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ORIGINAL ARTICLE

Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios can Predict Treatment Response to Neoadjuvant Therapy in Esophageal Cancer

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Abstract

Introduction We hypothesized that serum neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios may predict pathologic complete response to neoadjuvant chemoradiotherapy in esophageal cancer patients. The ability to predict favorable treatment response to therapy may aid in determining optimal treatment regimens.

Materials and Methods A retrospective review of a prospective esophageal disease registry was conducted. Neutrophil-to-lymphocyte ratio was defined as the pre-chemoradiotherapy serum neutrophil count divided by lymphocyte count. Platelet-to-lymphocyte ratio was similarly defined. Logistic regression was applied to analyze these ratios and their effect on pathologic complete response. A Cox proportional-hazards model was used to analyze survival.

Results Sixty patients were included. Elevated neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio were both negative predictors of pathologic complete response (odds ratio: 0.62; 95% confidence interval: 0.37–0.89, $P = 0.037$ and odds ratio: 0.91; 95% confidence interval: 0.82–0.98, $P = 0.028$, respectively). Only platelet-to-lymphocyte ratio was predictive of decreased overall survival (hazard ratio: 1.05, 95% confidence interval: 0.94–1.16, $P = 0.40$).

Conclusion Elevated neutrophil and platelet-to-lymphocyte ratios were significant predictors of a poor treatment response to neoadjuvant therapy. Only elevated platelet-to-lymphocyte ratio was predictive of worse overall survival. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios may offer a simple serum test to assess the likelihood of a pathologic complete response after neoadjuvant therapy in esophageal cancer.

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Keywords Esophageal cancer · Oesophageal cancer · Pathologic complete response · Neutrophil-to-lymphocyte ratio · Platelet-to-lymphocyte ratio

Introduction

Esophageal cancer is a deadly malignancy with a poor prognosis. Five-year survival rates after diagnosis are currently reported to be less than 18%.[1] Rates of esophageal adenocarcinoma in the USA have increased by over 450% in the last 40 years.[2] Esophagectomy, with or without neoadjuvant chemoradiotherapy (CRT), remains the mainstay of treatment.[3,4] Recent advances in chemotherapy and radiation regimens have helped improve overall survival for locally advanced disease,[3,4] but discriminative treatment pathways for esophageal cancer patients remain sub-optimal. It is now recognized that up to 30% of esophageal cancer patients will have a

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pathologic complete response (pCR) after neoadjuvant CRT. Unfortunately, there is currently no accurate method to reliably predict which patients will manifest a pCR prior to undergoing an esophagectomy.[3–5] If clinicians could reliably predict who will respond favorably to CRT, then select high-risk surgical patients may be spared the morbidity and mortality associated with surgery. Conversely, non-responders may be offered surgery without undergoing CRT or alternative systemic regimens.

An increasing body of evidence suggests certain unique characteristics of malignancy, including tumor. Microenvironment and systemic inflammation play an important role in cancer biology.[6] Inflammation has been shown to be associated with local invasion, distant metastasis, and response to systemic treatment.[7–11] Measures of systemic inflammation offer a promising area of study that may give clinicians insight into predicting tumor behavior. Two simple measures of systemic inflammation, serum neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) appear to offer utility as predictors of treatment response and prognosis in a number of solid tumors.[7–10,12] Furthermore, a small number of studies have shown decreased survival with elevated NLR and PLR in esophageal squamous cell cancer, but the impact on treatment response has yet to be clearly defined.[1,12,13]

In this study, we aimed to determine if NLR and PLR were predictive of pCR after neoadjuvant therapy in patients undergoing treatment for esophageal cancer at a single academic center. In addition, we sought to determine the prognostic impact of these ratios on overall survival after esophagectomy for cancer.

Materials and Methods

The study was approved by the Oregon Health and Science University (OHSU) Institutional Review Board (OHSU1759). Data were collected from the Esophageal Cancer and Related Diseases (ECRD) database. The ECRD is an institutionally based, prospectively maintained registry of demographic, clinical, and pathologic information for all esophageal cancer patients who consented to participate and underwent treatment at OHSU. Patients treated with neoadjuvant CRT followed by esophagectomy for esophageal cancer between January 2005 and June 2015 were included in the study. Demographic, staging, and treatment data were extracted and analyzed. Each patient's medical record was reviewed, and pre-treatment complete blood count (CBC) with differential was recorded in order to calculate NLR and PLR. Patients with CBCs drawn within 90 days prior to initiation of chemotherapy or radiation were included. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Similarly, PLR was calculated by dividing the platelet count by the absolute lymphocyte count. All eligible patients had their post-operative pathology reviewed by a single experienced pathologist. Outcomes investigated were pCR to CRT and overall survival from date of surgery. A pCR was defined as no evidence of carcinoma on final pathologic examination of the resected esophagus or lymph nodes per our previously validated protocol.[14] All patients with any residual carcinoma on final pathology were considered non-responders to CRT. Overall survival was based on date of known death; if death status was unknown, patients were contacted via telephone to confirm living status at the time of data collection. For living patients, date of last clinic follow-up was used as the censoring value in the survival analysis.

Univariable and multivariable logistic regressions were performed to determine the effect of NLR and PLR on response to neoadjuvant treatment and to adjust for important confounders. Hosmer and Lemeshow's purposeful-selection procedure was used to select the best fit models for NLR and PLR on treatment response.[15] Additional variables included in the regression models selection procedure were age, race, gender, pathologic subtype, pre-treatment clinical stage, and chemotherapy regimen. Cox proportional-hazard modeling was used to assess survival. The risk of death per one unit of NLR and per ten units increase in PLR was represented as a hazard ratio of time from surgery to death. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using the R statistical software (version 3.2, R-project, Vienna, Austria).

Results

A total of 343 patients underwent esophagectomy for cancer and agreed to participate in ECRD at our institution between January 2005 and June 2015. Of these 343 patients, 217 were treated with tri-modality therapy (neoadjuvant chemoradiation followed by esophagectomy). Sixty subjects had a pre-treatment CBC with differential available to calculate NLR and PLR (Fig. 1). These patients did not differ significantly from the 157 patients who did not have NLR and PLR values with respect to age, gender, pathologic subtype, or cancer stage. No significant differences were seen between non-responder and the pCR group with respect to age, race, gender, chemotherapy regimen, or cancer stage (Table 1). There was a trend towards elevated median values of NLR and PLR for non-responders compared to pCRs (3.38 vs 2.53, $P = 0.070$ and 189 vs 133, $P = 0.064$, respectively, (Fig. 2). Two outliers were excluded from statistical analysis due to elevated Cook's distance and leverage.[15] Based on Hosmer and Lemeshow's purposeful-selection procedure, the univariable regression model was determined to be the best fit model; therefore, age, sex, race, pathologic subtype, chemotherapy regimen, and stage were not included as co-variates in the final analysis. Both increases in NLR (odds ratio (OR): 0.62,

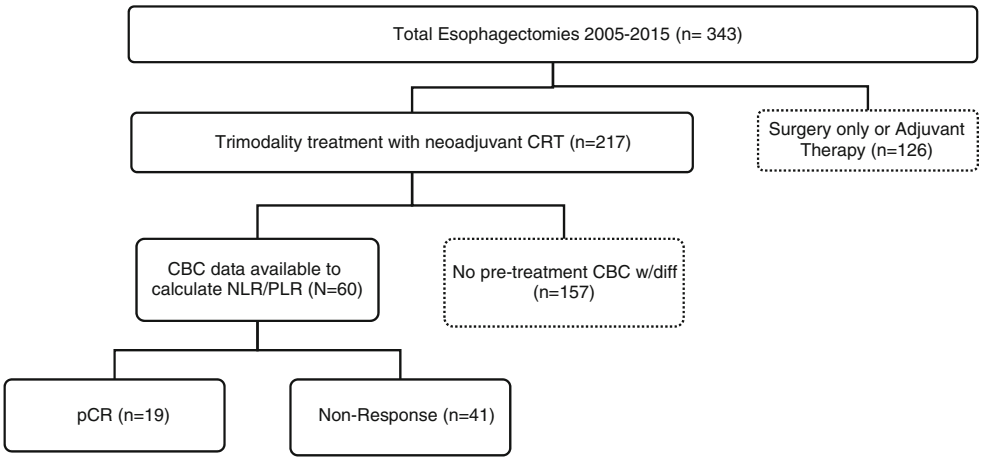

Fig. 1 Patient selection criteria for inclusion for statistical analysis

confidence interval (CI): 0.37–0.89, $P = 0.037$) and PLR (OR: 0.91 CI: 0.82–0.98, $P = 0.028$) were significant negative predictors of a pCR (Table 2). Each one unit increase in NLR predicted 37.8% lower odds of complete response. Each ten unit increase in PLR predicted 9.3% lower odds of pCR. In addition, PLR had a significant association with decreased overall survival (HR: 1.05, 95% CI: 1.01–1.08, $P = 0.005$), but NLR was not predictive of decreased overall survival (HR: 1.05, 95% CI: 0.94–1.16, $P = 0.40$) (Table 3). A ten unit increase in PLR predicted 4.7% increased odds of death at any time post operatively.

Discussion

This study attempts to define the predictive role of NLR and PLR on pCR after neoadjuvant CRT and the impact the NLR and PLR have for predicting survival after esophagectomy. We have demonstrated that pre-chemotherapy elevations in NLR and PLR are associated with a decreased likelihood of a pCR. In addition, elevated PLR was associated with a decreased overall survival. These findings are consistent with what has been observed in previous studies of NLR and PLR.[7–10] In these studies, NLR and PLR elevations have been shown to be predictive of poor outcomes in other tumors, including rectal cancer, gastric cancer, and urologic cancers.[7,10,16] Furthermore, a poor response to treatment has been demonstrated with an elevated NLR in pancreatic cancer.[8] In the case of esophageal cancer, a recent systematic review concluded that both high NLR and PLR were predictive of decreased overall survival.[5,13] That study also concluded that NLR and PLR were associated with deeper tumor invasion and lymph node metastasis.[5,13] Our study did not observe similar upstaging with elevations in NLR and PLR. One notable difference between prior studies and ours is that previous studies primarily investigated squamous cell pathology,[13] whereas our patient population reflects primarily North American adenocarcinoma as the majority of cases.[1] In addition, the role of NLR and PLR on response to systemic and regional treatment in esophageal cancer was not investigated in these prior studies.

Individual tumor biology, microenvironment, and patient systemic factors play an important role in our understanding of malignancies. NLR and PLR offer simple, readily available measures of systemic inflammation that may assist clinicians in the treatment of solid tumors. Inflammation can result from activation of oncogenes and the initiation of a cascade that potentiates cancer growth, invasion, and metastasis.[11] Tumorigenesis and proliferation are driven by the production of inflammatory cytokines, chemokines, and prostaglandins.[11,17] Cytokines, in turn, recruit inflammatory cells, such as neutrophils and activated platelets.[11] Platelets then serve as a major source of growth factors, such as TGF-β and VEGF, which promote angiogenesis and invasion.[17] In parallel, neutrophils and other myelomonocytic cells activate transcription factors that influence the production of more inflammatory mediators.[11] Taken together, these cellular perturbations can lead to an inhibition of the patient's adaptive immune system and subsequent downregulation of T cell response.[11,17] In essence, the tumor itself initiates an inflammatory cascade that feeds back on the host immune response in a manner that contributes to a favorable environment for tumor progression and continued inflammation.[17] It is no surprise that we see elevated levels of innate inflammatory cells, such as neutrophils and platelets, and associated decreases in lymphocytes associated with aggressive tumor behavior. Presumably, an increased NLR and PLR reflect an activated innate inflammatory system in opposition to a lessened anti-tumor lymphocyte effect. In the long term, a better understanding of this process may allow physicians to take advantage of host immune systems and offer additional targets for systemic therapy.[17]

Esophageal cancer patients with a pCR after neoadjuvant CRT have a significantly improved overall survival, as compared to patients without pCR.[5] Consequently, the ability to predict which patients will manifest a pCR may provide important prognostic information and could aid clinicians in treatment decision pathways. The ability to evaluate the

Table 1 Baseline demographic, treatment, and staging make up of study population by responder group

	N	No or partial response	Pathologic complete response	Combined	*P* value
Age	60	66 (60, 69)	64 (61, 69)	66 (60, 69)	0.765[a]
Sex	60				0.493[b]
F		17% (7)	26% (5)	20% (12)	
M		83% (34)	74% (14)	80% (48)	
Race	60				1.0[b]
Asian		2% (1)	0% (0)	2% (1)	
White		95% (39)	100% (19)	97% (58)	
N. American		2% (1)	0% (0)	2% (1)	
Pathologic subtype	59				0.416[b]
EAC		90% (36)	79% (15)	88% (51)	
SCC		10% (4)	21% (4)	12% (8)	
Chemotherapy regimen	54				0.58[b]
Caboplatin/paclitaxel		61% (22)	50% (9)	57% (31)	
5-FU/cisplatin		17% (6)	33% (6)	22% (12)	
Cisplatin/paclitaxel		3% (1)	6% (1)	4% (2)	
		6% (2)	0% (0)	4% (2)	
5-FU/carboplatin/paclitax-el		14% (5)	11% (2)	13% (7)	
Other					
Clinical stage	58				0.155[b]
IA		2% (1)	0% (0)	2% (1)	
IB		0% (0)	5% (1)	2% (1)	
IIA		10% (4)	26% (5)	15% (9)	
IIB		20% (8)	21% (4)	20% (12)	
III		2% (1)	0% (0)	2% (1)	
IIIA		49% (20)	42% (8)	47% (28)	
IIIB		15% (6)	0% (0)	10% (6)	
IIIC		2% (1)	0% (0)	2% (1)	
IV		0% (0)	5% (1)	2% (1)	
Median NLR	60	3.38 (2.33,6.20)	2.53 (2.10,3.08)	3.17 (2.29, 4.21)	0.070[a]
Median PLR	60	189 (116,297)	133 (102, 180)	172 (112, 242)	0.064[a]
Vital status	60				0.025[b]
Living		54% (22)	84% (16)	63% (38)	
Deceased		46% (19)	16% (3)	37% (22)	
Total	60	68% (41)	32% (19)	100% (60)	

[a] Wilcoxon rank-sum test. Numbers in parentheses represent upper and lower quartiles

[b] Fisher's exact test. Numbers in parentheses following percent represent frequencies

inflammatory state of the patient and the relationship with treatment response has clinical implications. This information provides information for clinicians and patients about the aggressiveness of the tumor. Furthermore, the ability to predict response to treatment may prove useful in certain high-risk surgical patients where a watchful waiting approach is preferred to a large operation. If we are able to predict treatment response, patients who are unlikely to respond favorably to current treatment regimens can be offered additional or alternative systemic therapies. Furthermore, these patients may benefit from proceeding directly to surgery without inordinate delay for neoadjuvant therapy.

Esophagectomy is a procedure that can be associated a high morbidity and mortality due to pulmonary, cardiac, and anastomotic complications.[18,19] There have been no randomized control trials that have directly compared outcomes of esophagectomy versus definitive chemoradiotherapy in esophageal adenocarcinoma, so outcome data can only be extrapolated from randomized trials on squamous cell pathology. The majority of our patient population (88%) was the adenocarcinoma subtype, which tends to be less responsive to CRT, so any benefit to non-surgical management is expected to be less in adenocarcinoma.[3] Nonetheless, two fairly recent randomized control trials have compared CRT alone versus CRT plus

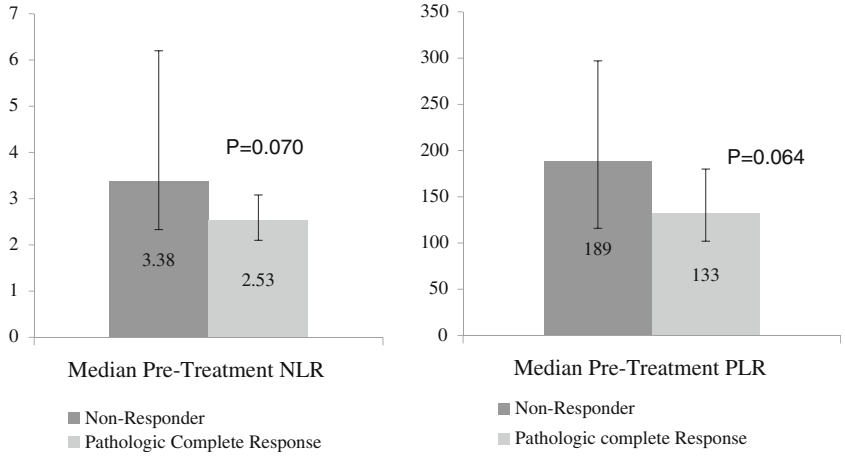

Fig. 2 Median NLR values for non-responders vs patients with pCR ($P = 0.070$) and median PLR values for non-responders vs patients with pCR ($P = 0.064$). *Error bars* represent interquartile range

surgery for esophageal squamous cell cancer.[20,21] Neither study demonstrated a survival difference between the two arms.[20,21] Both studies found significantly higher local recurrence rate in patients receiving CRT alone.[20,21] The lack of a survival benefit associated with surgery may well be due to complications associated with esophagectomy. To this end, improved selection of patients for esophagectomy has the potential to improve outcomes. In one retrospective case–control study, CRT followed by esophagectomy compared to definitive CRT has been shown to be superior with respect to both local recurrence and survival in patients who have a clinical complete response based on imaging and endoscopy.[22] These modalities alone may not be sensitive enough to detect a true pCR. It is only after an esophagectomy with a thorough histopathologic exam can a pCR be confirmed. The ability to confidently predict treatment response may allow clinicians to further individualize cancer treatment for each patient and his or her desires and goals. Patients who are high-risk surgical candidates with a high probability of achieving a pCR based on imaging, endoscopy, and NLR and PLR blood work could potentially be spared the morbidity of surgery, and instead choose definitive CRT with close surveillance. Despite improved prognostic information gained from NLR and PLR tests, more definitive evidence is needed before recommending CRT alone. Esophagectomy should remain the mainstay of treatment and can have acceptably low morbidity and mortality profiles in experienced hands at high-volume centers.

There are limitations to this study. Our cohort is retrospective in nature. In addition, our sample size was small. Although 217 patients treated with esophagectomy at our institution qualified for the study, only 60 patients had laboratory data available to calculate NLR and PLR. This was due in large part to the fact that our treatment center is a tertiary care facility that receives referrals from across a wide geographical area. Consequently, complete laboratory records were not always available to investigators. In response to this shortcoming, our esophageal cancer care group now requires documentation of a CBC with differential prior to initiation of treatment, which will increase the number of patients for inclusion in future investigations. Furthermore, the study did include a heterogeneous population with regards to histology. Eight squamous cell tumors were included in the analysis in addition to 52 adenocarcinomas. There were no significant differences between NLR and PLR values between the two subtypes, as such we felt it was appropriate to include these patients. To exclude these, eight squamous cell patients may under power our data. Analysis with more patients of a single histology would offer clearer evidence for application of these ratios to specific clinical situations. In addition, two patients did not fit the logistic regression model during data analysis and were excluded. Both excluded individuals were in the pCR group and were outliers with elevated NLR and PLR values. The first excluded patient had calculated NLR and PLR values of 6.8 and 203, respectively. The second excluded patient had an NLR value of 5.8 and a PLR of 305. These values were greatly elevated when compared to similar patients from the pCR group. Review of their medical records

Table 2 Univariable logistic regression model for NLR and PLR on pathologic complete response

	Odds ratio (95% CI)	*P* value
NLR[a]	0.622 (0.367, 0.893)	0.037
PLR[b]	0.907 (0.821, 0.977)	0.028

[a] Odds ratio for each 1 unit increase in NLR

[b] Odds ratio for each 10 unit increase in PLR

Table 3 Cox proportional-hazards model of overall survival

	Hazard ratio (95% CI)	*P* value
NLR[a]	1.05 (0.942, 1.162)	0.398
PLR[b]	1.05 (1.014, 1.082)	0.005

[a] Hazard ratio for each one unit increase in NLR

[b] Hazard ratio for each 10 unit increase in PLR

showed that the first patient had a history of acute myelogenous leukemia (AML), with a subsequent allogenic stem cell transplant, and multiple episodes of graft versus host disease, which were treated with steroids. These medical conditions substantiate derangements we observed in this patient's NLR and PLR. The second patient had previously undergone a kidney transplant for glomerulonephritis and was taking long-term immune suppressive therapy with azathioprine. Lymphopenia is a well-recognized effect of azathioprine,[23,24] and explains elevated NLR and PLR in this patient. Deviations from the expected values of NLR and PLR can be explained by these concomitant medical issues; excluding these patients from our analysis, however, further limited the sample size that could be included. We have also found that there is incomplete data available on the chemotherapy regimen used for six patients. Only 54 of our 60 patients had data available that detailed the type and duration of chemotherapy. This is due to the fact that these patients received neoadjuvant therapy at other institutions; consequently, detailed records were not available to investigators. Although our study showed no differences in pCR rates observed between the different chemotherapy regimens, the data remains incomplete. Finally, the findings from this study can only provide prognostic significance about tumor behavior and cannot not yet be used to alter current treatment recommendations. Despite these limitations, our findings were consistent with reported studies in other tumors and other survival studies with esophageal cancer with regard to NLR and PLR.[7–10,12]

Conclusions

Our study demonstrated that increasing NLR and PLR significantly decrease the odds of a pCR to neoadjuvant chemoradiotherapy in patients with esophageal cancer. Similarly, an elevated PLR was predictive of decreased overall survival. NLR and PLR may offer a simple and widely available laboratory test to assess likelihood of pCR after CRT in esophageal cancer. By predicting which patients will have a favorable treatment response, clinicians may be able to individualize cancer treatment plans to avoid over or undertreating patients. Evaluating NLR, PLR, and other predictive biomarkers may prove useful in future recommendations for individualized esophageal cancer care.

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Author's Contributions Study design conception: McLaren, Bronson, Vaccaro, Gatter, Thomas, Hunter, Dolan.
Data acquisition: McLaren, Bronson.
Data analysis: McLaren, Hart.
Interpretation of data: McLaren, Bronson, Hart, Dolan.
Manuscript drafting and revision: McLaren, Bronson, Hart, Vaccaro, Gatter, Thomas, Hunter, Dolan.
Final Approval: McLaren, Bronson, Hart, Vaccaro, Gatter, Thomas, Hunter, Dolan.

Compliance with Ethical Standards

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