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Immunological Predictors Of Complicated Postopera-Tive Course In Diffuse Peritonitis

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ABSTRACT

Objectives. To identify immunological predictors of complicated postoperative course in patients with diffuse peritonitis (DP) and to assess their prognostic value in the early postoperative period.
Methods. A total of 58 patients undergoing emergency surgery for DP were in-cluded. Based on postoperative outcomes, patients were stratified into two groups: complicated course (n=38) and uncomplicated course (n=20). On postoperative day 1, immune monitoring included cellular immunity ($CD3^+$, $CD4^+$, $CD8^+$, NK cells), humoral immunity (IgA, IgM, IgG, circulating immune complexes [CIC], and the IgA×IgM/IgG index), and cytokine profile (IL-6, IL-10, TNF-α, IFN-γ). Multivariable logistic regression with Firth's correction and ROC analysis were ap-plied to identify independent predictors of adverse outcomes.
Results. Complicated course was observed in 65.5% of patients; mortality reached 24.1% and occurred exclusively in this group. Patients with complications demon-strated significant reductions in $CD4^+$ T-helper cells (25.3±4.5% vs. 34.1±4.7% without complications; $p<0.05$), NK cells (8.9±2.1% vs. 13.2±2.3%; $p<0.05$), se-rum IgM (0.83±0.17 g/L vs. 1.05±0.21 g/L; $p<0.05$), and the IgA×IgM/IgG index (0.11±0.02 vs. 0.16±0.02; $p<0.05$). These changes were accompanied by elevated IL-6 (79.4±19.7 pg/mL vs. 35.8±11.2 pg/mL; $p<0.01$), IL-10 and TNF-α levels. Multivariable analysis identified IL-6 >60 pg/mL (OR 4.72; 95% CI 1.61–13.84; $p=0.005$), $CD4^+$ <30% (OR 3.42; 95% CI 1.28–9.16; $p=0.015$), NK cells <10% (OR 2.87; 95% CI 1.05–7.83; $p=0.041$), IgM <0.9 g/L (OR 2.64; 95% CI 1.01–6.94; $p=0.048$), and IgA×IgM/IgG index <0.12 (OR 3.95; 95% CI 1.36–11.44; $p=0.011$) as independent predictors. The ROC curve yielded an AUC of 0.87 (95% CI 0.78–0.96), with sensitivity of 82% and specificity of 80%.
Conclusions. The combination of hypercytokinemia and immunosuppression rep-resents a major determinant of complicated postoperative outcomes in DP. Early immune monitoring (IL-6, IL-10, $CD4^+$ T-cells, NK cells, IgM, and the IgA×IgM/IgG index) provides reliable risk stratification and may guide preventive strategies. Consideration of environmental and occupational factors influencing immune competence further enhances the prognostic value and highlights the in-terdisciplinary relevance of immune assessment in abdominal sepsis.

KEYWORDS: diffuse peritonitis; immunological predictors; IL-6; $CD4^+$ T-lymphocytes; NK cells; complicated postoperative course.

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INTRODUCTION

Diffuse peritonitis (DP) remains one of the most severe conditions in emergency abdominal surgery, associated with a high rate of postoperative complications and mortality, which according to recent studies reaches 20-30% even in specialized centers [1,

2]. Despite advances in surgical techniques, antimicrobial therapy, and intensive care, patient outcomes are largely determined not only by timely source control but also by the status of systemic defense mechanisms. In most patients, a complicated postoperative course develops within the first 7-14 days after surgery and is accompanied by both peritoneal and systemic complications, including sepsis, multiple organ dysfunction syndrome (MODS), and thromboembolic events [3]. This highlights the need for reliable biomarkers capable of predicting adverse outcomes at the earliest stages of the postoperative period.

Particular attention in recent years has been focused on immunological predictors, since the imbalance between innate and adaptive immunity is considered a key factor in the development of complications [4, 5]. A pronounced decrease in $CD4^+$ T-helper cells and NK cells, coupled with elevated IL-6 and TNF-α levels, as well as dysfunction of humoral immunity, have been proposed as early indicators of systemic inflammatory response and sepsis [6, 7]. The concept of "immune paralysis," characterized by the paradoxical coexistence of hypercytokinemia and immunosuppression, is now actively discussed in the context of surgical infection and multiple organ failure [8].

In addition to purely clinical determinants, external and environmental factors play a significant role in the pathogenesis of complicated outcomes. It is well established that adverse environmental conditions, chronic exposure to toxicants, and occupational stressors can lead to persistent dysregulation of immune responses and reduced adaptive capacity [9, 10]. In urban populations with high levels of air pollution and increasing prevalence of chronic inflammatory diseases, the risk of severe courses of surgical infection is further amplified [11]. Thus, the investigation of immunological mechanisms in DP acquires interdisciplinary significance, linking clinical surgery with environmental and occupational health.

Based on these considerations, the aim of the present study was to identify immunological predictors of complicated postoperative course in diffuse peritonitis and to evaluate their prognostic significance during the early postoperative period.

MATERIALS AND METHODS

Study design. A single-center cohort study was conducted to identify immunological predictors of complicated postoperative course in diffuse peritonitis (DP) during the early postoperative period. Patient enrollment was performed prospectively at the surgical department between 2022 and 2024.

Patients. A total of 58 patients with DP who underwent emergency laparotomy were included. Based on postoperative outcomes, patients were stratified into two groups: complicated course (n=38; 65.5%); uncomplicated course (n=20; 34.5%).

Inclusion criteria: clinically and intraoperatively confirmed diagnosis of DP; age ≥18 years; emergency surgical intervention.

Exclusion criteria: terminal condition at admission, hematological malignancies, secondary immunodeficiency, or refusal to participate.

Clinical assessment. Demographic data, etiology of peritonitis, type of peritoneal exudate, and stage of inflammation were recorded. Postoperative complications were classified as: peritoneal (intra-abdominal abscesses, anastomotic leakage, early postoperative peritonitis); systemic (SIRS, multiple organ dysfunction syndrome, sepsis, pneumonia); combined.

Immunological assessment. Venous blood samples were collected on postoperative day 1. Cellular immunity: total lymphocyte count, $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ ratio, NK cells ($CD16^+/CD56^+$). Humoral immunity: serum IgA, IgM, IgG, circulating immune complexes (CIC). Cytokine profile: IL-6, IL-10, TNF-α, IFN-γ. Measurements were performed using flow cytometry (BD FACSCalibur™) and enzyme-linked immunosorbent assay (ELISA, HUMAN kits) in accordance with international protocols.

Outcomes. The primary outcome was the development of a complicated postoperative course within 14 days after surgery. Secondary outcomes included the structure of complications and mortality.

Statistical analysis. Data were analyzed using SPSS Statistics (IBM, USA) and R (version 4.3). Continuous variables were expressed as mean ± standard deviation (M±SD). Student's t-test and Mann-Whitney U test were used for group comparisons, while categorical variables were analyzed with the χ^2 test.

Independent predictors of complicated course were identified using multivariable logistic regression. Considering the limited sample size, the model was restricted to 3-4 predefined immunological variables ($CD4^+$ T-cells, NK cells, IgM/IgA×IgM/IgG index, IL-6 or IL-10). To reduce overfitting, Firth-penalized regression was applied, and robustness was assessed by bootstrap validation with 1000 resamples.

Model performance was evaluated by the area under the ROC curve (AUC), sensitivity and specificity, and calibration using the Hosmer-Lemeshow test.

Ethical approval. The study was approved by the Local Ethics Committee (Protocol № 25/3, dated December 23, 2021). Written informed consent was obtained from all patients or their legal representatives.

RESULTS

Clinical and surgical characteristics

Among the 58 enrolled patients, a complicated postoperative course of diffuse peritonitis was documented in 38 cases (65.5%). The remaining 20 patients (34.5%) experienced a relatively favorable course without complications requiring re-intervention or intensive care.

The most frequent complications were intra-abdominal abscesses (39.5%), early postoperative peritonitis (31.6%), and anastomotic leakage (18.4%). Among systemic disorders, the leading conditions were prolonged systemic inflammatory response syndrome (SIRS) (42.1%), hospital-acquired pneumonia (36.8%), multiple organ dysfunction syndrome (31.6%), and sepsis (26.3%). The cumulative mortality rate reached 24.1% (14 out of 58 patients), all occurring in the group with complicated postoperative course.

Immunological parameters

By postoperative day 1, patients with complicated outcomes demonstrated pronounced disturbances in both cellular and humoral immunity (Table 1).

Table 1.
Cellular immune parameters in patients with diffuse peritonitis

PARAMETER	Reference (n=20)	Uncomplicated (n=20)	Complicated (n=38)
Lymphocytes, %	28.2±3.6	21.3±4.1*	16.5±3.8*#
$CD3^+$, %	68.4±4.3	61.2±5.4*	48.6±6.1*#
$CD4^+$, %	40.1±4.9	34.1±4.7*	25.3±4.5*#
$CD4^+/CD8^+$ ratio	1.65±0.21	1.51±0.19	1.19±0.17*#
NK-cells ($CD16^+/CD56^+$), %	14.8±2.5	13.2±2.3	8.9±2.1*#

Notes: * p<0.05 vs. reference; # p<0.05 vs. patients without complications.

In patients with a complicated postoperative course, the most pronounced reductions were observed in $CD4^+$ T-helper cells (1.6-fold decrease compared to normal) and NK cells (1.5-fold decrease), accompanied by a reduction in the $CD4^+/CD8^+$ ratio, indicating a marked imbalance between adaptive and innate immunity (Table 2).

Table 2.
Humoral immune parameters in patients with diffuse peritonitis

PARAMETER	Reference (n=20)	Uncomplicated (n=20)	Complicated (n=38)
IgA, g/L	1.9±0.4	1.61±0.35	1.18±0.29*#
IgM, g/L	1.2±0.3	1.05±0.21	0.83±0.17*#
IgG, g/L	11.5±1.9	10.4±1.7	9.2±1.8*#
CIC, units	41±12	54±17*	79±23*#
IgA×IgM/IgG index	0.20±0.03	0.16±0.02*	0.11±0.02*#

Notes: * p<0.05 vs. reference; # p<0.05 vs. patients without complications.

In patients with a complicated postoperative course, there was a significant decrease in IgA and IgM levels, as well as in the integrated immunoglobulin index, accompanied by an increase in circulating immune complexes, reflecting functional insufficiency of antibody-mediated defense (Table 3).

Table 3.
Cytokine levels in patients with diffuse peritonitis

PARAMETER	Reference (n=20)	Uncomplicated (n=20)	Complicated (n=38)
L-6, pg/mL	8.5±3.1	35.8±11.2*	79.4±19.7*#
IL-10, pg/mL	4.1±1.2	8.6±3.3*	18.2±5.6*#
TNF-α, pg/mL	7.2±2.0	17.9±4.5*	32.6±7.1*#
IFN-γ, pg/mL	5.6±1.6	9.8±3.1*	14.7±4.2*#

Notes: * p<0.05 vs. reference; # p<0.05 vs. patients without complications.

The most pronounced differences were observed in IL-6 levels, which in patients with complicated outcomes exceeded the normal values by more than ninefold. Simultaneous elevation of IL-10 indicated the development of compensatory immunosuppression, typical for the later phases of systemic inflammatory response.

Multivariable analysis and prognostic significance

To identify independent risk factors for complicated postoperative course of diffuse peritonitis during the early postoperative period, a multivariable logistic regression analysis was performed. Variables included in the model were those with the highest significance in univariate analysis and supported by biological plausibility: $CD4^+$ T-helper cells, NK cells ($CD16^+/CD56^+$), serum IgM, IgA×IgM/IgG index, and IL-6 level. Considering the limited number of events, Firth-penalized regression was applied to reduce the risk of overfitting (Table 4).

Table 4.
Independent predictors of complicated postoperative course in diffuse peritonitis (logistic regression)

Variable	OR (95% CI)	p-value
$CD4^+ < 30\%$	3.42 (1.28-9.16)	0.015
NK cells < 10%	2.87 (1.05-7.83)	0.041
IgM < 0.9 g/L	2.64 (1.01-6.94)	0.048
IgA×IgM/IgG index < 0.12	3.95 (1.36-11.44)	0.011
IL-6 > 60 pg/mL	4.72 (1.61-13.84)	0.005

Multivariable analysis confirmed five independent immunological predictors of complicated postoperative course. Elevated IL-6 emerged as the strongest factor (OR 4.72), followed by low $CD4^+$ T-helper cells, reduced NK cells, low IgM levels, and a decreased IgA×IgM/IgG index.

The predictive performance of the model was high, with an AUC of 0.87 (95% CI 0.78-0.96), sensitivity of 82%, and specificity of 80%. Calibration by the Hosmer–Lemeshow test showed good agreement between predicted and observed probabilities (p=0.47).

Thus, the combined assessment of cellular, humoral, and cytokine components of immunity allowed us to identify a set of independent immunological predictors of complicated postoperative course in diffuse peritonitis.

DISCUSSION

In our cohort, the complicated postoperative course of diffuse peritonitis was consistently associated with a triad of hypercytokinemia, reduced $CD4^+$ T-helper cells, and a pronounced decline in humoral immunity. IL-6 emerged as the strongest predictor, while the IgA×IgM/IgG index and the proportion of NK cells also demonstrated stable prognostic value. Taken together, this constellation of factors appeared to drive patients toward a multi-wave trajectory of complications during the first 7-14 postoperative days. Numerically, our data confirmed this: elevated IL-6 and IL-10, decreased $CD4^+$ and NK cells, and reduced IgM and immunoglobulin index were consistently observed in patients with adverse outcomes.

These findings align with the contemporary view of intra-abdominal infections. Current guidelines continue to emphasize early recognition, adequate source control, timely antibiotic therapy, and rapid hemodynamic stabilization. However, it is increasingly recognized that outcomes are determined not only by surgical techniques but also by the host's capacity to regulate systemic inflammation. Our data support this perspective: when immune regulation fails, the cascade of complications accelerates [12].

Essentially, this reflects the phenomenon of "immune paralysis," a paradoxical coexistence of hypercytokinemia and functional immunosuppression. Recent literature has explored this phenomenon in detail, from effector cell dysfunction to T-cell exhaustion and innate immune dysregulation. The profile observed in our study-low $CD4^+$ and NK cells-fits well into this framework. In such patients, complications become systemic and self-reinforcing [13].

IL-6 deserves particular emphasis. Elevated baseline levels and, more importantly, their sharp rise within the first 24 hours have long been associated with unfavorable trajectories in critically ill patients. Recent studies underline the prognostic relevance of early IL-6 dynamics during the first 48–72 hours. Our findings are consistent with this: a threshold above 60 pg/mL served as a «red flag» beyond which the likelihood of a complicated postoperative course markedly increased [14].

The decline in $CD4^+$ T-helper and NK cells among high-risk patients provides a straightforward explanation for why local complications so readily evolve into systemic ones. Inadequate adaptive coordination and impaired cytotoxic clearance coincide with a background of uncontrolled cytokine activity. Humoral dysfunction adds another dimension: decreased IgM and a low IgA×IgM/IgG index practically abolish early antibody-mediated defense, facilitating secondary bacterial burden. This pattern has been described as a hallmark of post-septic immunosuppression, involving multiple arms of immune regulation [13].

Environmental and occupational exposures may also play a role beyond the surgical domain. Long-term exposure to air pollution and chemical agents has been associated with immune dysregulation at the molecular level and increased risk of immune-mediated diseases. Patients living or working under such conditions may have reduced «reserve capacity» to withstand critical inflammatory events. While this does not mean that peritonitis is caused by environmental factors, it may explain why two clinically similar patients follow different complication trajectories. In the context of occupational and environmental medicine, this interdisciplinary connection appears justified [15].

For practicing surgeons, the implications are twofold. First, immune screening within the first postoperative day should be considered an essential component of risk stratification: IL-6, IL-10, $CD4^+$, NK cells, and the IgA×IgM/IgG index are feasible for routine measurement. Second, this approach must be combined with strict adherence to the basic principles of intra-abdominal infection management -source control, antimicrobial therapy, and hemodynamic support. In essence, surgical management is complemented by personalized host assessment, aiming to reduce systemic complications in the vulnerable window of 1-4 postoperative days [12].

This study has limitations. It was single-center with a limited sample size, raising the risk of overfitting when multiple predictors are analyzed. We mitigated this with penalized regression and bootstrap validation, but external validation remains indispensable.

The next step should involve an expanded cohort and independent multicenter validation, moving beyond associations toward readiness for clinical implementation.

Finally, one broader observation deserves attention: the «biography» of the patient outside the hospital. Place of residence, air quality, and occupational exposures are silent modifiers of immune response. They are difficult to measure yet easy to overlook but may subtly influence the probability of severe outcomes even after technically successful surgery [15].

In summary, our findings confirm that the immunological profile assessed within the first postoperative day is not merely descriptive. It represents a predictive tool. Integrating this information with established principles of intra-abdominal infection management, while accounting for environmental and occupational factors, can enhance patient stratification and improve outcomes.

CONCLUSION

The immunological profile assessed on the first postoperative day in patients with diffuse peritonitis is clearly associated with the risk of a complicated course. The most informative predictors were elevated IL-6 and decreased parameters of adaptive and innate immunity ($CD4^+$ T-cells and NK cells) supplemented by reductions in IgM and the IgA×IgM/IgG index. The combination of these markers provided high discrimination of adverse outcomes and reflected the pathogenic link of «hypercytokinemia + immunosuppression», associated with systemic complications during postoperative days 1-14.

From a practical standpoint, early immune monitoring (IL-6/IL-10, $CD4^+$, NK cells, immunoglobulin profile) may serve as a basis for risk stratification and personalized management from intensified source control and antimicrobial therapy to proactive prevention of secondary infections and multiple organ dysfunction. Considering the potential impact of adverse environmental and occupational exposures on immune resilience, integration of this context into risk assessment appears justified.

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KEY MESSAGES

What is already known on this topic.

Diffuse peritonitis remains one of the most severe forms of surgical infection, with mortality rates up to 30%.

Adverse outcomes are often related not only to technical aspects of surgery but also to systemic inflammatory response and immunosuppression.

The role of immunological predictors of complicated postoperative course remains insufficiently studied.

What this study adds
Key immunological markers of complicated outcomes were identified: elevated IL-6, decreased $CD4^+$ and NK cells, reduced IgM and IgA×IgM/IgG index.

The combination of these parameters predicted complications with high accuracy (AUC 0.87).

The concept of "immune paralysis" is substantiated as a central mechanism in the development of systemic complications after surgical treatment of peritonitis.

How this study might affect research, practice or policy
Immune monitoring on the first postoperative day may be used as a tool for risk stratification and early prevention of complications.

Incorporating immunological parameters into clinical protocols for DP may improve prognostic accuracy and reduce the incidence of systemic complications.

Considering environmental and occupational factors influencing immune responses could promote a more personalized approach in surgical infection management.

Ethics approval. The study was approved by the Local Ethics Committee of the Tashkent State Medical University (Protocol № 25/3, dated December 23, 2021). Written informed consent was obtained from all participants or their legal representatives.

Patient consent for publication. Not required.

Data availability statement. Data supporting the findings of this study are available from the corresponding author on reasonable request. Due to ethical and privacy restrictions, individual patient data cannot be shared publicly.

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