = 0.024$).

The cut-off point for the $\triangle rSO_2 24$ parameter was set at 4%, with a sensitivity of 50%, specificity of 88%, and overall classification accuracy of 73.2% (Fig. 2). Based on this threshold, the cohort was divided into two groups: $\triangle rSO_2 24 < 4\%$ and $\triangle rSO_2 24 \geqslant 4\%$.

Fatal outcome was observed in 4 patients (8.9%). Among surviving patients, good functional recovery was documented in 25 cases (61%) with the following distribution between groups: in the $\triangle rSO_2 24 < 4\%$ group, favorable outcomes were observed in 22 cases (73%) compared to 3 cases (27%) in the $\triangle rSO_2 24 \geqslant 4\%$ group ($P = 0.012$).

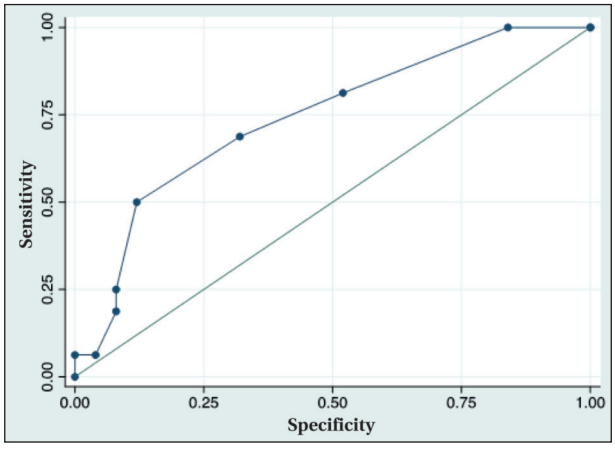

Fig. 2. ROC curve: sensitivity and specificity of interhemispheric difference in cerebral oximetry values 24 hours after systemic thrombolysis for predicting good functional recovery.
Note. The area under the curve (AUC) is 0.741 [95% CI, 0.570 to 0.857].

Table 1. Clinical and demographic characteristics of the sample and outcomes.

	Entire sample, *N* = 45	△rSO$_2$24 < 4%, *N* = 31	△rSO$_2$24 ⩾ 4%, *N* = 14	*P*-value
Age, years	70.9±10.9	71.1±10.4	70.4±12.4	0.570
Sex, male, *N* (%)	27 (60)	20 (64.5)	7 (50)	0.357
NIHSS on admission, points, *Me (Q1; Q3)*	9 (6; 16)	7 (6; 13)	14.5 (9; 20)	0.002
Comorbidities				
Hypertension, *N* (%)	38 (84.4)	26 (83.9)	12 (85.7)	0.874
Atrial fibrillation, *N* (%)	16 (35.6)	10 (32.3)	6 (42.9)	0.492
Diabetes mellitus, *N* (%)	11 (24.4)	7 (22.6)	4 (28.6)	0.717
Coronary heart disease, *N* (%)	15 (33.3)	11 (35.5)	4 (28.6)	0.743
Chronic heart failure, *N* (%)	6 (13.3)	5 (16.1)	1 (7.1)	0.648
Outcomes				
Death, *N* (%)	4 (8.9)	1 (3.2)	3 (21.4)	0.082
mRS score on day 90, points, *Me (Q1; Q3)*	2 (1; 3)	2 (1; 3)	3.5 (3; 5)	0.01

Note. mRS — modified Rankin score.

Table 2. Predictors of favorable functional recovery after thrombolytic therapy.

Predictor	Preliminary analysis			Adjusted analysis		
	OR	95 % CI	*P*-value	aOR	95 % CI	*P*-value
△rSO$_2$24 < 4 %	7.3	1.5–34.7	0.012	12	1.6–93.7	0.017
Age, years	0.9	0.8–0.9	0.029	0.9	0.8–0.9	0.016
NIHSS on admission, points	0.9	0.8–1.1	0.093	0.9	0.8–1.1	0.551

Note. Here and Tables 2, 3: △rSO$_2$24 — interhemispheric difference in cerebral oximetry; aOR — adjusted odds ratio.

Table 3. Predictors of mortality after thrombolytic therapy.

Predictor	Preliminary analysis			Adjusted analysis		
	OR	95 % CI	*P*-value	aOR	95 % CI	*P*-value
△rSO$_2$24 < 4 %	0.12	0.1–1.3	0.082	0.25	0.01–3.9	0.301
Age, years	1	0.9–1.1	0.902	1	0.9–1.1	0.964
NIHSS on admission, points	1.2	1–1.4	0.049	1.2	0.9–1.4	0.163

△rSO$_2$24 as a predictor of favorable functional outcome. △rSO$_2$24 < 4% was associated with favorable functional recovery in univariate analysis (OR, 7.3 [95% CI, 1.5 to 34.7], *P* = 0.012). In multivariate analysis, △rSO$_2$24 < 4% also was an independent predictor of favorable functional outcome (adjusted OR, 12 [95% CI, 1.6 to 93.7], *P* = 0.017). Variables included in the model are listed in Table 2.

△rSO$_2$24 as a predictor of mortality. △rSO$_2$24 < 4% was not a predictor of mortality in either univariate analysis (OR, 0.13 [95% CI, 0.01 to 1.3]; *P* = 0.082) or multivariate analysis (adjusted OR, 0.25 [95% CI, 0.01 to 3.9]; *P* = 0.301) (Table 3).

In this post hoc analysis of an RCT investigating the optimization of blood pressure during the first 24 hours after TLT for IS, it was demonstrated that △rSO$_2$ values significantly decreased after TLT. This reduction illustrates the effectiveness of reperfusion techniques in restoring blood flow to the affected cerebral hemisphere. However, the observed decrease in △rSO$_2$ was modest in absolute terms, limiting its utility as a marker of reperfusion. These findings are consistent with those reported by Hametner et al. in which △rSO$_2$ increased in the affected hemisphere in only 2 of 25 patients after successful recanalization by MT. Therefore, the applicability of △rSO$_2$ monitoring to assess reperfusion during the hyperacute phase of acute IS remains uncertain.

To date, several studies have investigated the prognostic ability of △rSO$_2$ levels in predicting functional recovery and mortality in patients with IS. According to S. E. Eroğlu et al. [25], △rSO$_2$ values were not associated with stroke severity in acute cerebrovascular events. This lack of association may be due to the inclusion of both ischemic and hemorrhagic stroke patients in their cohort. This is partially supported by Flint et al. who demonstrated that △rSO$_2$ values did not differ between hemispheres in patients with ICH [15]. In contrast, for IS specifically, △rSO$_2$ values of 3% or greater have been identified as a potential predictor of large intracranial vessel occlusions, such as in the intracranial internal carotid artery, M1 segment of the middle cerebral artery, and A1 segment of the anterior cerebral artery [15]. Our results further suggest that △rSO$_2$24 values of 4% or greater serve as an independent predictor of poor functional recovery in IS. This observation may reflect a higher prevalence of patients with large-vessel occlusion in the cohort, resulting in larger ischemic volumes and consequently worse outcomes.

The 90-day mortality rate in our cohort was 8.9%, which is consistent with published data [26]. Our results suggest that △rSO$_2$24 is not a predictor of mortality in patients after thrombolysis. However, C. Hametner et al. reported △rSO$_2$24 as a predictor of mortality, which may be attributed to the higher mortality rate of their cohort (32.6%) and the inclusion of patients undergoing MT for large intracranial vessel occlusions. In addition, the baseline

severity of illness was significantly higher in the C. Hametner et al. study, with a median NIHSS score of 19 on admission compared to 9 in our cohort [18]. This difference likely contributed to the worse functional outcome in cases of unsuccessful recanalization in their study.

To our knowledge, this study is among the first to investigate the prognostic value of rSO_2 values in patients after TLT for IS. Nevertheless, several limitations must be acknowledged. These include the modest sample size and single-center design, which limit the generalizability of the findings. In addition, we did not assess the prevalence of large intracranial vessel occlusion, which could be a significant confounding factor influencing our results.

Conclusion

Thrombolytic therapy in IS is associated with a reduction in the interhemispheric difference in rSO_2 between the intact and affected hemispheres. A $\triangle rSO_2 24$ of 4% or greater is an independent predictor of poor functional recovery in patients after IS, but is not associated with increased mortality. Further research is needed to elucidate the role of rSO_2 monitoring in the hyperacute phase of IS.

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Diagnosis of Brain Death in a Multidisciplinary Hospital

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Summary

Brain death diagnosis (BDD) remains a challenge for anesthesiologists and intensive care physicians despite existing regulatory frameworks.

Objective. To evaluate the frequency of BDD procedure and identify factors limiting its implementation in a multidisciplinary hospital setting.

Materials and Methods. A single-center retrospective study was conducted including 698 patients by total sampling. Of these, 98 (14%) had brain injury and were selected for further analysis. From this cohort, patients who died within 15 days of hospital admission ($N = 61$) were identified. A subgroup of patients with a Glasgow Coma Scale (GCS) score of 3–5 was then selected ($N = 38$). For comparison, a literature search was performed in PubMed using the query «brain death criteria» and in eLibrary.ru using the keywords «brain death diagnosis».

Results. BDD was initiated in 12 (31.6%) cases within the GCS 3–5 subgroup, with brain death confirmed in 8 (21.1%) patients, including 5 (63%) women and 3 (37%) men. Complete BDD procedures were performed in 6 (75%) patients with non-traumatic intracerebral hemorrhage (ICH), 1 with non-traumatic subarachnoid hemorrhageь (SAH), and 1 with traumatic brain injury (TBI) (12.5% each). The median patient age was 59 [43; 65] years, the median GCS score was 3 [3; 3], and the median FOUR score was 0 [0; 0]. Median hospital length of stay was 1.5 [1; 2.5] days, and median intensive care unit (ICU) stay was 1 [1; 2] day.

Conclusion. Insufficient pupil diameter (5 mm) is a limiting factor for the performance of BDD procedures in grade III coma patients.

Keywords: brain death diagnosis; transplantation

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

The main results were presented in a poster session on «Education and Organizational Issues in Anesthesiology and Critical Care» at the Forum of anesthesiologists and reanimatologists of Russia (FARR), October 12–14, 2024, St. Petersburg.

Introduction

Advances in medical care have led to an increase in the number of patients receiving intensive therapy despite irreversible brain damage of primary or secondary origin. For anesthesiologists and intensivists, the timely diagnosis of death based on neurological criteria is critical. This practice helps to discontinue futile intensive care and prevents the emotional burden on health care professionals who recognize the unfavorable prognosis but continue to provide care [1].

Failure to diagnose brain death results in the loss of potential organ donors who meet neurological criteria, depriving patients awaiting transplantation of a chance at life. It is estimated that the annual need for kidney transplants is approximately 40 cases per million population, while the need for heart and liver transplants is 20 cases each. Consequently, the annual need for kidney transplants in the population is about 4,000–5,000, and for liver and heart transplants, 1,500–2,000 each. Patients in need of organ transplantation are treated in specialized centers, where the mortality rate of patients on the waiting list ranges from 10% to 35% [2].

The aim of the study was to evaluate the frequency of brain death determination by intensivists and to identify factors limiting its implementation in a multidisciplinary hospital.

Materials and Methods

We conducted a single-center retrospective study that included a comprehensive sample of 698 patients who died between September 4, 2023, and March 22, 2024 (201 days). The study focused on seven anesthesiology and intensive care units (112 beds) within a large multidisciplinary hospital with a catchment population of approximately 300,000 people. The hospital includes a vascular center and performs neurosurgical procedures for neuro-oncological and cerebrovascular conditions.

Of the total patient sample, 98 cases (14%) involved brain damage and were selected for further analysis (see Figure). The types of brain injury are detailed in Table 1.

From the cohort of selected patients, a group of patients who died within 15 days of hospital admission was identified (*N*=61; see Figure and Table 1). This group was selected because in patients with a hospital stay longer than 15 days, the cause of death was primarily progression of the organ failure syndrome secondary to infectious complications.

In the next step, a subgroup consisting of patients with an ICU stay of 0–15 days and a reduced level of consciousness scoring 3–5 on the Glasgow Coma Scale (GCS) was identified from this group (subgroup, *N*=38).

The study cohort had 48 women (49%) and 50 men (51%). The study group included 32 women (52%) and 29 men (48%), while the subgroup consisted of 17 women (45%) and 21 men (55%).

Decisions on the determination of brain death (DBD) were made in accordance with the Order of the Ministry of Health of the Russian Federation dated December 25, 2014, No. 908n, «On the Procedure for Determining Human Brain Death» [3]. The biochemical criteria required to initiate the DBD procedure included pH 7.35–7.45, sodium 135–145 mmol/L, potassium 3.5–5.0 mmol/L, blood glucose 3.0–8.3 mmol/L, and magnesium and calcium concentrations within their reference ranges, excluding brain death due to their abnormal levels [4].

We evaluated the length of hospital stay, time spent in the intensive care unit (ICU), duration of mechanical ventilation, patient age, and level of consciousness on admission to the ICU using the Glasgow Coma Scale (GCS) and the Full Outline of UnResponsiveness (FOUR) scale.

To compare our results with published data, a literature search was performed in the PubMed database using the query «brain death criteria» and in the eLibrary.ru system using the query «констатация смерти мозга» («determination of brain death»). A total of 5,939 sources were identified, covering the period from 1968 to 2024. Full-text publications from 2014 to 2024 were selected for detailed analysis.

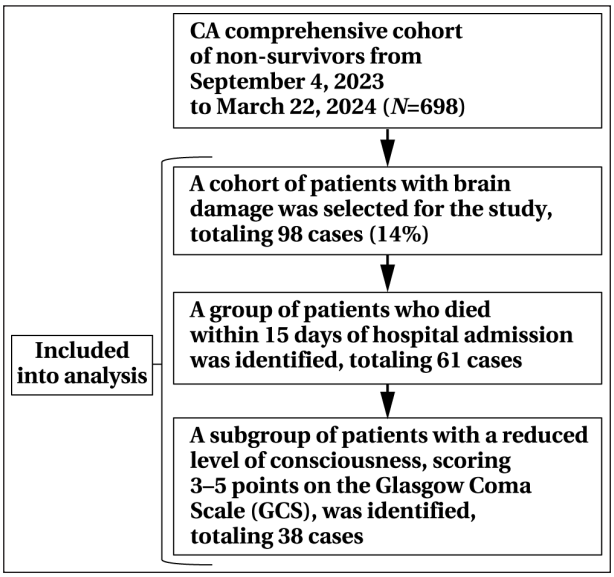

Fig. Study flowchart.

The collected data were processed using IBM SPSS Statistics 22 for Windows (SPSS, Chicago, Illinois) and Microsoft Office Excel 2013. Shapiro–Wilk test was used to determine the normality of data distribution. Quantitative data are presented as median *(Me)* and interquartile range *(Q1; Q3)*.

Results

Patient characteristics, length of hospital stay, length of ICU stay, and duration of mechanical ventilation are summarized in Table 2.

In the subset of patients, determination of brain death (DBD) was initiated in 12 cases (31.6%). Brain death was confirmed in 8 patients (21.1%), including 5 females (63%) and 3 males (37%).

Table 1. Distribution of patients by diagnosis, *N* (%)

Diagnosis	Participants		
	Entire cohort (*N* = 98)	Group (*N* = 61)	Subgroup (*N* = 38)
Ischemic stroke	35 (35.7)	18 (29.5)	9 (23.7)
Intracerebral nontraumatic hemorrhage	27 (27.6)	19 (31.1)	14 (36.8)
Subarachnoid hemorrhage	7 (7.1)	6 (9.8)	4 (10.5)
Traumatic brain injury	15 (15.3)	9 (14.8)	9 (23.7)
Brain tumor (primary or metastatic, operated or not operated)	10 (10.2)	5 (8.2)	0
Secondary meningoencephalitis	1 (1.0)	1 (1.6)	1 (2.6)
Cardiopulmonary resuscitation (secondary brain damage)	3 (3.1)	3 (4.9)	1 (2.6)

Table 2. Characteristics of included patients, *Me* [*Q1*; *Q3*].

Parameter	Participants		
	Entire cohort (*N* = 98)	Group (*N* = 61)	Subgroup (*N* = 38)
Age, years	67 [55; 76]	64 [50; 70]	61 [47; 68]
GCS, points	6 [3; 9]	3 [3; 6]	3 [3; 3]
FOUR, points	6 [0; 16]	0 [0; 16]	0 [0; 0]
Length of stay in hospital, days	9 [3; 27]	4 [3; 8]	3 [2; 6.7]
Length of stay in ICU, days	5 [2; 11]	4 [2; 7]	3 [2; 5.5]
Duration of lung ventilation, days	4 [1; 10]	3 [1; 6]	3 [2; 6]

Complete DBD was performed in 6 patients with intracerebral hemorrhage (75%), 1 with subarachnoid hemorrhage (12.5%), and 1 with traumatic brain injury (12.5%). The median age of these patients was 59 years [43; 65]. The Glasgow Coma Scale (GCS) score was 3 [3; 3] and the Full Outline of UnResponsiveness (FOUR) score was 0 [0; 0]. The median length of hospital stay was 1.5 days [1; 2.5], and ICU stay was 1 day [1; 2].

DBD was discontinued in four cases for the following reasons:

— Patient P. V. I., male, age 65 years, with the diagnosis of intracerebral hemorrhage and community-acquired pneumonia complicated by severe acute respiratory distress syndrome ($PaO_2/FiO_2 < 100$ mmHg). Apnea oxygenation testing was not initiated.

— Patient Z. R. S., male, age 24 years, with the diagnosis of TBI with ruptured tympanic membrane. EEG recording was not possible due to inability to apply electrodes.

— Patient K. M. V., a 55-year-old male with a diagnosis of intracerebral hemorrhage, developed hemodynamic instability during the apnea-oxygenation test, leading to termination of the test. Death occurred 30 minutes later.

— Patient Z. T. V., female, age 66, diagnosed with ischemic stroke with type 4 hemorrhagic transformation (intracerebral hematoma), developed hemodynamic instability during the apnea-oxygenation test. Death occurred 12 hours later.

DBD could not be initiated in 26 patients for various reasons:

— 19 (50.0%) patients had a pupil diameter less than 5 mm, of them 2 patients had pupil diameter less than 5 mm, preserved photoreaction and preserved breathing pattern, 4 patients had pupil less than 5 mm and preserved breathing pattern, and 13 patients had only diameter less than 5 mm;

— in 1 patient (2.6%) diazepam was administered during emergency medical care, and the length of hospital stay was less than 3 days;

— 5 (15.8%) patients with out-of-hospital/nosocomial pneumonia developed septic shock;

— 1 (2.6%) patient developed hypotension that was not corrected by 2 sympathomimetics after CPR.

After DBD in 8 potential organ donors, organ procurement was performed in 6. Organ procurement was not performed for a 44-year-old patient admitted with ICH who had previously undergone surgery for breast cancer, and an 88-year-old patient with ICH.

Discussion

According to the findings of The World Brain Death Project, the minimum criteria for diagnosing brain death include the presence of coma, absence of brainstem reflexes, and apnea. Assessment of cerebral blood flow and electroencephalography (EEG) should be used if the clinical examination does not provide sufficient information [5].

It is important to note that these criteria for determining brain death are fully described in the Russian Ministry of Health Order No. 908n of December 25, 2014, «On the Procedure for Determining Human Brain Death» [3]. In addition, the criteria specified in this order are reflected in the diagnostic algorithm for brain death proposed by M. Piradov and E. Gnedovskaya in 2010 [6], which remains a practical and informative tool.

There are significant differences in brain death criteria around the world, as demonstrated by the comprehensive study by A. Lewis et al. that analyzed data from 136 countries [7]. The study found that 83 countries have established brain death determination protocols; however, 78 of these have unique characteristics, and 53 countries have no such protocols at all.

Clinical signs that are evaluated in confirming brain death include the following:

— Pupil response to light: assessed in 70 (90%) countries.

— Corneal reflex: assessed in 68 (87%) countries.

— Oculovestibular reflex: assessed in 67 (86%) countries.

— Gag reflex: assessed in 64 (82%) countries.

— Cough reflex: assessed in 62 (79%) countries.

— Oculocephalic reflex: assessed in 58 (74%) countries.

— Cranial trigger point pain stimulation: assessed in 37 (47%) countries.

— Pain stimulation in extremities: assessed in 22 (28%) countries.

— Assessment of other reflexes: in 22 (28%) countries.

The apnea oxygenation test (AOT) is included in 91% of brain death protocols worldwide. However, there is variability in both the methodology of its performance and the target arterial carbon dioxide tension ($PaCO_2$) levels required. Ancillary tests to confirm brain death are required in 22% of protocols.

An interesting comparison of the frequency of diagnosis of brain death using national protocol criteria versus American or Chinese criteria was presented in a study by clinicians from Beijing Tiantan Hospital, which examined 37 patients with primary brain injury [8].

In the protocol used in China, confirmation of brain death requires the use of at least two of three ancillary tests: transcranial Doppler ultrasonography (TCD), electroencephalography (EEG), or somatosensory evoked potentials (SEP). AOT is mandatory and serves as the final step in the determination process. The interval between the first

confirmatory step and repeat ancillary testing is 12 hours.

In the United States, ancillary tests are used only when the clinical examination or apnea test cannot be performed due to special circumstances.

According to the Chinese national protocol, brain death was diagnosed in 9 of 37 potential organ donors, while according to the US criteria, brain death was diagnosed in 33 of the same group. Notably, intracranial infection leading to Grade III coma (with absence of brainstem reflexes) is not a reason for «non-inclusion» into brain death protocol under the Chinese recommendations on DBD.

These findings highlight significant differences in national guidelines on DBD, which may affect the frequency of brain death diagnoses.

The primary cause of brain death in our study was acute cerebrovascular event (ACVE), which accounted for 10 of 12 (83.3%) cases in which the brain death protocol was initiated and 7 of 8 (87.5%) cases in which it was successfully completed.

A decreasing proportion of traumatic brain injuries (TBI) among potential organ donors after determination of brain death has been observed in most European and North American countries. This trend has been attributed to improved vehicle safety, advances in traffic management, and a reduction in traffic accidents [9–11].

In our study, among potential donors diagnosed with brain death due to ACVE, intracerebral hemorrhage (ICH) was the leading cause, accounting for 75% of cases. ICH was present in 66.6% of brain death protocol initiations. The predominance of ICH as a cause of brain death has also been reported by other investigators. For example, D. Escuderoa et al. [10] and A. Sanchez-Vallejo et al. [12] identified ICH as the cause of brain death in 49% of cases.

Several studies have documented a temporal decrease in subarachnoid hemorrhage (SAH) as a cause of brain death. This trend has been attributed to improvements in the management and treatment of patients with SAH [13].

In our study, only one patient in whom the DBD protocol was initiated but not completed presented with ischemic stroke (IS) as the underlying cause of brain death, although this case also involved a type IV hemorrhagic transformation.

The low number of patients with IS progressing to brain death may be due to the presence of «reserve spaces» in the elderly population. In these cases, the development of a large cerebral infarct does not always lead to transtentorial herniation, despite the displacement syndrome. An important factor in reducing mortality in patients with IS is the widespread use of decompressive craniectomy to treat life-threatening cerebral edema [11].

The median age of potential donors undergoing DBD procedure in our study was 59 years, which is consistent with previously reported findings of 60.7 years [8, 9]. In Switzerland, P. Grzonka et al. reported a mean age of 57 years for brain-dead individuals [13]. However, younger donor ages have been documented; for example, A. Seifi et al. found a mean age of 47.83 ± 20.93 years [14], and M. Sahin et al. reported a mean age of 43 years [15] among potential donors. The researchers attributed this lower age to the relatively younger population in Turkey compared to Europe [14, 15].

According to M. Minina [16], the median age of brain-dead donors in Moscow between 2009 and 2013 was approximately 40 years.

In our study, the median time from admission to the intensive care unit to initiation of DBD was 1.5 days, and the median duration of mechanical ventilation was 1 day.

According to the literature, the time from hospital admission to determination of brain death varies significantly between countries. In Turkey, 69.69% of DBD procedures are performed in patients who stay in the ICU up to 7 days, 22.17% in those who stay 7–14 days, and 8.14% in those who stay longer than 14 days [17]. D. Escuderoa et al. report that when the DBD protocol is initiated within the first 24 hours of admission, brain death is diagnosed in 48% of cases in hospitals with neurosurgical services and in 59% of cases in hospitals without such services [10].

A major factor preventing DBD in 13 patients in our study was a pupil diameter of less than 5 mm. These patients also showed absence of light reflex, response to painful stimuli, spontaneous breathing patterns (making apneic oxygenation testing impossible), and oculocephalic and oculovestibular reflexes.

A retrospective study by P. Lenga et al. [17] of 17 potential donors over 18 years of age with confirmed brain death reported a mean age of 57.3 years. Using the NPi®-200 pupillometer (Neuroptics, Laguna Hill, USA), the mean right pupil diameter was 4.9±1.3) mm and the mean left pupil diameter was 5.2±1.2) mm. In countries such as Australia, New Zealand and Japan, a pupil diameter of less than 4 mm is a prohibitive factor for initiating DBD protocols [19].

In the study by D. Shlugman et al. [19], some of the 148 potential organ donors with a confirmed diagnosis of BD had pupils less than 4 mm in diameter. Similarly, A. Khandelwal et al. [18] described several challenging cases of patients with pupils less than 3 mm in diameter. However, after careful evaluation of the brainstem reflexes, the DBD protocols were successfully performed in these cases.

In our study, three brain death determinations (25%) were terminated due to the inability to perform

AOT. Of these, two cases (16.6%) were related to hemodynamic instability during the test, and one case (8.4%) was due to the inability to maintain the target gas exchange parameters specified in Russian Ministry of Health Order No. 908n due to the development of acute respiratory distress syndrome (ARDS). All three patients died soon after.

The incidence of symptomatic arterial hypotension during AOT was 9% (8 of 94 patients) in the study by X. L. Wu et al. [20]. The authors attributed this to inadequate preoxygenation prior to testing. A previous study by J. L. Goudreau et al. [21] reported arterial hypotension in 24% of 145 AOT cases. In both studies, patients had PaO_2 values greater than 200 mmHg, but target blood pressure was maintained with vasopressor infusions.

Neurogenic lung injury associated with severe brain injury occurs in 2% to 42.9% of cases according to various authors [22, 23] and often prevents the achievement of target oxygenation levels. I. Stulin et al. reported that maintaining the required blood gas parameters was not possible in 11% of cases, making the DBD protocol impossible [24].

In one case, the DBD protocol was not performed in a patient with TBI because it was not possible to place electrodes for electroencephalography (EEG) due to significant cranial bone deformities and ruptured tympanic membranes, which also precluded performance of the oculovestibular reflex test. A literature search of PubMed and eLibrary did not reveal any similar cases of DBD failure due to such factors in patients with TBI [25], suggesting that this is an extremely rare cause of protocol noncompliance.

The incidence of DBD varies considerably between countries and even between regions within the same country. In Spain, regional rates range from 55 to 25 protocols per 1 million population [10]. Time trends also play a role; in the United States, the number of confirmed cases of brain death increased from 12,575 in 2012 to 15,405 in 2016 [5].

In Moscow, according to I. D. Stulin et al. [24], mobile neurodiagnostic teams confirmed brain death in more than 500 cases between 1995 and 2010, including 282 cases between 2007 and 2010. In addition, M. Minina [16] reported that from 2011 to 2013, 243 effective donors were recorded after DBD procedure in Moscow.

The study of I. Voznyuk et al. [26] presented data on the application of the protocol of DBD at the St. Petersburg Research Institute of Emergency Medicine named after I. I. Dzhanelidze. Between 2014 and 2019, 48 DBD protocols were initiated in 313 patients with grade III coma, representing 15.3% of cases.

The proportion of completed DBD protocols among initiated cases (8 out of 12) in our study is consistent with reported data from Russia.

Study limitations. This study did not consider the presence of comorbidities or associated conditions, which limits the generalizability of the results.

Conclusion

The primary factor limiting performance of the procedure of brain death determination was a pupil diameter of less than 5 mm in patients with grade III coma.

The leading cause of brain death were cerebral vascular conditions, particularly intracerebral hemorrhage.

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Genetic, Metabolic, and Proteomic Polymorphisms and Clinical Phenotypes of Sepsis

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Summary

The heterogeneity of sepsis patient populations remains an unresolved issue, hindering the development of effective therapeutic strategies and disease prognostic tools. Classification of diverse sepsis patients by molecular endotypes, together with multi-omics profiling, enables a more personalized treatment approach. Studying the immune response, genomic, metabolomic and proteomic profiles of sepsis patients will enable clinical phenotyping of this diverse population and the development of a precision approach to the diagnosis, prognosis and treatment of sepsis and septic shock.

The aim of the review was to discuss sepsis subtypes as identified by profiling of patient genomic, metabolic, and proteomic data and present the latest approaches addressing the heterogeneity of sepsis patient populations, such as multi-omics endotyping and clinical phenotyping, which may aid in targeted therapy and optimization of diagnosis and therapy. The keywords «sepsis omics», «sepsis endotypes», and «sepsis heterogeneity» were used to search PubMed databases without language restrictions. From over 300 sources, 120 were selected for analysis as being most relevant to the aim of the review. More than half of these were published within the last five years. Criteria for excluding sources were their inconsistency with the aims of the review and their low informativeness.

This review discusses the different types of immune responses, the impact of patient population heterogeneity on therapeutic interventions, and current perspectives on phenotyping sepsis patients. Despite the limitations of centralized collection of clinical information, cluster analysis of large data sets and the role of immune response genomics, metabolomics, and proteomics are beginning to dominate the prognosis and treatment of sepsis. Establishing links between all these elements and attempting clinical phenotyping of sepsis, including subtype analysis, appear to be critical in the search for personalized treatment approaches in the near future.

Conclusion. Currently, the widely accepted goal in sepsis management is early detection and initiation of therapy to prevent the development of irreversible septic shock and multiorgan failure syndrome. Personalized genetic, metabolomic and proteomic profiling of the patient seems to be an intriguing and promising avenue in the search for new treatment strategies in sepsis.

Keywords: sepsis; omics studies, genomics of the immune response; metabolomics of the immune response; proteomics of the immune response; phenotypes of sepsis

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

Introduction

Sepsis does not progress or manifest in the same way in all patients due to the marked heterogeneity of septic patients and differences in pathophysiological and immunological responses.

Heterogeneity is a major feature of the sepsis patient population, and if one can stratify them into distinct groups (phenotypes), the latter will differ not only in pathophysiological patterns but also in responses to therapy.

Specific characteristics such as sex, age, race, comorbidities, smoking, alcohol consumption, medications, obesity, and nutritional status, as well as the source of infection, the type of infectious agent, the treatment administered, the nature of the underlying disease, and the conditions that cause immune dysfunction (liver cirrhosis, cancer, and autoimmune diseases) are obvious, but not exclusive, reasons for patient heterogeneity. Individual variability in the nature of the immune and pathophysiological response accounts for the wide range of clinical variants of sepsis.

Patients with sepsis were dying in the mid-twentieth century, despite the discovery of penicillin and the absence of antibiotic resistance problems as we know them today. Numerous disparate ob-

servations from those years led an increasing number of researchers to conclude that the root of the problem was not only the pathogen itself, but also (perhaps to a greater extent) the patient's inflammatory response, consistent with Osler's views. In the years that followed, this view of the pathophysiology of sepsis became dominant.

Sepsis was defined in 1992 as a clinical syndrome that included both infection and systemic inflammatory response syndrome (SIRS) as measured by temperature, heart rate, respiratory rate, and leukocytosis [1]. These criteria were so broad that almost any patient with an acute respiratory viral infection or, for example, pancreatitis met the definition of sepsis. However, it was the high mortality rate from sepsis during those years that forced the scientific community to act in this way, allowing any intensivist to suspect sepsis before the onset of septic shock and make an early clinical diagnosis. However, the low specificity of the SIRS diagnostic criteria resulted in an extremely large population of patients meeting the diagnostic criteria for sepsis, posing significant challenges in both clinical practice and research.

In 2001, the updated definition of sepsis was published, which was almost identical to the previous one; it simply expanded the list of sepsis criteria [2]. Despite the introduction of another definition in 2016, which emphasized that sepsis is a life-threatening organ dysfunction caused by an unregulated host response to infection [3], it remains very difficult to describe this response in detail because we lack the tools to objectively assess whether a given organism's response to infection is normally regulated or not. Because immune responses are unique, answering the question «What should be considered immune dysfunction?» can be challenging. Indeed, in this context, heterogeneity becomes a hallmark of sepsis [4].

As a result, future studies of the efficacy of different therapeutic interventions in sepsis should use endo- and phenotyping to stratify sepsis patients in clinical trials and to develop treatment strategies that are more precisely targeted to specific endo- and phenotypes of sepsis.

The primary objective of this review is to familiarize the reader with the stratification of different endotypes obtained using omics technologies (genomic, transcriptomic, proteomic, metabolomic, etc.) as well as the phenotyping of sepsis patients using large clinical datasets.

The literature search was performed in the bibliographic database PubMed without language restrictions. The keywords «sepsis omics», «sepsis endotypes», and «sepsis heterogeneity» were used in the search queries to link the topics of omics research and sepsis phenotyping. The analysis included 120 sources that were most relevant to the main objective of the review.

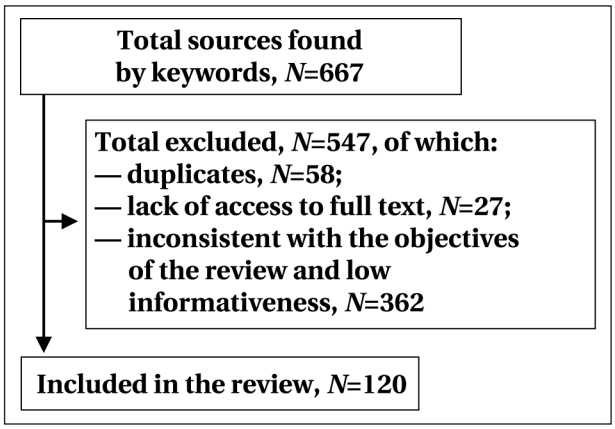

Fig. 1. Flow chart for searching and selecting papers for inclusion in the review.

Criteria for excluding sources were irrelevance to the review objective and low informativeness. The current review included 6 comparative studies, 3 prospective cohort studies, 17 observational studies, 51 original studies, 6 commentaries, 20 reviews, 1 meta-analysis, and results from 16 clinical trials. The source selection scheme is shown in Fig. 1.

Genomics of the sepsis-related immune response. Individual transcriptome variations during sepsis have been evaluated by various authors in several large cohorts based on a dysfunctional (immunosuppressive) endotype of the immune response to sepsis. Data from clinical and laboratory studies included peripheral blood leukocyte counts obtained within the first hours of admission to the intensive care unit in patients with probable infection. These studies used an unsupervised hierarchical clustering method for approximately 25,000 transcriptomic profiles across the genome (gene expression microarray and RNA sequencing). These complex methods, based on large amounts of genetic data, have enabled the identification of patterns among expressed genes that define molecular subgroups representing different abnormal conditions that are not necessarily associated with specific clinical outcomes, but may be related to them. This approach can also identify clusters based on a patient's premorbid status (age, comorbidities), stage and severity of disease, likelihood of mortality, and genetic predisposition to severe sepsis.

One of the first studies to use unsupervised hierarchical clustering to investigate subgroups of sepsis patients in the general ICU population was conducted in a cohort of children admitted with septic shock to pediatric ICUs in the United States [5]. The attempt by Wong et al. to develop a clinically feasible personalized medicine approach to pediatric septic shock resulted in the first genetic profiling of a heterogeneous group of septic shock patients. According to differential patterns of full genomic expression, 2 subclasses were defined using a spe-

cially developed gene expression parameter. This method of patient categorization was prospectively analyzed in a separate cohort of patients: out of 132 patients, 63 patients were classified as endotype A and 69 patients as endotype B. Initially, these two subclasses differed in age and leukocyte count distribution: patients with endotype A were significantly younger (mean age 1.4 years vs. 4.1 years for subclass B), and endotype A had a lower total leukocyte and neutrophil count than endotype B. The clinical phenotypes of the subtypes also differed: endotype A had a significantly higher 28-day mortality in the ICU (11% vs. 4% for endotype B), and endotype A had a more complicated course (27% vs. 11%) [5]. In a previous study by the same authors using the same patient sample, patients in the endotype A group showed the greatest disruption of immune defense pathways, specifically the suppression of key genes essential for the adaptive immune system, including those involved in glucocorticoid receptor pathways [6].

In 2016, an updated perspective of leading intensive care specialists on the phenomenon of immune dysregulation in sepsis was published [7]. Davenport et al. performed a transcriptomic analysis of peripheral blood leukocytes from patients admitted to the intensive care unit. Transcriptomic profiles of 265 patients admitted to 29 ICUs in the UK as part of the Genomic Advances in Sepsis (GAinS) study demonstrated two endotypes of the immune response to sepsis: SRS1 (41%) and SRS2 (59%) [8]. Patients with the SRS1 endotype had a higher 14-day mortality rate than those with the SRS2 endotype (22% vs. 10%). SRS1 was also associated with relative immunosuppression, endotoxin tolerance, T-cell depletion, HLA class II suppression, and metabolic disturbances (shift from oxidative phosphorylation to glycolysis). Only seven of the more than 3000 differentially expressed genes accurately predicted classification into a specific SRS endotype. The Davenport research group hypothesized that in future studies, patients with a prospectively defined SRS1 endotype might benefit from therapy that increases the pro-inflammatory response in sepsis. The same investigators later replicated this analytical approach to examine gene expression patterns in 117 patients with fecal peritonitis (FP) [9]. Again, two distinct groups were identified: SRS1(FP) — 46% and SRS2(FP) — 54%, with patients in the SRS1(FP) group having a higher 14-day mortality rate (19% vs. 4%). The results were consistent with those found in the previous study, which included patients with sepsis caused by community-acquired pneumonia [8], indicating an increased tolerance to LPS in the SRS1(FP) patient group. A simpler set (this time consisting of 6 genes) was obtained from over 1000 expressed genes that predicted classification into a particular SRS endotype. It should be noted that the patterns of SRS gene expression that distinguish the «immunosuppressive» SRS1/SRS1(FP) endotype in adults did not correspond to the similar endotype A in children [5].

Several other studies have shown that more than 80% of the transcriptomic response in sepsis is independent of the source or pathogen of the primary infection [9,10]. Furthermore, these patterns are similar to those observed in patients with trauma or burns [11], as well as in critically ill patients with non-infectious respiratory distress syndrome [12].

In a prospective observational cohort study of 306 patients admitted to two intensive care units in the Netherlands between January 1, 2011, and July 20, 2012, as part of the Molecular Diagnosis and Risk Stratification of Sepsis (MARS) project (discovery and first validation cohorts), and patients hospitalized with sepsis due to community-acquired pneumonia in 29 intensive care units in the United Kingdom (second validation cohort), whole-genome blood gene expression profiles were generated from samples collected on admission [13]. The obtained data were analyzed using unsupervised consensus clustering and machine learning software. Four molecular endotypes were found to be associated with 28-day mortality ($P = 0.022$): on day 28, mortality was highest in the Mars1 group (39%), followed by 22% in the Mars2 group, 23% in the Mars3 group, and 33% in the Mars4 group [13].

The Mars1 endotype showed decreased expression of genes related to key innate and adaptive immune cell functions, including Toll-like receptors, NFκB1 signaling, antigen presentation, and T cell receptor signaling. However, an increased expression of trigger genes for specific metabolic pathways, including heme biosynthesis was seen in this endotype. The Mars2 endotype showed increased expression of genes related to pattern recognition, cytokine signaling, cell growth, and motility, such as NF-κB, IL-6, inducible nitric oxide synthase, and N-formylmethionyl peptide signaling. The Mars4 endotype was also associated with increased expression of genes involved in pattern recognition and cytokine interactions, specifically interferon signaling, RIG1-like receptors, and TREM1 signaling. The Mars3 endotype was primarily associated with increased expression of genes in the adaptive immune pathway, such as T helper cells, NK cells, IL-4 signaling, and B cells. The combinations of the AHNAK and PDCD10 genes were selected as biomarkers for this endotype [13]. To facilitate potential clinical use, for each endotype, specific biomarkers were used: BPGM and TAP2 reliably identified patients with the Mars1 endotype, GADD45A and PCGF5 with Mars2, and IFIT5 and GLTSCR2 with Mars4 [13]. The primary aim of our study was to identify sepsis endotypes and compare their clinical signs and survival outcomes. The study also identified

candidate biomarkers for further identification of specific sepsis endotypes in clinical practice [13].

Recent cost reductions in whole exome sequencing (WES) technologies have made genomic research more accessible. In one such study, researchers hypothesized that certain variations in specific genes involved in the pathogenesis of syndromes such as macrophage activation syndrome (MAS) and atypical hemolytic uremic syndrome (aHUS) would be more common in sepsis patients, resulting in marked inflammation. The researchers used ferritin levels above 7000 ng/ml as a screening marker and performed WES in six patients [14]. All patients inherited at least one abnormal (or likely abnormal) genomic variant previously identified in the literature as a cause of hereditary immunologic diseases. For example, three of six patients had the UNC13D variant, which causes abnormal natural killer (NK) cell degranulation and altered cytolytic activity. The autosomal recessive inheritance of this variant results in familial hemophagocytic lymphohistiocytosis type 3. Three patients had a series of aHUS-associated mutations in complement pathway genes, including two in the CD46 gene, one in C3, and one in CFHR5, all of which were associated with nucleotide substitutions [14].

There are distinct patterns of gene expression among granulocyte and lymphocyte subpopulations, reflecting the specialized function of each immune cell [15]. Because the transcriptome profile varies between immunocompetent cell types, gene expression patterns may reflect different leukocyte populations rather than intracellular differences in gene expression. These findings also need to be validated in larger cohorts from different countries, as ethnic background is a strong predictor of gene expression [16].

Currently, ncRNAs (non-coding RNAs) and miRNAs (microRNAs) are being investigated for their prognostic value in sepsis. A non-coding RNA molecule is one that is transcribed from DNA but not translated into proteins. miR is a small non-coding RNA molecule that regulates post-transcriptional gene expression. Huang et al. found that lncMALAT1 (long non-coding transcript 1 associated with lung adenocarcinoma metastasis) and miR-125a were elevated in septic patients compared to healthy controls, while in non-survivors they were positively correlated with APACHE II and SOFA scores and serum creatinine levels [17,18].

V. M. Pisarev et al. found that increased plasma levels of extracellular DNA (ecDNA) were associated with 30-day mortality in sepsis patients [19]. In turn, ecDNA acts as a ligand for one of the toll-like receptors (TLR9). Patients with the TLR9 CC genotype had the highest levels of cfDNA compared to other genotypes. The C allele of the TLR9 genetic variant (s352162) has been associated with multiple organ failure and increased TNF-α production [19,20]. The simultaneous use of markers such as cfDNA and the genetic marker TLR9 most accurately predicts the fatal outcome of ICU patients [19]. Thus, in the future, targeted therapy using TLR9 receptor inhibitors could be developed as one of the personalized treatment approaches.

In 2020, the results of a Russian prospective study on the prognostic potential of aquaporin AQP5 as a biomarker for the course and outcome of sepsis were published [21]. Among all ICU patients, the homozygous AA variant of AQP5 genotype was most frequent. Sepsis patients with AQP5 AC and CC genotypes had a higher survival rate than those with the AA variant. In non-abdominal sepsis, however, mortality was not affected by single nucleotide substitution (AQP5). Only in patients with abdominal sepsis was there a significant difference in survival between genotypes: patients with the AQP5 AA genotype had higher mortality than patients with the AC and CC genotypes. The authors concluded that the C allele predicts a better outcome in abdominal sepsis [21]. The results of another Russian study on the relationship between sepsis severity and the prognostic significance of the aquaporin 4 (AQP4) genetic variant were published in 2023 [22]. The study included patients from three intensive care units. The majority of patients carried the GG AQP4 genetic variant, while homozygous carriers of the minor T allele were rare. The frequency of septic shock was significantly lower in patients with the GT and TT genetic variants than in patients with the GG genotype [22]. Interestingly, when the frequency of septic shock was compared between patients in different ICUs, it was found that the protective effect of the T allele was not statistically significant for patients in ICU-1, contrary to the patients in ICU-2 and ICU-3 who had a higher frequency of comorbidities and a higher SOFA score on admission [22]. Thus, the presence of the T allele in the 3' region of the AQP4 gene had a protective effect only in patients with severe multiple organ failure and comorbidities and was associated with a better course of sepsis in these patients.

In 2021, a Russian study was conducted to evaluate the contribution of the angiotensin II receptor 1 gene (AGTR1) polymorphism to outcomes in patients with sepsis and various comorbidities [23]. In the patient cohort studied, CIRS and Charlson Scale scores were significantly associated with sepsis mortality. Among all patients, homozygotes with the TT AGTR1 genotype dominated, while homozygotes with the AA AGTR1 genotype had the lowest frequency.

There were no significant differences in comorbidity between patients with different AGTR1 genotypes. No significant differences in mortality rates between the different AGTR1 variants were

found; however, patients with the TT genotype had a lower incidence of septic shock. In patients with cardiovascular comorbidities, carriers of the TA and AA variants had a higher mortality rate (16 of 16 cases) than carriers of the TT variant (25 of 33 cases) [23]. The TA and AA variants also had a higher risk of developing septic shock. The presence of the AGTR1 genotype determined the severity and outcome of sepsis in patients with type 2 diabetes: mortality was significantly lower with the TT variant compared to the TA and AA variants. When patients with severe cardiovascular disease and diabetes mellitus were combined into a single group, the mortality rate among carriers of the TT genetic variant was 69%, while carriers of the A allele had a mortality rate of 96% [23]. The association of the AGTR1 polymorphism with disease progression and outcome in septic ICU patients with severe comorbidities may become an important prognostic indicator in the future.

The presented studies provide evidence for the existence of distinct categories of the body's immune response to infection in the context of sepsis and potential therapeutic targets, with a differential approach to interpreting the clinical picture of sepsis based on the expressed molecular pathways that distinguish immune response endotypes in different patients [5, 8, 13, 15, 16, 24]. Furthermore, each of the cited studies proposed a potential «dimensionality reduction» of the multidimensional data from whole genome expression analysis into manageable prognostic clusters that could be incorporated into a simpler test applicable at the point of care, thereby facilitating the translation of the presented basic research results into real clinical practice.

Metabolomics of the immune response in sepsis. Epigenetic regulation of gene function has been identified as a key mechanism controlling myeloid cell function in sepsis patients. Transcriptional regulation involves the organization of gene loci on chromatin into transcriptionally active or «silent» states [25]. Transcriptionally active euchromatin is accessible to transcription factors and polymerases, whereas transcriptionally «silent» heterochromatin is inaccessible and inhibits gene transcription. Histone modifications such as acetylation, methylation, ubiquitination and phosphorylation all affect chromatin activation. Thus, various cellular metabolites serve as cofactors for epigenetic enzymes that induce chromatin and DNA modifications, modulate gene transcription, and promote different functional programs in sepsis: immunoparalysis or excessive inflammation [26–29]. A specific example of such epigenetic regulation is the Warburg effect, a shift from oxidative phosphorylation to glycolysis that leads to succinate accumulation, which in turn is critical for increasing the stability of hypoxia-inducible factor 1α (HIF1α), a transcription factor that increases IL1b transcription (which encodes IL-1β) [27].

Finally, in addition to the immune, genetic, and cellular regulatory pathways discussed above, a variety of other mechanisms influence the overall inflammatory response system in sepsis. These include neuroinflammation (which involves transmission of a peripheral sensory signal via the afferent vagus nerve to the brainstem, stimulation of the efferent vagus nerve, and subsequent activation of the splenic nerve in the celiac plexus, which leads to the release of norepinephrine in the spleen and the secretion of acetylcholine by a subpopulation of CD4+ T lymphocytes [30] with acetylcholine inhibiting the release of proinflammatory cytokines by macrophages) and a shift in the acid-base balance of the internal environment towards acidosis [31].

Several studies have investigated the metabolomic profiles of patients with sepsis. Schmerler et al. used targeted metabolomics to identify molecules that distinguish sepsis from non-infectious SIRS. They used liquid chromatography-mass spectrometry (LC-MS) to analyze 186 metabolites found in 74 SIRS patients and 69 sepsis patients, including acylcarnitine, amino acids, biogenic amines, glycerophospholipids, sphingolipids, and carbohydrates. In this study, acylcarnitine and glycerophospholipid activities were found to be significantly different in patients with sepsis compared to SIRS. Using these two markers, the researchers correctly identified SIRS and sepsis in 80% of patients [32].

Another study found metabolic differences between healthy individuals, patients with SIRS, and patients with sepsis. Patients with sepsis had significantly lower concentrations of lactitol dehydrate and S-phenyl-D-cysteine, but higher concentrations of S-(3-methylbutanoyl)dihydrolipoamide E and N-nonanoylglycine than patients with SIRS. This study also found that 2-phenylacetamide, dimethyllysine, glyceryl phosphoryl ethanolamine, and D-cysteine were associated with the severity of sepsis. In addition, the profiles of sepsis patients 48 hours before death showed a clear state of metabolic derangement, with levels of metabolites such as S-(3-methylbutanoyl)dihydrolipoamide E, phosphatidylglycerol, glycerophosphocholine, and S-succinylglutathione significantly reduced ($P < 0.05$) [33].

The gut microbiota deserves special attention because it is thought to influence systemic immune responses by translocating microbial components from the gut into the bloodstream. The research of N.V. Beloborodova et al. contributes to our understanding of the role of the intestinal microbiota in normal and pathological conditions, including sepsis [34-37]. There are several microbial metabolites that may influence the body's response to infection in sepsis. For example, hydroxylated aromatic mi-

crobial metabolites have been found to dominate the metabolic profile of serum phenolic metabolites in sepsis patients. These metabolites may affect neutrophil function by suppressing their activity, which may contribute significantly to the development of immunosuppression.

The regulatory mechanisms described above are not only the result of genetic and cellular regulation of immune system responses to infectious agents (based on individual characteristics), but also of factors that can have a significant impact on these responses.

Proteomics of the immune response in sepsis. Biological profiling of sepsis patients is based on the measurement of proteins in various biological samples, which is more widely accepted and feasible than genetic or metabolomic profiling. Each method for testing a biological sample has advantages and disadvantages. Plasma and serum samples are the most readily available for clinical evaluation. As a result, a considerable amount of information has already been gathered from studies that have attempted to classify sepsis using their analysis [38–50].

One notable method that may provide a new way to categorize a heterogeneous group of septic patients is the use of molecular and protein biomarkers to predict outcome in septic shock patients. This approach has been used to stratify the risk of pediatric septic shock using a previously validated risk score consisting of 5 plasma protein biomarkers (PERSevere) [40] and their combination with 4 genes, including DDIT4, HAL, PRC1, and ZWINT, which are directly linked to TP53 and are likely to be associated with adverse outcomes [41]. Parameters used to assess 28-day mortality risk showed improved prediction ability. Plasma biomarkers were associated with dysfunctional inflammation and cellular damage, while genes were associated with the p53 protein, a transcription factor that acts as a tumor suppressor: activated when DNA damage accumulates, it causes the cell cycle arrest or induces apoptosis when cells are irreversibly damaged.

The first proteomic analysis of serum from sepsis and septic shock patients was performed by A. Kalenka et al. [42]. This study compared the proteomic profiles of survivors and non-survivors with the goal of identifying early differences in serum composition that might predict survival at day 28. Several differentially expressed proteins were identified, including complement factor Bb, α-1-B-glycoprotein, and clusterin [42]. The Bb segment of factor B, a component of the alternative complement pathway, plays a key role in the body's initial defense against infection. Factor B is essential for the activation of this pathway, serves as a cofactor in antibody-dependent monocyte-mediated cytotoxicity, and enhances macrophage adhesion and plasminogen activation [51, 52]. The study found higher activity of these proteins in survivors compared to non-survivors. Meanwhile, α-1-B-glycoprotein — a member of the immunoglobulin superfamily and a well-known plasma protein with an unclear biological function — was elevated to a greater extent in non-survivors. Haptoglobin, an acute-phase protein with molecular heterogeneity resulting from genetic polymorphism, is elevated during inflammation, infection, and cancer, making it a biomarker for several diseases [53, 54]. There are two common haptoglobin alleles, Hp1 and Hp2. Homozygous individuals for these alleles express Hp 1-1 and Hp 2-2, respectively, whereas heterozygotes express Hp 2-1 [55]. Notably, Hp 1-1 has greater antioxidant activity compared to Hp 2-2 [56]. One study investigated the effects of haptoglobin isolated from healthy individuals with the Hp 1-1 phenotype on cytokine production by lipopolysaccharide (LPS)-stimulated monocytes. In vitro results showed that haptoglobin inhibited the release of TNF-α, IL-10 and IL-12 from LPS-stimulated human monocytes, but did not significantly affect IL-6 or IL-8 levels. In vivo models further confirmed the potent anti-endotoxic properties of haptoglobin. The authors suggested that haptoglobin acts as a selective modulator of inflammation by preventing excessive production of proinflammatory cytokines. In particular, inhibition of IL-12 release was proposed to promote a T helper type 2-dominant environment. Because of its anti-endotoxic effects, haptoglobin is considered a potential therapeutic agent for inflammation [57]. Sepsis survivors showed a more pronounced upregulation of haptoglobin, possibly reflecting a stronger immune response. Clusterin activity was also increased in survivors, with expression dependent on specific factors (26.5 and 14.9) [42]. Clusterin is thought to play a role in the clearance of toxic substances through its ability to bind unfolded proteins, cellular debris, and immune complexes [58].

In a prospective observational study, M. S. Raju et al. analyzed changes in the serum proteome from early to late stages of sepsis in survivors compared to non-survivors [43]. The study identified differences in the levels of several proteins, including haptoglobin (Hp), transthyretin (TTR), orosomucoid glycoprotein 1/α1-acid glycoprotein (ORM1), α1-antitrypsin (A1AT), serum amyloid A (SAA), and S100A9. These proteins showed distinct expression patterns between survivors and non-survivors, particularly during the early stages of sepsis. The results highlight significant differences in the proteome of survivors and non-survivors, suggesting that dysregulation of the inflammatory response may be a key factor contributing to mortality in sepsis [43].

N. K. Sharma et al. compared the proteomic profiles of sepsis patients with community-acquired

pneumonia to those of healthy volunteers of the same age and sex. Bioinformatic analysis of differentially expressed proteins in sepsis patients revealed changes in proteins involved in cytoskeleton and cell motility, lipid metabolism, immune response, and other processes [44].

A separate plasma proteomics study of sepsis patients with hospital-acquired pneumonia identified dysregulated lipid metabolism as a key abnormality. The study found lower expression of PON1 and apolipoproteins (ApoA1, ApoC, and ApoE) associated with HDL and higher expression of Hp and SAA1/SAA2. A validation study found lower plasma levels of total cholesterol, HDL-C, LDL-C, non-HDL cholesterol, apolipoproteins (ApoA1 and ApoB100), and PON1 in patients with hospital-acquired pneumonia. These findings are consistent with previous research highlighting the importance of lipid metabolism in the pathogenesis of sepsis [45].

L. Su et al. used proteomic analysis to identify 34 differentially expressed urinary proteins in patients with sepsis and systemic inflammatory response syndrome (SIRS) using iTRAQ (isobaric tags for relative and absolute quantitation) labeling and 2D-LC-MS/MS. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses revealed that these proteins are involved in inflammation, immune response and cytoskeletal organization. A protein-protein interaction network identified five specific proteins: cadherin-1 (involved in actin cytoskeleton remodeling), Hp (with anti-inflammatory properties), complement component 3, SERPINA1 (with pro-inflammatory activity), and ceruloplasmin (which provides antioxidant and anti-inflammatory protection) [46].

The same research group published the results of another study in which proteomic and bioinformatic analyses of urine from sepsis patients with different outcomes (survivors vs. non-survivors) revealed significant differences in protein expression. Five proteins (SELENBP-1, HSPG-2, A-1-BG, HPR, and LCN) were upregulated, while two (LAMP-1 and DPP-4) were downregulated in non-survivors. Three previously unknown differentially expressed proteins (LAMP-1, SBP-1, and HSPG-2) were validated by immunoblotting. LAMP-1 expression was significantly lower in non-survivors, whereas SBP-1 and HSPG-2 levels were similar between survivors and non-survivors. These findings suggest that urinary LAMP-1 levels may be used as a prognostic marker for sepsis outcome [47].

Inflammation-induced blood coagulation amplifies the inflammatory response, resulting in a positive feedback loop [59]. Neutrophils, monocytes, macrophages, platelets, and other inflammatory cells play important roles in the pathogenesis of sepsis. Platelets, as anucleated cellular fragments, are particularly well suited for proteomic analysis to detect protein changes in sepsis. Liu and colleagues used 2-DE (two-dimensional electrophoresis) and MALDI-TOF-MS (matrix-assisted laser desorption/ionization time-of-flight mass spectrometry) to identify proteins differentially expressed in platelets from sepsis patients versus healthy controls. The study found increased expression of five platelet proteins in sepsis patients: EFCAB7 (calcium ion binding), actin (cytoskeletal protein), IL-1β (cytokine), GPIX (membrane receptor), and GPIIb (integrin). These proteins are involved in inflammatory response and coagulation activation, highlighting the critical role of platelets in sepsis-induced inflammation and coagulation [48].

H. Zhang et al. used iTRAQ-based quantitative proteomic analysis to compare changes in the monocyte membrane proteome before and after LPS exposure. A total of 1,651 proteins were identified, of which 53.6% were membrane proteins. Subcellular analysis revealed that more than 90% of mitochondrial membrane-associated proteins were significantly downregulated. This finding suggests that mitochondria may be a primary target of bacterial infection in sepsis [49].

P. M. De Azambuja Rodrigues et al. used LC-MS/MS to detect monocyte proteins in patients with septic shock. Downregulated proteins in sepsis include those involved in oxidative phosphorylation and the Krebs cycle (ATP5C1, DLST, ETFB, NDUFA11, NDUFA2, NDUFS7, NDUFS8, PDK3, PDP1, PDPR, RXRA, SUCLG2, TACO1, and UQCRQ), β-oxidation of fatty acids (ACADM, DECR1, PCCA, and PCCB), and the interferon signaling pathway (EIF2AK2, EIF4A3, EIF4E2, HLA-DPA1, HLA-DQA2, HLA-DRA, HLA-DRB1, IFIT1, MX1, NUP35, OAS3, PSMB8, and UBE2L6), as well as the MHC II antigen presentation pathway (CD74, CTSH, DCTN3, DYNC1LI2, HLA-DMA, HLA-DMB, HLA-DPA1, HLA-DQA2, HLA-DRA, HLA-DRB1, KIF2A, and OSBPL1A). Glycolysis-associated proteins (enzymes PGK1, ALDOA, ALDOC, GADPH, PKLR, GPI, and LDHA) were found to be upregulated. These proteomic findings suggest significant disturbances in monocyte energy metabolism in septic shock patients [50].

In a study of brain autopsies of patients who died from sepsis, the absence of occludin expression in the brain microvascular endothelium was associated with more severe disease progression. Occludin is an essential integral protein for tight junctions in endothelial cells. Erikson and colleagues found that endotoxin and pro-inflammatory cytokines significantly reduced occludin expression *in vitro* in a human brain vascular endothelium model [60]. Thus, blood occludin levels may be a promising biomarker for predicting blood-brain barrier (BBB) damage in sepsis [18].

The role of various cluster of differentiation (CD) receptors as prognostic bio-

markers is also being investigated. For example, in a study by W.-P. Yin et al., nCD64 combined with SOFA score predicted 28-day mortality more accurately than procalcitonin measurement and SOFA score [61]. Resistin and myeloperoxidase (MPO) levels are strongly associated with the development of multiorgan failure. A. Bonaventura et al. found that elevated plasma concentrations of resistin and MPO from the first day of sepsis were associated with the development of organ dysfunction de novo. However, only MPO elevation from day 1 predicted 90-day mortality in sepsis [62].

C. Cao et al. [63], and B. J. Anderson et al. [65] performed studies on the prognostic significance of specific soluble receptors. According to a meta-analysis of 2,418 patients by C. Cao et al., serum sTREM-1 (soluble triggering receptor expressed on myeloid cells-1) had moderate specificity for identifying septic patients. However, when combined with other clinical parameters, it was more predictive of sepsis-related mortality than clinical parameters alone [64]. In a multicenter prospective cohort study by Anderson et al., an sTNFR1 (soluble tumor necrosis factor receptor-1) concentration > 8,861 pg/mL predicted 30-day mortality.

For the first time, the molecular dynamic profiles of serum exosomes and their potential role in the development of sepsis were investigated in 2022 [66]. A multi-omics analysis revealed that the onset of the «cytokine storm» is closely associated with circulating exosomes in the serum of sepsis patients. Specifically, mRNAs (messenger RNAs) in serum exosomes of sepsis patients were associated with cytokine synthesis and secretion. Pre-administration of serum exosomes to septic mice reduced TNF-α and IL-6 mRNA expression in multiple organs, resulting in organ protection. This finding supported the authors' previous study, which found that exosomes isolated from the serum of LPS-induced mice significantly reduced inflammation and improved survival in CLP mice (a septic model involving cecal ligation and puncture) [67].

Furthermore, exosomes from sepsis patients were found to be associated with complement and coagulation cascades, containing proteins from both the classical and alternative complement pathways [66]. This study also demonstrated the role of serum exosomes in modulating the immune response in sepsis by regulating specific vitamin metabolism pathways.

Several studies on increased intestinal permeability in sepsis found elevated levels of zonulin, I-FABP (intestinal fatty acid binding protein) and the D-isomer of lactic acid.

Taken together, metabolomic and proteomic approaches to sepsis provide a plausible framework for describing the biological pathways leading to adverse outcomes.

Clinical phenotyping of sepsis. Clinical phenotyping is required to identify specific groups of patients who may benefit from targeted interventions. Several approaches to phenotyping sepsis patients in the ICU have been proposed, including phenotyping based on temperature trends [70–85], hemodynamic characteristics [86–90], response to fluid therapy (in septic shock) [91–95], ICU outcome (favorable or fatal) [96–101], and characteristics of multiple organ dysfunction [91, 102–109], often using artificial intelligence and machine learning.

The key findings of these studies are discussed below.

In recent years, attempts have been made to classify sepsis based on body temperature parameters. According to research in this area, hypothermia (or absence of fever) in sepsis patients is independently associated with higher mortality [70, 72, 73]. A 2017 meta-analysis found that fever in septic patients is a protective factor that reduces mortality compared to normothermia [71]. A Russian retrospective study found that hypothermia in sepsis patients was associated with more severe arterial hypotension, acidosis, and increased INR [85].

This supports the idea that therapeutic hyperthermia in patients with hypothermia may improve sepsis survival. Several clinical trials have found an association between improved outcomes and warming of hypothermic sepsis patients [83, 84]. However, the study by A. M. Drewry et al. [83] has a significant limitation that prevents its findings from being directly translated into routine clinical practice. Specifically, almost twice as many patients in the hyperthermia group tested positive for pathogens susceptible to empirically prescribed antibiotics. Honore et al. pointed out this limitation in a letter to the editor of *Critical Care Medicine* [110].

Before discussing the results of the following sepsis phenotyping studies, it is necessary to briefly explain machine learning and cluster analysis, which serve as the methodological basis for many of these investigations.

In recent years, artificial intelligence (AI) has been increasingly applied in medicine. The basic idea behind AI, particularly machine learning in biomedicine, is to train an information system on large data sets (clinical, laboratory, imaging, etc.) to recognize and extract specific patterns. This allows for the grouping and subsequent analysis of these patterns.The next step in this process is cluster analysis.

Cluster analysis quantifies the similarities among patients in a heterogeneous population. This method generates groups of patients (essentially representing different phenotypes) without relying on predetermined hypotheses [111]. However, a limitation of cluster analysis is the difficulty in determining the optimal number of data clusters.

Group-based modeling is an extension of cluster analysis that identifies groups of patients who exhibit similar trends with respect to a particular variable of interest [112].

A study by S. V. Bhavani et al. used group-based modeling to identify sepsis subphenotypes based on temperature trend patterns. Four distinct subphenotypes were identified: normothermic, hyperinflammatory («hyperthermic, slow resolvers»), hypoinflammatory («hypothermic»), and a balanced inflammatory subphenotype («hyperthermic, fast resolvers») — the latter being associated with the lowest mortality rate [74]. The same research group validated their findings in a separate retrospective study that identified four similar phenotypes in COVID-19 patients [78].

Hemodynamic characteristics in sepsis and septic shock, as shown in recent studies, may also help to address the clinical heterogeneity of sepsis patient populations.

The introduction of continuous hemodynamic monitoring in routine ICU practice has made it possible to define different phenotypes based on hemodynamic profiles.

In a study by R. M. Nowak et al., cluster analysis of invasive hemodynamic monitoring data from 127 patients identified three phenotypes with distinct hemodynamic profiles:

- Phenotype I (56.7%): High cardiac index (CI) and normal systemic vascular resistance index (SVRI).
- Phenotype II (39.4%): Low CI and elevated SVRI.
- Phenotype III (3.9%): Very low CI and very high SVRI.

The three phenotypes differed significantly in terms of 30-day mortality: 5.6% for patients with phenotype I and 20% for patients with phenotypes II and III [86].

J.-L. Zhu et al. analyzed trends in systolic blood pressure (SBP) in more than 3,000 sepsis patients admitted to the ICU and identified seven distinct phenotypes [90]. The lowest mortality was observed in patients with phenotype 3. The authors suggest that the SBP trend characteristic of phenotype 3 should be considered as a hemodynamic target for sepsis patients during the first 10 hours after admission to improve outcomes. In addition, when comparing phenotypes 2 and 6, they found that persistent hypotension was associated with a worse prognosis than a rapid decline in SBP. Applying the findings of this study, clinicians could use SBP trend monitoring to earlier identify high-risk patients [90].

A multicenter study investigating the relationship between septic cardiomyopathy phenotypes — defined by echocardiographic characteristics — and sepsis outcomes is ongoing [89]. Preliminary results from this study have identified phenotypes with different responses to fluid therapy.

In addition, a multicenter randomized controlled trial (RCT) is underway to determine whether a strategy based on clinical hemodynamic phenotyping, with a focus on capillary refill time (CRT), can improve clinical outcomes compared to standard of care [95].

Thus, approaches to hemodynamic management of sepsis and septic shock can be tailored by identifying distinct phenotypes among the diverse population of sepsis patients. Infusion and catecholamine support protocols can be modified based on phenotype, allowing for individualized and adaptive care for each ICU patient.

In 2019, C. W. Seymour et al. published the SENECA study [104]. The study used machine learning to analyze data from more than 63,000 patients and identified four novel sepsis phenotypes (α, β, γ, and δ). These phenotypes were distinguished by unique demographic profiles, laboratory markers, and patterns of organ dysfunction. Treatment outcomes modeled with data from three randomized clinical trials (including 4,737 patients) demonstrated sensitivity to changes in phenotype distribution. The phenotypes include:

- α phenotype: Approximately one-third of sepsis patients have minimal laboratory abnormalities, limited organ dysfunction, and the lowest in-hospital mortality (23%).
- β phenotype: Found in 27% of patients, associated with advanced age, chronic comorbidities, and higher risk of acute kidney injury.
- γ phenotype: Approximately 25% of patients, similar to the β phenotype but with elevated inflammatory markers and a prevalence of pulmonary dysfunction.
- δ phenotype: The least common (13%) and most severe phenotype, characterized by severe multi-organ failure, including liver dysfunction and refractory shock, with the highest in-hospital mortality (32%).

Retrospective analysis revealed persistent differences between phenotypes. The cumulative 28-day mortality rates were 5% for the α phenotype, 13% for β, 24% for γ, and 40% for δ. In all cohorts and studies, the δ phenotype had significantly higher 28-day and 365-day mortality rates than the other three phenotypes ($P < 0.001$). Early targeted therapy according to the Rivers protocol [113] was found to be detrimental in patients with the δ phenotype, based on retrospective analyses of more than half of the RCTs included in the study. The endophenotypes aHUS and MAS, which comprise a significant proportion of the δ phenotype as defined by C. W. Seymour et al., may share a common pathogenesis. Endotoxin is an important molecular target for the δ phenotype, activating both the complement and cytokine pathways. Patients susceptible to endotoxin may develop MAS, aHUS-like syndrome, or both [114,115].

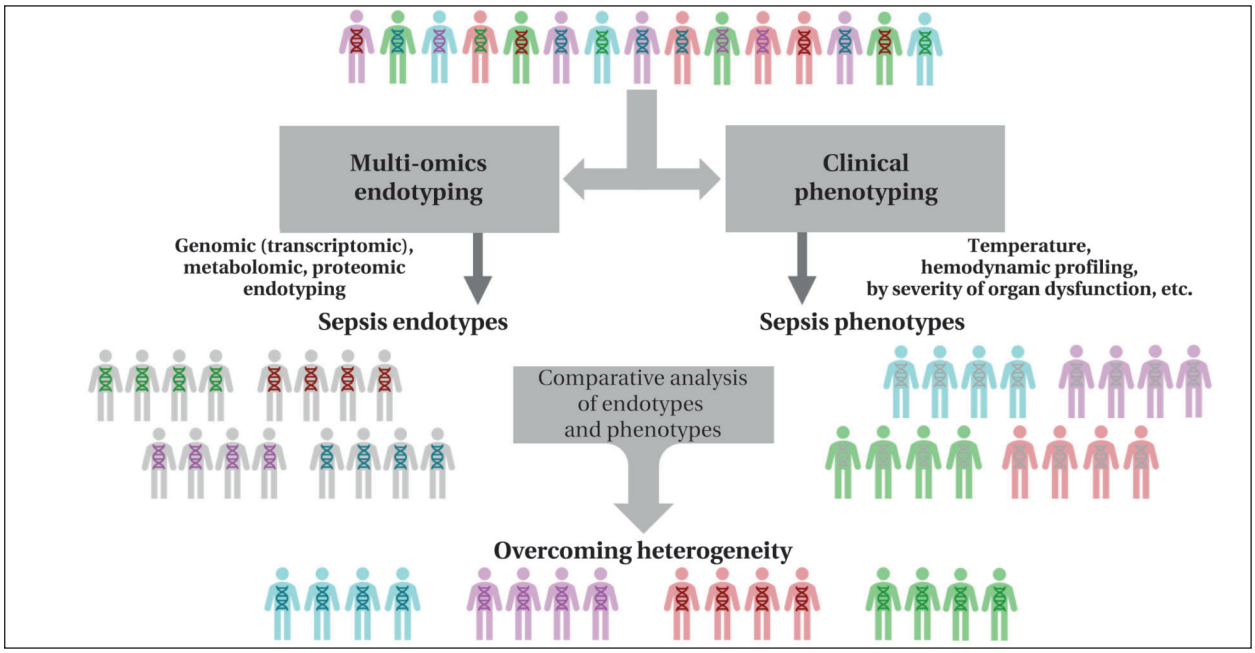

Fig. 2. A possible way to overcome the heterogeneity of sepsis patients.

It is worth noting that the study by C. W. Seymour et al. [104] was neither the first nor the only attempt to identify patterns in the population of patients with sepsis. We identified three studies in which the authors attempted to phenotype the heterogeneous syndrome of multiple organ dysfunction syndrome (MODS) in sepsis [91, 102, 103]. All three studies used machine learning methods, resulting in four phenotypes that significantly differed in the profile of organ dysfunction within MODS. Since 2019, the results of five additional studies on clinical phenotyping of MODS in sepsis have been published [105–109].

Recently, the results of a Russian study on the identification of clinical phenotypes of sepsis in patients with severe community-acquired pneumonia based on the SENECA system proposed by C. W. Seymour et al. were published [104, 116]. Four sepsis phenotypes were identified in all patients: α (48.6%), β (19.3%), γ (13.1%) and δ (19%). The majority of patients with viral pneumonia belonged to the α phenotype (51.9%), whereas the δ phenotype predominated in patients with bacterial pneumonia (55.2%). The highest mortality rates were observed in patients with the β phenotype of sepsis associated with bacterial (7 deaths out of 7 cases) and viral pneumonia (115 deaths out of 121 cases). Interestingly, in patients with the α phenotype of sepsis and severe community-acquired pneumonia caused by COVID-19, therapy with interleukin-6 receptor-targeting monoclonal antibodies resulted in favorable sepsis outcomes in 87.5% of cases [116].

The research of Y. Qin et al. has practical implications. The authors used 24-hour machine learning techniques to identify four computable pediatric sepsis phenotypes. Among these, the authors identified one phenotype (PedSep-D) as particularly suitable for inclusion in early personalized research focused on multiple organ dysfunction associated with thrombocytopenia and macrophage activation syndrome. The study resulted in a mathematical model capable of identifying pediatric sepsis phenotypes using 25 parameters available within the first 24 hours of hospitalization [117].

Although incorporating phenotyping into routine clinical practice may seem difficult due to the complexity of centralized clinical data collection and the sophistication of machine learning and cluster analysis methods, initial steps in this direction are already underway. Clinical phenotyping of the diverse sepsis patient population will enable a more personalized approach to care, significantly improving the precision and selectivity of treatments. There is no doubt that this global trend will continue and the amount of research in this area will only increase.

Analysis of sepsis subtype combinations as a potential strategy to overcome heterogeneity A secondary analysis of the prospective MARS cohort study [13] aimed to compare sepsis subtypes using clinical, biomarker, and transcriptomic data from sepsis patients [118]. While molecular subtypes derived from transcriptomic data can now be reliably identified, finding meaningful correlations between these molecular subtypes and clinical phenotypes remains challenging. The concordance between subtypes defined in studies such as SENECA [104], ARDS [119, 120], MARS [13] and SRS [8] was moderate to low, suggesting that each subtype represents a distinct patient cohort.

These findings suggest that the identified endotypes and phenotypes represent distinct, potentially complementary aspects of sepsis subtypes. The authors propose a combined approach that includes molecular genetic endotyping and clinical phenotyping of the diverse sepsis population. This integrated strategy improves the accuracy of patient assessment. However, as R. B. E. van Amstel et al. note, it also presents significant challenges.

First, effective stratification requires large sample sizes. Second, the lack of alignment between omics and non-omics data types creates inherent difficulties in integrating them. Nevertheless, the long-term goal of all sepsis typing methods should be the same: to stratify patients into as homogeneous subgroups as possible [118].

Ultimately, improving the accuracy of stratification techniques has the potential to help overcome the inherent heterogeneity of sepsis in the future.

Conclusion

Classification of heterogeneous populations based on molecular endotypes and multi-omics profiling of sepsis patients may soon provide effective tools for targeted therapies tailored to specific subgroups of patients. This approach may allow the use of molecular biomarkers in sepsis both for patient selection and for monitoring the efficacy of specific (immunobiologic) therapies.

The identification of distinct biological patterns has the potential to facilitate the rational inclusion of sepsis patients in clinical trials, as well as to improve diagnosis, prognosis and personalized therapeutic strategies. This includes modulation of the immune response to sepsis (Fig. 2).

Future efforts must focus on developing new strategies based on a personalized assessment of the patient's genetic, metabolomic and proteomic response to infection, as well as the clinical sepsis phenotype. Establishing links between these elements and identifying targets for precision sepsis therapies are among the most critical challenges for the medical research community in the coming years.

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«The Brain as a Whole» Concept: Facilitating Approaches to Brain Death Understanding (Short Communication)

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Summary

James Bernat claimed that «the formulation of whole-brain death provides the most congruent map for our correct understanding of death». However, the author has recently proposed the categorization of another phrase: «brain as a whole (BAAW)». This is because patients with primary brainstem lesions who otherwise meet the clinical criteria for BD may still have EEG, CBF, evoked potentials, and hypothalamic-pituitary neurosecretion.

Bernat and colleagues suggested «tightening the clinical tests for brain death or loosening the whole-brain criterion of death». They emphasize that the BAAW criterion is an intermediate standard between the whole-brain and brainstem views, tolerating the irreversible cessation of critical brain functions, whereas the BD/DNC determination does not require the cessation of all brain functions or the death of every neuron.

In this paper, we have revised the concept of BAAW, which is intuitive and facilitates a conceptual and practical approach, but requires further refinement to specify precisely which brain functions must cease at brain death and which may continue.

Keywords: brain death; clinical criteria; hypothalamus; brainstem; autonomic nervous system

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In recent decades, three main brain-oriented formulations of death have been discussed: whole-brain death, brainstem death, and higher brain standards [1, 2]. James Bernat claimed that «the formulation of whole-brain death provides the most congruent map for our proper understanding of the concept of death» [3]. He argued that «the irreversible cessation of clinical functions of the brain constitutes death because the brain is responsible for the functioning of the organism as a whole» [4–6]. Thus, tightening the clinical tests for brain death may require a neuroimaging study demonstrating the absence of CBF, but there is a notable worldwide variation in the use of adjunctive tests [3, 7, 8].

Bernat and colleagues' defense of the whole-brain formulation of death was cited by the United States President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research as the conceptual basis for BD/DNC [4–6]. The Commission recommended that all US states adopt the Uniform Determination of Death Act (UDDA) [9].

Recently, Bernat proposed another term: «brain as a whole (BAAW)». This was suggested because patients with primary brainstem lesions who otherwise meet the clinical criteria for BD may retain EEG, CBF, evoked potentials, and hypothalamic-pituitary neurosecretion. Bernat and coworkers recommended «tightening the clinical tests for brain death or loosening the whole-brain criterion for death». They emphasized that the BAAW criterion is an intermediate standard between the whole-brain and brainstem views, allowing for the irreversible cessation of critical brain functions, while stating that the BD/DNC determination does not require the cessation of all brain functions or the death of every neuron [10].

The term BAAW was also used by Mohandas and Chou, who argued that «in patients with known and irreparable intracranial lesions, irreversible damage to the brainstem is the 'point of no return'» [11]. Pallis fully developed the brainstem criteria of BD/DNC [12]. This view is flawed because it does not consider the function of the cerebral hemispheres [13].

A major argument against «whole brain» is that some brain-dead patients retain residual hypothalamic neurosecretory function [14]. Varela affirms that the requirement of residual hypothalamic neurosecretory function in the declaration of BD/DNC is meaningless [15]. Nair-Collins states that «an individual with preservation of any function of any part of the brain is not dead under the UDDA. There is no argument, and no evidence, that can escape this conclusion. To deny it is to deny logic itself» [16].

We have recently discussed that the hypothalamus plays a key role in the central control of the autonomic nervous system (ANS). The hypothalamus contains neurons that send axons to preganglionic neurons for both the sympathetic and parasympathetic nervous systems, thereby regulating autonomic outflow. If there is residual hypothalamic function in brain dead patients, it is possible to find residual autonomic function [13].

How does the hypothalamus regulate the autonomic nervous system?

In autonomic control, the hypothalamus contains neurons that send axons directly to preganglionic neurons for both the sympathetic and parasympathetic nervous systems. These autonomic control neurons are located in the paraventricular and arcuate nuclei and the lateral hypothalamic area. The dorsal longitudinal fasciculus is the major pathway from the hypothalamus for autonomic control [16].

Magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus secrete the hormone arginine vasopressin (AVP) via the posterior pituitary into the peripheral circulation in response to an increase in plasma osmotic pressure or hypovolemia. In the absence of AVP or the ability of the kidneys to respond to it, diabetes insipidus (DI) develops, characterized by the excretion of large amounts of dilute urine, often accompanied by hypernatremia [17–20].

In contrast, the hypothalamus indirectly controls the anterior pituitary by secreting hypophysiotropic hormones into the local portal circulation.

The functions of the anterior pituitary hormones, their target organs, and the peripheral hormones they control are complex, diffuse, and subject to multiple interrelated feedback loops that affect metabolic functions throughout the body.

Several forebrain, hypothalamus, and brainstem structures are interconnected to organize the output of the autonomic nervous system. Collectively, this is referred to as the central autonomic network, which is further organized into a hierarchy of functional loops. The body temperature regulation is an example of hypothalamic control over brainstem and spinal autonomic nuclei related to longer-term autonomic reflexes [21, 22].

Using HRV methodology, it is possible to assess the ANS objectively. The high-frequency (HF) component is considered a marker of the parasympathetic cholinergic central system, with ambiguous responses generated mainly in the nucleus. The low-frequency (LF) band is associated with vagal and sympathetic influences. The mid-frequency (MF) band has been correlated with biofeedback of baroreceptor function and Meyer blood pressure waves.

Meanwhile, the very low frequency (VLF) range has been associated with the pressor arm of the sympathetic adrenergic system, central thermoregulatory centers, and the renin-angiotensin system. The loss of all HRV power has characterized BD/DNC. I reported a brain-dead case in which the VLF oscillations were the last to disappear, possibly related to residual sympathetic vasomotor activity that progressively disappeared due to the extension of necrosis affecting the nerve centers of the lower part of the spinal cord and the first 2–3 cervical spine segments. Therefore, this patient's preservation of HRV bands this patient's preservation of HRV bands demonstrated persistent medullary autonomic activity within the vagal and other central autonomic nuclei [13].

We have reported a patient who showed residual very low-frequency waves in heart rate variability (HRV) after completing the clinical diagnosis of BD/DNC [23]. All HRV bands were preserved in Jahi, and we showed autonomic reactivity to «Mother Talks» stimulation, suggesting enduring awareness. Therefore, we described a new state of disordered consciousness and proposed that death is the «irreversible loss of both components of consciousness — arousal and awareness.» We suggested rephrasing the definition of the World Brain Death Project (WBDP) as: «the complete and permanent loss of brain function as defined by an unresponsive coma with loss of both components of consciousness — arousal and awareness — and the ability to breathe» [13].

This discussion also examines the use of ancillary tests to confirm BD/DNC. If residual autonomic function is doubtful, the ANS should be assessed, which may provide some emotional awareness.

We also agree with Bernat that the BAAW is intuitive and facilitates a conceptual and practical approach. However, «further refinement is needed to specify precisely which brain functions must cease at brain death and which may continue» [10].

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Gender Gap in Bibliometric Indices of Academic and Non-Academic Italian ICU Physicians

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Summary

Hirsch-index, better known as H-index is an important bibliometric index for Italian critical care physicians.

Aim of our study was to collect the H-index of all Italian critical care academic physicians and compare it with the Italian Ministry of University and Research thresholds necessary to be eligible as Professor, and to investigate potential gender disparities in such bibliometric indices.

Materials and Methods. We collected all the names of academic ICU physicians on June 24th, 2023 from the official Italian Ministry of University and Research website. We added non-academic ICU physicians searching on Scopus or among academic physicians' collaborators. Minimum thresholds to be eligible as Professor were identified through the official Italian Ministry of University and Research website. Median H-index of men and women were compared.

Results. The total number of included physicians was 237 (46 Full Professors, 88 Associate Professors, 79 Researchers and 22 Non-academic physicians). Minimum threshold to be eligible as Associate Professor was 6 and to be eligible as Full Professor was 13. The median H-index in men versus women in every subgroup was: Full Professors (38 [27–49] vs 29 [21–34]), Associate Professors (25 [18–32] vs 22 [18–28]), Researchers (12 [7–21] vs 9 [6–16]) and Non-academic physicians (27 [25–37] vs 26 [25–29]).

Conclusion. Current median H-index of Italian academic ICU physicians is considerably greater than minimum thresholds released by the Italian Ministry of University and Research to be eligible as Professor. Gender gap in bibliometric indices of academic ICU physicians remains.

Keywords: bibliometric indices; H-index; gender gap; ICU physicians

Conflicts of interest. The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Fundings. The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work.

Introduction

Hirsch index, better known as H-index is an important quotation for Italian critical care physicians as it is one of the criteria to participate in grant applications, to compete for academic career and to be admitted as commissioner in public calls.

Aim of our study was to collect the H-index of all Italian critical care academic physicians and compare it with the median values identified by the Italian Ministry of University and Research back in the year 2018 to see whether these thresholds are still applicable nowadays, and to investigate potential gender disparities in such bibliometric indices.

Materials and Methods

We collected all the names of academic ICU physicians on the 24th of June 2023 from the official Italian Ministry of University and Research website [1]. To this list we added non-academic ICU physicians A) searching between non-academic physicians who obtained National Scientific Qualification («Abilitazione Scientifica Nazionale») in the last 3 years; B) searching on Scopus, using the keywords «anesthesia», «intensive care» and «critical care» and limiting to authors with > 60 publications; C) looking for collaborators of the academic authors enlisted before.

We extracted sex and affiliation, and we calculated the median H-index from Scopus of Full Professors, Associate Professors, Researchers and Non-academic authors. Then, we compared it to the threshold defined by the Italian Ministry of University and Research to be eligible for the positions of Full Professor and Associated Professor.

In the analyses, we reported H-index as medians and interquartile ranges [IQR].

The total number of included physicians was 237 of which 46 were Full Professors, 88 Associate Professors, 79 Researchers and 22 Non-academic physicians (Supplemental Table).

Table. Median H-index in each subgroup, both for men and women.

Subgroup	Overall , *N* = 237		Men, *N* = 172		Women, *N* = 65	
	H-index	Total	H-index	Total	H-index	Total
Full Professors	37 [26–47]	46	38 [27–49]	40	29 [21–34]	6
Associate Professors	25 [21–31]	88	25 [18–32]	68	22 [18–28]	20
Researchers	21 [19–24]	79	12 [7–21]	46	9 [6–16]	33
Non-academic physicians	27 [25–36]	22	27 [25–37]	16	26 [25–29]	6

Results and Discussion

Full Professors had a median H-index of 37 (26–47), Associate Professors 25 (21–31), Researchers 21 (19–24) and Non-academic physicians 27 (25–36). Notably, men were overrepresented (172, 73%) overall and within every subgroup: Full Professors (40, 87%), Associate Professors (68, 77%), Researchers (46, 58%) and Non-academic physicians (16, 73%). The median H-index in men versus women in every subgroup is shown in the Table.

In our study, we found that median H-index of Italian academic ICU physicians ranges from 21 (for Researchers) to 37 (for Full Professors) with important discrepancies between men and women.

We found that current median H-index of Italian academic ICU physicians is considerably greater than minimum thresholds released by the Italian Ministry of University and Research to be eligible as Associate or Full Professor: in 2016 they required an H-index of 11 (in the previous 15 years) to become Full Professor and an H-index of 3 (in the previous 10 years) to become Associate Professor. These thresholds were updated in 2018 with an H-index of 13 for Full Professor and 6 for Associate Professor, keeping the same time ranges [2].

To the best of our knowledge, this is the first report of this kind regarding Italian academic physicians. Several reports of bibliometric analysis for anesthesia and critical care researchers have been published in the last 10–15 years, but none focused on the correlation between H-index and eligibility for academic positions.

Studies published in early 2010s reported a median H-index for UK researchers in the field of anesthesia of 13, while median H-index of editorial board members of anaesthesiology journals was 14 [3].

More recently, an analysis of most prolific authors worldwide in the field of critical care medicine reported a median h-index of 41, which is only slightly higher than median H-index of Italian full professors [4].

Our data therefore confirm that scientific productivity of highest-ranked Italian academic is in line with worldwide trends, and that H-index of top-ranked scientist is growing.

In the Italian academic system, in order to be eligible as Full or Associate Professor, clinicians must first obtain a certification of eligibility («Abilitazione Scientifica Nazionale», National Scientific Qualification) by the Italian Ministry of University and Research. Among the other parameters, a minimum H-index threshold is required to obtain the qualification. Certified clinicians are then allowed to participate in public calls for applications released by each individual Italian university. The threshold required by the Ministry were updated from 2016 to 2018, mostly for Associate Professor for which the H-index value doubled from 3 to 6. Consistent with data from other countries, the median H-index of Academic authors has increased further so the Ministry should consider a new update.

Interestingly, we found that median H-index of non-academic clinicians is higher than the H-index of Associate Professors and Researcher. This data suggests that also several non-academic clinicians actively and regularly participate in conduction and dissemination of high-impact research. However, it also implies that there are numerous colleagues with remarkable curricula who have no access to academic career.

Gender analities and disparities are increasingly investigated, and generally suggest presence of a gender gaps and differences in both access and response to treatments, as well as access to academic career [5–8]. We found that the number of women is enormously underrepresented (28%), with the bigger discrepancy observed inside the higher academic position, Full Professors (13%), and a decreasing discrepancy going towards lower positions: Associate Professors (23%), Researchers (42%). This data is in line with recent reports and bibliographic analyses [9].

Conclusion

H-index is important for academic career in Italy, and it has generally increased in recent years. Gender gap in bibliometric indices of academic and non-academic ICU physicians still remains.

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Supplement

Supplemental Table. Full Professors, Associate Professors, Researchers and Non-academic critical care physicians ordered by H-index.

#	Name	Gender	H-Index (June 2023)	Degree
1	Antonelli Massimo	M	91	Full Professor
2	Ranieri Vito Marco	M	91	Full professor
3	Zangrillo Alberto	M	70	Full professor
4	Landoni Giovanni	M	70	Full professor
5	Cecconi Maurizio	M	69	Full professor
6	Stocchetti Nino	M	67	Full professor
7	Mercadante Sebastiano	M	65	Non-Academic Physician
8	Citerio Giuseppe	M	62	Associate professor
9	Ranucci Marco	M	61	Non-Academic Physician
10	Conti Giorgio	M	56	Full professor
11	Chiumello Davide Alberto	M	53	Full professor
12	Casuccio Alessandra	F	51	Non-Academic Physician
13	Bellani Giacomo	M	49	Full professor
14	Girardis Massimo	M	49	Full professor
15	Navalesi Paolo	M	49	Full professor
16	Fumagalli Roberto	M	48	Full professor
17	Sandroni Claudio	M	48	Researcher
18	Guarracino Fabio	M	48	Non-Academic Physician
19	Latronico Nicola	M	46	Full professor
20	Patroniti Nicolo' Antonino	M	46	Associate professor
21	Foti Giuseppe	M	45	Associate professor
22	Grasselli Giacomo	M	45	Full professor
23	Ricci Zaccaria	M	43	Associate professor
24	Mascia Luciana	F	42	Associate professor
25	Robba Chiara	F	42	Researcher
26	Bignami Elena Giovanna	F	41	Full professor
27	Mojoli Francesco	M	41	Associate professor
28	Morelli Andrea	M	41	Full professor
29	Scolletta Sabino	M	40	Full professor
30	Volta Carlo Alberto	M	40	Full professor
31	Beretta Luigi	M	39	Full professor
32	Cortegiani Andrea	M	39	Associate professor
33	Della Rocca Giorgio	M	39	Full professor
34	Maggiore Salvatore Maurizio	M	39	Full professor
35	Ristagno Giuseppe	M	39	Associate professor
36	Spadaro Savino	M	39	Associate professor
37	Della Corte Francesco	M	38	Full professor
38	Grasso Salvatore	M	38	Full professor
39	Pappalardo Federico	M	38	Non-Academic Physician
40	Bilotta Federico	M	37	Researcher
41	Cabrini Luca	M	37	Associate professor
42	Mauri Tommaso	M	37	Associate professor
43	Protti Alessandro	M	37	Associate professor
44	Zanier Roncati	M	37	Non-Academic Physician
45	Giarratano Antonino	M	36	Full professor
46	Gregoretti Cesare	M	36	Associate professor
47	Tritapepe Luigi	M	36	Associate professor
48	Caironi Pietro	M	35	Associate professor
49	Piastra Marco	M	35	Associate professor
50	Brazzi Luca	M	34	Full professor
51	De Pascale Gennaro	M	34	Associate professor
52	Lionetti Vincenzo	M	34	Associate professor
53	Pugliese Francesco	M	34	Full professor
54	Rocco Monica	F	34	Full professor
55	Cinnella Gilda	F	33	Full professor
56	Ball Lorenzo	M	32	Researcher
57	Monaco Fabrizio	M	32	Non-Academic Physician
58	Coluzzi Flaminia	F	31	Associate professor
59	Corradi Francesco	M	31	Associate professor
60	Donati Abele	M	31	Full professor
61	Mazzeo Anna	F	31	Associate professor
62	Vaschetto Rosanna	F	31	Associate professor
63	Zanella Alberto	M	31	Associate professor
64	Feltracco Paolo	M	30	Associate professor
65	Donadello Katia	F	29	Associate professor
66	Greco Massimiliano	M	29	Researcher
67	Monti Giacomo	M	29	Associate professor
68	Tonetti Tommaso	M	29	Associate professor
69	Valenza Franco	M	29	Full professor
70	Pasin Laura	F	29	Non-Academic Physician
71	Biancofiore Giandomenico Luigi	M	28	Associate professor
72	Bove Tiziana	F	28	Associate professor
73	Finco Gabriele	M	28	Full professor
74	Forfori Francesco	M	28	Associate professor
75	Lucangelo Umberto	M	28	Full professor
76	Scandroglio Anna Mara	F	28	Non-Academic Physician
77	Franchi Federico	M	27	Associate professor
78	Longhini Federico	M	27	Associate professor
79	Mistraletti Giovanni	M	27	Associate professor
80	Romagnoli Stefano	M	27	Full professor
81	Servillo Giuseppe	M	27	Full professor
82	Severgnini Paolo	M	27	Associate professor

Continuation Supplemental Table.

#	Name	Gender	H-Index (June 2023)	Degree
83	Belletti Alessandro	M	27	Non-Academic Physician
84	Covello Remo Daniel	M	27	Non-Academic Physician
85	Semeraro Federico	M	27	Non-Academic Physician
86	Berlot Giorgio	M	26	Full professor
87	De Robertis Edoardo	M	26	Full professor
88	Fanelli Vito	M	26	Associate professor
89	Montini Luca	M	26	Researcher
90	Pace Maria Caterina	F	26	Full professor
91	Paladini Antonella	F	26	Associate professor
92	Agnoletti Vanni	M	25	Researcher
93	Cammarota Gianmaria	M	25	Associate professor
94	Langer Thomas	M	25	Associate professor
95	Lorini Ferdinando Luca	M	25	Researcher
96	Pennisi Mariano Alberto	M	25	Associate professor
97	Raineri Santi Maurizio	M	25	Associate professor
98	Rasulo Francesco Antonio	M	25	Associate professor
99	Villa Gianluca	M	25	Associate professor
100	Grieco Domenico L	M	25	Non-Academic Physician
101	Gemma Marco	M	25	Non-Academic Physician
102	Calabrò Maria Grazia	F	25	Non-Academic Physician
103	Battaglini Denise	F	25	Non-Academic Physician
104	Disdma Nicola	M	25	Non-Academic Physician
105	Agro' Felice Eugenio	M	24	Full professor
106	De Blasi Roberto Alberto	M	24	Associate professor
107	Fodale Vincenzo	M	24	Associate professor
108	Marinangeli Franco	M	24	Full professor
109	Pasero Daniela	F	24	Associate professor
110	Ruberto Franco Gennaro Maria	M	24	Researcher
111	Sanfilippo Filippo	M	24	Researcher
112	Tavazzi Guido	M	24	Researcher
113	Lamperti Massimo	M	24	Non-Academic Physician
114	Busani Stefano	M	23	Associate professor
115	Garofalo Eugenio	M	23	Associate professor
116	Gottin Leonardo	M	23	Associate professor
117	Mattia Consalvo	M	23	Full professor
118	Mirabella Lucia	F	23	Associate professor
119	Pieri Marina Laura Grazia	F	23	Researcher
120	Vetrugno Luigi	M	23	Associate professor
121	Mirabella Lucia	F	23	Non-Academic Physician
122	Cascella Marco	M	23	Non-Academic Physician
123	Aceto Paola	F	22	Researcher
124	Adembri Chiara	F	22	Associate professor
125	Alessandri Francesco	M	22	Researcher
126	Dauri Mario	M	22	Associate professor
127	David Antonio	M	22	Full professor
128	Freo Ulderico	M	22	Associate professor
129	Polati Enrico	M	22	Full professor
130	Ragazzi Riccardo	M	22	Associate professor
131	Rezoagli Emanuele	M	22	Researcher
132	Terragni Pierpaolo	M	22	Full professor
133	Adrario Erica	F	21	Associate professor
134	Boscolo Bozza Annalisa	F	21	Researcher
135	Russotto Vincenzo	M	21	Researcher
136	Zoerle Tommaso	M	21	Researcher
137	Bruni Andrea	M	20	Associate professor
138	De Rosa Silvia	F	20	Researcher
139	Evangelista Maurizio	M	20	Researcher
140	Melotti Rita Maria	F	20	Full professor
141	Musu Mario	M	20	Associate professor
142	Noto Alberto	M	20	Associate professor
143	Piazza Ornella	F	20	Full professor
144	Piva Simone	M	20	Associate professor
145	Pota Vincenzo	M	20	Researcher
146	Vargas Maria	F	20	Associate professor
147	Siniscalco Antonio	M	20	Non-Academic Physician
148	Catena Emanuele	M	20	Non-Academic Physician
149	Magnoni Sandra	F	20	Associate professor
150	Baldini Gabriele	M	19	Associate professor
151	Cavaliere Franco	M	19	Associate professor
152	Cotoia Antonella	F	19	Researcher
153	Damiani Elisa	F	19	Researcher
154	Passavanti Maria Beatrice	F	19	Associate professor
155	Scaravilli Vittorio	M	19	Researcher
156	Biasucci Daniele Guerino	M	18	Researcher
157	Bufi Maurizio	M	18	Associate professor
158	Draisci Gaetano	M	18	Associate professor
159	Puntillo Filomena	F	18	Associate professor
160	Ragazzoni Luca	M	18	Associate professor
161	Sansone Pasquale	M	18	Associate professor
162	Scapigliati Andrea	M	18	Researcher
163	Sollazzi Liliana	F	18	Associate professor
164	Baciarello Marco	M	17	Associate professor

Continuation Supplemental Table.

#	Name	Gender	H-Index (June 2023)	Degree
165	Carassiti Massimiliano	M	17	Associate professor
166	Caricato Anselmo	M	17	Researcher
167	Cataldo Rita	F	17	Associate professor
168	Messina Antonio	M	17	Researcher
169	Natoli Silvia	F	17	Associate professor
170	Pasqualucci Alberto	M	17	Full professor
171	Carsetti Andrea	M	16	Associate professor
172	Di Filippo Alessandro	M	16	Associate professor
173	Di Marco Pierangelo	M	16	Associate professor
174	Giglio Maria Teresa	F	16	Researcher
175	Pulitano' Silvia Maria	F	16	Researcher
176	Tellan Guglielmo	M	16	Associate professor
177	Cardia Luigi	M	15	Researcher
178	Carron Michele	M	15	Associate professor
179	Chelazzi Cosimo	M	15	Associate professor
180	Rossi Marco	M	15	Associate professor
181	Schweiger Vittorio	M	15	Associate professor
182	Marra Annachiara	F	14	Associate professor
183	Mercieri Marco	M	14	Associate professor
184	Santini Alessandro	M	14	Researcher
185	Alampi Daniela	F	13	Researcher
186	Ciccozzi Alessandra	F	13	Researcher
187	Piroli Alba	F	13	Associate professor
188	Vergari Alessandro	M	13	Researcher
189	Gaspari Rita	F	13	Researcher
190	De Pasquale Maria	F	12	Researcher
191	Leonardis Francesca	F	12	Researcher
192	Montrucchio	F	12	Researcher
193	Sales Gabriele	M	12	Researcher
194	Ferraro Fausto	M	11	Associate professor
195	Martinelli Lorenzo	M	11	Researcher
196	Modesti Cristina	F	11	Researcher
197	Peluso Lorenzo	M	11	Researcher
198	Rauseo Michela	F	11	Researcher
199	Scaramuzzo Gaetano	M	11	Researcher
200	Barbieri Alberto	M	10	Associate professor
201	Buonanno Pasquale	M	10	Researcher
202	Iacovazzo Carmine	M	10	Researcher
203	Roman-Pognuz Erik	M	10	Researcher
204	Samolsky Dekel Boaz Gedaliahu	M	10	Associate professor
205	Coniglione Filadelfo	M	9	Researcher
206	Sardo Salvatore	M	9	Researcher
207	Adducci Enrica	F	8	Researcher
208	Bellini Valentina	F	8	Researcher
209	Collino Francesca	F	8	Researcher
210	De Vico Pasquale	M	8	Researcher
211	Amato Arianna	F	7	Researcher
212	Coppolino Francesco	M	7	Researcher
213	Costamagna Andrea	M	7	Researcher
214	Fiorelli Silvia	F	7	Researcher
215	Mascia Antonio	M	7	Researcher
216	Pusateri Angela	F	7	Researcher
217	Vagnoni Salvatore	M	7	Researcher
218	Crea Maria Antonietta	F	6	Researcher
219	Falsini Silvia	F	6	Researcher
220	Guarneri Sergio	M	6	Researcher
221	Cannelli Giorgio	M	5	Researcher
222	Caviglia Marta	F	5	Researcher
223	Fattorini Fabrizio	M	5	Researcher
224	La Camera Giuseppa	F	5	Researcher
225	Pistidda Laura	F	5	Researcher
226	Corrado Michele	M	4	Researcher
227	Fegiz Alessandra	F	4	Researcher
228	Galletti Claudio	M	4	Researcher
229	Mangoni Giuseppe Salvatore	M	4	Researcher
230	Perotti Valerio	M	4	Researcher
231	Sparacia Benedetta	F	4	Researcher
232	Borgia Maria Luisa	F	3	Researcher
233	Leonardis Carlo	M	3	Researcher
234	Valenti Mario	M	3	Researcher
235	Palmeri Di Villalba Cesira	F	1	Researcher
236	Pedulla' Eugenia	F	1	Researcher
237	Stancanelli Vito	M	1	Researcher

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Main information for the manuscript submission

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

ФОРУМ АНЕСТЕЗИОЛОГОВ И РЕАНИМАТОЛОГОВ РОССИИ ФАРР-2024

СЪЕЗД ФЕДЕРАЦИИ АНЕСТЕЗИОЛОГОВ И РЕАНИМАТОЛОГОВ

более 17 000
очных и зочных участников

Доклады	394
Лекции	132
Секционные заседания	37
Симпозиумы	6
Семинаров и круглых столов	3
Коммерческих докладов	34

25 стран

Россия
Абхазия
Азербайджан
Армения
Беларусь
Венгрия
Германия
Грузия
Израиль
Казахстан
Киргизия
Китай
Латвия
Ливан
Республика Молдова
Новая Зеландия
Сомали
США
Таджикистан
Турция
Узбекистан
Украина
Эстония
Южная Корея

340 городов РОССИИ

В РАМКАХ ФОРУМА ПРОШЕЛ
II Всероссийский конкурс ординаторов по специальности анестезиология и реаниматология
«Профессионалы 2024»

49 команд участие в отборе

16 команд очный раунд

ФОРУМЫ АНЕСТЕЗИОЛОГОВ И РЕАНИМАТОЛОГОВ РОССИИ
2022, 2023 и 2024 года

количество очных участников
3470
3725
4015

количество онлайн подключений
14893
15323
13281

количество компаний на выставке
52
58
63

2022	2023	2024
387 докладчиков и модераторов	395 докладчиков и модераторов	394 докладчиков и модераторов
38 секционных заседаний	35 секционных заседаний	37 секционных заседаний
125 лекций	151 лекция	132 лекции
6 сателлитных симпозиумов и мастер классов	11 сателлитных симпозиумов и мастер классов	6 сателлитных симпозиумов и мастер классов
12 постерных секций	11 постерных секций	12 постерных секций
Олимпиада по регионарной анестезии «Навигатор 2022»	Всероссийский конкурс ординаторов по специальности анестезиология и реаниматология «Профессионалы 2023»	Конкурс научно-исследовательских работ молодых ученых II Всероссийский конкурс ординаторов по специальности анестезиология и реаниматология «Профессионалы 2024»

24 страны
347 городов

23 страны
412 городов

25 стран
340 городов