Can the leukocyte's parameters in peripheral blood smear predict risk of in-hospital death of patients undergoing high-risk gastrointestinal surgery?

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

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ABSTRACT:

Introduction: White blood cell (WBC) count constitutes a part of routine peripheral blood examination (FBC; full blood count). Precise analysis of leukocytes' parameters in blood smear is usually performed only when leukopenia or leukocytosis is found. We aimed to assess the usefulness of leukocytes' smear test in predicting in-hospital death of patients undergoing high-risk gastrointestinal (GI) surgery.

Materials and methods: We prospectively enrolled 101 subjects undergoing high-risk GI surgery from 01.01.2017 till 31.12.2017. Blood tests were performed preoperatively, with analysis focused on the assessment of total WBC count, as well as the count of neutrophils (NEUT), lymphocytes (LYM), monocytes (MONO), eosinophils (EOS) and basophils (BASO). Indices of NEUT/LYM (NLR) and MONO/LYM (MLR) were calculated. In-hospital mortality was considered the outcome.

Results: Mortality reached 5%. There was no significant difference in WBC count between survivors and the deceased ($p = 0.2$) and WBC failed to predict the outcome (AUC = 0.69; $p = 0.3$). MONO ($p = 0.009$) and BASO ($p = 0.02$) counts, as well as MLR ($p = 0.007$) were significantly higher in patients who died. MONO count and MLR index predicted in-hospital death with good accuracy, respectively: AUC(MONO) = 0,85 (p <0,001) i AUC(MLR) = 0.86 (p <0.001). Other investigated parameters played no significant role in outcome prediction.

Conclusion: Routine peripheral blood smear evaluation should be considered in all patients undergoing high-risk GI surgery, because the number of monocytes can be a valuable predictor of in-hospital death.

KEYWORDS: peripheral blood morphology, perioperative medicine, risk, monocytes

INTRODUCTION

Every year, there are over 300 million surgical procedures performed in the world [1], after which the recovery of 3-17% of patients is prolonged or even impossible due to serious complications [2]. Their occurrence significantly worsens the quality of life, increases the risk of death, generates high costs and is often an indication for admitting patients to the intensive care unit (ICU) [3].

The risk of complications should be estimated pre-operatively based on the knowledge about the patient's functional conditional and individual patient burdens, the degree of control over co-morbidities or deviations in laboratory tests. Such analysis should meet the screening criteria.

It is therefore justified to seek cheap and easily accessible methods available at every reference stage, the assessment of which will allow to identify patients requiring special attention and to attempt to optimize their clinical condition. This is particularly important in patients undergoing high-risk procedures, such as GI surgeries.

Routine FBC, or full blood count usually focuses on the analysis of parametrical deviations of the erythrocyte system. On the other hand, in-depth analysis of platelet or white blood cell parameters is rarely performed, especially in the context of death risk modeling. Hence, the aim of the study was to assess the usefulness of leukocyte parameters in predicting in-hospital death of patients undergoing GI surgery with high risk of complications.

METHODS AND CLINICAL MATERIAL

Studied population

A single center study was conducted from January 1, 2017 till December 31, 2017. One hundred and one patients hospitalized and operated in the gastrointestinal surgery department of the university hospital were prospectively observed. Patients with high risk (> 5%) of cardiovascular complications due to the type of procedure (i.e., death within 30 days of surgery, taking into account only the specifics of surgery, regardless of individual patient risk) were qualified for the study. Risk was assessed on the basis of the current ESC/ESA guidelines (European Society of Cardiology/European Society of Anesthesiology) [4]. The analysis included the following high-risk procedures: duodenal and pancreatic surgeries (n = 76), liver resections and bile duct surgeries (n = 17), surgeries due to gastrointestinal perforation (n = 5), and resection of the esophagus (n = 3). Patients' individual risk was assessed using the functional status scale of the American Society of Anesthesiologists (ASA-PS, American Society of Anesthesiologists Physical Status) [5]. Patients with ASA-PS III or more were qualified to the high-risk individual group and/or underwent an "E", or emergency surgery [6]. The analysis also includes: age, sex, Body Mass Index (BMI) and the mode of surgery (planned, accelerated, urgent, immediate).

The in-hospital death was assumed as the main endpoint. Furthermore, the necessity of admitting ICU patients, duration of ICU stays and total time of hospitalization (regardless of ICU stay) were analyzed.

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Morphological blood test

Blood collected pre-operatively, in accordance with the procedures in force at the center, was transferred to the laboratory, where it was analyzed using the XT-1800i device (Sysmex, Japan). For the purpose of the study, the following parameters of the white blood cell system were analyzed: total white blood cell count (WBC) and the number of neutrophils (NEUT), basophils (BASO), eosinophilia (EOS), lymphocytes (LYM) and monocytes (MONO). In addition, the following values of indicators were calculated: NEUT/LYM (NLR) and MONO/LYM (MLR).

Statistical analysis

Statistical analysis was performed using MedCalc v.18 software (MedCalc Software, Ostend, Belgium). The Shapiro-Wilk test was used to verify the character of the distribution of quantitative variables. Quantitative variables with normal distribution are presented in the form of arithmetic mean and standard deviation. In the case of non-normal distribution, the results were shown in the form of a median and interquartile range (IQR, interquartile range). Qualitative variables are presented in the form of absolute values and percentage.

Evaluation of differences between quantitative variables was carried out using the analysis of variance or the Kruskal-Wallis test. Chi-square test was used for qualitative variables. Furthermore, the appropriate odds ratios with their 95% confidence intervals were estimated for dichotomous variables. Correlations were evaluated based on the value of the Spearman rank coefficient. Diagnostic accuracy was assessed by means of ROC curves and area under curve (AUC). Observations from simple analyzes were verified in the logistic regression model, in which the dependent variable was the hospital death, while the independent variables were constituted by the values of the white blood cell system parameters. The criterion of statistical significance p<0.05 was adopted.

Bioethical committee approval

Due to the observational character of the study, the consent of the bioethical commission for its implementation was not required [7].

RESULTS

Characteristics of the studied group

A hundred and one patients were included in the analysis, including 48 men. The median age of respondents was 64 (IQR 55-70) years. Detailed characteristics of the examined group are shown in Table I. Results of the morphological examination in the scope of the white blood cell system in the examined group are shown in Table II. Medians and/or averages of all analyzed parameters fell in the range of reference values.

Leukocytic parameters and the individual risk of patients

High-risk patients (ASA-PS≥III and/or "E") had higher MONO values and NLR and MLR indices than patients with low individual risk (Table III). Differences in the values of other leucocytes were statistically insignificant (p> 0.05). In a more detailed analysis, statistically significant differences between WBC, NEUT, MONO MLR and NLR values were found in individual ASA-PS classes – patients with higher scores presented higher values of these parameters (Table IV).

Tab. I. Clinical and demographic data.

VARIABLE	VALUE	
Male (n, %)	48	48%
Age [years]	64 (55–70)	
BMI [kg/m²]	24.8 (22.7–29.3)	
Hospital admission mode: (n, %)		
planned / accelerated	87	86%
urgent / immediate	14	14%
ASA-PS class: (n, %)		
I	2	2%
II	35	35%
III	56	55%
IV	7	7%
V	1	1%
E	8	8%
Individual risk: (n, %)		
large	64	
small	37	
Total hospitalization time [days]	12 (9–18)	
Patients admitted to ICU after surgery (n, %)	18	18%
Time of hospitalization in ICU [days]	4 (2–8)	
Death: (n, %)		
total	5	5%
including ICU	1	1%

Quantitative variables were presented using median and interquartile range (IQR), qualitative variables using absolute value and percentage

Tab. II. Peripheral blood morphology – white blood cell system

PARAMETER	VALUE	LABORATORY NORM
WBC [10³/µL]	**7.14** (5.95–8.72)	4–10
BASO [10³/µL]	**0.02** (0.01–0.04)	0.02–0.1
% basophils	**0.3** (0.2–0.5)	0–1
EOS [103/µL]	**0.11** (0.06-0.21)	0.04–0.4
% eosinophils	**1.5** (0.78–2.43)	1–5
NEUT [10³/µL]	**4.6** (3.53–6.15)	2.5–5
% neutrophils with segment nuclei.	**64.9** ± 11.4	45–70
LYM [10³/µL]	**1.82** ± 0.64	1.5–3.5
% lymphocytes	**24.8** ± 9.9	20–45
MONO [10³/µL]	**0.55** (0.39–0.79)	0.2–0.8
% monocytes	**7.8** ± 3.1	3–9

The values of quantitative variables are presented in the form of a median and interquartile range (IQR) or mean and standard deviation (± SD).

Leukocytic parameters and time of hospitalization

None of the leukocytic parameters analyzed correlated with the total time of hospitalization and the time of patient's stay in ICU (Table V).

Leukocytic parameters and hospitalization in ICU

Patients requiring hospitalization in ICU had higher values of the NLR index. Differences in other parameters did not reach statistical significance (Table VI)

Leukocytic parameters vs. risk of death

Patients who died had statistically significantly higher MONO, BASO, and MLR values. There was no such difference for WBC (table VII).

WBC had no predictive mortality (AUC = 0.68, 95% CI 0.58-0.77, p = 0.31). MONO and MLR predicted in-hospital death with high accuracy, respectively: AUC(MONO)=0.85; 95%CI 0.76-0.91; p<0.001, at the cut-off point >0.95 (sensitivity 80%, specificity 92%) and AUC(MLR)=0.86; 95%CI 0.88-0.92; p<0.001, at the cut-off point >0.37 (sensitivity 100%, specificity 65%) (Figure 1). These observations were verified in a multi-variable model: considering the interfering effects of WBC and other smear parameters, the risk of death was almost 18-fold higher in people with monocytosis: logOR = 17.95; 95% CI 2.64-121.85; p = 0.003, at AUC=0.849; 95% CI 0.76-0.91; p = 0.09.

Tab. III. Differences in the values of other leucocytes were statistically insignificant (p> 0.05).

PARAMETER	INDIVIDUAL RISK		OR (95% CI)	'P'
	LARGE	SMALL		
WBC [10³/µL]	7.48 (5.98–9.38)	6.9 (5.78–8.02)	1.13 (0.98–1.29)	NS
BASO [10³/µL]	0.02 (0.01–0.04)	0.02 (0.01–0.04)	11.28 (0–5603723.8)	NS
EOS [10³/µL]	0.11 (0.07–0.19)	0.12 (0.06–0.22)	0.39 (0.01–12.4)	NS
NEUT [10³/µL]	4.81 (3.61–6.54)	4.37 (3.15–5.45)	1.15 (0.98–1.36)	NS
LYM [10³/µL]	1.72 (1.19–2.29)	1.79 (1.48–2.2)	0.63 (0.32–1.21)	NS
MONO [10³/µL]	0.66 (0.46–0.83)	0.50 (0.37–0.62)	9.07 (1.67–49.37)	0.01
MLR	0.36 (0.23–0.64)	0.24 (0.15–0.40)	21.58 (2.46–189.18)	0.004
NLR	2.84 (1.97–5.08)	2.17 (1.61–2.87)	1.29 (1.01–1.66)	0.008

The values of quantitative variables are presented in the form of a median and interquartile range (IQR). Odds ratios are presented including 95% confidence intervals. MONO - monocytes; MLR - monocytes/lymphocytes ratio; NLR - neutrophil/lymphocyte index; NS - statistically insignificant (p> 0.05).

DISCUSSION

Our work aimed to assess the usefulness of determining the parameters of the white blood cell system in the prediction of death, in patients undergoing high-risk GI surgeries. Although the mortality rate was only 5%, we have clearly demonstrated that the number of monocytes may constitute a valuable prognostic indicator, which should encourage routine FBC analysis in this specific group of patients. The scope of examinations necessary to be performed in patients prepared for anesthesia and surgery is still the topic of discussion [8]. In the light of the current guidelines of scientific societies, physicians are expected to consider the choice of additional tests and reduce the costs of hospitalization [9]. It is known that only 1 in 10,000 patients benefit from the FBC test in the form of a change in pre-operative strategy [10].

The standard FBC study is based on the evaluation of the white blood cell system by calculating the total white blood cell count (WBC). Making a smear requires a separate order, increases costs and is usually carried out only in case of discovering irregularities in the field of WBC (i.e., leukopenia, leukocytosis). In the presented study, the WBC value did not provide significant predictive information, while the selected smear parameters, determined in all patients, regardless of WBC, allowed very good accuracy to predict in-hospital death. Our study ended with a successful verification of the accepted hypothesis that patients undergoing GI surgery belong to a group that could benefit from routine pre-operative FBC testing with leukocyte smear. This is in line with current recommendations, as is visible - not always respected [4,8,11].

The study showed a correlation between selected white blood cell parameters and the ASA-PS class – patients with more aggravating medical history presented higher values of selected parameters, although they did not always exceed the accepted norms. The risk of death is not the same in patients with results close to the extreme reference values, but grows with the increase of these values, therefore the dichotomous, zero-one interpretation of laboratory tests (normal result/abnormal result) may result in omission of important information. Our observations in this respect coincide with the results of other authors [12].

The conducted study revealed an interesting relationship between monocytosis and an increased risk of death, but it did not explain its causes, which is a significant limitation of the study. Referring to the current knowledge on the role of monocytes in maintaining homeostasis of the body, in our opinion, the cause of death should be seen in the impaired functioning of the immune system, severe and uncontrolled inflammation, and the resulting excessive activation of the coagulation system [13, 14]. This hypothesis seems to be partially confirmed by the studies carried out so far, in which the association of an increased number of monocytes, including with the occurrence of venous thromboembolism, increased cardiovascular risk and higher overall mortality [14-16].

Waterhouse et al. [16] showed that the number of monocytes constitutes a useful predictor of cardiovascular disease development in previously asymptomatic patients, which in the light of the planned high-risk surgery may be a valuable clue for the anesthetic team regarding the biological reserves of the body. Routine, serial determination of markers of myocardial injury in patients after high-risk procedures now seems difficult to achieve for financial reasons. Nevertheless, in view of the obtained results, the monitoring of myocardial injury (MINS, myocardial injury after noncardiac surgery) in the group of patients with elevated monocytes should be considered [17].

Perhaps this will explain this causal link. Other causes of the increased number of monocytes include bacterial and viral infections, connective tissue diseases, inflammatory bowel diseases, hematological proliferative diseases, as well as the use of glucocorticoids [18].

Tab. IV. Values of leukocytic parameters in individual ASA-PS classes.

PARAMETER	VALUE IN INDIVIDUAL ASA CLASSES (IQR)					`P`
	I	II	III	IV	V	
WBC [$10^3/\mu L$]	6.2 (5.3–7.14)	6.9 (5.92–8.07)	7.0 (5.8–8.96)	10.7 (8.6–21.85)	37.0 (37–37)	0.006
BASO [$10^3/\mu L$]	0.01 (0.01–0.01)	0.02 (0.01–0.04)	0.02 (0.01–0.04)	0.03 (0.02–0.06)	0.3 (0.3–0.3)	NS
EOS [$10^3/\mu L$]	0.04 (0.02–0.05)	0.13 (0.07–0.23)	0.11 (0.07–0.21)	0.09 (0.07–0.12)	0.02 (0.02–0.02)	NS
NEUT [$10^3/\mu L$]	3.82 (3.28 –4.37)	4.42 (3.04–5.47)	4.63 (3.51–6.22)	8.74 (6.08–19.53)	33.32 (33.32–33.32)	**0.007**
LYM [$10^3/\mu L$]	1.99 (1.79–2.20)	1.78 (1.47–2.19)	1.79 (1.31–2.33)	1.2 (1.11–1.3)	1.39 (1.39–1.39)	NS
MONO [$10^3/\mu L$]	0.37 (0.19–0.54)	0.5 (0.37–0.63)	0.58 (0.44–0.81)	1.04 (0.71–1.31)	1.94 (1.94–1.94)	**0.009**
MLR	0.18 (0.11–0.25)	0.24 (0.15–0.42)	0.35 (0.21–0.56)	0.79 (0.41–1.1)	1.4 (1.4–1.4)	**0.002**
NLR	1.91 (1.83–1.99)	2.19 (1.58–2.94)	2.48 (1.94–4.14)	7.05 (4.83–21.63)	23.97 (23.97–23.97)	**0.004**

The values of quantitative variables are presented in the form of a median and interquartile range (IQR). WBC - total number of leukocytes, NEUT - neutrophils, MONO - monocytes; MLR - monocytes/lymphocytes ratio; NLR - neutrophil/lymphocyte index; NS - statistically insignificant (p> 0.05).

Tab. V. Correlation between leukocytic parameters and time of hospitalization (including ICU).

	WBC	NEUT	BASO	EOS	LYM	MONO	NLR	MLR
Hospitalization time	R = -0.08 NS	R = -0.04 NS	R = -0.12 NS	R = 0.08 NS	R = -0.16 NS	R = 0.04 NS	R = 0.06 NS	R = 0.1 NS
Time of stay in ICU	R = 0.1 NS	R = 0.19 NS	R = 0.39 NS	R = -0.15 NS	R = -0.38 NS	R = 0.17 NS	R = 0.31 NS	R = 0.29 NS

R – Spearman's rank correlation coefficient, NS – not statistically significant (p>0.05).

Tab. VI. Leukocytic parameters and risk of hospitalization in ICU.

PARAMETER	HOSPITALIZATION IN ICU		OR (95% CI)	'P'
	YES	NO		
WBC [$10^3/\mu L$]	7.83 (6.4–10.7)	7.06 (5.9–8.6)	1.07 (0.99–1.16)	NS
BASO [$10^3/\mu L$]	0.02 (0.01–0.03)	0.02 (0.01–0.04)	0.0001 (0–7271332.55)	NS
EOS [$10^3/\mu L$]	0.11 (0.08–0.15)	0.11 (0.06–0.21)	0.51 (0.005–48.58)	NS
NEUT [$10^3/\mu L$]	5.18 (3.48–8.74)	4.59 (3.55–5.86)	1.08 (0.99–1.17)	NS
LYM [$10^3/\mu L$]	1.68 (1.2–2.16)	1.79 (1.4–2.29)	0.87 (0.39–1.96)	NS
MONO [$10^3/\mu L$]	0.59 (0.38–0.82)	0.54 (0.40–0.77)	1.74 (0.45–6.8)	NS
MLR	0.36 (0.18–0.65)	0.30 (0.20–0.47)	2.75 (0.61–12.42)	NS
NLR	2.63 (2.02–4.75)	2.41 (1.75–3.90)	1.11 (1–1.22)	**0.04**

The values of quantitative variables are presented in the form of a median and interquartile range (IQR). Odds ratios are presented including 95% confidence intervals. WBC - total number of leukocytes, NEUT - neutrophils, MONO - monocytes; MLR - monocytes/lymphocytes ratio; NLR - neutrophil/lymphocyte index; NS - statistically insignificant (p> 0.05).

Retrospective analysis of the medical history of the examined group contradicts such assumptions in relation to our project. While the assessment of the usefulness of MLR as a prognostic parameter in various disease entities has been the subject of many studies [19,20], it seems that its use in predicting patients' death in the perioperative period has not been analyzed. The obtained results confirm that MLR is as effective in predicting death as the preoperative number of monocytes. Due to the automatic analysis of leukocytic smears, errors in the count of individual leukocyte subpopulations cannot be excluded [21]. A more reliable method

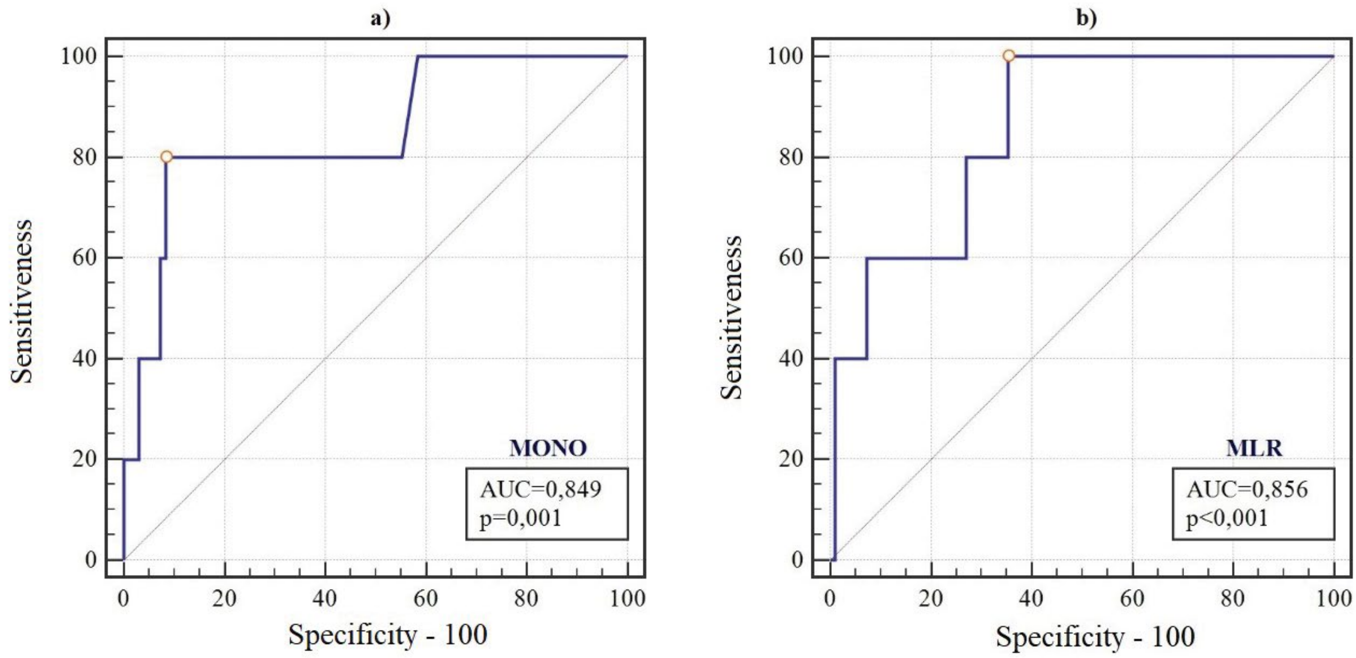

Fig. 1. The predictive accuracy of monocytes (a) and MLR (b) in predicting in-hospital death.

Tab. VII. Leukocytic parameters and risk of hospital death.

PARAMETER	END OF HOSPITALIZATION		OR (95% CI)	'P'
	IN-HOSPITAL DEATH	DISCHARGE		
WBC [10³/µL]	8.58 (7.14–34.35)	7.03 (5.93–25.17)	1.17 (1.05–1.31)	NS
BASO [10³/µL]	0.06 (0.05–0.12)	0.02 (0.01–0.04)	61.3 (0.43–867)	**0.02**
EOS [10³/µL]	0.08 (0.04–0.28)	0.11 (0.07–0.21)	0.98 (0–2276.25)	NS
NEUT [10³/µL]	6.02 (3.77–31.41)	4.59 (3.51–6.01)	1.18 (1.05–1.31)	NS
LYM [10³/µL]	1.2 (1.17–1.72)	1.79 (1.39–2.24)	0.42 (0.09–2.03)	NS
MONO [10³/µL]	1.05 (0.89–1.54)	0.54 (0.38–0.76)	18.14 (2.66–123.57)	**0.009**
MLR	0.87 (0.44–1.22)	0.30 (0.19–0.47)	21.83 (2.29–207.55)	**0.007**
NLR	5.06 (1.61–24.39)	2.41 (1.84–3.91)	1.18 (1.05–1.31)	NS

The values of quantitative variables are presented in the form of a median and interquartile range (IQR). Odds ratios are presented including 95% confidence intervals. WBC - total number of leukocytes, NEUT - neutrophils, MONO - monocytes; MLR - monocytes/lymphocytes ratio; NLR - neutrophil/lymphocyte index; NS - statistically insignificant (p> 0.05).

would be to perform a manual smear, but this involves increasing costs, extended time to obtaining results, and requires an experienced laboratory diagnostician. In spite of the mentioned limitations, there are grounds for continuing research on the optimal use of data obtained from laboratory tests in the process of perioperative risk management [12].

CONCLUSIONS

Routine evaluation of peripheral blood smear should be considered in all patients undergoing high-risk gastrointestinal surgery, because the number of monocytes may be a valuable predictor of in-hospital death.

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