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Prediction of Local Infectious and Inflammatory Complications After Reconstructive Surgery of Aorta

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Summary

Aim. To identify biomarkers for prediction and early diagnosis of infectious and inflammatory complications in patients after aortic surgery.

Materials and methods. The study included 57 patients who underwent surgical procedures on the aorta and its branches under cardiopulmonary bypass and myocardial ischemia. The cohort was divided into two groups: patients with an uneventful postoperative period (group 1, *N*=35) and patients with local infectious and inflammatory complications after surgery (group 2, *N*=22). Serum levels of procalcitonin (PCT), interleukins (IL-6 and IL-10), and aromatic microbial metabolites (AMM) were measured before surgery, upon admission, and six hours after admission to the ICU. On postoperative days 3 and 6 neutrophil, lymphocyte, and platelet counts were assessed, and neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated.

Results. There were no significant differences in sex, age, or comorbidities between groups 1 and 2. Patients in group 2 had a more severe intraoperative period and required a longer ICU stay. Predictive markers of complications included IL-6>143.35 pg/mL at ICU admission (sensitivity 42.9%, specificity 90.9%, AUC 0.789, 95% CI 0.669–0.909, $P<0.001$); PCT>0.12 ng/mL 6 hours after ICU admission (sensitivity 90.9%, specificity 54.3%, AUC 0.762, 95% CI 0.634–0.891, $P<0.001$); NLR >7.8 on postoperative day 3 (sensitivity 72.7%, specificity 68.6%, AUC 0.710, 95% CI 0.571–0.850, $P=0.003$); and △AMM (before and after surgery) >0.185 (sensitivity 77.3%, specificity 71.4%, AUC 0.780, 95% CI 0.651–0.909, $P<0.001$).

Conclusion. Values of IL-6, PCT, NLR, and AMM reflect different features of the inflammation and can be used for prediction and early diagnosis of infectious and inflammatory complications in cardiac surgery patients.

Keywords: infectious and inflammatory complications; biomarkers; interleukin-6; aromatic microbial metabolites; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio; cardiac surgery

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

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Introduction

Infections and inflammation account for 4.9% to 30.8% of all complications after cardiac surgery [1]. A large study analyzing the outcomes of more than 30.000 patients undergoing cardiac and vascular surgery reported the following incidences of infectious complications: urinary tract infection (2.8%), sepsis (2.2%), pneumonia (1.7%), surgical site infection (0.4%), and sternal wound infection (0.86%) [2]. Although these complications are relatively rare, they significantly prolong hospital stays, increase treatment costs [3], and reduce patients' quality of life. In some cases, these infections are diagnosed after discharge and may contribute to delayed adverse outcomes [4].

The inflammatory response plays a central role in the body's protective response to surgical stress. However, when this response is dysregulated — due to factors such as the patient's baseline

condition or specific characteristics of surgeries involving cardiopulmonary bypass (CPB) [5–8] — it can lead to tissue and organ damage, increasing the risk of infectious complications [9–14].

This study hypothesized that assessment of biomarker fluctuations related to immune, inflammatory, and metabolic homeostasis can differentiate between appropriate and dysregulated responses to surgical stress. This approach aims to establish a diagnostic panel for the prediction of infectious and inflammatory complications in the early postoperative period.

Materials and Methods

This prospective, minimally interventional study used data collected during the first phase of the scientific project «Microbiota Modulation» conducted at the Russian Scientific Center of Surgery named after Academician B. V. Petrovsky (Local Ethics Committee Meeting Protocol No. 7 dated April 15, 2021); registered at ClinicalTrials.com as NCT04921436 [15]. From 2021 to 2023, the study included patients (*N*=81) who underwent reconstructive aortic surgery under CPB and had myocardial ischemia (MI) without prolonged antibiotic prophylaxis.

Inclusion criteria:

— Age between 18 and 75 years;

— Reconstructive aortic surgery performed by the same surgical and anesthesia team;

— The patient's voluntary informed consent to participate in the study.

Exclusion criteria:

— Loss to follow-up due to patient transfer to another hospital (*N*=2);

— Development of postoperative complications such as bleeding in the early postoperative period requiring reoperation, severe hemodynamic instability, acute cerebrovascular events, and others (*N*=22) (Fig. 1).

Data from 57 patients were analyzed, including 43 males and 14 females (24.6%). The median age of the participants was 57 years (IQR: 46–64), with a Charlson Comorbidity Index (CCI) score of 4 (IQR: 2–5). The median duration of CPB was 124 minutes (IQR: 99.5–161), and the median duration of MI was 97 minutes interquartile range (IQR: 67.5–120.5). All patients were monitored in the intensive care unit (ICU) for at least 24 hours postoperatively.

The primary endpoint of the study was the occurrence of local infectious and inflammatory complications (e. g., pneumonia, surgical site infection) during the postoperative period, collectively referred to as «complications». According to national clinical guidelines [16], the diagnosis of pneumonia was made on the basis of the presence of new focal infiltrative changes in the lungs observed on radiological imaging, combined with at least two clinical and laboratory criteria:

— Acute fever of 38.0°C or higher;

— Cough with sputum;

— Physical signs such as focal crepitus/crackles, bronchial breath sounds, dullness on percussion;

— Leukocytosis $> 10 \times 10^9$/L and/or neutrophilic shift to the left > 10%.

The diagnosis of surgical site infection was made in collaboration with the surgeons based on inspection of the postoperative wound at dressing changes, including the results of microbiologic analysis of wound exudate.

Secondary endpoints included ICU length of stay and total hospital length of stay.

Group 1 included patients with an uncomplicated postoperative period (*N*=35), while group 2 included patients with complications (*N*=22). Of the patients in group 2, 19 (86.4%) were diagnosed with hospital-acquired pneumonia and 2 presented with purulent tracheobronchitis. Surgical site infections were observed in 3 patients (13.6%).

Blood samples for biomarker assessment were collected both pre- and post-operatively: immediately upon

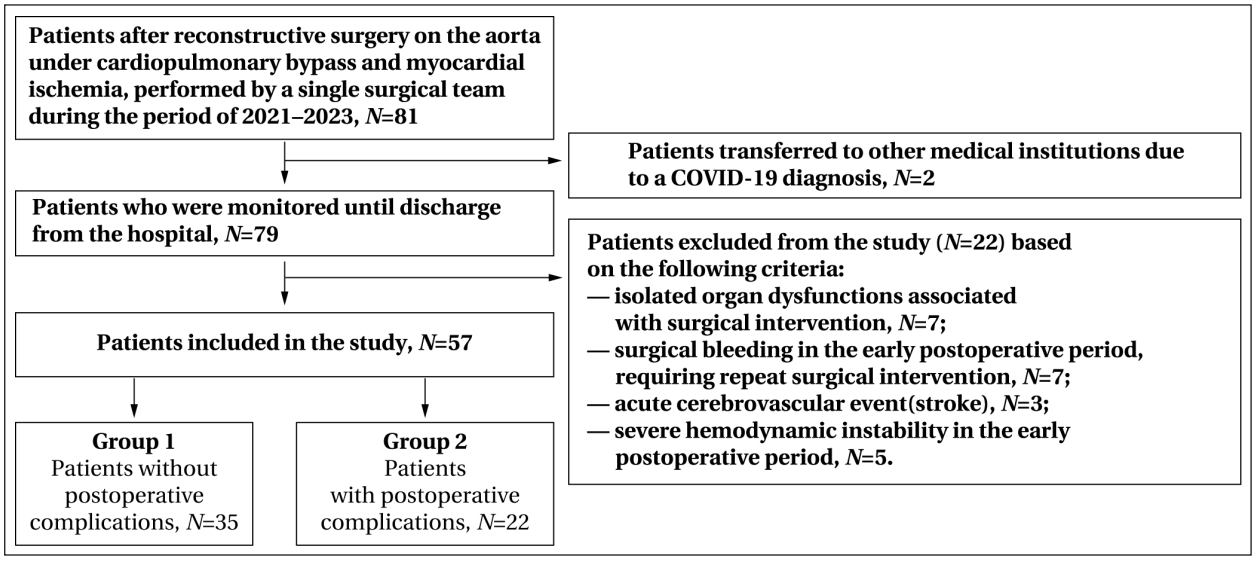

Fig. 1. Flowchart of patient inclusion in the study.

admission to the ICU and 6 hours after ICU admission. Levels of procalcitonin (PCT, cutoff < 0.05 ng/mL) were measured by immunochemistry, while tumor necrosis factor-alpha (TNF-α, cutoff < 50 pg/mL) and interleukins (IL-6 < 7 pg/mL and IL-10 < 9.1 pg/mL) were measured by enzyme-linked immunosorbent assay (ELISA).

At the same time points, serum samples were analyzed for clinically relevant aromatic microbial metabolites (AMM), including 2-hydroxy-3-phenylpropionic (phenyllactic), 3-(4-hydroxyphenyl)-2-hydroxypropionic (p-hydroxyphenyllactic), and 4-hydroxyphenylacetic (p-hydroxyphenylacetic, or p-HPAA) acids. AMM levels were determined in μM using gas chromatography-mass spectrometry after liquid-liquid extraction and derivatization. These metabolites were then summed to calculate an integral indicator: total aromatic microbial metabolites (∑AMM).

Dynamic changes in the parameters were calculated using the formula:

$$\triangle \text{Parameter} = 100\% \times \frac{\text{Value of the repeated measurement} - \text{Value of the previous measurement}}{\text{Value of the previous measurement}}$$

On postoperative days 3 and 6, a complete venous blood count was performed to assess neutrophil, lymphocyte, and platelet counts. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated from these values.

Microsoft Excel was used to construct the database and create graphical materials. Statistical data analysis was performed using IBM SPSS Statistics 26 software. The distribution pattern for each quantitative variable was determined using the Shapiro–Wilk test. All quantitative data with non-normal distribution were presented as median *(Q2)* and IQR *(Q1; Q3)*. Differences between two independent samples were assessed using the Mann–Whitney test, differences between paired samples were evaluated using the Wilcoxon test, and differences between three independent samples were analyzed using the Kruskal–Wallis test. Correlation analysis was performed by calculating Spearman's correlation coefficient (*R*). To evaluate variables as predictors, ROC analysis was performed and all results were accumulated in the Appendix (Table A2). In all cases, statistical analysis results were considered significant at $P<0.05$ (two-tailed *P*-value).

Results and Discussion

The age, sex, and comorbidity profile of the patients did not differ significantly between the groups being compared (Table 1). Although males predominated in both groups, male sex was not identified as a risk factor for developing complications (OR 1.8, 95% CI 0.49–6.66).

There were no fatal outcomes during the study. Comparison of parameters showed that group 2 patients experienced longer duration of CPB and MI, and significantly higher intraoperative and postoperative blood loss. In addition, this group required more intensive monitoring in the ICU during the early postoperative period and a longer overall hospital stay (Table 1).

The complete list of laboratory parameters studied is provided in the Appendix (Table A1). In the first step of data analysis, biomarkers and calculated parameters that could potentially serve as predictors of infectious complications were selected. Subsequently, only those parameters with statistically significant differences between groups 1 and 2 in at least one of the steps were considered (Table 2).

Correlation analysis was performed both between the studied markers and between the markers and parameters such as ICU length of stay, blood loss volume, CPB duration, MI duration, CCI, and patient age. A significant positive correlation was found between IL-6 levels on ICU admission immediately after surgery and PCT levels on postoperative day 6 ($R=0.543$, $P<0.005$). Further analysis results are shown in the Appendix (Tables A3, A4).

It was demonstrated that patients with complicated and uncomplicated postoperative course differ in the nature and intensity of the inflammatory response to surgical stress, allowing the development of a diagnostic biomarker panel. This panel could help to assess the likelihood of complications and contribute to their early diagnosis:

- A significant increase in IL-6 levels on admission to the ICU above 143.35 pg/mL (sensitivity 42.9% and specificity 90.9%) may indicate the de-

Table 1. Demographic characteristics, comorbidities, and features of the perioperative period in the study groups.

Parameter	Values in groups		*P*-value
	Group 1, *N*=35	Group 2, *N*=22	
Demographic characteristics and comorbidities			
Age, years	58 (45; 63)	53.5 (48; 65.75)	0.634
CCI, points	3 (2; 5)	4 (2; 5)	0.451
Proportion of men in the group, %	72%	82%	
Features of intra- and postoperative periods			
CPB, minutes	112 (73; 141.5)	161 (136; 206.5)	<0.001
MI, minutes	84.5 (53.75; 104.5)	122.5 (90.5; 151.75)	0.002
Intraoperative blood loss, mL	800 (600; 900)	1000 (725; 1875)	0.011
Blood loss in drains within the first 24 hours, mL	200 (140; 300)	325 (207.5; 500)	0.005
Follow-up time after surgery in ICU, days	1 (1; 1)	3.5 (2; 5)	<0.001
Follow-up time after surgery in the ward, days	7 (6; 8)	10 (7.25; 14.75)	0.001

Table 2. Levels of markers and calculated parameters in the study groups.

Parameter	Values in groups		*P* value
	Group 1, *N*=35	Group 2, *N*=22	
Before surgery			
p-HPAA, μM	0.4 (0.3; 0.6)	0.6 (0.4; 0.8)	0.078
∑AMM, μM	2.3 (1.9; 3.1)	2.4 (2.0; 3.2)	0.876
TNF-α, pg/L	6.20 (5.35; 7.05)	7.00 (5.00; 8.30)	0.349
IL-6, pg/mL	2.25 (1.50; 7.33)	7.70 (2.90; 17.20)	0.058
IL-10, pg/mL	5.00 (5.00: 5.00)	5.00 (5.00: 5.00)	0.281
IL-6/ IL-10 ratio	0.45 (0.30; 0.99)	0.90 (0.30; 2.42)	0.207
PCT, ng/mL	0.02 (0.02; 0.02)	0.02 (0.02; 0.04)	0.657
Upon admission to ICU			
p-HPAA, μM	0.3 (0.3; 0.6)	0.6 (0.4; 1.1)	0.018
∑AMM, μM	2.3 (1.9; 3.3)	3.2 (2.6; 4.5)	0.008
ΔAMM (before vs, after surgery), %	7 (–1; 21)	31 (19; 75)	<0.001
TNF-α, pg/L	6.10 (5.43; 7.98)	6.80 (5.40; 7.80)	0.527
IL-6, pg/mL	51.30 (34.10; 85.00)	125.50 (66.30; 218.30)	<0.001
IL-10, pg/mL	263.50 (135.00; 603.50)	253.00 (114.00; 773.00)	0.979
IL-6/ IL-10 ratio	0.17 (0.08; 0.56)	0.38 (0.18; 1.27)	0.031
6 hours after ICU admission			
p-HPAA, μM	0.3 (0.2; 0.4)	0.5 (0.3; 1.3)	0.001
∑AMM, μM	2.7 (2.3; 3.9)	4.1 (3.0; 5.6)	0.010
ΔAMM (before surgery vs, 6 hours after surgery), %	10 (–5; 32)	12 (–5; 23)	0.889
ΔAMM (before surgery vs, 6 hours after surgery), %	24 (3; 46)	49 (31; 116)	0.007
TNF-α, pg/L	5.20 (4.43; 6.93)	7.40 (5.20; 8.20)	0.030
IL-6, pg/mL	78.85 (51.60; 102.95)	86.20 (53.60; 135.60)	0.716
IL-10, pg/mL	15.70 (5.18; 46.48)	66.60 (6.70; 138.00)	0.068
IL-6/ IL-10 ratio	4.51 (1.71; 13.67)	0.96 (0.65; 15.18)	0.042
PCT, ng/mL	0.11 (0.06; 0.25)	0.42 (0.18; 0.87)	0.001
3rd day post-op			
Neutrophil count, 10^3 cells/μL	8.60 (6.50; 11.65)	8.85 (7.10; 10.00)	0.544
Lymphocyte count, 10^3 cells/μL	1.40 (1.05; 1.85)	1.00 (0.83; 1.18)	0.004
NLR	6.14 (4.05; 8.66)	9.52 (7.36; 12.14)	0.008
6th day post-op			
Neutrophil count, 10^3 cells/μL	6.50 (5.00; 8.35)	8.65 (6.43; 9.98)	0.017
Lymphocyte count, 10^3 cells/μL	1.80 (1.25; 2.05)	1.20 (1.00; 1.65)	0.028
NLR	3.78 (2.89; 4.96)	6.09 (4.50; 8.28)	0.002

velopment of a dysregulated hyperinflammatory response to surgical stress.

- PCT levels > 0.12 ng/mL six hours after ICU admission, with relatively high sensitivity (90.9%) but low specificity (54.3%), may identify patients at increased risk of complications.
- The blood level of an aromatic microbial metabolite p-HPAA > 1.1 μM on ICU admission and six hours later shows the highest specificity (94.3% and 94.1%, respectively) but low sensitivity (27.3% and 36.4%, respectively) for predicting the development of infectious inflammation.
- ∑AMM (sum of aromatic microbial metabolites), both as an absolute value on ICU admission and its changes pre- and postoperatively, as well as changes from preoperative levels to six hours after ICU admission, shows the highest sensitivity (81.8%, 77.3%, and 72.7%, respectively) and specificity (60%, 71.4%, and 71.4%, respectively) for predicting the development of infectious inflammation.
- An NLR > 7.8 on the third day after ICU admission has a predictive value for the development of infectious complications with a sensitivity of 72.7% and a specificity of 68.6%. By day 6 after ICU admission, NLR > 5.4 shows lower sensitivity (68.2%) but higher specificity (80%), suggesting that NLR at day 6 is a better marker of ongoing inflammation.

Patients in group 2 had longer CPB duration, greater blood loss and a marked pro-inflammatory response immediately after surgery. This response subsequently shifted to an immunosuppressive trajectory of the systemic inflammatory response, predisposing them to complications.

In contrast, patients in group 1 showed a less pronounced increase in IL-6 levels after surgery, although a slight upward trend was observed six hours postoperatively. The ratio of IL-6 to IL-10 was higher in group 1 than in group 2, reflecting preserved protective inflammatory mechanisms. By day 6, NLR levels returned to values typical of a relatively healthy population in group 1, whereas they remained elevated in patients with complications (Fig. 3).

Classic clinical signs of infection and biomarker levels are not always sufficiently informative; for example, fever in cardiac surgery patients may have both infectious and non-infectious origins.

In a prospective study conducted in an intensive care unit, changes in C-reactive protein (CRP) levels were not shown to be a reliable marker of infection, in contrast to elevated body temperature and leuko-

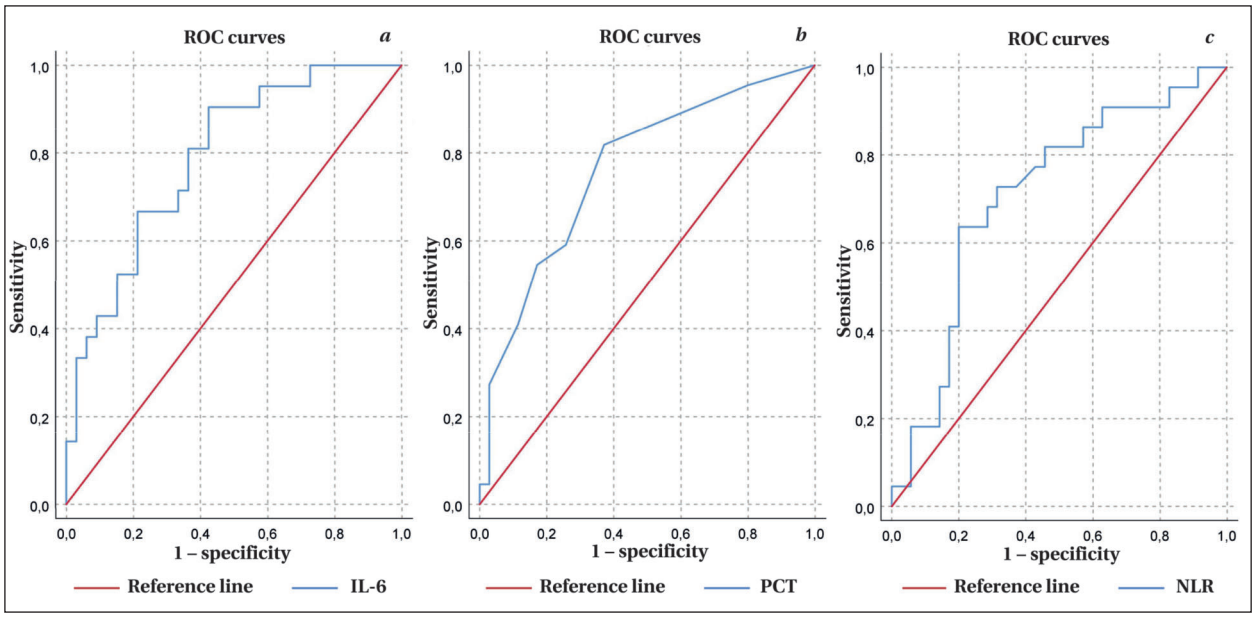

Fig. 2. Results of ROC analysis.
Note. *a* — IL-6 upon ICU admission; *b* — PCT 6 hours after ICU admission; *c* — NLR on the 3rd day after surgery.

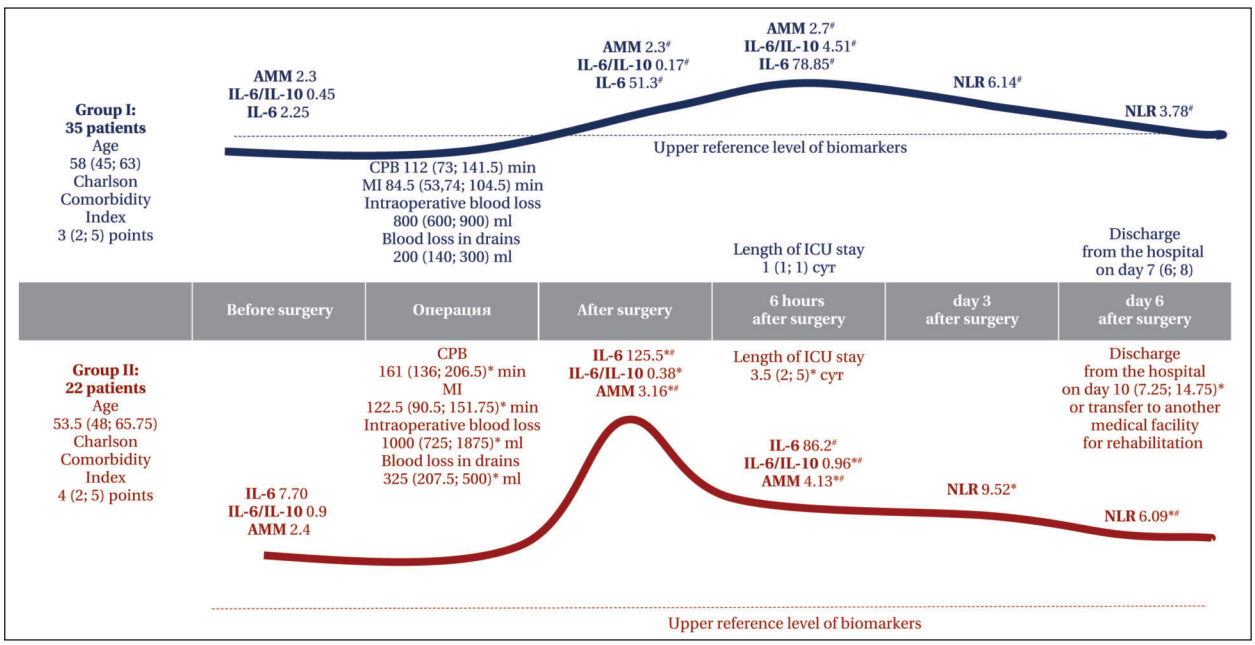

Fig. 3. Original flow chart of the perioperative course in patients without complications (group 1) and with complications (group 2).
Note. * — $P<0.005$ compared to previous measurements; # — $P<0.005$ compared to the other group.

cyte count [21]. In patients undergoing open-heart surgery, significant differences in body temperature, leukocyte count, and CRP levels were observed during the first three days, but these did not reflect the development of infection. Only after the sixth day did a renewed increase in these parameters indicate the presence of infection [22].

There were no differences in leukocyte counts between the groups studied. More informative markers included PCT, IL-6, aromatic microbial metabolites, and hematologic indices (HI).

According to other research groups, PCT thresholds vary widely depending on the presence of comorbidities, the timing of marker assessment, and other factors [23]. For example, P. Sharma and colleagues reported that on the first postoperative day, a PCT concentration > 7 ng/mL indicates a high risk of infectious complications [24].

In our study, PCT levels in the very early postoperative period (6 hours after ICU admission) showed high sensitivity (90.9%) with relatively low specificity (54.3%), making it a convenient marker for initial assessment. A PCT concentration < 0.12 ng/mL in the early postoperative period suggests an adaptive response to surgical stress and a low likelihood of complications. However, when evaluating PCT concentrations, it is important to adjust diagnostic thresholds in the presence of renal dysfunction [25].

In cases of uncertainty, additional biomarkers with high specificity can be used, such as tumor necrosis factor-alpha (TNF-α) and IL-6/IL-10 measured 6 hours after surgery. Among these, IL-6 at ICU admission showed the most optimal combination of sensitivity and specificity (> 143.35 pg/mL; 42.9% and 90.9%, respectively). The high specificity of IL-6 for early infectious complications has been confirmed in other studies [26, 27]. Elevated IL-6 levels after CPB have also been associated with hyperdynamic cardiovascular instability and metabolic disturbances [28].

Notably, the changes of IL-6 as a pro-inflammatory marker may be more clinically relevant than the absolute level above a certain threshold. IL-6 levels at ICU admission correlated with almost all biomarkers studied (PCT levels, AMM levels and their perioperative variations, NLR), as well as with CPB and MI duration, total blood loss, and ICU length of stay.

One of the circulating metabolites of the microbiota is p-hydroxyphenylacetic acid (p-HPAA). During sepsis, microbial metabolism of aromatic amino acids occurs not only in the gastrointestinal tract but also in inflammation sites. This leads to an excessive release of metabolic intermediates into the bloodstream, increasing the levels of sepsis-associated circulating metabolites, including p-HPAA [29].

In our study, p-HPAA concentrations exceeded 1.1 μM immediately after ICU admission and 6 hours later. This marker showed the highest specificity (94.3% and 94.1%, respectively) but relatively low sensitivity (27.3% and 36.4%, respectively). According to the findings of N. Beloborodova et al., healthy volunteers typically have p-HPAA concentrations below 0.5 μM, whereas patients with sepsis have significantly higher levels, averaging 2.1 μM (1.7–7.0 μM) [29].

Thus, a p-HPAA level > 1.1 μM after surgery indicates a high risk of developing inflammatory complications, even if it does not reach levels characteristic of septic patients.

In a previous study, the risk of all types of postoperative complications in cardiac surgery patients was evaluated, including the total concentration of aromatic microbial metabolites (∑AMM) six hours after surgery. The prognostic value of ∑AMM was found to be moderate, with an area under the curve (AUC) of 0.717, a threshold of 2.9 μM, a sensitivity of 81%, and a specificity of 56% [30].

In the present study, the same threshold of 2.9 μM demonstrated a lower prognostic significance (AUC of 0.705, sensitivity of 77.3% and specificity of 51.1%). However, after ICU admission, this parameter showed a higher prognostic significance with a sensitivity of 81.8% and a specificity of 60%, which is crucial for timely diagnostic and therapeutic decisions. In addition, the dynamic changes in total aromatic microbial metabolite levels before and after surgery, as well as from preoperative levels to six hours after ICU admission, showed some of the highest sensitivities (77.3% and 72.7%, respectively) and specificities (71.4% and 71.4%, respectively) among all biomarkers analyzed.

Hematological indices, calculated from routine complete blood counts available in any hospital, provide a practical tool for monitoring throughout the postoperative period, especially in the absence of more advanced laboratory diagnostics. On the one hand, HI reflect the body's response to CPB (since CPB significantly alters neutrophil and lymphocyte counts and their characteristics) [31]. On the other hand, they have already been established as predictors of adverse outcomes after various cardiac surgical procedures [32–34].

According to Y. Zhu et al., a postoperative NLR > 7.5 in patients undergoing CPB surgery is associated with higher 30-day mortality rates [35]. In our study, an NLR > 7.8 on postoperative day 3 demonstrated predictive value for the development of infectious complications with a sensitivity of 72.7% and a specificity of 68.6%. At postoperative day 6, an NLR > 5.4 showed decreased sensitivity (68.2%) but increased specificity (80%), suggesting that at postoperative day 6, NLR is more appropriately considered a marker of an active infection rather than a predictor of potential infection.

Study limitations. Limitations of this study include the lack of a priori sample size calculation, the small number of observations, and the high degree of heterogeneity in the population of cardiac surgery patients undergoing aortic reconstruction. Patient recruitment is ongoing to address these limitations.

Conclusion

Dysregulated systemic inflammatory responses immediately after aortic reconstructive surgery are detected by elevated PCT levels > 0.12 ng/mL, IL-6 levels > 143.35 pg/mL, and the presence of AMM, especially p-HPAA > 1.1 μM. NLR values > 7.8 and > 5.4 on the third and sixth postoperative day, respectively, serve as markers of a developing infection and inflammation.

Appendix

Table A1. Comprehensive list of measured biomarkers.

Name	Units of measurement
Basophils, absolute count	10^3 cells/μL
BA — Benzoic acid	μM
HVA — Homovanillic acid	μM
Leukocytes, absolute count	10^9 cells/L
Lymphocytes, absolute count	10^3 cells/μL
Monocytes, absolute count	10^3 cells/μL
Immature granulocytes, absolute count	10^9 cells/L
Neutrophils, absolute count	10^3 cells/μL
p-HBA — p-hydroxybenzoic acid	μM
p-HPLA — p-hydroxyphenyllactic acid	μM
p-HPPA — p-hydroxyphenylpropionic acid	μM
p-HPAA — p-hydroxyphenylacetic acid	μM
NLR — Neutrophil-to-lymphocyte ratio	
Platelets	10^9 cells/L
PLA — Phenyllactic acid	μM
TNF-α — Tumor necrosis factor-alpha	pg/L
PPA — Phenylpropionic acid	μM
Eosinophils, absolute count	10^3 cells/μL
TSH — Thyroid-stimulating hormone (high-sensitivity)	μIU/mL
IL-10	pg/mL
IL-1β	pg/mL
IL-6	pg/mL
IL-8	pg/mL
NLR — Neutrophil-to-lymphocyte ratio	
NSE — Neuron-specific enolase	ng/mL
NT-proBNP — N-terminal pro-brain natriuretic peptide	pg/mL
PCT — Procalcitonin	ng/mL

Table A2. Results of ROC analysis.

Parameter	Threshold Level	Sensitivity	Specificity	AUC	95% CI	*P* value
p-HPAA						
— Upon admission to ICU	>1.1	27.3	94.3	0.685	0.538–0.832	0.013
— 6 hours after admission to ICU	>1.1	36.4	94.1	0.765	0.634–0.896	<0.001
∑AMM						
— Upon admission to ICU	>2.5	81.8	60	0.710	0.576–0.845	0.002
— 6 hours after admission to ICU	>2.3	77.3	51.1	0.705	0.562–0.847	0.005
△AMM						
— Pre- and post-operation	>0.185	77.3	71.4	0.780	0.651–0.909	<0.001
— Pre-op and 6 hours post-admission	>0.354	72.7	71.4	0.713	0.565–0.861	0.005
PCT						
— 6 hours after admission to ICU	>0.1185	90.9	54.3	0.762	0.634–0.891	<0.001
IL-6						
— Upon admission to ICU	>143.35	42.9	90.9	0.789	0.669–0.909	<0.001
IL-6/IL-10						
— Upon admission to ICU	>3.865	14.3	94.1	0.671	0.531–0.818	0.017
— 6 hours after admission to ICU	—	—	—	0.665	0.494–0.835	0.058
TNF-α						
— 6 hours post-operation	>9.6	9.5	91.2	0.676	0.534–0.818	0.015
Neutrophils						
— 6th day post-operation	>5.45	95.5	37.1	0.688	0.548–0.828	0.008
Lymphocytes						
— 3rd day post-operation	<1.25	81.8	65.7	0.727	0.589–0.865	0.001
— 6th day post-operation	<1.05	36.4	85.7	0.673	0.525–0.822	0.022
NLR						
— 3rd day post-operation	>7.8350	72.7	68.6	0.710	0.571–0.850	0.003
— 6th day post-operation	>5.424	68.2	80	0.742	0.609–0.874	<0.001

Table A3. Results of correlation analysis.

Parameter 1	Parameter 2	*R*	*P* value
PCT before surgery, ng/mL	p-HPAA 6 hours after ICU admission, μM	0.360	0.006
IL-6 upon ICU admission, ng/mL	p-HPAA upon ICU admission, μM	0.404	0.002
IL-6 upon ICU admission, ng/mL	p-HPAA 6 hours after ICU admission, μM	0.423	0.002
TNF-α 6 hours after ICU admission, pg/L	p-HPAA 6 hours after ICU admission, μM	0.421	0.002
IL-6/IL-10 upon ICU admission	p-HPAA upon ICU admission, μM	0.345	0.010
IL-6/IL-10 upon ICU admission	p-HPAA 6 hours after ICU admission, μM	0.356	0.008
PCT 6 hours after ICU admission, ng/mL	∑AMM upon ICU admission, μM	0.312	0.018
PCT 6 hours after ICU admission, ng/mL	∑AMM 6 hours after ICU admission, μM	0.411	0.001
IL-6 upon ICU admission, ng/mL	∑AMM upon ICU admission, μM	0.422	0.001
IL-6 upon ICU admission, ng/mL	∑AMM 6 hours after ICU admission, μM	0.317	0.020
PCT 6 hours after ICU admission, ng/mL	△AMM (pre-surgery vs, post-surgery)	0.480	<0.001
PCT 6 hours after ICU admission, ng/mL	△AMM (pre-surgery vs, 6 hours post-surgery)	0.461	<0.001
IL-6 upon ICU admission, ng/mL	△AMM (pre-surgery vs, post-surgery)	0.364	0.007
IL-6 upon ICU admission, ng/mL	PCT 6 hours after ICU admission, ng/mL	0.543	<0.001
IL-6 upon ICU admission, ng/mL	TNF-α 6 hours after ICU admission, pg/L	0.381	0.004
IL-6/IL-10 upon ICU admission	TNF-α 6 hours after ICU admission, pg/L	0.307	0.023
△AMM (pre-surgery vs, post-surgery)	Neutrophils (absolute count), 6th day post-surgery, 10^3 cells/μL	0.280	0.035
PCT 6 hours after ICU admission, ng/mL	Neutrophils (absolute count), 6th day post-surgery, 10^3 cells/μL	0.387	0.003
p-HPAA 6 hours after ICU admission, μM	Lymphocytes (absolute count), 3rd day post-surgery, 10^3 cells/μL	–0.285	0.034
△AMM (pre-surgery vs, 6 hours post-surgery)	Lymphocytes (absolute count), 6th day post-surgery, 10^3 cells/μL	–0.362	0.006
PCT 6 hours after ICU admission, ng/mL	Lymphocytes (absolute count), 3rd day post-surgery, 10^3 cells/μL	–0.296	0.025
IL-6 upon ICU admission, ng/mL	Lymphocytes (absolute count), 6th day post-surgery, 10^3 cells/μL	–0.330	0.015
p-HPAA 6 hours after ICU admission, μM	NLR, 3rd day post-surgery	0.272	0.042
△AMM (pre-surgery vs, post-surgery)	NLR, 3rd day post-surgery	0.299	0.001
△AMM (pre-surgery vs, 6 hours post-surgery)	NLR, 3rd day post-surgery	0.424	0.001
IL-6 upon ICU admission, ng/mL	NLR, 6th day post-surgery	0.358	0.008
PCT 6 hours after ICU admission, ng/mL	NLR, 6th day post-surgery	0.368	0.005

Table A4. Results of correlation analysis of biomarkers with perioperative characteristics.

Parameter	Days in ICU	Days in the ward	Days total	Age	CCI	CPB	MI	Intra-operative blood loss	Drains	Total blood loss
Preoperative p-HPAA					0.261*					
p-HPAA upon ICU admission					0.295*					
∑AMM upon ICU admission	0.346#				0.291*	0.290*			0.291*	
∑AMM 6 hrs after ICU admission	0.398#				0.288*		0.312*	0.311*	0.362#	0.335*
△AMM (pre- and post-op)	0.550#		0.327*			0.371#	0.284*			
△AMM (pre-op and 6 hrs post-op)	0.410#		0.268*				0.292*			
PCT 6 hrs after ICU admission	0.525#		0.369#			0.385#	0.415#	0.441#	0.314*	0.478#
IL-6 upon ICU admission	0.472#		0.402#			0.376#	0.455#		0.279*	0.312*
IL-6/IL-10 upon ICU admission			0.300*				0.287*			
TNF-α 6 hrs after ICU admission			0.276*	0.348#	0.361#				0.308*	
Neutrophils 6 days post-op	0.384#		0.315*					0.261*		
Lymphocytes 3 days post-op	–0.443#		–0.342#		–0.265*	–0.356#	–0.346*			
Lymphocytes 6 days post-op	–0.291*	–0.264*	–0.370#			–0.306*	–0.360*	–0.322*	–0.274*	–0.375#
NLR 3 days post-op	0.314*			0.377#	0.317*					
NLR 6 days post-op	0.438#	0.291*	0.462#			0.352#	0.436#	0.395#	0.324*	0.426#

Note. * — $P<0.05$; # — $P<0.001$.

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