Clinical and prognostic significance of preoperative and postoperative neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in patients undergoing major abdominal surgery

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ABSTRACT

Aims: Acute inflammatory processes are associated with perioperative complications. Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) were reported to have prognostic importance in various diseases. We aimed to investigate the clinical importance of preoperative (preop) and postoperative (postop) NLR and PLR as predictors of morbidity and surgical or nonsurgical complications after major abdominal surgery.

Methods: Patients who had a major abdominal surgery were retrospectively evaluated. Age, gender, American Society of Anesthesiologist (ASA) score, and the type of operation were recorded. Preop and postop days 1, 3 and 5 white blood cell (WBC), neutrophil, lymphocyte and platelet counts, duration of intensive care unit stay and hospitalization, Clavien Dindo classification, and surgical or non-surgical complications were determined.

Results: The study included 462 subjects. Concerning increased need for red blood cell transfusions, NLR was significantly higher on postop day 3 but lower on day 5, and PLR was higher on postop day 1 compared to preop state. Regarding a worse Clavien-Dindo classification, NLR was higher on postop day 3 but lower on day 5, and PLR was higher on postop day 1 and 3 compared to baseline. In those with increased surgical complications, NLR was lower on postop day 5, and postop day 1 and 3 PLR were higher compared to baseline values. In subjects with higher non-surgical complications, NLR was higher on postop day 3 but lower on day 5 compared to preop measurements. PLR was similar across the days of follow up in terms of non-surgical complications.

Conclusions: Higher NLR on postoperative day 5, and higher PLR on postoperative days 1 and 3 compared to preop values were the indicators of increased complications in this study.

Introduction

Major abdominal surgeries are procedures which are lasting more than 30 minutes, performed under general anesthesia and necessitate a hospital stay of at least six days (1). Operations of the following categories of the gastrointestinal system were called as major abdominal surgery: esophagectomy, gastrectomy, pancreatectomy, hepatectomy, colectomy, small bowel resection, tumor resection, and laparoscopic gastrointestinal operations. Abdominal tumor resection constitutes a wide variety of operations for benign and malignant intraabdominal tumors. Laparoscopic gastrointestinal resection includes small bowel and colon resections. These operations were highly associated with a red blood cell (RBC) transfusion (2). Inflammation is a nonspecific response of the organism to endogenous or exogenous stimulants to maintain the survival. The biological aim of this response is to restore the cellular injury caused by a stimulant, clean the residue of cellular debris and foreign body, confine the bacteria and/or stimulant for the prevention of dangerous effects on the body. Although many different infectious or noninfectious mechanisms trigger inflammation, the response is quite the same. White blood cells (WBCs) play a key role in the formation of inflammation. Activation of leukocytes by any stimulant causes the secretion of important mediators from these cells which are taking part in the inflammatory process (3). Physiological response of the leukocytes against stress is an increase in neutrophil count and a decrease in lymphocyte count. Surgery triggers an acute inflammatory process over a stress response and some serious complications like surgical site infection, sepsis, and multiple organ failure may come out in the early postoperative period despite advanced surgical techniques and preventive perioperative medicine (4). The response can partially be estimated by some biomarkers which help the clinician to monitor the patient. Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) are two cheap, reproducible and measurable markers of systemic inflammation (5,6). NLR has been suggested as a simple biological parameter to stratify the risk of mortality after major cardiac events and to predict cancer outcomes(7,8). Currently, the prognostic importance of inflammatory markers has been investigated in various cancers. It was shown that NLR was associated with poor prognosis and overall survival in some cancer types (9).

Many studies have demonstrated a significant relation between NLR, PLR, and prognosis, especially in colorectal cancers. In this study, we aimed to investigate the clinical importance of preoperative and postoperative NLR and PLR as independent parameters of morbidity and development of surgical or non-surgical complications in major abdominal surgery.

Methods

This was a retrospective cohort study which included 510 patients admitted to the general surgery clinic of a training and research hospital between January 2012 and December 2016. All patients underwent major abdominal surgery. Subjects who were operated at another hospital, having insufficient data, findings of immunosuppression, ongoing antibiotic and/or chemoradiotherapy, or multiple operations were excluded. The final analyses included 462 patients. Sex, age, American Society of Anaesthesiologists' score (ASA), operation type and date, preoperative and postoperative white blood cell (WBC), neutrophil, lymphocyte and platelet counts, intensive care unit (ICU) and length of hospital stay, Clavien-Dindo classification, and surgical and non-surgical complications were examined. Surgical complications were categorized by Clavien-Dindo classification into 5 grades (10). Preoperative blood count measurements were executed in the last 7 days before surgery. Postoperative blood counts obtained 1, 3, and 5 days after the operation were recorded. Primary staging 18-F fluorodeoxyglucose (FDG) positron emission tomography (PET) / computed tomography (CT) (FDG-PET/CT) was performed for cancer patients before the operation. The operability of these cases was decided by the PET findings. Patients having distant metastasis were not included. The study was designed according to the Helsinki declaration and patient rights regulations and was also approved by the institutional ethics committee. Data were processed with SPSS 15.0 (Statistical Package for Social Science) for Windows. Descriptive statistics were presented by the number and percentage, mean with standard deviation or median value. Normality was measured with Kolmogorov-Smirnov test. The relation of ICU and hospital stay with NLR, PLR was examined with Pearson's correlation analysis. Chi-square test was used for categorical variables (RBC transfusion, morbidity, surgical and non-surgical complications). For continuous variables, comparisons between multiple groups with normal distribution were analyzed by the ANOVA test. Post-hoc analysis was performed with the Tukey test. For intergroup comparisons between the groups without normal distri-

Table 1. Major abdominal disease and major abdominal surgery types.

		Number (n)	Percentage (%)
Major abdominal disease	Esophagus cancer	5	1
	Gastric cancer	62	13
	Colon cancer	150	33
	Rectal cancer	88	19
	Liver malignant tumor	31	7
	Liver benign disease	15	3
	Pancreatic cancer	25	5
	Spleen disease	4	1
	Retroperitoneal mass	2	0
	Trauma	1	0
	Gallbladder disease	12	3
	Incisional hernie	10	2
	Others	55	12
Major abdominal surgery	Esophagectomy	5	1
	Gastrectomy	63	14
	Colectomy	128	28
	LAR-APR*	103	22
	Major liver resection	28	6
	Minor liver resection-hydatid disease tretament	16	3
	Pancreatectomy	27	6
	Splenectomy	4	1
	Retroperitoneal mass resection	1	0
	Exploratory laparatomy	18	4
	Open cholecystectomy	11	2
	Incisional hernie repair	13	3
	Others	41	9

*Low anterior resection - abdominoperineal resection

bution, Kruskal-Wallis test or Mann-Whitney U test wer used. p values <0.05 were accepted as statistically significant.

Results

Mean age of the patients was 59.5±15 (20-92) years. 280/462 (60.5%) of the subjects were male, and 182/462 (39.5%) were female. Major abdominal surgery types and their indications for the patients were indicated in Table 1. Preoperative and postoperative (days 1,3 and 5) mean and median values of WBC, neutrophil, lymphocyte, platelet counts, NLR and PLR results are shown in Table 2.

Table 2. Preoperative and postoperative (days 1,3 and 5) mean and median values of white blood cell, neutrophil, lymphocyte and platelet counts; NLR and PLR.

Parameters	Mean	Median
Preoperative white blood cells (WBC) (/mm^3)	6195	6100
Preoperative neutrophil count (NC) (x1000/mm^3)	5.11	4.21
Preoperative lymphocyte count (LC) (x1000/mm^3)	1.77	1.71
Preoperative platelet count (PC) (x1000/mm^3)	278	259
Preoperative NLR	4	2.44
Preoperative PLR	195	61
Postoperative WBC		
Day 1	7699	8100
Day 3	5623	6000
Day 5	4864	5200
Postoperative NC		
Day 1	13.3	9.89
Day 3	7.33	6.64
Day 5	5.95	5.35
Postoperative LC		
Day 1	1.14	1.03
Day 3	1.14	1.25
Day 5	1.39	1.13
Postoperative PC		
Day 1	238	225
Day 3	217	201
Day 5	259	247
Postoperative NLR		
Day 1	11.6	9.07
Day 3	6.89	5.77
Day 5	5.44	4.24
Postoperative PLR		
Day 1	39.73	23.74
Day 3	61.03	29.83
Day 5	63.33	45.42

Median ASA score was 2. Mean hospital stay was 12±7.2 days, mean ICU stay was 4.2 (MV: 3) days. Hospital stay was correlated with PLR positively (r=0.192, p=0.034), although its correlation coefficient was not high. The statistical relation between NLR, PLR and ICU/hospital stay was shown in Table 3.

Table 3. The correlation of ICU days/hospital stay with NLR and PLR.

	NLR		PLR	
	r	p	r	p
ICU Stay	0.055	0.241	0.008	0.826
Hospital Stay	-0.031	0.621	0.192	0.034

NLR:Neutrophil/lymphocyte ratio, PLR:Platelet/lymphocyte ratio, ICU: Intensive care unit
r: Correlation coefficient

NLR and PLR values calculated before the operation and on the days 1, 3 and 5 after the operation are given in Table 4 according to the prespecified study outcomes which RBC transfusions, Clavien-Dindo classification, surgical complications, and non-surgical complications. In subjects with increased RBC transfusions, NLR was higher on postoperative day 3 but lower on day 5, and PLR was higher on postoperative day 1 compared to baseline values. Regarding a worse Clavien-Dindo classification, NLR was higher on postoperative day 3 but lower on day 5, and PLR was higher on postoperative day 1 and 3 compared to baseline values. Concerning increased surgical complications, NLR was significantly lower on postoperative day 5 compared to preoperative measurement. Postoperative day 1 and 3 PLR were significantly higher compared to baseline values. In terms of higher non-surgical complications, NLR was significantly higher on postoperative day 3 but lower on day 5 compared to preoperative measurement. PLR was similar across the days of follow up in terms of non-surgical complications.

Discussion

Leukocytes respond physiologically to stress with an increased neutrophil count, decreased lymphocyte count resulting in a concomitant lymphopenia and neutrophilia.

Their count rate has been used as an inflammatory marker in recent studies (11). Historically, upon revealing the relation between inflammation and surgery, the prognostic importance of inflammatory markers in various types of cancers and a few major operations have been investigated recently. NLR is the first inflammatory marker ever researched, but the relation of its increase with poor prognosis was not completely defined at the beginning. It was studied in malignancies like colorectal, lung, over, kidney, urinary bladder, liver cancers (treated by liver transplantation) and its relation with their survey was demonstrated. NLR was reported to associate with poor outcome and survival in some cancers (9). Yamanaka et al. showed that NLR was an independent parameter and useful marker for survival estimation in advanced stage gastric cancer (9). However, some questions remain unanswered when the literature is examined as some contradictory results were published later. Moreover, the same questions also apperared for PLR. While increases in preoperative NLR and PLR were found as prognostic in some cancers in a few studies, only PLR emerged as a prognosticator in other reports (12,13). He et al. found NLR and PLR increase a poor prognostic factor in colorectal cancer (14). Kwon et al. declared that PLR increase was a good prognosticator in colorectal cancer (15) when compared with NLR. In his study, it is concluded that PLR reflects better the increased inflammatory response against tumor biology according to NLR (15).

Platelets are the first cellular corpuscles cementing the processes of hemostasis, inflammation and tissue repair within

Table 4. Preop and postop NLR and PLR according to RBC transfusions, Clavien-Dindo classification, surgical complications and non-surgical complications.

		Preop				Postop day 1				Postop day 3				Postop day 5			
		NLR		PLR		NLR		PLR		NLR		PLR		NLR		PLR	
		Mean	p value	Mean	p value	Mean	p value	Mean	p value	Mean	p value	Mean	p value	Mean	p value	Mean	p value
RBC transfusion	No	3.7		180		11		245		6.4		208		0.02		233	
	<3 pacs	4.4	0.66	214	0.115	10.2	0.47	243	0.005	6.9	0.013	193	0.224	0.03	<0.001	214	0.426
	>3 pacs	4.5		228		11.5		312		8.6		178		0.04		213	
Morbidity (Clavien-Dindo classification)	1	3.5		178		11.1		253		6		199		0.02		220	
	2	4.4		203		10.5		233		7.2		185		0.02		219	
	3	3.1	0.412	180	0.017	11	0.994	261	<0.001	8.4	0.003	253	0.003	0.05	<0.001	226	0.125
	4	7.4		320		11.5		458		10.5		188		0.05		290	
	5	5.8		383		11.2		430		9.4		359		0.05		365	
Surgical complication	Exist	3.1	0.105	208	0.483	11.5	0.511	300	0.025	8.1	0.067	234	0.045	0.05	0.01	230	0.769
	Nonexist	4.1		193		10.8		249		6.7		195		0.02		223	
Non-surgical complication	No	4.2		197		11.1		252		6.4		200		0.02		227	
	Pulmonary	3.6		175		9.2		237		10.2		199		0.04		209	
	Urinary	3.6		229		9.9		289		7		166		0.03		179	
	Cardiac	2.5	0.923	165	0.882	12.4	0.488	244	0.536	8.1	0.001	197	0.266	0.03	<0.001	190	0.052
	Gastrointestinal	2.8		154		8.7		265		5.4		156		0.12		169	
	Others	3		204		9.7		311		9.8		263		0.02		309	

NLR:Neutrophil/lymphocyte ratio, PLR:Platelet/lymphocyte ratio

seconds upon specific signals generated by tissue injury or invasion of pathogens (16). They accumulate at the site of damage of vascular wall and surrounding tissue. Platelets express receptors for adhesive proteins and release a plethora of cytokines, mediators with this stimulation. Activated platelets directly contact with endothelial cells, granulocytes, monocytes and lymphocytes. They either stimulate or inhibit the functions of other cellular elements of inflammation and mediate the transendothelial migration of leukocytes into injured tissue (17). Surgical stress itself and its developing complications create the very same environment just as in a variety of diseases and conditions resulting in platelet activation. Whether or not stimulation of platelets is causative in these diseases is not fully clear, but platelets certainly contribute to the development of clinical symptoms due to complications following the surgical process.

Lymphopenia, a vigorous component of the immune system was reported to worsen the prognosis of cancer patients in current papers (18). Presence of T-lymphocytes in a tumor is the indicator of an evident immune response to the lesion. Recent data suggest decreased T-lymphocyte count is associated with poor prognosis in colorectal cancer (19). Urging evidence about the subject that lymphopenia and resulting increased NLR are beneficial to estimate the prognosis of some clinical settings, has been flourishing day by day. Therefore, attempts of vital supports for the fortification of lymphocytes were inaugurated. Parameters like NLR, PLR, NPS (neutrophil / platelet score) based on hematologic markers, are simple and rapid laboratory findings which are reflecting the inflammatory response of immune system to surgical stress. Although NLR and PLR can portray the ongoing course and balance in the inflammatory process, association of increased preoperative NLR and/or PLR with poor prognosis has not been established fully in major surgery. NLR and PLR were also evaluated as a risk factor for early outcome and late survival prediction in a very limited number of major surgeries such as cardiac or abdominal ones. But these are very scarce. Sibelmans et al assessed prognostic impact of NLR in heart surgery (20). Elevated NLR was shown to present adverse outcomes and reduced survival in a wide spectrum of disease including a variety of surgical settings like coronary artery disease, acute myocardial infarction, percutaneous coronary intervention and coronary artery bypass graft surgery (21). Lai et al conducted a study in which NLR and PLR were investigated as new parameters of transplant failure and recurrence after liver transplantation for hepatocellular cancer (22). They stated that NLR is a good predictor for the dropout risk of transplant, while PLR is a good predictor for recurrence after the transplantation (22). Our preoperative finding are in line with them.

During the surgery, lymphocyte count, platelet count and PLR decrease; neutrophil count and NLR increase physiologically according to preoperative period and we normally expect PLR decrease together with NLR increase in the early phase of complications. These events happened samely in our study and we observed a PLR decrease at postoperative period according to preoperative status. This postoperative decrease was more prominent at 1st day and recovered slightly on ensuing days in complication-developed cases. We also found a positive correlation between hospital stay and PLR decrease. PLR decrease is seen in complication and complication means

prolonged hospital stay. A clear increase in NLR at postoperative 1st day recovering markedly on the following period was observed in complicated patients. When we compared NLR and PLR statistically, a decreased postoperative PLR at 1st day, an equilibrium with NLR at postoperative 3rd day and a NLR increase at postoperative 5th day were strong indicators of complication development. Unfortunately, many of the studies associated with PLR and NLR were conducted in malignancies. Besides, there are very few papers in major operations to compare our results. Consequently, our findings are in accordance with the normal physiological response of the body to surgical stress.

There are many reports containing debating results about the subject in literature. So comprehensive studies with large samples are needed to elaborate the issue. Our study investigated them as prognostic parameters in major abdominal surgery also including PLR in its design. Additionally, postoperative NLR and PLR were used as new independent variables. To the best of our knowledge, our study is the first one in literature in this context. Our patient population was very large and consisted of cases incurring a serious abdominal surgery. 78% of the surgical indication was a gastrointestinal cancer.

Pioneer studies asserted that these factors can't be considered as independent prognosticators alone. However, they may be used in multivariate analysis together with other factors and thus provide a guiding additional perspective for prediction of outcome and complications. On the contrary, we found preoperative and postoperative 1. day PLR, postoperative 3. day and postoperative 5. day NLR as independent variables. Besides their relation with other prognostic factors like metastatic lymph nodes, ASA score, operation type, ICU and hospitalization duration, RBC transfusion, Clavien-Dindo classification, surgical or non-surgical complications, DFS, OS and validity of treatment in the follow-up was not researched widely in previous studies. We tried to fulfill this deficiency. Hospitalization duration, RBC transfusion, Clavien-Dindo classification, surgical or non-surgical complications were statistically meaningful according to our study.

PLR domination exists in preoperative and postoperative 1st day, they reach equilibrium in postoperative 3rd day, consequently NLR overruns in postoperative 5th day according to morbidity. This condition predicts poor prognosis. Predominance of PLR in postoperative 1st and 3rd days, NLR in postoperative 5th day imply a surgical complication. NLR increase in postoperative 3rd and 5th days strongly indicates a non-surgical complication. All these epilogues and postulates must be kept in mind during the first week monitorization of such patients for appropriate intervention. Preoperative and postoperative NLR and PLR measurements are simple, noninvasive methods which predict patient outcome. You can easily estimate complication risk with them during the postoperative period. They can be considered safe and practicable predictor biomarkers basing on their intrinsic role in natural physiological response of the body to any kind of stress like surgery. This paper should be supported by wider designs to unveil the little-known greyzone of the subject in the future.

Conclusions

A decreased PLR on postop day 1 in conjunction with NLR lower on postop day 3 but higher on postop day 5 were strong indicators of complication development. Preoperative and postoperative NLR and PLR measurements are simple, noninvasive methods which predict patient outcome.

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Conflict of Interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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