

Preoperative Neutrophil to Lymphocyte Ratio Predicts Complications After Esophageal Resection That Can Be Used as Inclusion Criteria for Enhanced Recovery After Surgery: a Multi-Center Observational Study

Bowen Shi

Changhai Hospital

Xinyu Wang

Changhai Hospital

Yue Zhao

Changhai Hospital

Xiang Fei

Changhai Hospital

Ji Zhu

Changhai Hospital

Fu Yang

Shanghai First People's Hospital: Shanghai Jiaotong University First People's Hospital

Yudong Han

The Affiliated Hospital of Qingdao University

Hezhong Chen

Changhai Hospital

Chunguang Li (✉ poman001@163.com)



Changhai Hospital

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Preoperative neutrophil to lymphocyte ratio predicts complications after esophageal resection that can be used as inclusion criteria for enhanced recovery after surgery

A Multi-center Observational Study

BO-WEN SHI^{1*}, XIN-YU WANG^{1*}, YUE ZHAO^{1*}, XIANG FEI¹, JI ZHU¹, FU YANG², YU-DONG HAN³, HE-ZHONG CHEN¹ and CHUN-GUANG LI^{1#}

1Department of Thoracic Surgery, Changhai Hospital, The Second Military Medical University, Shanghai 200433, P.R. China; 2Department of Thoracic Surgery, Shanghai First People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200080, P.R. China; 3 Department of Thoracic Surgery, Affiliated Hospital of Qingdao University, Qingdao, 266000, P.R. China;

Abstract

Background The neutrophil to lymphocyte ratio (NLR) has been reported as an indicator for poor prognosis in many cancers including esophageal cancer. However, the relationship between the NLR and postoperative complications after esophageal cancer resection remains unclear. At present, enhanced recovery after surgery (ERAS) lacks inclusion criteria. The aim of this study is to determine whether the preoperative NLR ($_{pre}NLR$) can predict complications after esophageal cancer resection, which could represent the criteria for ERAS.

Methods This was a retrospective study on 171 patients who underwent esophagectomy at Hospital between November 2019 and November 2020 (68 patients from Changhai Hospital, 65 patients from Shanghai General Hospital and 38 patients from Affiliated Hospital of Qingdao University). Univariate and multivariate logistic regression analyses were performed to demonstrate that the $_{pre}NLR$ could predict complications after esophagectomy.

Results A $_{pre}NLR$ cutoff value of 2.30 was identified as having the greatest ability to predict complications with a sensitivity of 76% and specificity of 65%. Moreover, the Chi-squared test results showed that the $_{pre}NLR$ was significantly associated with complications ($\chi^2=13.641$, $p<0.001$), and multivariate logistic regression analysis

#Correspondence to: Dr Chunguang Li, Department of Thoracic Surgery, Changhai Hospital, The Second Military Medical University, 168 Changhai Road, Shanghai 200433, P.R. China

*Contributed equally

E-mail: xwlicg@hotmail.com

Key words: Neutrophil to lymphocyte ratio, esophageal resection, complications, enhanced recovery after surgery

showed that body mass index (BMI), p stage and $_{pre}$ NLR were independent variables associated with the development of postoperative complications ($p < 0.05$).

Conclusion The $_{pre}$ NLR can predict complications after esophagectomy, and these predicted complications can represent the criteria for recruiting patients for ERAS.

Keywords Neutrophil to lymphocyte ratio, esophageal resection, complications, enhanced recovery after surgery

1. Introduction

Esophageal cancer is the 6th leading cause of death from cancer and the 8th most common cancer in the world associated with high rates of morbidity and mortality; the 5-year survival is approximately 15%-25%, and the best prognoses are related to early diagnosis [1]. Early detection and intervention can reduce adverse effects and improve the survival of patients. Although advancements in endoscopic techniques, such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), have greatly benefited patients with early-stage disease, surgical resection remains the most important treatment measure. Esophagectomy is a complex procedure associated with complications such as pneumonia and anastomotic leakage that can restrict oral feeding, leading to short postoperative survival rates [2]. With improvements in surgery and perioperative care resulting in reduced mortality after esophageal cancer [3], there is an urgent need to identify patients who are eligible for enhanced recovery after esophageal carcinoma resection. Enhanced recovery after surgery (ERAS) is based on a suite of clinical processes and evidence that benefit patients by reducing complications and the duration of hospital stay following a major surgery; it was initially established for colorectal surgery [4, 5, 6]. Currently, ERAS has gained attention with regard to esophagectomy, and an increasing number of retrospective and prospective studies and clinical protocols are being reported. Accelerated recovery with ERAS is associated with not only reduction in the duration of hospital stay, pulmonary complications and anastomotic leakage but also decreased pain after surgery and faster return to normal life, especially oral feeding. However, to our disappointment, despite enhancement in the interventions during anesthesia and postoperative rehabilitation exercise, there is no consensus on when patients should return to oral feeding, as many patients suffer from anastomotic leakage during ERAS [7, 8, 9, 10, 11]. Except for severe malnutrition and adverse reactions after neoadjuvant chemotherapy being considered in the exclusion criteria, there are no official guidelines to select the patients undergoing esophagectomy who are eligible for ERAS.

Systemic inflammatory responses have been demonstrated to be associated with cancer initiation and progression and poor outcomes in various malignant tumors [12, 13, 14, 15, 16]. Inflammatory indicators such as the neutrophil to lymphocyte ratio (NLR) is suggested to include critical information that makes the NLR suitable as a serum biomarker that can reflect early complications associated with recovery, so that we may implement appropriate treatment strategies to address adverse outcomes in a wide range of patients [17, 18, 19, 20]. However, the relationship between preoperative or postoperative NLR and complications after esophagectomy is still uncertain. In this

study, we aimed to determine the association between the NLR and postoperative complications to determine the potential of the NLR as an indicator for patients who are eligible for ERAS.

2. Materials and methods

2.1 Patients and perioperative management

The work has been reported in line with the PROCESS criteria [21]. This was a retrospective study, and a total of 668 patients who underwent video-assisted laparo-thoracoscopy via cervical anastomosis esophagectomy at three hospitals between November 2019 and November 2020 were recruited. The patients' eligibility for surgery was evaluated by a multidisciplinary team meeting following appropriate disease staging; meanwhile, physical fitness for surgery was evaluated by the operating surgeon and anesthetist. The exclusion criteria of this study were as follows: patients who underwent surgical procedures except video-assisted laparo-thoracoscopy via cervical anastomosis; patients who had advanced cardiopulmonary dysfunction; patients who used hemopoietin internally for two weeks; patients who had donated blood or underwent blood transfusion in the prior two weeks; patients who recently used glucocorticoids or human granulocyte colony stimulating factor; patients with unknown elevated or reduced white blood cell count and neutrophil or lymphocyte count; patients with hematological disease or autoimmune disease; patients with previous or concomitant cancer; patients who exhibited clinical evidence of infection or other inflammatory conditions; patients who used anti-inflammatory medicines within 1 week of surgery; patients with penicillin or cephalosporin allergy and who used other antibiotics during the operation; and patients suffering from bleeding, chylothorax, recurrent laryngeal nerve paralysis (RLNP) or pneumothorax. Ultimately, 171 patients were included in the study. All patients were subjected to white blood cell counting and neutrophil, lymphocyte, and albumin quantification within one week before surgery (the preoperative neutrophil to lymphocyte ratio was designated $_{pre}NLR$). Samples were obtained on the day of surgery ($_{D0}NLR$) and on the first day after surgery ($_{D1}NLR$), and the data were included in the analysis (laboratory inspection was performed by the Experimental Diagnostic Department; reference ranges at our institution were $4.0\text{--}10.0\times 10^9/l$ for white blood cell counts, $2.0\text{--}7.0\times 10^9/l$ for neutrophil count, and $0.8\text{--}4.0\times 10^9/l$ for lymphocyte count. The NLR was calculated by dividing the number of neutrophils by the number of lymphocytes).

The patients' clinical pathological parameters were collected from being admitted to hospital to being discharged. All patients had been given the same antibiotics at the induction of anesthesia to prevent infection and cure potential infections, enteral nutrition or total parenteral nutrition, proton pump inhibitor, and none of them were administered intravenous infusion of albumin during the study. The patients were routinely admitted to the intensive care unit after surgery. Warm water nasal feeding was performed the day after surgery; when patients felt uncomfortable, enteral nutrition was administered as early as possible to maintain normal physiology. X-ray of the chest and clinical characteristics (temperature, blood routine, drainage of chest

tube) were used to evaluate eligibility to resume oral feeding. Informed consent was obtained from each patient, and the study procedures were approved by the Institutional Review Board.

2.2 Pathological analysis and definitions

The data were obtained from hospital records and retrospectively analyzed. All recruited patients underwent pathological diagnosis via gastroscopy and biopsy before surgery. The American Society of Anesthesiologists (ASA) grade was assessed by the anesthetist in charge, and tumor size, invasion, operation time, intraoperative blood loss and other data were assessed by the surgeon in charge and the first assistant and recorded in the operation notes. Then, the specimens were sent for pathological examination after preservation in 10% formalin. Tumor staging was based on the American Joint Committee on Cancer (AJCC) Staging Manual (7th edition; Springer, New York) [22], combined with computed tomography scanning of the chest and abdomen. Complications were mainly defined according to mortality and morbidity, including pulmonary infection ((respiratory symptoms and infiltration on chest radiography associated with fever requiring antibiotic treatment), superficial or deep tissue infection, sepsis[23], anastomotic leakage and gastric fistula (based on video-assisted fluoroscopy or computerized tomography after oral contrast agent administration), anastomotic stricture, small bowel obstruction, postoperative, hemorrhage, arrhythmia, pneumothorax, and deep vein thrombosis). These complications were confirmed and recorded accurately by the doctor in charge.

2.3 Statistical analysis

We determined the optimal discriminator value for the NLR using receiver operating characteristic (ROC) curve analysis. An area under the curve (AUC)>0.7 was considered clinically relevant. Chi-squared tests were used to compare proportions. Nonparametric variables were analyzed by the Mann–Whitney U-test. Multivariate logistic regression analyses were used to examine the effect of variables on the development of postoperative complications. p values were reported to three decimal places, and a two-tailed p value of <0.05 was taken as significant.

Statistical analysis was conducted with SPSS 22.0 (IBM Corporation, Armonk, NY, USA).

3. Results

3.1 Clinicopathological features

A total of 171 patients (122 men and 49 women) met the inclusion criteria and were recruited for analysis; their age ranged from 45 to 76 years, with an average of 62.43 ± 6.60 years. The average body mass index (BMI) was 23.49 ± 2.86 kg/m²; the average operation time was 289.27 ± 56.22 min; the average blood loss was 225.50 ± 114.52 ml; and the average postoperative hospital stay duration was 11.11 ± 6.18 days. Twenty-one patients had complications, including respiratory infection in 5 (23.8%), anastomotic fistula in 7 (33.3%), catheter infection in 3 (1.8%), wound infection in 1 (4.8%), and other complications in 5 (36.3%) patients. None of the patients died during the operation. Meanwhile, 3 patients underwent re-intubation for pulmonary infection and respiratory failure.

3.2 Relationship between the NLR and complications

The preNLR showed the greatest discriminatory ability with an AUC of 0.72 (95% confidence interval 0.583–0.846, $p=0.001$). A preNLR cutoff value of 2.30 was identified as having the greatest ability to predict complications (Figure 1) with a sensitivity of 76% and specificity of 65%. The average preNLR was 2.45 ± 1.36 .

3.3 Relationship between clinicopathological and complications

The Chi-squared test and Mann–Whitney U-test results showed that BMI ($\chi^2=8.794$, $p=0.003$), ASA grade ($\chi^2=7.735$, $p=0.021$), operation time ($\chi^2=4.485$, $p=0.034$), intraoperative blood loss ($\chi^2=3.909$, $p=0.048$), tumor size ($\chi^2=3.909$, $p=0.048$), T stage ($\chi^2=10.552$, $p=0.014$), N stage ($\chi^2=12.028$, $p=0.007$), p stage ($\chi^2=28.117$, $p<0.001$), postoperative hospital stay ($z=-7.257$, $p<0.001$) and preNLR ($\chi^2=13.641$, $p<0.001$) were significantly associated with complications. There were no significant difference regarding age, sex, neoadjuvant chemotherapy, forced expiratory volume 1 (FEV1), albumin, or histological differentiation ($p>0.05$) (Table 1).

3.4 Multivariate logistic regression analysis of clinicopathologic characteristics in patients with complications

The results of univariate analysis for factors associated with postoperative complications after esophagectomy are shown in Table 2. We next analyzed the clinicopathologic characteristics for which Chi-squared test and Mann–Whitney U-test results showed $p<0.15$. In addition to BMI, ASA grade, operation time, intraoperative blood loss, tumor size, T, N, and p stage, postoperative hospital stay and preNLR , we included FEV1/predicted FEV1 ($z=-1.509$, $p=0.131$) and tumor location ($z=3.866$, $p=0.145$) in our analyses. Indeed, BMI, p stage and preNLR were independent variables associated with the development of postoperative complications ($p<0.05$).

4. Discussion

To the best of our knowledge, this is the first study demonstrating that the NLR (in addition to surgical factors) is a potential indicator of complications in patients after esophageal cancer resection.

In the past years, several studies have demonstrated that the Glasgow Prognostic Score (GPS) (the combination of an elevated C-reactive protein (CRP) level and hypoalbuminemia) is associated with poor survival in various cancers [24], but as the primary limitation, CRP level is not a normal examined factor in many institutions. Until now, the systemic inflammatory prognostic marker, the NLR, has received great interest because it is convenient, inexpensive and easy to evaluate by clinical doctors [25]. Neutrophils infiltrate in tumor tissues that produce high levels of vascular endothelial growth factor (VEGF). Neutrophils can also produce carcinogenic element to stimulate tumor cells to secrete VEGF. High levels of VEGF can provide a suitable environment for tumor growth and proliferation and promote the formation of tumor blood vessels, thus accelerating tumor growth [26]; additionally, a decrease in lymphocytes in the tumor stroma can contribute to tumor cell growth and migration and is associated with poor prognosis [27]. The NLR is proven to be an effective

predictive factor of prognosis in many malignant tumors [28, 29, 30]. An increasing number of studies have demonstrated that inflammation plays a critical roles in malignant tumor progression and prognosis; in other words, the regulation of inflammation may benefit patients by preventing the formation of tumors and improving outcomes [31, 32]. A study demonstrated that pneumonia has a negative impact on overall survival after esophagectomy, and strategies to prevent pneumonia after esophagectomy can improve outcomes after this operation [33]. Several studies demonstrate that inflammation is associated with the prognosis of esophageal cancer. A study from Japan on gastric carcinoma demonstrated that the $_{pre}NLR$ can independently predict the development of postoperative infection-associated complications and reduced survival after gastrectomy. An elevated NLR could trigger postoperative infection and increase the risk of recurrence in patients with these postoperative complications after gastrectomy [34]. An study from UK on sixty-five patients showed that an elevated NLR as early as 48 h following surgery was a highly sensitive and significant predictor of postoperative complications [35]. One meta-analysis from China comprising nine studies containing 2513 patients concluded that a high NLR might represent poor prognosis and unfavorable clinicopathologic characteristics for patients with esophageal squamous cell carcinoma (ESCC) [36]. These results suggest that the $_{pre}NLR$ might be a precise indicator of the balance between the tumor inflammatory response and host immune response.

In this study, we first analyzed the relationship between the NLR and main complications after esophagectomy. We investigated factors that had never been studied in this context before. To eliminate the confounding effect of the operation technique, we excluded patients with complications such as postoperative bleeding, recurrent laryngeal nerve injury and pneumothorax. To eliminate the effect of injury from different surgical procedures, we excluded a large number of patients who underwent Ivor-Lewis esophagectomy, nonendoscopic esophageal cancer resection and some other surgical procedures. Additionally, we excluded patients who had taken glucocorticoids, erythropoietin, or human granulocyte colony stimulating factor, patients who recently underwent blood donation or transfusion or patients with hematological diseases or autoimmune diseases to prevent the effect or routine changes in blood. Our study demonstrated the NLR along with BMI and p stage is an independent risk factor for complications. BMI has been proven to be a risk factor of complications and prognosis after resection in many cancers [37, 38]. In this study, we analyzed the $_{pre}NLR$, $_{D0}NLR$ and $_{D1}NLR$ and found that the $_{pre}NLR$ was most significant indicator for the occurrence of complications. We consider that the NLR after operation is likely highly influenced by the inflammatory reaction, and thus, it is unable to accurately indicate the condition of the patient. Our univariate analysis revealed that complications after esophagectomy are related to BMI, ASA grade, operation time, intraoperative blood loss and tumor stage. For patients undergoing thoracic surgery, postoperative rehabilitation exercise is important for promoting lung function recovery and can reduce complications such as pneumonia. Patients with high BMI have difficulty reaching effective cough and sputum production and performing early activities, and thus, these patients are likely to develop pneumonia

and deep vein thrombosis. Because the operation time is much longer for esophagectomy than for other surgeries and because single lung ventilation is used, anesthesia can aggravate injury to the body, especially the lung, and is more likely to cause pneumonia and other complications.

Overall, this study has some limitations. We need to perform multicenter observational studies to prove that the $_{pre}NLR$ is an objective indicator of complications after esophagectomy, and it may be much more appropriate to introduce reference indicators such as CRP level and interleukin levels for comparison. Then, we can proceed with survival analysis and prognostic assessment. Additionally, we can find whether non-infection complications are associated with poor prognosis.

Importantly, in most cases, the indicators are present long before the complications can be identified. Therefore, we can use these indicators as early predictive markers. As esophagectomy is a complicated and traumatic procedure, more careful evaluation and intervention are needed to improve the postoperative outcomes. ERAS is a patient-centered, surgeon-led protocol combining anesthesia, nursing, nutrition and psychology. During recent years, ERAS has obtained much attention in the field of cancer resection [39, 40]. ERAS can benefit patients by reducing the discomfort of tube detention, promoting quicker recovery to the physiological status, and reducing hospital stay duration and cost. ERAS is not commonly implemented in esophagectomy because of the complexity of the surgical procedure and high morbidity associated with postoperative complications, which have limited the progress in esophagectomy. The primary factors that influence the time to oral feeding and tube removal are pneumonia, anastomotic leakage and pleural effusion. If we can detect the indications for complications, we can identify patients undergoing esophagectomy who are suitable for ERAS, and this can significantly enhance recovery and reduce the cost after surgery; additionally we can implement early interventions to address postoperative complications.

5. Conclusion

The $_{pre}NLR$ as an early predictor of complications can reduce postoperative mortality and improve survival rates. Herein, we consider $_{pre}NLR$ can be used as inclusion criteria for enhanced recovery after surgery

Abbreviations

ESCC: Esophageal squamous cell carcinoma; NLR: neutrophil to lymphocyte ratio; ERAS: enhanced recovery after surgery; $_{pre}NLR$: preoperative neutrophil to lymphocyte ratio; BMI: body mass index; EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection; AJCC: American Joint Committee on Cancer; ASA: American Society of Anesthesiologists; GPS: Glasgow Prognostic Score; VEGF: vascular endothelial growth factor.

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Availability of data and materials

Not applicable

Authors' contributions

BWS, YZ and XYW conceived and designed the study. JZ, FY and YDH were responsible for clinical data collection. XF, JZ, CGL and HZC analyzed the data. BWS, YZ, XYW wrote the manuscript and all authors have read and approved the final version of manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors have no competing interests to disclose.

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Figures

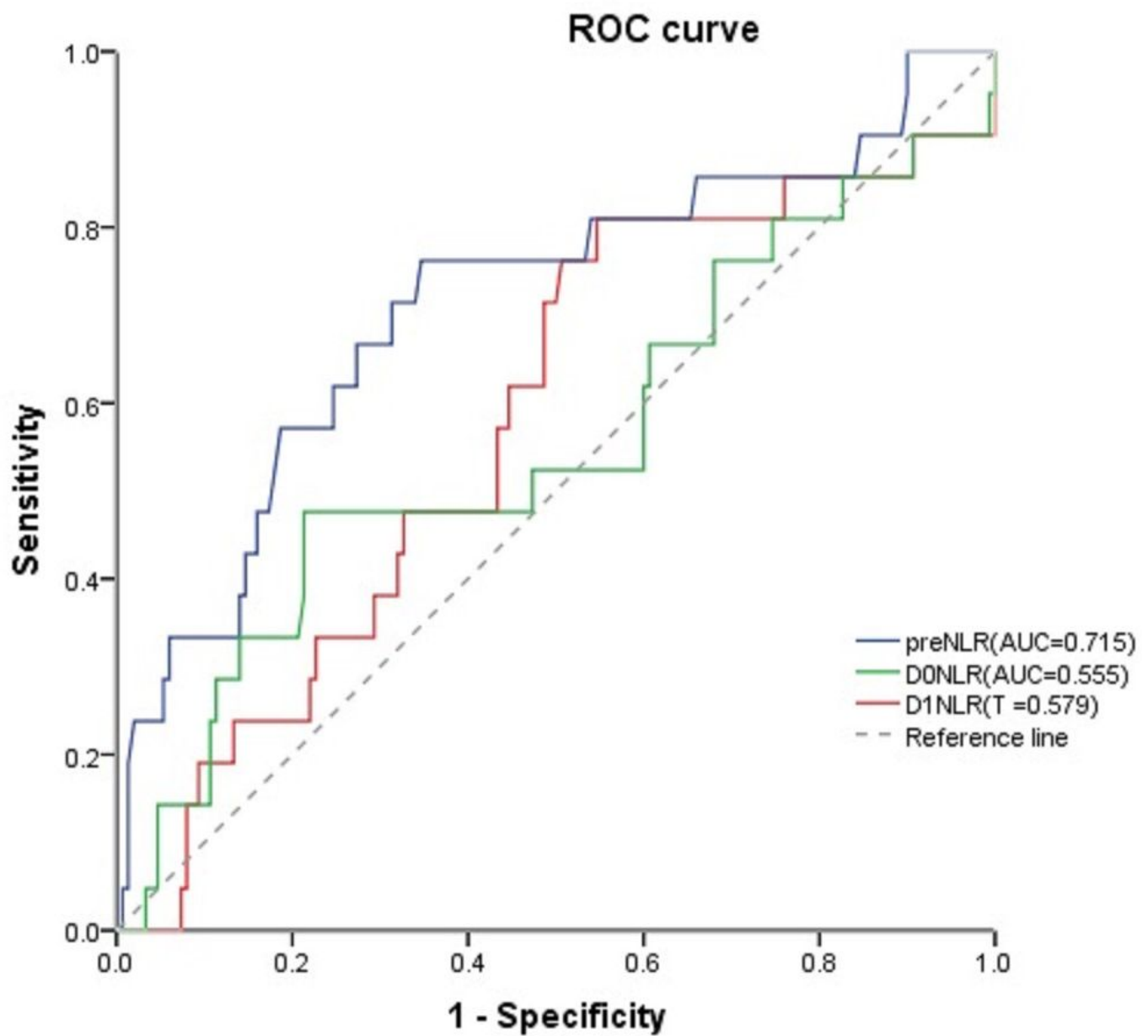


Figure 1

The preNLR showed the greatest discriminatory ability with an AUC of 0.72 (95% confidence interval 0.583–0.846, $p=0.001$). A preNLR cutoff value of 2.30 was identified as having the greatest ability to predict complications with a sensitivity of 76% and specificity of 65%. preNLR, pre-operative neutrophil to lymphocyte ratio; DONLR, the day of surgery neutrophil to lymphocyte ratio; D1NLR, the first day after surgery neutrophil to lymphocyte ratio.