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**Research Article**

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# The Dynamics of Platelet Content in Patients with Diffuse Peritonitis as a Predictor of Disease Outcome

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**BACKGROUND** Absolute numbers of platelets are of key importance for determining the severity of multiple organ failure in sepsis, while their fluctuations within normal values are not taken into account. At the same time, early detection of a downward trend in this parameter may have greater predictive value in predicting disease outcomes.

**AIM OF STUDY** To identify trends in changes in platelet levels in patients with widespread peritonitis and determine the possible relationship of these changes with the outcome of the disease.

**MATERIAL AND METHODS** The basis of the work was an analysis of the results of treatment of 220 patients with diffuse secondary peritonitis who were treated at the Elizavetinskaya Hospital in 2013–2019. A correlation analysis was conducted to identify relationships between disease outcomes, assessed according to the severity of postoperative complications, and the degree of platelet reduction, expressed in platelet ratio. The further ROC analysis allowed us to identify a threshold value of the platelet ratio, which excess indicated a high risk of an unfavorable outcome.

**RESULTS** Based on the data obtained, the threshold value of the platelet ratio in the first two days has no clinical significance. At the same time, starting from the third 3rd day of the postoperative period, the quality of the resulting classifier increased, which confirms the prognostic significance of the threshold value of the platelet ratio, which was 1.72 on the third 3rd day after surgery. In other words, a decrease in platelet levels more than 1.72-fold on the 3rd day indicates a high risk of an unfavorable outcome, which may be associated primarily with intra-abdominal complications. This provision also indirectly confirms the fact that among patients with platelet ratio (PR) values exceeding 1.72 on the 3rd day, 68.7% ultimately underwent repeated surgical interventions (33 patients out of 48 with high PR values, and the overall mortality rate was 72.1%.Similar indicators in the subgroup with low PR values were 27.6% of reoperated patients (29 of 105) and 26.7% of unfavorable outcomes.

**CONCLUSION** The results obtained indicate that the degree of platelet reduction, rather than their absolute levels, has greater predictive value in patients operated on for diffuse peritonitis.

**Keywords:** platelet level, platelet ratio, sepsis, peritonitis

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CI – confidence interval
PR – platelet ratio

## RELEVANCE

According to the conclusions of the third international consensus on the definition of sepsis and septic shock, platelet count should be performed routinely as part of the assessment of the level of multiple organ failure in accordance with the SOFA scale [1]. The mechanisms of development of thrombocytopenia in sepsis are diverse, among which peripheral consumption of blood platelets due to their activation in the microvasculature and immune cytolysis prevail [2, 3].

In this case, a decrease in platelet level to $150\times10^9$/l is considered prognostically significant, and a value of $50\times10^9$/l is regarded as severe thrombocytopenia, associated with a high risk of adverse outcome in septic patients [4, 5]. However, the decrease in platelet levels is often progredient, so the rejection of systemic inflammatory response syndrome criteria in favor of the SOFA indicator may hinder the early recognition of patients who require intensive treatment before the development of organ failure, ultimately resulting in underdiagnosis of sepsis [6].

In addition, a number of pathological conditions are accompanied by absolute thrombocytosis, which also devalues this parameter when determining the degree of organ failure. It is likely that early assessment of the dynamics of platelet levels, rather than absolute values, carried out before the development of significant thrombocytopenia, may have greater predictive value in predicting disease outcomes.

**Aim of study:** to identify trends in changes in platelet levels in patients with widespread peritonitis and determine the possible relation of these changes with the outcome of the disease.

## MATERIAL AND METHODS

The basis of the work was an analysis of the results of treatment of 220 patients with widespread secondary peritonitis who were treated at the St. Petersburg State Budgetary Institution "Yelizavetinskaya Hospital" in 2013–2019. Patients who died on the first day of hospital admission, incurable patients with total necrotic lesions of the small intestine due to occlusion of mesenteric blood flow, as well as pancreatogenic peritonitis were excluded from the study. In addition, the study did not include several patients with initial thrombocytopenic syndrome due to chemotherapy. In the case of clinically significant thrombocytopenia, the genesis of which could not be explained by the use of drugs or other anamnestic information, these patients were also included in the study, and platelets were counted using the Fonio method.

Among the studied patients there were 116 men (52.7%), the average age was 64.9±18.1 years. Taking into account the predominance of patients in the middle and elderly age groups, in most cases the general somatic background was burdened by various diseases of the cardiovascular, respiratory and nervous systems. A significant contribution to the overall comorbidity was also made by cancer, diagnosed in 37.7% of cases (83 patients), among which malignant neoplasms of the digestive system predominated. The structure of nosological units that led to the development of a generalized infectious process in the abdominal cavity is shown in Fig. 1.

All patients were operated on as soon as possible from the moment of admission, the duration of preparation in all cases did not exceed 6 hours. The volume and nature of the primary surgical interventions performed were selected in each case individually and were determined by a number of factors, in particular the severity of the patient's condition, the degree of anesthetic risk and intraoperative findings. In all cases, a median laparotomy was performed as the main surgical approach. The scope of surgical interventions performed in all cases consisted of eliminating the source of peritonitis with further mechanical sanitation and drainage of the abdominal cavity with tubular drainages. Information about the operations performed is summarized in Fig. 2.

Fig. 1. Sources of secondary peritonitis

The definitions of the third international consensus conference were used as criteria for sepsis, according to which a dysregulated response to infection was determined by a score of 2 or more on the SOFA scale. In the study group of patients, 88 patients (40%) had SOFA values that did not exceed score 2, which is why these patients were not interpreted as septic. In the remaining 132 patients, SOFA values upon admission to intensive care units ranged from 2 to 9, averaging 3.48 ± 1.55 points, which, along with the identified source of infection, served to establish a diagnosis of sepsis in 60% of patients.

Further treatment measures for operated patients consisted of standard therapy, carried out in intensive care units, and dynamic observation, which included, among other things, daily monitoring of laboratory parameters. The platelet level at the time of admission to the hospital and the first 5 days of the postoperative period were analyzed. Later time periods were not considered, since in this case the very meaning of determining the prognostic value of the studied parameter is lost. The outcomes were mortality and the presence of postoperative complications, the severity of which was assessed according to the Clavien–Dindo classification [7], which made it possible to include this indicator in the correlation analysis as an ordinal parameter.

The study results were processed using statistical methods, including the calculation of arithmetic means, standard deviations and 95% confidence intervals (CI) for parametric criteria, the normality of distribution of which was determined according to the Kolmogorov–Smirnov test. Statistical processing of treatment results consisted of the following procedures:

— correlation analysis of the relationship between the absolute level of platelets on days 0–5 of the postoperative period and the outcome of the disease;

— correlation analysis of the relationship between the ratio of platelet levels on days 1–5 to the value at the time of admission and the outcome of the disease;


Fig. 2. Characteristics of the surgical interventions performed

— ROC analysis aimed at identifying the cut-of value of the ratio of platelet levels, which has the best combination of sensitivity and specificity in terms of predicting an unfavorable outcome of the disease.

All statistical procedures were performed using SPSS ver. 26.0.

## RESULTS AND DISCUSSION

The Table 1 summarizes information on the main treatment outcomes, stratified according to the presence and severity of complications, as well as the average platelet level measured upon admission and on days 1–5 of the postoperative period. In addition, the last row provides significance tests for the difference in means in each subgroup, calculated by performing one-way analysis of variance.

The data obtained indicate that statistically significant differences in the average platelet level within the compared subgroups with complications of varying severity are observed from the second day of the postoperative period and over time the level of significance shows a downward trend, i.e. the statistical significance of the differences increases over time. In other words, the worse the prognosis of the disease, the more pronounced the thrombocytopenic disorders. However, the maximum detected difference in platelet content within the compared subgroups was only 46 (95% CI 22–70) ×10 9/l, and focusing on such changes in clinical practice is quite problematic due to the small absolute values.

Table 1

**Average platelet level in patients with complications of varying severity up to the 5th day of the postoperative period**

| Severity of complications* | Average platelet level ± σ , ×10⁹/l | | | | | |
|---|---|---|---|---|---|---|
| | Upon admission | Days of postoperative period | | | | |
| | | 1 | 2 | 3 | 4 | 5 |
| No | 285±150 | 312±144 | 286±140 | 303±150 | 365±160 | 358±160 |
| I | 339±177 | 238±93 | 240±87 | 295±176 | 299±157 | 313±147 |
| II | 314±148 | 240±167 | 256±167 | 210±71 | 193±98 | 255±89 |
| III a | 267±83 | 248±78 | 305±174 | 281±261 | 237±176 | 294±100 |
| III b | 363±162 | 286±133 | 260±97 | 265±90 | 291±91 | 275±109 |
| IV a | 478±201 | 242±117 | 152** | 176** | 107** | 70** |
| IV b | 409±130 | 273±105 | 278±116 | 259±103 | 247±107 | 258±117 |
| V | 335±178 | 256±125 | 212±97 | 185±102 | 185±131 | 164±111 |
| p | 0.09 | 0.372 | **0.048** | **0.008** | **0.002** | **<0.001** |

Notes: * — according to Clavien-Dindo classification; ** — not enough data to calculate standard deviations

Subsequently, the correlation between the level of blood platelets and the course of the disease was analyzed in accordance with the presence and severity of postoperative complications. The information obtained generally confirms the previously made conclusions that over time the correlation tends to strengthen. Thus, if the correlation coefficient (Pearson in this case) at the time of admission and on the 1st day of the postoperative period was 0.11 and 0.06, respectively, then by the 5th day this indicator gradually increased to 0.37, which corresponds to the presence of a moderate positive relationship between the studied parameters. In addition, in order to test the working hypothesis, the correlation between the course of the disease and the platelet ratio (PR), by which we mean the value obtained by dividing the platelet level at each time point of the study by a similar parameter at the time of admission, was analyzed in a similar way. A graphical representation of the results obtained is shown in Fig. 3.

The information obtained suggests that during the first 5 days of the postoperative period, the correlation between PR and the course of the disease tends to increase, reaching a maximum value of 0.48, corresponding to a relationship of moderate severity. In addition, in any of the time periods studied, the prognostic significance of PR turned out to be higher compared to the absolute level of platelets due to larger values of the correlation coefficient. Based on this, the threshold value of PR is interesting, indicating an increased risk of unfavorable outcome in patients with widespread peritonitis. To calculate the latter, the dependent variable was transformed into a dichotomous scale in which postoperative mortality was considered as an unfavorable outcome, and all other options for the course of the disease, including non-fatal complications, as a neutral option. After this, an ROC analysis was carried out aimed at determining the cut-off value of PR, which combined the best values of sensitivity and specificity (according to Youden's statistics) in terms of predicting the occurrence of an unfavorable outcome. The visual result is shown in Fig. 4, and the numerical interpretation of the obtained graphs is in Table 2.

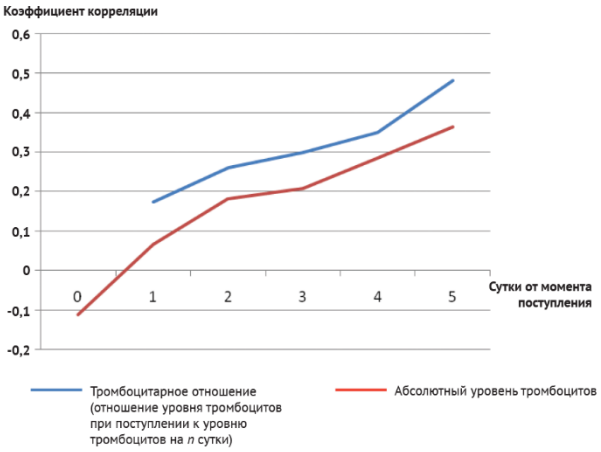


Fig. 3. The dynamics of the correlation between platelet levels and platelet ratio, and the outcome of the disease

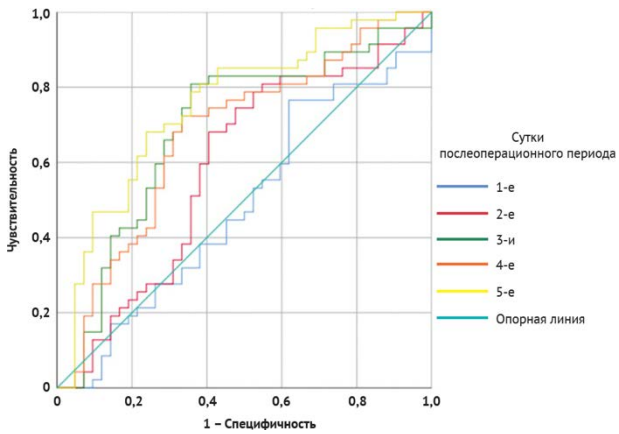


Fig. 4. ROC curves for assessing the relationship between treatment outcomes for diffuse peritonitis and platelet ratio on days 1–5 of the postoperative period

Based on the data obtained, the threshold value of PR in the first two days has no clinical significance due to the fact that 95% CI of the areas under the curves include values 0.5 and below, i.e. predicting the outcome of the disease in the early stages based on PR is not appropriate. At the same time, starting from the 3rd day of the postoperative period, the quality of the resulting classifier increases: AUC increases from 0.69 (95% CI 0.58–0.81) on the 3rd day to 0.76 (95% CI 0.65–0.86) on the 5th day of the postoperative period. This fact confirms the prognostic significance of the threshold value of PR, which was 1.72 on the 3rd day after surgery. In other words, a decrease in platelet levels more 1.72-fold on day 3 indicates a high risk of an unfavorable outcome, which may be associated primarily with intra-abdominal complications requiring repeated surgical interventions.

This provision also indirectly confirms the fact that among patients with PR values exceeding 1.72 on the 3rd day, 68.7% (33 patients out of 48 with high PR values) ultimately underwent repeated surgical interventions, and the overall level mortality rate was 72.1%. Similar indicators in the subgroup with low PR values were 27.6% of reoperated patients (29 out of 105) and 26.7% of unfavorable outcomes. Threshold values for the 4th and 5th days of the postoperative period are 1.64 and 1.39, respectively, while maintaining similar sensitivity and specificity values, which indicates a greater prognostic significance of PR at later follow-up periods. However, the predictive value of any factor is lost over time, and, as a consequence, with the natural progression of the outcome of the disease, so assessing the level of PR is most appropriate precisely on the 3rd day of the postoperative period.

## CONCLUSION

The results obtained indicate that the degree of platelet reduction, rather than their absolute levels, has greater predictive value in patients operated on for diffuse peritonitis. The threshold values of the platelet ratio, indicating a high risk of an unfavorable outcome, are 1.72, 1.64 and 1.39 for the 3rd, 4th and 5th days of the postoperative period, respectively. However, focusing solely on this parameter, predicting the outcome of the disease in the early stages of observation (days 1–2) is not possible due to the weakness of the resulting classifier, so the search for additional prognostic criteria seems to be a promising direction.

Table 2

**Threshold values of the platelet ratio at various times of the postoperative period, indicating their sensitivity, specificity, as well as the AUC-corresponding ROC curve**

| Days after surgery | Cut-off PR value | AUC (95% CI) | Sensitivity | Specificity |
|---|---|---|---|---|
| 1 | 1.47 | 0.49 (0.36–0.61) | 0.77 | 0.23 |
| 2 | 1.45 | 0.59 (0.47–0.71) | 0.68 | 0.32 |
| 3 | 1.72 | 0.69 (0.58–0.81) | 0.81 | 0.19 |
| 4 | 1.64 | 0.68 (0.56–0.79) | 0.72 | 0.28 |
| 5 | 1.39 | 0.76 (0.65–0.86) | 0.68 | 0.32 |

Notes: CI – confidence interval; PR – platelet ratio; AUC – area under curve

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