https://doi.org/10.15360/1813-9779-2025-1-2517

Correlation of Immune Parameters in Breast Cancer Patients Undergoing General Anesthesia: Post-hoc Analysis of the TeMP Study

Kristina K. Kadantseva[1,2]*, Valery V. Subbotin[2], Mikhail Y. Yadgarov[1]*, Elizaveta M. Korolenok[1], Levan B. Berikashvili[1], Roman A. Akchulpanov[2], Nikolay S. Karnaukhov[2], Ksenia S. Korchagina[2], Polina I. Kukina[3], Oksana A. Svitich[3], Artem N. Kuzovlev[1], Anna S. Barmina[4], Valery V. Likhvantsev[1,5]

[1] Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology, 25 Petrovka Str., Bldg. 2, 107031 Moscow, Russia
[2] A. S. Loginov Moscow Clinical Research Center, Moscow Department of Health, 86 Enthusiasts Highway, 111123 Moscow, Russia
[3] I. I. Mechnikov Research Institute of Vaccines and Serums, 5a Maly Kazenny per., 105064 Moscow, Russia
[4] N. I. Pirogov Russian National Medical Research University, Ministry of Health of Russia, 1 Ostrovityanov Str., 117513 Moscow, Russia
[5] I. M. Sechenov First Moscow State Medical University, Ministry of Health of Russia, 8 Trubetskaya Str., Bldg. 2, 119991 Moscow, Russia

For citation: *Kristina K. Kadantseva, Valery V. Subbotin, Mikhail Y. Yadgarov, Elizaveta M. Korolenok, Levan B. Berikashvili, Roman A. Akchulpanov, Nikolay S. Karnaukhov, Ksenia S. Korchagina, Polina I. Kukina, Oksana A. Svitich, Artem N. Kuzovlev, Anna S. Barmina, Valery V. Likhvantsev.* Correlation of Immune Parameters in Breast Cancer Patients Undergoing General Anesthesia: Post-hoc Analysis of the TeMP Study. *Obshchaya Reanimatologiya = General Reanimatology.* 2025; 21 (1): 15–27. https://doi.org/10.15360/1813-9779-2025-1-2517 [In Russ. and Engl.]

***Correspondence to:** Kristina K. Kadantseva, kristina161093@gmail.com; Mikhail Y. Yadgarov, mikhail.yadgarov@mail.ru

Summary

Aim: to study the correlation of immune parameters in breast cancer patients undergoing general anesthesia and to evaluate the 1-year overall and recurrence-free survival after surgery depending on general anesthesia technique.

Materials and Methods. A post hoc analysis of data from a double-blind, randomized, controlled clinical trial involving 98 patients with operable breast cancer was performed. Patients were divided into two groups: 48 received inhalational anesthesia (IA) and 50 received total intravenous anesthesia (TIVA). Immune parameters (CRP, IgA, IgM, IgG, C3, C4, MMP-9, neutrophil and lymphocyte counts, etc.) were assessed before induction of anesthesia, 1 hour postoperatively, and 24 hours postoperatively. Spearman correlation coefficients and heat maps were used for analysis.

Results. In the IA group, significant uniform increases were observed in all immunoglobulin types at 1 and 24 hours postoperatively (all $P<0.001$; for IgA-IgG, $R=0.928$; for IgA-IgM, $R=0.837$; for IgG-IgM, $R=0.815$). A positive correlation was found between complement components (C3, C4) and immunoglobulins ($P=0.011$ — 0.023; $R=0.313$–0.363). In the TIVA group, changes were variable: immunoglobulin levels increased at 1 hour ($P<0.001$) but decreased at 24 hours ($P<0.001$). A strong positive correlation was identified between cytotoxic T cells and NK cells ($P<0.001$; $R=0.722$). Neutrophil count showed no significant correlation with cytotoxic T or NK cells. One year after surgery, both groups demonstrated 100% overall and recurrence-free survival.

Conclusion. IA was associated with synchronized changes in humoral immunity components, whereas TIVA resulted in variable immune responses, suggesting potential differences in IA and TIVA effects on the immune system. However, no impact of anesthesia technique on overall or recurrence-free survival was observed. More research is needed to better understand how different anesthetics affect immune function and the potential impact of anesthesia technique on long-term cancer outcomes.

Keywords: immune parameters; inhalational anesthesia; total intravenous anesthesia; breast cancer; humoral immunity;, cellular immunity; overall survival; recurrence-free survival

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

Funding. The study was supported by a grant from the Russian Science Foundation, No. 23-25-00219 (https://rscf.ru/project/23-25-00219).

Information about the authors:
Kristina K. Kadantseva: ORCID 0000-0002-6593-8580
Valery V. Subbotin: ORCID 0000-0002-0921-7199
Mikhail Ya. Yadgarov: ORCID 0000-0003-3792-1682
Elizaveta M. Korolenok: ORCID 0009-0007-5731-9273
Levan B. Berikashvili: ORCID 0000-0001-9267-3664
Roman A. Akchulpanov: ORCID 0000-0001-9983-0925
Nikolay S. Karnaukhov: ORCID 0000-0003-0889-2720
Ksenia S. Korchagina: ORCID 0000-0003-3181-1191
Polina I. Kukina: ORCID 0000-0002-0054-6754

Oksana A. Svitich: ORCID 0000-0003-1757-8389
Artem N. Kuzovlev: ORCID 0000-0002-5930-0118
Anna S. Barmina: ORCID 0009-0005-4429-4244
Valery V. Likhvantsev: ORCID 0000-0002-5442-6950

Introduction

Surgery is the primary treatment strategy for most patients with solid tumors. However, early tumor recurrence occurs in approximately one third of patients after surgery [1]. The stress response to surgery, involving activation of pro-inflammatory pathways and stimulation of angiogenesis, promotes cancer cell growth and metastasis, potentially leading to locoregional recurrence or distant metastasis [1]. While the negative impact of surgical stress on metastasis and oncologic outcomes is well understood, the effects of various anesthetic agents on these processes are less clear [2, 3]. Anesthetics can modulate the immune status of patients, significantly influencing postoperative complications such as infection and delayed tumor recurrence [2, 4]. Inhalation anesthetics have been shown to affect hypoxia-inducible factor-1 (HIF-1) and insulin-like growth factor-1 (IGF-1), with potential mechanisms involving downregulation of genes associated with angiogenesis, proliferation, and cell metabolism, leading to unfavorable oncologic prognosis [5]. Consequently, more randomized controlled trials are investigating the impact of the two most commonly used types of anesthesia (inhalation and total intravenous) on long-term oncologic outcomes and the mechanisms of immune suppression [6–9].

Current evidence suggests that inhaled anesthetics may affect both adaptive immune components (including T lymphocytes, CD4+ and CD8+ cells, and B lymphocytes) and innate immune elements (such as phagocytes including macrophages and neutrophils, and NK cells). Inhalation anesthesia (IA) and total intravenous anesthesia (TIVA) are thought to have distinct effects on various aspects of the immune system. To accurately determine how anesthesia influences immune responses, a comprehensive array of immune markers must be examined [10, 11].

The aim of this study was to investigate the relationship between immune parameters in breast cancer patients undergoing anesthesia. In addition, the one-year overall and recurrence-free survival rates following breast cancer surgery were to be assessed, taking into account the type of anesthesia used.

Materials and Methods

Study design. A post hoc analysis of a prospective, randomized, controlled, double-blind clinical trial was performed. The protocol was approved by the local ethics committee (No. 2/2021) and registered on clinicaltrials.gov (NCT04800393). Detailed descriptions of the study population, anesthesia methods, blood sampling, and data collection are available in the original publication [12].

Anesthesia methods. Patients enrolled in the study were not premedicated. Intraoperative monitoring included electrocardiography (ECG), pulse oximetry, and noninvasive arterial blood pressure measurement. Anesthesia induction in both the total intravenous anesthesia (TIVA) and inhalation anesthesia (IA) groups was performed with propofol (1.5–2.2 mg/kg), fentanyl (3–5 mcg/kg), and a neuromuscular blocking agent (rocuronium bromide or cisatracurium). Neuromuscular blockade was maintained at a train-of-four (TOF) ratio of 10–0%. Tracheal intubation was performed with an appropriately sized tube.

After induction and tracheal intubation, patients in both groups received pressure-controlled, volume-guaranteed lung ventilation (LV) using General Electric Avance CS2 or General Electric Medical Systems (USA) anesthesia machines. Ventilation parameters included: fraction of inspired oxygen (FiO_2) 35–40%, tidal volume (V_t) 6–8 mL/kg, positive end-expiratory pressure (PEEP) 5 cm H_2O, inspiratory-to-expiratory ratio (I:E) 1:2, and a respiratory rate sufficient to maintain normocapnia (35–45 mmHg).

In the TIVA group, anesthesia was maintained with propofol at a continuous infusion rate of 0.1–0.2 mg/kg/min delivered via a Braun Infusomat Space infusion pump using the Schneider model. In the IA group, anesthesia was maintained with sevoflurane administered endotracheally at 1 minimum alveolar concentration (MAC). The gas mixture consisted of 35–40% oxygen and air without nitrous oxide (N_2O). Gas flow rates were adjusted as needed to optimize oxygenation and ventilation parameters. Mean arterial pressure was maintained above 60 mmHg throughout the procedure.

After skin closure, patients were transferred to Pressure Support Ventilation-Pro (PSV-Pro) mode with the following settings: flow trigger sensitivity of 0.2 L/min, pressure support tailored to achieve a tidal volume of 6–8 mL/kg, peak airway pressure limit of 35 cm H_2O, and positive end-expiratory pressure (PEEP) of 5–8 cm H_2O. Normocapnia was maintained during this period. Tracheal extubation was performed when the TOF ratio reached $\geqslant 0.95$.

Patients were transferred to the recovery room when a modified Aldrete score of 9 or greater was achieved.

Postoperative analgesia was administered according to local standard practice with the goal of maintaining a Visual Analog Scale (VAS) pain score below 3.

Assessment of immunologic markers. Immune cell populations were characterized by flow cytometry using specific CD markers on a BD FACSCanto II

platform (Becton Dickinson Biosciences, USA). Cell populations were identified based on forward and side scatter light parameters combined with fluorescence emission profiles. Gating strategies allowed precise delineation of immune subsets including T cells (CD3+), T helper cells (CD3+CD4+), cytotoxic T cells (CD3+CD8+), B cells (CD19+CD3-), and natural killer (NK) cells (CD3-CD16+CD56+) based on specific morphological and expression (fluorescent) profiles.

Serum levels of inflammatory and immune markers, including C-reactive protein (CRP), IgA, IgM, IgG, complement components C3 and C4, were quantified by nephelometry using a BN ProSpec laser nephelometer (Siemens Healthcare Diagnostics Products GmbH). Matrix metalloproteinase-9 (MMP-9) levels were measured by enzyme-linked immunosorbent assay (ELISA) using the Human MMP-9 Quantikine ELISA Kit (Cloud-Clone Corp.).

Endpoints. The study evaluated the correlation and dynamic changes of the following immunological parameters: C-reactive protein (CRP), IgA, IgM, IgG, complement components C3 and C4, matrix metalloproteinase-9 (MMP-9), neutrophil and lymphocyte counts, neutrophil-to-lymphocyte ratio (NLR), the proportion of T cells (CD3+), T helper cells (CD3+CD4+) and cytotoxic T cells (CD3+CD8+), the immunoregulatory index (the ratio of T helper cells to cytotoxic T cells, CD3+CD4+/CD3+CD8+), the proportions of B cells (CD19+CD3-) and natural killer (NK) cells (CD3-CD16+), and the total proportions of T, B, and NK cells.

All parameters were measured at three time points: before induction of anesthesia, 1 hour after surgery, and 24 hours after surgery.

In addition, long-term patient survival outcomes, including recurrence-free survival (RFS) and overall survival (OS), were assessed one year after randomization. Data were collected through telephone interviews and review of electronic medical records, including comprehensive instrumental and laboratory findings. Overall survival (OS) was defined as the time from enrollment to death from any cause, while recurrence-free survival (RFS) was defined as the time from enrollment to either disease recurrence or death.

Statistical Analysis. All statistical calculations were performed using IBM SPSS Statistics for Windows, version 27.0 (Armonk, NY: IBM Corp.). Quantitative variables with a normal distribution were presented as means ± standard deviation *(SD)*, while variables that did not meet the assumption of normality were reported as medians with interquartile ranges *(IQR)*. Normality was assessed using the Shapiro–Wilk test and histogram analysis.

Binary variables were analyzed using the two-tailed χ^2 test or Fisher's exact test, with the Fisher–Freeman–Halton extension applied when appropriate. Independent groups of quantitative variables were compared using the Mann–Whitney *U* test. For paired samples, analysis was conducted using the Friedman test, Dunn's post hoc test, or the Wilcoxon signed-rank test.

Correlation analysis was performed to assess the relationship between each pair of parameters by calculating Spearman's rank correlation coefficient with a 95% confidence interval *(CI)*. Correlations were evaluated for baseline parameter values across patients, within groups, and for relative changes in parameters at 1 hour and 24 hours. The strength of the correlation was interpreted according to the following scale [13]:

- $0 < |R| < 0.2$: very weak
- $0.2 \leqslant |R| < 0.4$: weak
- $0.4 \leqslant |R| < 0.6$: moderate
- $0.6 \leqslant |R| < 0.8$: strong
- $0.8 \leqslant |R| < 1$: very strong

Heatmaps were generated using Python 3.11 with the numpy (2.0.0), pandas (2.2.2), seaborn (0.13.2), and matplotlib (3.9.1) libraries.

Two-tailed tests were applied with a significance level of $P<0.05$.

Results

Patients. Between 2022 and 2023, a total of 324 patients were screened for eligibility based on the inclusion and exclusion criteria at the A. S. Loginov Moscow Clinical Scientific Center. Of these, 278 patients met the inclusion criteria, while 180 were excluded: 158 because of a history of autoimmune disease and 22 because of malignancy at another site. As a result, 98 patients were enrolled in the study, of whom 48 were assigned to the IA group and 50 to the TIVA group (Fig. 1).

Baseline demographic characteristics, clinicopathologic parameters, type of surgery, and duration of anesthesia were comparable between groups (Table 1). The median age was 62 years (interquartile range [IQR], 55–68). Radical mastectomy was performed in most patients (*N*=69, 70%). Length of stay in the post-anesthesia care unit (PACU) did

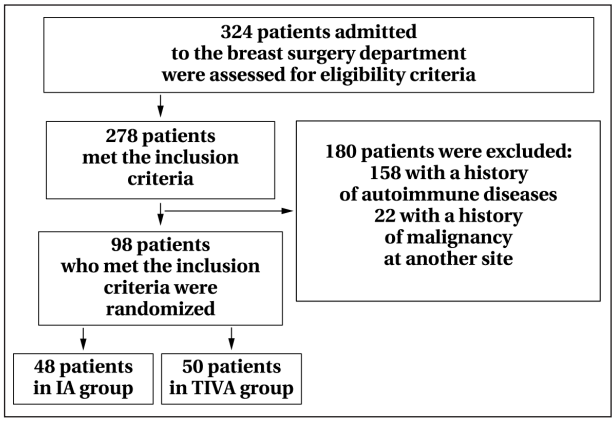

Fig. 1. Patient selection scheme for the study.
Note. For Fig. 1, 3 and Tables 1–3: TIVA — total intravenous anesthesia; IA — inhalation anesthesia.

Table 1. Main patient characteristics.

Parameter	Values in groups		*P*
	IA, *N*=48	TIVA, *N*=50	
Age, years; *N, Me (IQR)*	48, 62.5 (56–68)	50, 61 (54–68)	0.545[1]
BMI, kg/m²; *N, Me (IQR)*	46, 29 (23.8–32.0)	50, 27.6 (23.4–31.2)	0.687[1]
Comorbidities, *N* (%)			
History of COVID-19	29 (60)	27 (54)	0.521[2]
Uncontrolled diabetes mellitus	3 (6.3)	0 (0)	0.114[3]
Chronic obstructive pulmonary disease	1 (2.1)	1 (2)	0.999[3]
Cerebrovascular disease	1 (2.1)	0 (0)	0.490[3]
Peripheral arterial disease	1 (2.1)	0 (0)	0.490[3]
Diabetes mellitus	5 (10.4)	2 (4)	0.264[3]
Arterial hypertension	30 (63)	28 (56)	0.513[2]
Chronic kidney disease	0 (0)	1 (2)	0.999[3]
Coronary heart disease	3 (6.3)	4 (8)	0.999[3]
Atrial fibrillation	2 (4.2)	0 (0)	0.237[3]
Rhythm disturbances	3 (6.3)	1 (2)	0.357[3]
Heart failure	6 (12.5)	2 (4)	0.155[3]
Liver failure	0 (0)	0 (0)	NA
Dementia	0 (0)	0 (0)	NA
Rheumatic conditions	0 (0)	0 (0)	NA
Peptic ulcer disease	0 (0)	1 (2)	0.999[3]
Hemiplegia	0 (0)	0 (0)	NA
Leukemia	0 (0)	0 (0)	NA
Lymphoma	0 (0)	0 (0)	NA
AIDS/hepatitis	0 (0)	0 (0)	NA
Clinical and morphological characteristics, *N* (%) or Me (IQR)			
Tumor localization (right)	23 (48)	20 (40)	0.430[2]
TNM			
Tis	1 (2.2)	0.579[4]	0.579[4]
T1	34 (71)	31 (62)	
T2	13 (27)	17 (34)	
N0	48 (100)	NA	NA
M0	48 (100)	NA	NA
Tumor cell differentiation (G)			
G1	8 (17)	0.945[2]	0.945[2]
G2	25 (54)	26 (52)	
G3	13 (28)	14 (28)	
Stage			
0	1 (2.2)	0.204[3]	0.204[3]
IA	34 (71)	28 (56)	
IIA	13 (27)	20 (40)	
Molecular subtype			
Data not available	2 (4.2)	0.598[4]	0.598[4]
Luminal A	21 (44)	17 (34)	
Luminal B	23 (48)	28 (56)	
Triple negative	2 (4.2)	4 (8)	
Her2neu+	2 (4.2)	2 (4)	0.999[3]
TILs, %	37.3 (2–5)	38.3 (2–5)	0.961[1]
Perioperative characteristics, *N* (%) or *Me (IQR)*			
Type of surgery			
Partial resection	18 (37.5)	11 (22)	0.093[2]
Mastectomy	30 (62.5)	39 (78)	
Duration of anesthesia, minutes	87.5 (75.0–102.5)	90.0 (70.0–105.0)	0.839[1]
Duration of surgery, minutes	70.0 (60.0–90.0)	70.0 (60.0–90.0)	0.937[1]
Anesthetic injection time, min	85 (75–100)	90 (70–105)	0.908[1]
Intraoperative fentanyl dose, mg	0.3 (0.3–0.4)	0.4 (0.3–0.5)	0.534[1]
Intraoperative propofol dose, mg	1.5–2.2 mg/kg — induction of anesthesia. No — maintenance of anesthesia	800 (600–1000)	NA
Intraoperative sevoflurane dose for maintenance of anesthesia (MAC)	0.9 (0.8–1.0)	No	NA

Note. [1] — Mann–Whitney test; [2] — Chi-squared test; [3] — Fisher's exact test; [4] — Fisher–Freeman–Halton test. NA — not applicable; *Me* — median value; *IQR* — interquartile range; *N* — number of patients with the specified parameter.

not exceed 24 hours. The median length of hospital stay was 3 days (IQR, 3–5) in the IA group and 4 days (IQR, 3–5) in the TVA group (*P*=0.131).

Comparison of baseline immunologic blood markers. Statistically significant differences between the groups were found for the concentrations of

C-reactive protein, IgA and IgG, and the proportions of T and B lymphocytes and NK cells (Table 2).

Analysis of correlations of baseline immunologic parameters showed that all immunoglobulins were positively correlated with each other with moderate to strong correlation strength (R=0.515 to 0.783; all P<0.001) (Fig. 2). A weak positive correlation was observed between components of the complement

Table 2, Serum biomarkers of patients in the IA and TIVA groups, *Me [Q1; Q3]*.

Laboratory parameter		Values in groups		P^1
		IA, N=48	TIVA, N=50	
C-reactive protein, mg/L	Before surgery	**0.7 [0.29; 2.21]**	**1.49 [0.77; 3.91]**	**0.023**
	1 hour after surgery	**0.77 [0.31; 2.29]**	**1.45 [0.79; 4.01]**	**0.038**
	% change from baseline before 1 h	–3.19 [–11.29; 1.66]	–0.44 [–6.22; 6.14]	0.112
	24 h after surgery	5.84 [2.45; 10.75]	5.54 [2.87; 11.78]	0.848
	% of change from baseline to 24 h	**466.38 [191.73; 1015.35]**	**260.56 [73.29; 631.25]**	**0.044**
IgA, g/L	Before surgery	**2.33 [1.56; 3.06]**	**1.09 [0.47; 2.25]**	**<0.001**
	1 hour after surgery	**2.27 [1.55; 2.98]**	**1.42 [0.81; 2.45]**	**<0.001**
	% change from baseline before 1 h	**–3.01 [–9.34; 2.73]**	**6.22 [–8.09; 82.75]**	**0.011**
	24 h after surgery	**2.23 [1.67; 2.75]**	**1.11 [0.46; 1.99]**	**<0.001**
	% of change from baseline to 24 h	–5.64 [–15.32; 3.63]	–5.84 [–26.4; 6.48]	0.629
IgM, g/L	Before surgery	0.82 [0.51; 1.23]	0.74 [0.33; 1.11]	0.058
	1 hour after surgery	0.84 [0.61; 1.17]	0.72 [0.39; 1.22]	0.207
	% change from baseline before 1 h	**–4.55 [–13.07; 0.88]**	**9.3 [–12.04; 70.95]**	**0.031**
	24 h after surgery	**0.81 [0.58; 1.17]**	**0.57 [0.35; 0.89]**	**0.005**
	% of change from baseline to 24 h	–3.4 [–15.4; 10.84]	–9.63 [–35.68; 17.99]	0.298
IgG, g/L	Before surgery	**10.09 [8.22; 12.8]**	**5.76 [2.52; 10.6]**	**<0.001**
	1 hour after surgery	**10.05 [8.15; 11.8]**	**7.98 [3.95; 10.23]**	**<0.001**
	% change from baseline before 1 h	**–4.77 [–11.9; 1.49]**	**4.3 [–7.21; 85.7]**	**0.013**
	24 h after surgery	**9.76 [8.26; 11.2]**	**5.64 [2.11; 9.96]**	**<0.001**
	% of change from baseline to 24 h	–7.85 [–15.5; –0.76]	–8.53 [–32.06; 3.79]	0.589
C3, g/L	Before surgery	1.25 [1.08; 1.36]	1.3 [1.11; 1.49]	0.161
	1 hour after surgery	1.2 [1.03; 1.35]	1.34 [1.12; 1.48]	0.078
	% change from baseline before 1 h	–4.88 [–7.73; –0.2]	–2.41 [–8.76; 2.22]	0.350
	24 h after surgery	1.23 [1.02; 1.39]	1.31 [1.17; 1.48]	0.086
	% of change from baseline to 24 h	–2.52 [–7.65; 2.41]	0.27 [–4.5; 5.02]	0.111
C4, g/L	Before surgery	0.31 [0.25; 0.35]	0.31 [0.24; 0.36]	0.752
	1 hour after surgery	0.3 [0.23; 0.33]	0.31 [0.23; 0.35]	0.709
	% change from baseline before 1 h	–4.73 [–8.59; 0.6]	–1.86 [–7.64; 2.17]	0.346
	24 h after surgery	0.3 [0.26; 0.34]	0.31 [0.24; 0.39]	0.621
	% of change from baseline to 24 h	–2.33 [–9.56; 5.5]	1.22 [–5.94; 10.86]	0.105
MMP-9, ng/mL	Before surgery	29, 19.71 [13.71; 20]	11, 17.35 [13.38; 19.3]	0.254
	24 h after surgery	29, 20 [15.93; 20]	11, 17.39 [14.74; 20]	0.492
	% of change from baseline to 24 h	29, 0 [0; 22.3]	11, 0.2 [–1.69; 16.24]	0.905
Neutrophil count, 10^9/L	Before surgery	47, 3.7 [3.1; 4.6]	3.3 [2.5; 4]	0.086
	1 hour after surgery	47, 5.6 [4; 7]	49, 5.4 [4.2; 7.35]	0.866
	% change from baseline before 1 h	46, 60.09 [8.53; 94.55]	49, 66.67 [30.21; 131.74]	0.295
	24 h after surgery	45, 6.8 [5.2; 9.1]	49, 5.8 [4.55; 8.6]	0.217
	% of change from baseline to 24 h	44, 80.66 [36; 151.56]	49, 80 [37.52; 172.25]	0.681
Neutrophil percentage, %	Before surgery	47, 57.4 [48.4; 63.9]	55.45 [51.38; 62]	0.865
	1 hour after surgery	47, 77.9 [62.7; 87.4]	49, 78.5 [66.65; 83.75]	0.789
	% change from baseline before 1 h	47, 37.09 [10.56; 54.28]	33.13 [11.61; 53.35]	0.854
	24 h after surgery	45, 69.5 [64.35; 74.75]	49, 67.6 [63.05; 73.35]	0.440
	% of change from baseline to 24 h	47, 22.67 [6.26; 41.23]	16.85 [4.97; 38.58]	0.831
Lymphocyte count, 10^9/L	Before surgery	47, 2.06 [1.7; 2.6]	2.1 [1.5; 2.36]	0.237
	1 hour after surgery	47, 1.2 [0.7; 1.7]	1.3 [0.98; 1.62]	0.558
	% change from baseline before 1 h	46, –47.22 [–62.33; –10.48]	–36.55 [–50; –7.24]	0.055
	24 h after surgery	45, 2 [1.75; 2.45]	49, 2 [1.55; 2.5]	0.604
	% of change from baseline to 24 h	44, –7.42 [–16.79; 13.13]	49, 6.67 [–13.96; 19.7]	0.193
Lymphocyte percentage, %	Before surgery	47, 33.3 [26.5; 39]	33.75 [28.25; 38.28]	0.894
	1 hour after surgery	47, 17.2 [10.2; 26]	16.4 [11.88; 25.53]	0.928
	% change from baseline before 1 h	47, –58.61 [–65.37; –23.1]	–49.39 [–62.6; –25.05]	0.593
	24 h after surgery	45, 21.5 [15.6; 25.85]	49, 23 [18.6; 27]	0.269
	% of change from baseline to 24 h	47, –34.36 [–59.79; –21.92]	–29.41 [–47.22; –15.24]	0.165
Neutrophil-lymphocyte ratio (NLR)	Before surgery	47, 1.7 [1.24; 2.43]	1.65 [1.34; 2.18]	0.767
	1 hour after surgery	47, 4.54 [2.4; 9]	49, 4.42 [2.5; 6.78]	0.519
	% change from baseline before 1 h	47, 246.94 [36.4; 343.55]	135.74 [33.94; 263.89]	0.294
	24 h after surgery	45, 3.25 [2.46; 4.81]	49, 3 [2.3; 3.91]	0.333
	% of change from baseline to 24 h	47, 79.31 [19.61; 182.45]	64.38 [18.28; 140.62]	0.636

Continuation of the Table 2.

Laboratory parameter		Values in groups		P^1
		IA, *N*=48	TIVA, *N*=50	
T lymphocytes (CD3+), %	Before surgery	47, 70.4 [64.9; 78.9]	70.75 [62.1; 78.1]	0.829
	1 hour after surgery	47, 67.5 [54.1; 74.9]	65.95 [54.7; 72.63]	0.549
	% change from baseline before 1 h	47, –8.17 [–18.65; 2.02]	–6.41 [–20.62; 1.2]	0.657
	24 h after surgery	47, 73.8 [65.5; 81.2]	71.9 [66.78; 77.58]	0.654
	% of change from baseline to 24 h	47, 1.62 [–4.19; 6.78]	2.39 [–5.57; 10.66]	0.945
T helpers (CD3+CD4+), %	Before surgery	47, 61.5 [53.9; 66.8]	59.75 [52.88; 71.13]	0.798
	1 hour after surgery	47, 61.1 [53.7; 68.2]	56.8 [43.58; 69.38]	0.292
	% change from baseline before 1 h	47, –1.16 [–6.47; 7.46]	–3.18 [–16; 3.78]	0.136
	24 h after surgery	47, 65.7 [56.7; 71.5]	63.4 [52.6; 72.23]	0.518
	% of change from baseline to 24 h	47, 4.64 [–0.83; 12.86]	3.88 [–3.77; 14.23]	0.675
Cytotoxic T lymphocytes (CD3+CD8+), %	Before surgery	47, 32 [25.3; 38.6]	32.65 [22.2; 39.68]	0.940
	1 hour after surgery	47, 31 [26; 37.6]	36 [22.8; 45.7]	0.392
	% change from baseline before 1 h	47, –2.54 [–10.58; 11.93]	4.39 [–6.4; 23.74]	0.075
	24 h after surgery	47, 27 [22.7; 36.2]	30.15 [21.63; 38.7]	0.433
	% of change from baseline to 24 h	47, –8.15 [–17.38; 0.3]	–5.86 [–14.87; 9.2]	0.375
Immuno-regulatory index (CD4+/CD8+ ratio)	Before surgery	46, 1.85 [1.49; 2.5]	1.66 [1.34; 3.22]	0.872
	1 hour after surgery	47, 1.95 [1.47; 2.52]	1.54 [0.97; 2.88]	0.203
	% change from baseline before 1 h	**46, 1.58 [–16; 18.4]**	**–8.15 [–35; 10.16]**	**0.033**
	24 h after surgery	45, 2.57 [1.61; 3.06]	49, 2.13 [1.36; 3.2]	0.394
	% of change from baseline to 24 h	45, 11.26 [–4.98; 36.06]	49, 15.87 [–9.2; 35.84]	0.907
B lymphocytes, %	Before surgery	47, 8.9 [7; 11.5]	9.65 [6.18; 13.18]	0.762
	1 hour after surgery	47, 10.7 [8.1; 14.3]	10.8 [7.68; 16.88]	0.991
	% change from baseline before 1 h	47, 25.41 [2.53; 44.83]	29.7 [–6.3; 44.39]	0.765
	24 h after surgery	47, 12.7 [8.5; 15.7]	49, 12.3 [9; 17.1]	0.484
	% of change from baseline to 24 h	47, 40.59 [9.01; 61.18]	49, 30.88 [9.31; 68.73]	0.498
NK cells, %	Before surgery	47, 16.2 [11.8; 23.4]	14.9 [8.63; 22.3]	0.191
	1 hour after surgery	47, 16 [10.3; 27.9]	17.5 [10.48; 26]	0.988
	% change from baseline before 1 h	47, 14.42 [–29.71; 65.87]	20.21 [–14.58; 83.06]	0.259
	24 h after surgery	47, 11.3 [8; 16.6]	48, 8.95 [6.43; 14.78]	0.189
	% of change from baseline to 24 h	47, –35.91 [–53.82; 0.78]	48, –35.93 [–52.71; 6.72]	0.615
T lymphocytes (CD3+), B lymphocytes (CD19+CD3), NK cells (CD3–CD16+), %	Before surgery	**46, 98.5 [96.53; 99.95]**	**97.2 [95.18; 98.6]**	**0.021**
	1 hour after surgery	47, 98.3 [95.5; 99.9]	97.25 [93.78; 99.23]	0.151
	% change from baseline before 1 h	46, –0.3 [–3.22; 2.56]	0.36 [–2.54; 2]	0.668
	24 h after surgery	45, 98.4 [96.6; 99.55]	48, 97.4 [94.3; 99.08]	0.105
	% of change from baseline to 24 h	44, –0.35 [–1.87; 1.89]	48, 0.07 [–2.31; 2.76]	0.487

Note. [1] — Mann–Whitney test; *Me* — median; *Q1* and *Q3* — first and third quartiles, respectively. Missing data are represented by the number of observations.

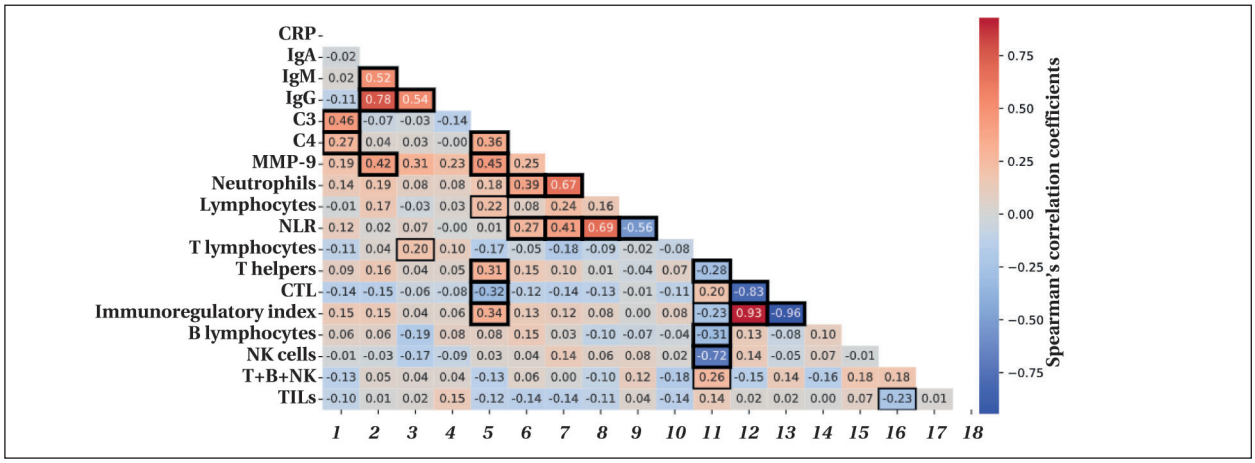

Fig. 2. Heat map of Spearman's correlation coefficients of preoperative (baseline) parameter values.
Note. *1* — CRP; *2* — IgA; *3* — IgM; *4* — IgG; *5* — C3; *6* — C4; *7* — MMP-9; *8* — Neutrophils; *9* — Lymphocytes; *10* — NLR; *11* — T lymphocytes; *12* — T helpers; *13* — CTL; *14* — Immunoregulatory index; *15* — B lymphocytes; *16* — NK cells; *17* — T+B+NK; *18* — TILS. Correlation is statistically significant for coefficients highlighted by a frame: thin frame at $P<0.05$, thick frame at $P<0.01$. CRP — C-reactive protein; MMP-9 — matrix metalloproteinase-9; NLR — neutrophil-lymphocyte ratio; CTL — cytotoxic lymphocytes; T+B+NK — total T, B lymphocytes and NK cells. TILs — tumor infiltrating lymphocytes.

system (C3, C4) ($P<0.001$; $R=0.36$). A strong positive significant correlation was found between MMP-9 and absolute neutrophil count ($P<0.001$; $R=0.673$), and a very strong negative correlation was found between the number of cytotoxic T cells and T helper cells ($P<0.001$; $R=–0.828$). NK cells showed a strong negative quantitative correlation with T cells ($P<0.001$; $R=–0.725$). No significant quantitative relationship was found between NK cells, T killers and neutrophils.

Detailed analysis results, including *P*-values and Spearman's correlation coefficients with their 95% confidence intervals, are available in the Supplementary Appendix at request from correspondence address.

Inhalation anesthesia

Changes at 1 hour. The results of the correlation analysis of the relative changes in the parameters at 1 hour after surgery in the IA group are presented as a heat map (Fig. 3, *a*).

All immunoglobulins showed a very strong positive correlation ($P<0.001$):

- IgA–IgG: $R=0.928$
- IgA–IgM: $R=0.837$
- IgG–IgM: $R=0.815$

This was accompanied by a concurrent decrease in the levels of all immunoglobulins.

The levels of complement system components (C3 and C4) also decreased. A strong positive correlation was observed between these components ($P<0.001$; $R=0.782$).

There was a weak positive correlation between the levels of complement system components and immunoglobulins, with statistically significant associations characterized by *P* values ranging from 0.011 to 0.023 and *R* values ranging from 0.313 to 0.363.

Thus, all components of the humoral immune system showed consistent changes (suppression) with varying degrees of correlation strength.

A significant positive moderate correlation was observed between T killers, NK cells and neutrophils, with R values ranging from 0.447 to 0.503 ($P\leqslant0.002$), as well as a moderate negative correlation between T helpers and NK cells ($P<0.001$; $R=–0.578$).

All significant correlations between components of the humoral immune system (IgA, IgM, IgG, C3, C4) and cells involved in «foreign body clearance» (T killers, NK cells, neutrophils) were positive, with strengths ranging from weak to moderate (*P* values between 0.003 and 0.049; *R* values between 0.291 and 0.427). A concomitant change in humoral immunity and the number of cells in the «foreign body clearance» system was observed.

The level of C-reactive protein (CRP) correlated positively with components of humoral immunity (IgA, IgM, IgG, C3, C4), as well as with the number of T killers, NK cells and neutrophils, with correlations ranging from weak to moderate ($P<0.001$ to 0.031; *R* values from 0.248 to 0.566).

Changes at 24 hours. The results of the correlation analysis of the relative changes in parameters 24 hours after surgery in the IA group are presented as a heat map (Fig 3, *b*).

The pattern and direction of changes in immunoglobulins and components of the complement system at 24 hours remained consistent with those observed at the previous measurement. The levels of all components of the humoral immune system continued to decrease, with varying degrees of correlation.

A strong positive correlation was observed between the number of T killers and NK cells ($P<0.001$; $R=0.743$), accompanied by a shift of the values to the lower range. Neutrophils no longer correlated quantitatively with T killers. A strong negative correlation remained between T helpers and T killers.

The relationship between humoral and cellular immunity disappeared. CRP level was no longer associated with other parameters.

Total intravenous anesthesia

Changes at 1 hour. The results of the correlation analysis of the relative changes in parameters at 1 hour after surgery in the TIVA group are presented as a heat map (Fig. 3, *c*).

All immunoglobulins showed strong or very strong positive correlations ($P<0.001$; *R* ranged from 0.802 to 0.907). This was accompanied by a concomitant increase in the levels of all immunoglobulins.

A moderate positive correlation was observed between the levels of complement components C3 and C4 ($P<0.001$; $R=0.596$). Plasma concentrations of these proteins 1 hour after surgery were lower than their baseline levels.

No significant correlations were found in five of six pairwise comparisons between complement components (C3, C4) and immunoglobulins (IgA, IgM, IgG). For one pair (IgA and C3), a weak positive correlation was observed ($P=0.039$; $R=0.293$).

Overall, different components of the humoral immune system responded in divergent directions: immunoglobulin concentrations increased simultaneously, whereas components of the complement system decreased in a coordinated manner. However, no significant correlations were observed between the parameters of these systems.

A strong positive correlation was observed between the number of T killers and NK cells ($P<0.001$; $R=0.722$), with a corresponding increase in the number of T killers in patient plasma. Neutrophils did not show a significant quantitative relationship with NK cells or T killers. However, a strong negative correlation was observed between NK cells and T helpers ($P<0.001$; $R=–0.759$).

For most pairwise comparisons between humoral immunity components (IgA, IgM, IgG, C3, C4) and cells involved in «foreign body clearance»

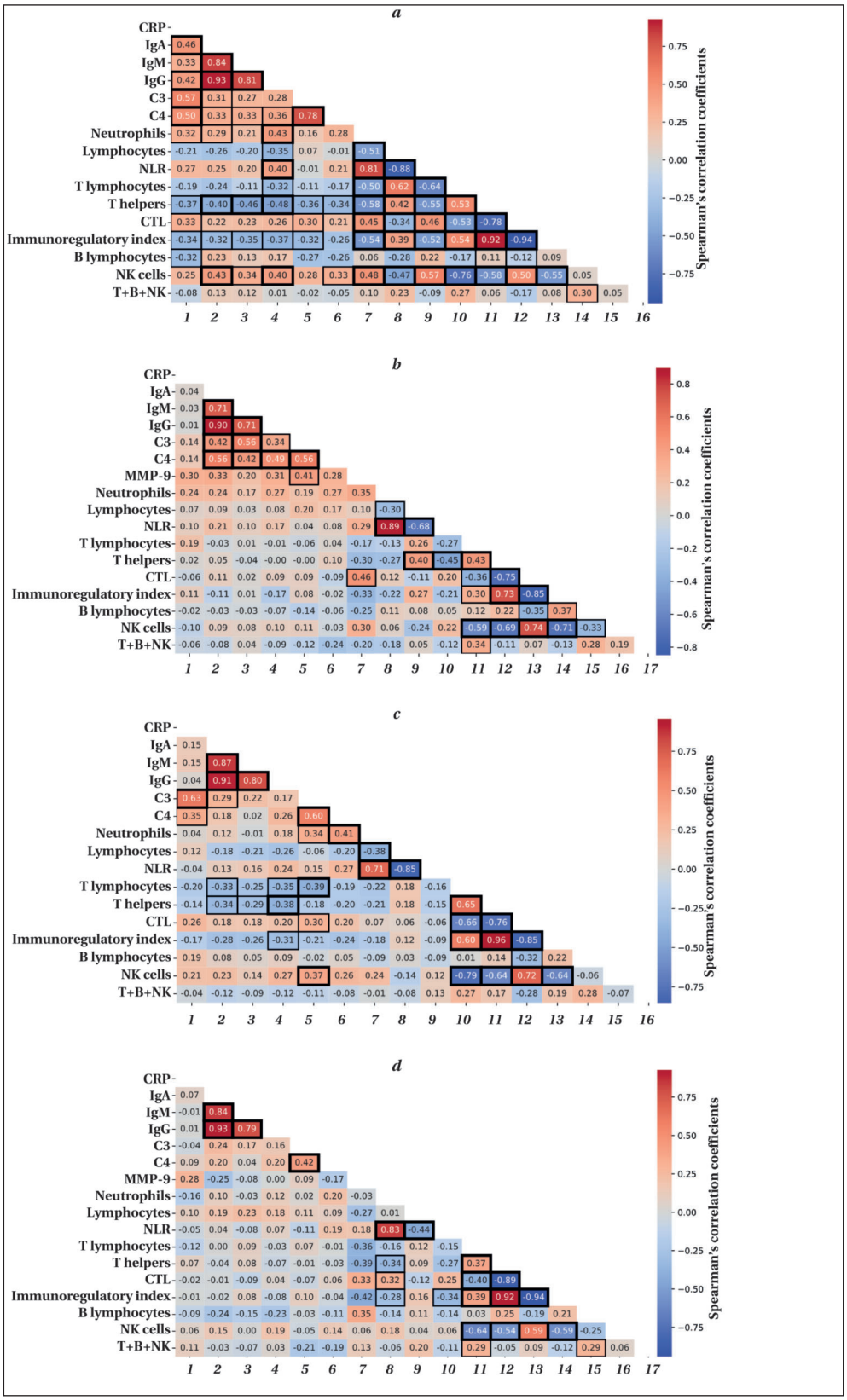

Fig. 3. Heatmaps of Spearman's correlation coefficients for relative changes in parameters at 1 hour (*a, c*) and 24 hours (*b, d*) in the inhalation anesthesia (IA; *a, b*) and total intravenous anesthesia (TIVA; *c, d*) groups.

Note. *1* — CRP; *2* — IgA; *3* — IgM; *4* — IgG; *5* — C3; *6* — C4; *7* — MMP-9; *8* — Neutrophils; *9* — Lymphocytes; *10* — NLR; *11* — T lymphocytes; *12* — T helpers; *13* — CTL; *14* — Immunoregulatory index; *15* — B lymphocytes; *16* — NK cells; *17* — T+B+NK. Correlation is statistically significant for coefficients highlighted by a frame: thin at $P<0.05$, thick at $P<0.01$. CRP — C-reactive protein; MMP-9 — matrix metalloproteinase-9; NLR — neutrophil-lymphocyte ratio; CTL — cytotoxic lymphocytes; T+B+NK — total T, B lymphocytes and NK cells. TILs — tumor infiltrating lymphocytes.

(T killers, NK cells, neutrophils), no significant correlations were identified. For a small subset of parameters (3 out of 15 pairs), weak positive correlations were found (P values ranging from 0.007 to 0.034; R values ranging from 0.301 to 0.374). In addition, neutrophils demonstrated a moderate correlation with C4 (P=0.003; R=0.415).

Overall, no concurrent changes between humoral and cellular immunity were observed in this group.

CRP levels did not correlate with markers of cellular immunity or immunoglobulin levels. However, a moderate positive association was observed with components of the complement system (with C3: $P<0.001$; R=0.63; with C4: P=0.012; R=0.354).

Changes at 24 hours. The results of the correlation analysis of the relative parameter changes at 24 hours postoperatively in the TIVA group are presented as a heat map (Fig. 3, *d*).

Immunoglobulin levels showed strong to very strong positive correlations with each other ($P<0.001$; R ranged from 0.786 to 0.926). Concurrently, their levels decreased.

Concentrations of complement system components (C3 and C4) increased and showed a moderate positive correlation (P=0.002; R=0.422).

No significant correlations were observed between complement proteins (C3, C4) and immunoglobulins (IgA, IgM, IgG). Thus, there was no systemic alignment in the changes of humoral immunity parameters.

A moderate positive correlation was observed between the number of T killers and NK cells ($P<0.001$; R=0.592), with an associated decrease in the number of T killers. Neutrophils showed a weak positive correlation with T killers (P=0.027; R=0.316), but not with NK cells. There was a moderate negative correlation between NK cells and T helpers.

No significant correlations were found between humoral and cellular markers of immunity.

CRP level was not associated with any immunologic parameter.

The correlations of the parameters in the IA and TIVA groups at 1 hour and 24 hours postoperatively are shown in Table 3.

Overall and recurrence-free survival. No recurrences or deaths were observed during the one-year follow-up period.

Discussion

In the IA group, strong correlations were observed between immunoglobulins (IgA, IgM, IgG) and complement system components (C3, C4), as well as their related dynamic changes.

Possible mechanisms underlying these effects include the direct influence of anesthetics on B lymphocytes, which are responsible for immunoglobulin production. Research suggests that anesthetics such as isoflurane and sevoflurane may suppress B lymphocyte function by modulating signaling pathways and inhibiting the transcription of genes essential for antibody synthesis [14]. In addition, elevated cortisol levels induced by anesthetics and surgical stress may affect the immune response by reducing antibody production through alterations in B lymphocyte activity [15]. The reduction in complement components (C3 and C4) may be due to their increased activation and subsequent depletion

Table 3. Comparison of correlations between parameters in the IA and TIVA groups at 1 hour and 24 hours postoperatively

Parameter	Values in groups							
	IA, *N*=48				TIVA, *N*=50			
	1 hour		24 hours		1 hour		24 hours	
	Correlation strength	Direction of change	Correlation strength	Direction of change	Correlation strength	Direction of change	Correlation strength	Direction of change
Immunoglobulins (IgA, IgM, IgG)	Very strong	↓↓	Strong/ very strong	↓↓	Strong/ very strong	↑↑	Strong/ very strong	↓↓
Complement systema (C3, C4)	Strong	↓↓	Moderate	↓↓	Moderate	↓↓	Moderate	↑↑
Humoral immunity	Weak	↓↓	Weak/ moderate	↓↓	5/6 no, 1 — weak (IgA and C3)	↑↑ (C3↓)	No	
T killers, NK cells, neutrophils	Moderate	↑↑ (T killers↓)	Strong (T killers and NK cells)	↓↓ (Neutrophils↑)	Strong (T killers and NK cells)	↑↑	Weak/ moderate	↓↓ (Neutrophils↑)
Humoral and cellular immunity	Weak/ moderate	↓↓(except NK cells and neutrophils)	No		No or Weak		No	
CRP with humoral and cellular immunity	Weak/ moderate	↓↓	No		Moderate with the complement system components	↓↓	No	

Note. Unidirectional arrows indicate positive correlation, bidirectional arrows indicate negative correlation.

in response to systemic inflammation associated with inhalation anesthetics. Alternatively, it may reflect the potential suppressive effects of anesthetics on liver function, which plays a critical role in protein synthesis [16]. The observed correlations between complement components and immunoglobulins highlight their joint contribution to humoral immunity and underscore the importance of a comprehensive investigation of the mechanisms underlying their interactions.

These findings differ from those of A. L. Kvarnström et al. who studied patients undergoing colorectal surgery and reported significant increases in C3a and SC5b-9 levels both intraoperatively and postoperatively in both the IA and TIVA groups. Such discrepancies underscore the significant role of surgical stress in complement activation. In their study, peak C3a levels occurred during surgery and remained elevated 24 hours postoperatively, suggesting a prolonged effect of surgical stress on the complement system [17].

Given the current lack of clinical studies demonstrating humoral immune suppression caused by reduced immunoglobulin levels under the influence of inhalational anesthetics, the findings presented here require further validation.

The strong negative correlation between NK cells and T-helper cells may reflect a form of «competition» between the innate and adaptive immune systems. NK cells, central players in innate immunity, have the ability to eliminate tumor cells without prior activation, although their functionality and efficiency can be significantly enhanced by specific cytokines. In contrast, T cells, essential components of adaptive immunity, require full activation to perform their functions. This divergent behavior may be explained by competition for limited resources, such as cytokines and growth factors, which could lead to suppression of one cell population while enhancing the activity of another [18, 19].

Literature suggests that both NK cells and T helper cells are dependent on IL-2 and IL-15 for activation. Imbalances in these cytokines could lead to preferential activation of one cell type at the expense of the other [20]. In addition, exposure to anesthetics can disrupt the production of IL-2 and other cytokines, potentially altering immune dynamics to favor NK cell activity over T cell responses — or vice versa — depending on the prevailing cytokine milieu [21].

Under normal conditions, T helper cells play a crucial role in the activation and support of cytotoxic T cells. By promoting the proliferation and differentiation of cytotoxic T cells, they ensure an effective immune response against tumor cells. However, exposure to inhalation anesthetics may suppress T helper cell function, thereby reducing the cytotoxic activity of CD8+ cells. This imbalance in the immune response could account for diminished antitumor activity and an increased risk of disease recurrence [22].

While the precise immune system targets of inhalation anesthetics remain undefined, several molecular and cellular mechanisms underlying their immunomodulatory effects have been identified. These mechanisms include the reduction of immune cell numbers through apoptosis and the suppression of cellular immune functions [16]. Given the complexity and variability of immune responses, the immunosuppressive effects of anesthetics are likely more intricate than previously recognized. Further clinical research, incorporating detailed analyses of blood immune parameters, is essential to clarify the mechanisms by which inhalation anesthetics modulate the immune system and their interrelated effects.

The weak correlations observed between humoral immune components (IgA, IgM, IgG, C3, C4) and cytotoxic immune cells (T killers, NK cells, neutrophils) suggest differing sensitivities of these immune subsystems to anesthetic exposure. This disparity may reflect distinct regulatory and activation mechanisms for humoral and cellular immunity. Moreover, individual variability in immune responses among patients likely contributes to the diverse reactions observed following anesthesia and surgical stress.

It seems that there was no single immunomodulatory factor in the TIVA group. At 1 hour postoperatively, some components of humoral immunity (immunoglobulins) increased in parallel, while other components (complement system) decreased. However, these changes were not related. At the same time, a subset of cellular immunity (T killers) was synchronously activated, resulting in an increased number of these cells 1 hour after surgery. By 24 hours postoperatively, components of humoral immunity (immunoglobulins and complement system) showed no correlation. The number of T killers decreased synchronously, but no associations were found between changes in cellular and humoral immunity.

Current literature suggests that propofol exerts less pronounced immunosuppressive effects compared to inhalation anesthetics. Specifically, propofol does not significantly suppress NK cell activity and has minimal effects on macrophage functions, including migration and polarization, thereby preserving immune function [23]. Despite the described immune changes, overall and recurrence-free survival at 1 year postoperatively was 100% in both the IA and TIVA groups.

The absence of mortality in this cohort is likely due to the low risk profile of patients with stage IA-IIA breast cancer (T1–2, N0, M0). However, the selection of this patient population inherently limits the external validity of the study and its applicability to long-term surgical outcomes.

The absence of adverse events may also be due to the limited sample size. Although post-hoc power calculations to assess overall and recurrence-free survival could not be performed due to the absence of recurrences and deaths, the low probability of these events in the study population combined with the small sample size highlights the limited power of the study to assess long-term outcomes, which is a major limitation.

Conclusion

Inhalation anesthesia was associated with synchronous changes in humoral immune components, whereas the total intravenous anesthesia resulted in divergent immune responses, suggesting potential differences in the effects of IA and TIVA on the immune system. However, no effect of anesthesia type on overall or recurrence-free survival was observed in patients with stage IA-IIA breast cancer during the one-year postoperative period. Further research is needed to elucidate the mechanisms by which different anesthetics influence immune status and to explore the relationship between anesthetic type and long-term oncologic outcomes.

References

1. *Hiller J. G., Perry N. J., Poulogiannis G., Riedel B., Sloan E. K.* Perioperative events influence cancer recurrence risk after surgery. *Nat Rev Clin Oncol*. 2018; 15 (4): 205–218. DOI: 10.1038/nrclinonc.2017.194. PMID: 29283170.
2. *Chang C.-Y., Wu M.-Y., Chien Y.-J., Su I.-M., Wang S.-C., Kao M.-C.* Anesthesia and long-term oncological outcomes: a systematic review and meta-analysis. *Anesth Analg*. 2021; 132 (3): 623–634. DOI: 10.1213/ANE.0000000000005237. PMID: 33105278.
3. *Степанов А. В., Шаповалов К. Г.* Мониторинг иммунной системы у пациентов в критическом состоянии (обзор). *Общая Реаниматология*. 2024; 20 (3): 42–52. *Stepanov A. V., Shapovalov K. G.* Monitoring the immune system in critically ill patients (review). *General Reanimatology = Obshchaya Reanimatologiya*. 2024; 20 (3): 42–52. (in Russ&Eng). DOI: 10.15360/1813-9779-2024-3-2388.
4. *Овечкин А. М., Политов М. Е., Сокологорский С. В., Евсюкова М. А.* Пропофол или ингаляционные анестетики: можно ли говорить о ренессансе тотальной внутривенной анестезии? *Анестезиология и Реаниматология*. 2021; (5): 71–79. *Ovechkin A. M., Politov M. E., Sokologorsky S. V., Evsyukova M. A.* Propofol vs inhalation anesthetics: can we talk about the renaissance of total intravenous anesthesia? *Russian Journal of Anaesthesiology and Reanimatology = Anesteziologiya i Reanimatologiya*. 2021; (5): 71–79. (in Russ.). DOI: 10.17116/ANAESTHESIOLOGY202105171.
5. *Sumi C., Matsuo Y., Kusunoki M., Shoji T., Uba T., Iwai T., Bono H., Hirota K.* Cancerous phenotypes associated with hypoxia-inducible factors are not influenced by the volatile anesthetic isoflurane in renal cell carcinoma. *PLoS One*. 2019; 14 (4): e0215072. DOI: 10.1371/journal.pone.0215072. PMID: 30986231.
6. *Efremov S. M., Kozireva V. S., Moroz G. B., Abubakirov M. N., Shkoda O. S., Shilova A. N., Yarmoshuk S. V., et al.* The immunosuppressive effects of volatile versus intravenous anesthesia combined with epidural analgesia on kidney cancer: a pilot randomized controlled trial. *Korean J Anesthesiol*. 2020; 73 (6): 525–533. DOI: 10.4097/kja.19461. PMID: 32098012.
7. *Cho J. S., Lee M.-H., Kim S. Il., Park S., Park H. S., Lee J. H., Koo B.-N.* The effects of perioperative anesthesia and analgesia on immune function in patients undergoing breast cancer resection: a prospective randomized study. *Int J Med Sci*. 2017; 14 (10): 970. PMID: 28924368.
8. *Buckley A., McQuaid S., Johnson P., Buggy D. J.* Effect of anaesthetic technique on the natural killer cell anti-tumour activity of serum from women undergoing breast cancer surgery: a pilot study. *Br J Anaesth*. 2014; 113 (suppl_1): i56–62. PMID: 25009196.
9. *Ситкин С. И.* Возможности ингаляционных анестетиков в блокировании чрезмерной воспалительной реакции: обзор литературы. *Вестник Интенсивной Терапии Имени А И Салтанова*. 2022; 2022 (3): 102–110. *Sitkin S. I.* Possibilities of inhalation anesthetics in blocking an excessive inflammatory response: a review. *Ann Crit Care = Vestnik Intensivnoy Terapii im AI Saltanova*. 2022; 2022 (3): 102–110. (in Russ). DOI: 10.21320/1818-474X-2022-3-102-110.
10. *Ackerman R. S., Luddy K. A., Icard B. E., Piñeiro Fernández J., Gatenby R. A., Muncey A. R.* The effects of anesthetics and perioperative medications on immune function: a narrative review. *Anesth Analg*. 2021; 133 (3): 676–689. DOI: 10.1213/ANE.0000000000005607. PMID: 34100781.
11. *Лихванцев В. В., Ландони Д., Субботин В. В., Каданцева К. К., Жукова Л. А., Ядгаров М. Я., Белетти А., с соавт.* Влияние выбора метода анестезии на иммунный ответ пациенток, перенесших радикальную операцию по поводу рака молочной железы (мета-анализ сравнительных клинических исследований). *Общая Реаниматология*. 2022; 18 (4): 20–28. *Likhvantsev V. V., Landoni D., Subbotin V. V., Kadantseva K. K., Zhukova L. A., Yadgarov M. Ya., Beletti A., et al.* Impact of anesthesia method on immune response in patients undergoing radical surgery for breast cancer (a meta-analysis of comparative clinical studies). *General Reanimatology = Obshchaya Reanimatologiya*. 2022; 18 (4): 20–28. (in Russ.&Eng.). DOI: 10.15360/1813-9779-2022-4-20-28.
12. *Kadantseva K., Subbotin V., Akchulpanov R., Berikashvili L., Yadgarov M., Zhukova L., Kvetenadze G., et al.* The impact of inhalation versus total intravenous anesthesia on the immune status in patients undergoing breast cancer surgery: a double-blind randomized clinical trial (TeMP). *Front Oncol*. 2024; 14. DOI: 10.3389/fonc.2024.1401910. PMID: 39132502.
13. Resources for Correlation > Spearmans Correlation Coefficient from statstutor n.d.: https://www.statstutor.ac.uk/topics/correlation/spearmans-correlation-coefficient/ (accessed July 29, 2024).
14. *Snyder G. L., Greenberg S.* Effect of anaesthetic technique and other perioperative factors on

cancer recurrence. *Br J Anaesth*. 2010; 105 (2): 106–115. PMID: 20627881.
15. *Rossaint J., Zarbock A.* Perioperative inflammation and its modulation by anesthetics. *Anesth Analg*. 2018; 126 (3): 1058–1067. DOI: 10.1213/ANE.0000000000002484. PMID: 28922235.
16. *Stollings L. M., Jia L.-J., Tang P., Dou H., Lu B., Xu Y.* Immune modulation by volatile nesthetics. *Anesthesiology*. 2016; 125 (2): 399–411. DOI: 10.1097/ALN.0000000000001195. PMID: 27286478.
17. *Kvarnström , Sarbinowski R. T., Bengtson J.-P., Jacobsson L. M., Bengtsson A. L.* Complement activation and interleukin response in major abdominal surgery. *Scand J Immunol*. 2012; 75 (5): 510–516. DOI: 10.1111/j.1365-3083.2012.02672.x. PMID: 22229650.
18. *Vivier E., Tomasello E., Baratin M., Walzer T., Ugolini S.* Functions of natural killer cells. *Nat Immunol*. 2008; 9 (5): 503–510. DOI: 10.1038/ni1582. PMID: 18425107.
19. *Griffith C. D., Kamath M. B.* Effect of halothane and nitrous oxide anaesthesia on natural killer lymphocytes from patients with benign and malignant breast disease. *Br J Anaesth*. 1986; 58 (5): 540–543. DOI: 10.1093/bja/58.5.540. PMID: 3964519.
20. *Ferlazzo G., Morandi B.* Cross-talks between natural killer cells and distinct subsets of dendritic cells. *Front Immunol*. 2014; 5: 159. DOI: 10.3389/fimmu.2014.00159. PMID: 24782864.
21. *Jafarzadeh A., Hadavi M., Hassanshahi G., Rezaeian M., Vazirinejad R.* General anesthetics on immune system cytokines: a narrative review article. *Anesthesiol Pain Med*. 2020; 10 (4): e103033. DOI: 10.5812/aapm.103033. PMID: 33134146.
22. *Chaudhry A., Rudra D., Treuting P., Samstein R. M., Liang Y., Kas A., Rudensky A. Y.* CD4+ regulatory T cells control TH17 responses in a Stat3-dependent manner. *Science*. 2009; 326 (5955): 986–991. DOI: 10.1126/science.1172702. PMID: 19797626.
23. *Perry N., Wigmore T.* Propofol (TIVA) versus volatile-based anesthetics: is there any oncological benefit? *Curr Anesthesiol Rep*. 2018; 8. DOI: 10.1007/s40140-018-0296-z.

Received 19.09.2024
Accepted 27.11.2024