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Neutrophil-to-lymphocyte Ratio and Platelet-to-lymphocyte Ratio can Predict Post-operative Complications and Mortality in Patients with Operable Esophageal and Gastric Malignancies

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Authors' contributions

This work was carried out in collaboration among all authors. Author MN designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors SB and BD managed the analyses of the study. Authors UM, KM and KB managed the literature searchers. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Postoperative complications are a major concern following surgery for upper GI malignancies. Studies have shown that high levels of preoperative inflammatory markers have a poor prognosis. However, the relationship between preoperative platelet-to-lymphocyte ratio (PLR),

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neutrophil-to-lymphocyte ratio (NLR) and postoperative complications after curative resection is unclear. This study aimed to evaluate the efficacy of PLR and NLR in predicting clinical outcomes and postoperative complications in these patients.

Study Design: Single-center prospective observational study

Place and Duration of Study: Sample: Department of Surgical Gastroenterology, Tirunelveli Medical College, between January 2021 and December 2022.

Methodology: This single-center prospective study included 70 patients out of which 55 with gastric cancer underwent D2 gastrectomy and 15 with esophageal cancer underwent transhiatal esophagectomy. We evaluated the relationship between PLR and NLR and postoperative complications (≥grade 1 Clavien-Dindo classification). Using a receiver operating characteristic curve, the area under the curve (AUC) for each parameter was calculated and the power to predict postoperative complications was compared.

Results: 35.71% patients experienced postoperative complications. The AUC values of NLR (0.825) and PLR (0.161) were higher when compared to other preoperative tests in predicting postoperative complications. The optimal cut-off for NLR was 1.71 (sensitivity 96% and specificity 84.4%) and for PLR was 0.56 (sensitivity 20% and specificity 84.4%). Patients in the high NLR group had an increased incidence of complications when compared to the low NLR group. 74% in the low PLR group experienced complications, whereas only 11.6% in the high PLR group experienced grade 1 or higher complications.

Conclusion: Both NLR and PLR may serve as valuable indicators of potential postoperative complications for patients receiving surgery for operable gastric and esophageal cancers.

Keywords: Gastric cancer; esophageal cancer; neutrophil-lymphocyte ratio; platelet-lymphocyte ratio; postoperative complications.

ABBREVIATIONS

PLR : Platelet-lymphocyte ratio;
NLR : Neutrophil-lymphocyte ratio;
PNI : Prognostic nutritional index;
SURPAS : Surgical Risk Preoperative Assessment System;
POSSUM : Physiologic and Operative Severity Score for the enUmeration of Mortality and morbidity;
CA : Carcinoma;
PRBC : Packed red blood cell;
TNM : Tumor Node Metastasis;
AJCC : American Joint Committee on Cancer;
GIST : Gastrointestinal stromal tumor;
BMI : Body mass index;
ICU : Intensive care unit;
GI : Gastrointestinal;
NK cell : Natural killer cell;
ECOG : European Co-operative Oncology Group;
ASA : American Society of Anaesthesiology;
CI : Confidence interval;
ROC : Receiver operative characteristic curve;
AUC : Area under the curve;
SD : Standard deviation.

1. INTRODUCTION

Cancers of the upper gastrointestinal tract pose a major health risk around the world [1]. Gastric cancer and esophageal cancer are one of the leading causes of cancer-related morbidity and mortality worldwide [2,3]. Surgery in the form of gastrectomy and esophagectomy plays a central role in the management of these cancers [4,5,6]. Despite advances in surgical techniques, significant postoperative complications such as anastomotic leaks, postoperative pneumonia, intra-abdominal abscess formation, postoperative pancreatic fistula, etc. occur. This can impede recovery, prolong the length of hospital stay, increase hospital costs, delay adjuvant therapy, and compromise the quality of life in these patients [7,8].

Systemic inflammatory response parameters are associated with cancer initiation and progression in various malignancies [9,10]. These parameters have also been shown to be associated with an overall poor prognosis in patients with various GI and non-GI malignancies [11-14]. Parameters such as the platelet-to-lymphocyte ratio(PLR), neutrophil-to-lymphocyte ratio(NLR), and prognostic nutritional index(PNI) are well-known predictors of poor prognosis in patients with gastric and esophageal cancers [15-18].

Moyes et al. [19] in their study demonstrated that "the presence of preoperative systemic inflammatory response itself independently predicted postoperative infectious complications in patients undergoing curative resection for colorectal cancer". Several studies have investigated "the use of preoperative inflammatory markers for predicting postoperative complications in cancer patients undergoing surgery" [19,20]. These parameters will help surgeons to provide precise informed consent information and optimize perioperative management.

However, there has been limited research on the role of preoperative PLR and NLR in predicting early postoperative complications, length of ICU stay and hospital stay following curative surgery for stage I-III esophageal and gastric cancers. This study was undertaken to assess the value of preoperative PLR and NLR in predicting postoperative clinical outcomes and complications in patients undergoing curative surgery for stage I-III gastric and esophageal cancers.

2. MATERIALS AND METHODS

This was a single-center prospective study that collected data from 70 consecutive patients of operable stage I-III gastric and esophageal cancers between January 2021 and December 2022 for a period of 24 months at a tertiary care center in South Tamil Nadu, India. Relevant demographic data included patient age, sex, smoking and alcohol consumption, and presence of comorbidities namely diabetes mellitus, systemic hypertension, and cardiovascular disease.

The inclusion criteria were surgically operable and histologically confirmed stage I-III gastric and esophageal cancers with no evidence of inoperability; R0 resection performed without multiorgan resection; a gap of six weeks between neoadjuvant therapy and surgery; standard D2 gastrectomy or transhiatal esophagectomy performed with curative intent. Exclusion criteria were patients with poor ECOG performance status >3; ASA grade IV and V disease; gastric lymphomas and GIST; patients with hereditary cancer syndromes; patients with acute infectious and inflammatory conditions; and metastatic tumors.

The institutional ethics committee approved the study (No: 20222430) and formal consent in addition to what the patients had given before hospitalization was obtained. This research complied with the principles outlined in the Helsinki Declaration of 1975, as revised in 2008.

"A first-generation cephalosporin antibiotic was administered 30 minutes before surgery and thereafter every 4th hourly during surgery. Oral intake was initiated on postoperative day 3 in gastrectomy patients and postoperative day 6 in esophagectomy patients if no obvious complications were found. Percutaneous drainage or the replacement of drainage tubes was done when there were signs of inadequate drainage on computed tomography or ultrasound scans. Clinically relevant postoperative complications were defined as those of grade II or higher according to the Clavien-Dindo classification" [21].

Relevant biochemical parameters including the preoperative complete blood count (including neutrophils, platelets, and lymphocytes) preferably obtained the day before surgery, were collected from the patient records.

The platelet-lymphocyte ratio and the neutrophil-lymphocyte ratio were calculated using the formulas:

PLR= absolute lymphocyte count/absolute platelet count × 100.

NLR= absolute neutrophil count/absolute lymphocyte count

Tumor characteristics for esophageal and gastric cancers included tumor location, histological grade, and clinical TNM stage [by the TNM staging system of the American Joint Committee on Cancer (AJCC 8th ed., 2016)} [22].

These data were imported into an Excel spreadsheet (Microsoft Excel 2016, Microsoft Corporation, Redmond, WA, USA) and used for the interpretation of results.

2.1 Definition of Post-Operative Complications

"Complications occurring within the first 30 days following surgery were defined as postoperative complications and were graded using the Clavien–Dindo classification system" [21]. "When an anastomotic leak or hemorrhage was suspected, computed tomography (CT) was performed to confirm these complications. A postoperative pancreatic fistula was diagnosed when the concentration of amylase in the

abdominal drain effluent was three times higher than the upper limit of the normal serum concentration on the third day after gastrectomy" [23]. "Postoperative pneumonia was diagnosed according to postoperative radiological findings, and one of the following clinical findings was required: body temperature 38 ^{C}, new or progressive and continuous coughing and expectoration with an abnormal white blood cell count (<4000 or >12000/mm^3), or positive respiratory cultures from sputum or blood" [24,25]. "A diagnosis of postoperative small bowel obstruction was based on the patient's symptoms and abdominal X–ray and CT findings. Postoperative chyle leakage was defined as >200 mL per day of milky white fluid discharge with a triglyceride content of >110 mg/dL" [26]. "Patients with upper abdominal distension and remnant stomach fullness on radiographic imaging were diagnosed with postoperative remnant gastric stasis" [27]. Postoperative cardiac arrhythmias were defined as cardiac complications.

2.1.1 Statistical analysis

A receiver operating characteristic (ROC) curve analysis was employed to calculate the area under the curve (AUC) and the sensitivity and specificity of PLR and NLR to predict postoperative complications. The optimal cut-off value for the variables was determined using the Youden index. After that, the study population was divided into two groups according to these cut-off points for each prominent variable. One group was representing those below the cut-off point, while the other group was representing those above the cutoff point.

At the final stage, categorical and continuous variables were evaluated by the Chi-square test and the Student-t-test where appropriate. In all analyses, a p-value of less than 0.05 was considered statistically significant.

All statistical analyses were performed using SPSS for Windows version 26.0.

3. RESULTS AND DISCUSSION

There were a total of 70 patients in our study out of which 55 patients were of gastric cancer and 15 patients of esophageal cancer. Only three patients of esophageal squamous cell carcinoma received neoadjuvant chemoradiation six weeks before surgery (Table 1).

Table 1. Preoperative characteristics of patients

Variables	Number of patients
Age in years (median)	50 (35-69)
Sex	
Male	41
Female	29
Comorbidities	
Diabetes	31
Hypertension	32
Cardiac	3
Preoperative symptoms	
Pain abdomen	55
Gastric outlet obstruction	20
Dyspepsia	31
Loss of appetite/weight	42
Dysphagia	15
Fatigue	41
Habits	
Smoking	62
Alcohol	63
Previous history of surgery	17
Preoperative BMI mean	21.21(SD ±0.88)
ECOG performance status	
0	13
I	46
II	11
Palpable lump	7

Variables	Number of patients
Endoscopic tumor location	
Stomach	
Proximal third	19
Middle third	15
Distal third	21
Esophagus	
Proximal esophagus	0
Middle esophagus	3
Distal esophagus	12
Endoscopic biopsy	
Stomach	
Well-differentiated adenoCA	13
Moderately differentiated adenoCA	28
Poorly differentiated adenoCA	14
Esophagus	
Well-differentiated squamous cell CA	6
Moderately differentiated squamous cell CA	5
Poorly differentiated squamous cell CA	0
Well-differentiated adenoCA	4
Preoperative tumor stage	
Stomach	
I	0
IIA	22
IIB	18
IIIA	6
IIIB	6
IIIC	3
Esophagus	
I	12
IIA	2
IIB	1

AUC. The area under the curve; NLR. Neutrophil-to-lymphocyte ratio; PLR. Platelet-to-lymphocyte ratio

In our study 25(35.71%) patients developed complications. Mild complications (Clavien-Dindo grade I) were seen in 2(2.85%) patients. Major complications (Clavien-Dindo grades 2,3,4 and 5) were seen in 23(32.85%) patients (Fig. 1).

When the AUC value which has the ability to predict postoperative complications, of the selected five parameters was calculated, the NLR demonstrated the highest AUC value (0.825, 95% CI 0.717-0.933) which was higher than the NLR components: neutrophil count(0.734, 95% CI 0.612-0.857) and lymphocyte count(0.158, 95% CI 0.055-0.261) (Fig. 2).

Based on the analysis of the ROC curve, the NLR cut-off value was established at 1.71 with a sensitivity of 96% and a specificity of 84.4% for predicting postoperative complications (Table 2).

Table 2. AUCs, and maximum sensitivity and specificity of the PLR and NLR with the optimal cut-off points

Results	NLR	PLR
AUC	0.825	0.161
95% CI	0.717-0.933	0.056-0.266
Youden index	0.8	0.04
Optimal cut-off	>1.71	<0.56
Sensitivity (%)	96	20
Specificity (%)	84.4	84.4

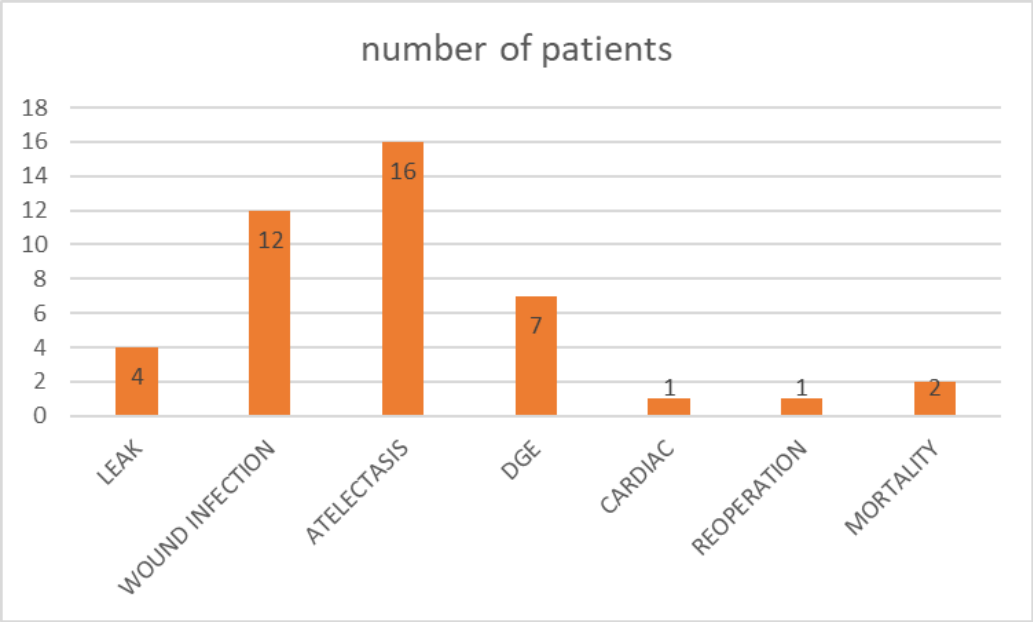

Fig. 1. Bar chart showing types of complications and their frequency

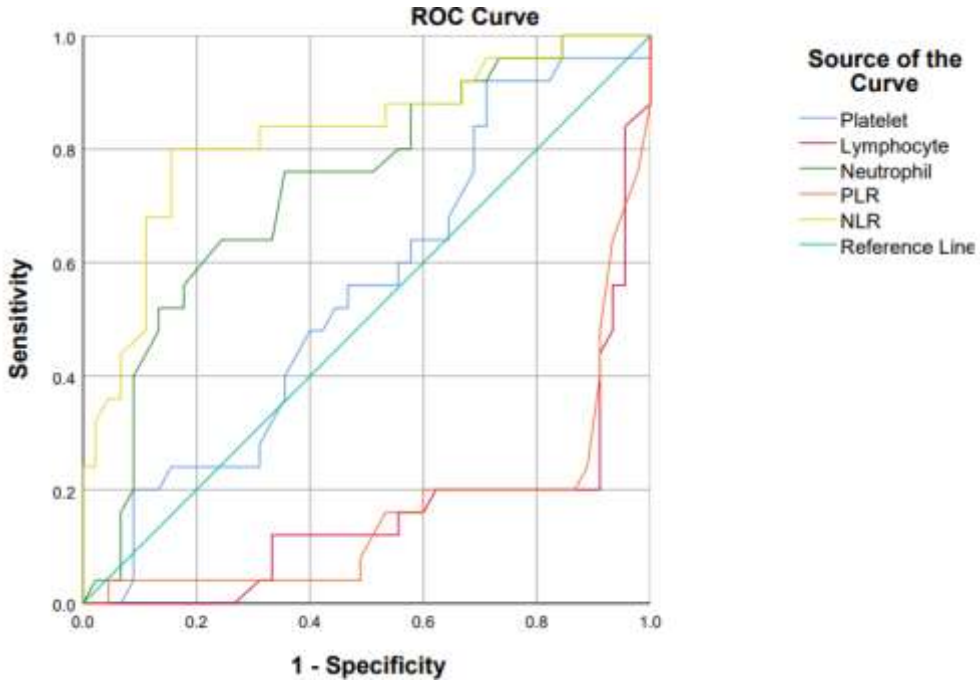

Fig. 2. The predictive powers of different laboratory variables were compared with the AUC values according to the postoperative complications grade ≥ 1 Clavein-Dindo classification

Using the cut-off point set by the ROC analysis, patients were divided into two subgroups, the high NLR group (>1.71) and the low NLR group (≤1.71). There were 61 patients in the high NLR group (n=61) and 9 patients in the low NLR group (n=9). 39.34% of patients in the high NLR group were found to have an increased incidence of postoperative complications, whereas only 11.11% of patients in the low NLR group experienced grade 1 or higher postoperative complications according to the Clavien -Dindo classification. According to the ROC analysis the NLR had greater power in predicting postoperative complications than the other preoperative laboratory values.

The AUC value of PLR was 0.161. Through ROC curve analysis, the cut-off point for PLR in predicting complications was established at 0.56, with a sensitivity of 20% and a specificity of 84.4%. As a result, patients were split into two subgroups, the high PLR group (>0.56) and the low PLR group (≤0.56). There were 27 patients in the low PLR group and 43 patients in the high PLR group. Out of all the patients, those in the low PLR group had a complication rate of 74%, while only 11.6% of patients in the high PLR group experienced grade 1 or higher complications based on the Clavien-Dindo classification (Table 3).

There has been widespread research on the relationship between systemic inflammatory mediators and solid cancers, yet the molecular mechanism behind this relationship is not completely understood [28-29]. “The role of laboratory markers like C-reactive protein and albumin in systemic inflammatory response has been extensively studied. These parameters have been used to construct the Glasgow Prognostic Score to predict clinical outcomes in patients with colorectal and esophageal cancers” [30-32].

Guthrie et al demonstrated the prognostic role of PLR and NLR in predicting postoperative complications in patients with colorectal cancers [33]. In another study, the role of elevated PLR and NLR for predicting overall morbidity in patients with head and neck cancer has been demonstrated [34]. In a study from the UK, Vulliamy et al. concluded that an elevated NLR can predict post-esophagectomy complications [35]. With this in mind, the role of NLR and PLR in predicting postoperative complications becomes more apparent in patients undergoing surgery for upper GI malignancies

When a patient undergoes surgical stress, there sets in a systemic inflammatory response which is characterized by an increase in the circulating neutrophils and a fall in the circulating lymphocytes [36]. This manifests as fever, immunologic changes, and tissue repair [37]. A decrease in lymphocyte count leads to immunosuppression and malnutrition [38]. Wound healing is delayed in patients with malnutrition [39]. This, along with an impaired lymphocyte-mediated antibacterial immune response predisposes the host to increasing bacterial invasion and growth [40]. Lymphocytes play an important role in the management of tumor cells in the host. Lymphocytes mediate increased tumor infiltration which is associated with improved response to chemotherapy and overall prognosis [40]. An increase in neutrophil count induces tumor progression and angiogenesis by suppression of the antitumor response of lymphocytes, activated T cells, and NK cells [41]. This leads to a pro-inflammatory state compromising the cell-mediated immunity and the T lymphocyte responses of the host [42]. An increase in platelet count is associated with a pro-inflammatory state and induces potential micro-vessel thrombosis. This also delays the process of wound healing [43]. All these factors put together to increase the incidence of postoperative complications in patients with malignancies.

The NLR, a ratio of circulating neutrophils to lymphocytes represents systemic inflammation and immune response [44]. Therefore, an increase in NLR value indicates both systemic inflammation and compromised immune response resulting in an increased incidence of postoperative complications in these patients. The PLR a ratio of platelets to lymphocytes in a similar way, is also a marker of systemic inflammation and deranged immune response in the host, as suggested by Inaoka K et al [38].

In this study, the AUC value of NLR for predicting post-operative complications was 0.825, (95% CI 0.717-0.933) and the AUC value of PLR was 0.161 (95% CI 0.056-0.266). These values were greater than the AUC values of all other biochemical parameters for predicting postoperative complications. The cut-off values were calculated using the ROC curves and the Youden index, to investigate the relations of the PLR and NLR with each of the variables such as mortality, anastomotic leaks, postoperative complications, length of hospital stay, and length of ICU stay. The cut off value for NLR was 1.71(sensitivity=96%, specificity=84.4%) and the cut off value for PLR was 0.56 (sensitivity=20% and specificity=84.4%).

Our study could credibly demonstrate a relationship between the preoperative PLR and NLR in predicting postoperative complications in patients undergoing surgery for upper GI malignancies. A high NLR and a low PLR were associated with the occurrence of complications such as mortality, anastomotic leaks, wound infections, pulmonary atelectasis, prolonged length of hospital stay, and ICU stay. Our results are similar to the results from the study conducted by Mungan I et al. [45].

Table 3. Comparison of complications between two subgroups according to PLR and NLR

Item	All	High NLR	Low NLR	P value	High PLR	Low PLR	P value
Number of patients	70	61	9		43	27	
Complications (number of patients)	25	24	1	0.09	5	20	0.000
Anastomotic leak	4	4	0		4	0	
Wound infection	12	12	1		3	11	
Atelectasis	15	15	0		3	12	
Pneumothorax	1	1	0		1	0	
DGE	7	7	0		2	5	
Cardiac	1	1	0		0	1	
Reoperation	1	1	0		0	1	
Pancreatitis	0	0	0		0	0	
Abdominal abscess	0	0	0		0	0	
ICU stay (days, mean±SD)	2.95±1.33	2.95±1.33	None		1.75±0.43	3.21±1.32	0.034
Hospital stay (days, mean±SD)	9.97±3	10.17±3.08	8.14±1.12	0.133	8.30±1.19	12.7±3.07	0.000
Mortality	2	2	0		0	1	

There have been various studies in the literature investigating the role of PLR and NLR in predicting postoperative complications and they have used different formulas to calculate PLR. Also, various cut-off points have been recommended for the PLR (ranging between 0.66 and 0.44) and NLR (ranging between 3 and 5) in these studies [36,46]. We used the method of calculating PLR as described by Inaoka et al. [38]. In our study the specificities of NLR and PLR for predicting complications were high, however, the sensitivities decreased the power of the analysis.

The NLR and PLR are simple biochemical parameters that can be determined in every hospital without adding extra cost burden to the patient. There have been several studies demonstrating the prognostic value of NLR and PLR in patients with upper GI malignancies [46-52]. However, there has been limited research on the influence of preoperative NLR and PLR on postoperative complications in patients undergoing surgery for gastric and esophageal malignancies.

According to our study, surgeons can provide precise informed consent information and identify patients at high risk of developing postoperative complications using NLR and PLR as a tool. This will help to tailor the perioperative care as an attempt to ultimately decrease postoperative complications for gastric and esophageal cancer patients undergoing surgery.

Various prediction models such as the Surgical Risk Preoperative Assessment System (SURPAS) and the Physiologic and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) have been used in the preoperative setting in clinical practice [53,54]. Our results suggest that the NLR and PLR can at least become valuable parameters of these scoring systems for the assessment of surgical risk in patients.

It is currently uncertain how an elevated NLR (neutrophil-to-lymphocyte ratio) correlates with a higher occurrence of complications following surgery. One possible explanation for this is that an increased NLR signifies an increased neutrophil count (systemic inflammation) and a decreased lymphocyte count (impaired cell-mediated immunity and malnutrition) [44]. These factors act in a synchronized manner to increase the incidence of postoperative complications.

It is unclear how a decreased PLR is linked to postoperative infectious complications. A decrease in PLR collectively indicates a lower total white blood cell count, which can result in compromised cell-mediated immunity and malnutrition. It also suggests an increase in platelet count, which can lead to inflammation and a high tendency for micro-vessel thrombosis [20,43]. Over time, the interaction between these intricate factors raises the likelihood of postoperative complications. This study raises an important question. Whether the preoperative modification of NLR and PLR by nutritional supplements and anti-inflammatory treatment will reduce the incidence of adverse postoperative events? Further studies are needed with a large sample size to answer this question.

This study is not without limitations. This study has been conducted at a single center with a small sample size(n=70). Further large-scale studies are required to validate our results.

4. CONCLUSION

The results of this study indicate that the preoperative NLR and PLR are simple and useful predictors of postoperative complications in patients undergoing a gastrectomy or esophagectomy for gastric or esophageal cancers. In the future, the construction of an integrated risk stratification system using the NLR and PLR can help physicians in decision-making and contribute to the informed consent process before performing these major surgeries.

CONSENT

All authors declare that ‘written informed consent was obtained from the patient (or other approved parties) for publication of this article. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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