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ORIGINAL ARTICLE

Clinical Application Values of Neutrophil to Lymphocyte and Platelet to Lymphocyte Ratios in Multiple Cancers

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SUMMARY

Background: **As the mechanism of systemic inflammatory response in the course of cancer progression is gradually revealed, research has begun to focus on the two indictors of neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) which may be associated with clinical disease development, treatment, and prognosis in patients who are undergoing surgery, chemotherapy, targeted therapy, and immunotherapy. We aim to define the clinical application values of those two biomarkers in multiple cancers.**
Methods: **PubMed and Web of Science are used to perform the systematic literature research. Related articles and references were identified for analyzing the association of between NLR and PLR with treatment outcome, as well as progression of cancers.**
Results: **NLR and PLR are convenient, easy to calculate, economical, and practical biomarkers, effectively predicting treatment outcome and risk of death based on inflammatory cells. Elevated NLR and PLR are significantly in line with worse clinical pathological characteristics, deeper invasiveness, more lymph node metastasis and advanced TNM stage. A significant association was observed that high NLR and PLR predict poor overall survival and disease-free survival.**
Conclusions: **NLR and PLR can be used as available biomarkers in prognostic survival and formulation of treatment strategy of multiple cancers.**
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INTRODUCTION

Cancer is a major threat to human health in the worldwide, and traditional research focuses on the characteristics of cancer itself, such as histology, cancer grading and gene mutations. In the 19th century Virchow [1] noted that white blood cells appeared in tumor tissue may be the source of cancer in the inflammatory site. Recent studies have confirmed the role of host inflammatory cells in the progressive microenvironment of tumors [2]. Tumors can not only occur or develop around inflammation, such as Helicobacter pylori [3], which can also trigger immune inflammatory responses around tumor. Tumor cells or tumor-related leukocytes and

platelets [4] can produce inflammatory factors that stimulate tumor cell proliferation and chemotaxis [5], promoting angiogenesis and tumor metastasis. Those factors may influence the tumor's response to systemic treatment [6]. It is generally believed that NLR and PLR can be used as indicators of the balance between inflammation of the body and the immune state of the body's anti-tumor response [46]. The predictive effect of NLR and PLR on disease progression and prognosis is more valuable than the vulnerable absolute counts. So, we reviewed the clinical research progress of PLR and NLR in tumor patients and provide the basis for future research.

Role in the prognosis of cancers

The prognostic role of PLR and NLR have been demonstrated in multiple types of tumors. Overall survival (OS) and progression-free survival (PFS) are commonly used as prognostic endpoint criteria. High-NLR patients with small-cell lung cancer (SCLC) the median OS time were 11.7 months [7], compared with 9.20 months in patients NLR < 4, and PFS in the high-NLR group was poor (high vs. low, 6.90 vs. 5.49 months, p = 0.005). Recently Suzuki et al. [8] reported that patients with higher NLR (≥ 2.9) and PLR (≥ 140.1) before treatment had shorter OS than those with lower patients in limits-stage small-cell lung cancer (LS-SCLC) (14.8 vs. 18.9 months). Another study [9] found that high NLR ≥ 1.89 and PLR ≥ 149 before treatment significantly predicted poor OS and PFS in pancreatic cancer (PC) patients. In addition, some studies using other indicators as the prognosis endpoint criteria. Preoperatively elevated NLR in patients with gastroesophageal independently predicted disease-specific survival (DSS) [10]. A significant association between poor cancer-specific survival (CSS) and recurrence-free survival (RFS) with high preoperative serum NLR was proved in esophageal squamous cell carcinoma (ESCC) [11]. To better understand the correlations reported in other human diseases, main studies have been executed (Table 1), such as gastric cancer [12], hepatocellular carcinoma [13,14], colorectal cancer [15], and ovarian cancer [16,17] et al., which suggested that those two indicators can be routinely included in prognostic assessment.

Early detection of tumors is difficult, and most of the visible lesions were found by physical examination. Therefore, it is very necessary to find a simple and effective diagnosis method. Cannon et al. [18] reported that patients with high NLR (> 2.98) and PLR (> 146) had shorter OS before treatment in patients with early stage non-small cell lung cancer (NSCLC). In recent studies, the combined score of NLR-PLR can better predict the survival rate of patients with stage I - II gastric cancer after radical resection. Importantly, the area under the ROC curve (0.66, p = 0.001) is greater than other indicators of inflammation such as mGPS [19]. Early stage patients with increased NLR or PLR had worse prognosis, so NLR and PLR were considered as important prognostic tools for early patients. Besides, the two markers are also used in advanced tumor studies. Grenader et al. [20] found that the median OS of patients with high baseline NLR (≥ 3) advanced esophageal cancer receiving first-line chemotherapy was 9.1 months (95% CI: 8.0 - 9.6) compared with 12.7 months (95% CI 10.8 - 14.4) in low baseline NLR (< 3). High baseline NLR regularly predicts negative prognostic effect on OS. Studies involving 14 types of advanced tumors proved that high NLR before treatment was associated with decreased OS and PFS [21]. Compared with early tumors, advanced tumors have higher levels of NLR [22], in the study from Gunaldi et al. [23], it was found that NLR and PLR parameters in peripheral blood was positively associated with larger tumor size and advanced tumor stage. Noteworthy, studies in patients with HBV-HCC have displayed that liver fibrosis affects the ability of NLR and PLR in prognostic assessment, the impact of the two markers on outcome was only in Ishak stage 0 - 5 patients and not in Ishak stage 6 patients [24]. It may be that the systemic inflammatory response is associated with increased NLR promoting end-stage non-fibrosis.

Tumor recurrence is a major obstacle in the current treatment of various types of cancer, and it is a problem that patients and doctors most worried about. Tumor recurrence is also an important reference for evaluating prognosis. Shao et al. [25] found that NLR was significantly associated with tumor stage (p = 0.033) and tumor recurrence (p = 0.014) in patients with SCLC. Besides, Xiao et al. [26] reported increased preoperative NLR was a significant predictor for tumor recurrence in HCC patients after liver transplantation (p = 0.002). Another study also had found that the NLR of pre-liver transplant recipients is a recurrence predictor of HCC after transplanting [27]. Yuan et al. [28] confirmed that preoperative NLR (≥ 5) independently predicted postoperative tumor recurrence, and showed poor DFS in patients with adenocarcinomas of the esophagogastric junction (AEG). In addition, a study found that the changes in NLR can predict tumor recurrence. High ΔNLR indicated a low response rate (HR = 0.77, 95% CI: 0.62 - 0.9, p = 0.004), which was positively associated with an increased risk of recurrence [29]. These dates showed the high NLR expression is a biomarker for poor clinical outcomes in patients with recurrence of cancers.

About which indicator is better prognostic marker, there is no unified conclusion at present. When Li et al. [30] retrospectively studied patients with non-metastatic rectal cancer, high NLR (> 2.3) and high PLR (> 144) predicted lower OS (p = 0.010) and DFS (p = 0.009), but PLR was only associated with the pN phase, and high NLR was associated with larger tumor size and poorer prognosis. In addition, patients with small cell lung cancer (SCLC) [31] showed that although high NLR (> 4.55) and high PLR (> 148) suggested poor overall prognosis, only NLR can be an independent prognostic factor for survival. Another study demonstrated that high NLR (> 3) rather than PLR in metastatic pancreatic

Table 1. Prognostic role of NLR and PLR in multiple cancers.

Cancer types	Test time	Number of patients	Biomarkers expression	Prognostic endpoint criteria	Outcome	Reference	Country
SCLC	diagnosis chemotherapy progression	187	NLR ≥ 4	OS/PFS	poor	Kang et al. (2014)	Korea
BC	pretreatment	5,542	high PLR	OS/DFS/ pathological characteristics	poor	Zhang et al. (2017)	China
CC	preoperative	372	high PLR	TTR/OS	shorter	Szkandera et al. (2014)	Austria
CRC	pretreatment	4,968	high PLR	OS/DFS/CSS/RFS/ clinicopathological characteristics	poor	Huang et al. (2017)	China
ESCC	Pretreatment/ posttreatment	217	ΔNLR	pathologic response/ recurrence	poor	Barbetta et al. (2018)	USA
ESCC	preoperative	483	NLR ≥ 3.5 PLR ≥ 150	OS	poor	Feng et al. (2014)	China
GC	preoperative	1,986	NLR (2 - 3) PLR (126 - 200)	OS/DFS	poor	Kim et al. (2015)	Korea
GC	preoperative	305	NLR - PLR	OS	poor	Sun et al. (2016)	China
GC	preoperative	245	NLR > 2.56 PLR > 160	OS/pathological characteristics	poor	Gunaldi et al. (2015)	Turkey
HCC	preoperative	375	NLR > 2.8	OS/recurrence	poor/high	Okamura et al. (2016)	Japan
HCC	pretreatment	2,449	high PLR	OS/DFS	poor	Lin et al. (2018)	China
HCC	pretreatment	86	NLR ≥ 3	disease control	worse	Taussing et al. (2017)	USA
LS-SCLC	pretreatment	122	NLR (≥ 2.9) PLR (≥ 140.1)	OS	shorter	Suzuki et al. (2019)	Japan
NSCLC	pretreatment	149	NLR > 2.98 PLR > 146	OS	poor	Cannon et al. (2015)	USA
NSCLC	pretreatment	101	NLR ≥ 3	PFS	poor	Nakaya et al. (2018)	Japan
NSCLC	baseline posttreament	54	NLR ≥ 5	PFS	poor	Suh et al. (2018)	Korea
OC	pretreatment	2,919	NLR/PLR	OS/PFS	poor	Zhu et al. (2018)	China
OC	pretreatment	344	NLR < 3.02 PLR < 207	OS/PFS	better	Miao et al. (2016)	China
PC	pretreatment	497	NLR ≥ 1.89 PLR ≥ 149	OS/PFS	poor	Lee et al. (2018)	Korea
RC	preoperative	161	NLR > 2.3 PLR > 144	OS/DFS/stage	poor	Li et al. (2016)	China
SCLC	pretreatment	112	NLR ≥ 4.15	OS/PFS/stage/ recurrence	poor/high	Shao et al. (2015)	China

CC - colorectal cancer, OC - ovarian cancer, RC - rectal cancer.

cancer associated with poor prognosis [32]. Investigators who support PLR serve as a better prognostic marker have elaborated their viewpoints. The results of Feng et al. [33] showed that the area under the ROC curve had a PLR greater than NLR (0.708 vs. 0.658), so PLR was considered to be superior to NLR as a prognostic survival factor for patients with ESCC. Similarly, the signification of preoperative PLR was proved in patients with early ESCC undergoing surgery and considered as an independent prognostic factor [34,35]. Further exploring need to be done to expound the values of NLR and PLR in a variety of clinical diseases.

Role in the progression of the cancer

As the study progressed, NLR and PLR not only used to predict tumor prognosis, but researchers found that they also play an important role in the development of cancer. Kang et al. [7] recorded NLR and PLR at the time of diagnosis, after the first cycle of chemotherapy and during disease progression, and found that patients with high NLR levels in disease progression had lower response rates to treatment compare with lower NLR.

NLR increased notably in the progression compared to the first cycle of chemotherapy, which suggest that NLR can reflects tumor burden to monitor the recurrence or progression of SCLC. Nakya et al. [36] found that NLR < 3 after 2 or 4 weeks is a predictive marker of advanced NSCLC patients with nivolumab treatment, and Suh et al. [37] found that NLR < 5 can better monitor the progression of anti-PD-1 antibody in patients with NSCLC after 6 weeks of treatment. Besides, another study [38] clarified that NLR may be a serum biomarker for early progression of HCC patients after intra-arterial treatment, the above trials suggested multiple types of treatment research may be focused in the future.

PLR has been found in a number of studies with worse clinical pathological changes, tumor invasion depth, lymph node positive, tumor metastasis and stage [23, 39]. Zhang et al. [40] showed that elevated PLR is not only predicting the poor survival of breast cancer patients and fully predicting the clinicopathological features of patients. Poor tumor differentiation is more serious damage to the body, which means that the anti-tumor ability of body is worse, and it may be the reason for PLR becoming a better prognostic marker [15]. Monitoring changes in PLR during clinical treatment can indicate the progression of the tumor and provide useful information for developing an effective treatment strategy.

The inflammatory response of the body runs through the development of any disease in the clinic. Corriere et al. [41] found that the probability of predicting carotid plaques NLR > 2.4 was 80% ($p < 0.01$), while the probability of NLR > 3.68 was 97% ($p = 0.013$), NLR between 2.4 and 3.68 was 80% ($p = 0.013$), so it was considered to be helpful in identifying the risk of occlusion of carotid plaque. A meta-analysis by Wang et al. [42] showed that NLR and PLR are significantly associated with mortality in patients with acute pulmonary embolism. The severity of coronary atherosclerosis is independently and positively correlated with elevated PLR [43], and PLR may also be a potential early prognostic marker for patients [44] with acute cerebral infarction (ACI). NLR is superior to conventional infection markers in the prognostic markers of community acquired pneumonia in the elderly, and it has been applied in the diagnosis of infection status in patients with SLE [45]. These two indicators have become the evaluation content of clinical doctor's choice for patients to make treatment strategies and monitoring care.

CONCLUSION

Adverse prognosis information provided by elevated NLR and PLR in cancer patients has been validated in most studies. Clinical evidence increasingly suggested that systemic inflammation response has a vital role in tumorigenesis and progression of multiple types cancer. Neutrophils can secrete cytokines, such as vascular endothelial growth factors (VEGF), leukocyte interleukins 6 (IL-6), and IL-8, which may help stimulate the malignant-cell growth and survival in the tumor microenvironment [46]. The decrease in lymphocytes indicates that the host immune cells have a poor response to the tumor cells, which may accelerate the progression of the tumor and lead to a worse prognosis. Platelets are also a major source of cytokines and provide an active surface and receptors to promote tumor cell metastasis [4]. Platelets also can be used to cover tumor cells and protect them from immune cells attacking [47]. The NLR and PLR calculated from the peripheral blood visually reflect the malignancy of the tumor and the ability of the body to resist inflammation in some non-neoplastic diseases.

We also found that most of the reports used pre-treatment NLR and PLR as predictors of prognosis, probably because drugs or other factors did not interfere with pre-treatment NLR and PLR, most likely to reflecting the initial state of the tumor before interventional therapy and the potential anti-tumor ability of the body. That is powerful evidence to assess prognosis survival and a key reason for NLR and PLR to be prognostic factors. In the study including enrolled patients receiving chemotherapy, the pre-treatment data should be used to evaluate the prognosis, because radiotherapy and chemotherapy greatly affect the immune status of the body, affecting the prognosis evaluation based on immune inflammation [48], and the ratio after treatment is not suitable for evaluation of prognosis. In addition, NLR and PLR are easy and economy to obtain compared with tumor size and stage, which are promising biomarkers for disease development and prognosis. In short, NLR and PLR can be used as available biomarkers and response to many clinical diseases of progression and survival outcomes, it is also necessary to apply in the formulation of treatment strategy and bedside monitoring.

Limitation and Prospects

We are aware of the limitations in the current studies, the most important is that the cutoff values of NLR and PLR are various. It was found that the prognosis may be affected by the increase of NLR cutoff value [22], which may be raised from tumor heterogeneity, regional, ethnic and analytical tools. Although many studies have stated that their cutoff values are most favorable, they have not been proven in all tumors, which require economically supported and well-planned research to performed in multiple regions in the future. Furthermore, due to the genetic and molecular biology characteristics of different disease groups, it is difficult to clearly determine that the progression of the cancer causes more inflammatory responses or the inflammation itself causes the tumorigenesis and spread, which one is the foremost. Zenan et al. [49] found that NLR and PLR were associated with different molecular subtypes of breast cancer. Studies of different tumor staging confirm the prognostic role of these two markers, but large-scale studies are still needed in tumors of dif-

ferent molecular subtypes. Although the both indicators have better stability, but cannot ignore the effects of concurrent blood system diseases and acute inflammation response. Articles that combine animal experiments and basic research validation was needed to contribute in this regard. In addition, we noticed that most researches are retrospective and susceptible to bias of investigators, therefore, it is necessary to conduct multicenter cohort studies. We can see obviously from above that the threshold of non-cancer patients is generally lower than the cancer groups. Luo et al. [50] have set the normal reference intervals of NLR and PLR in healthy adults. Consequently, we think these markers might have the potential to be a hematological parameter to identify patients between non-cancer and cancer or become an early warning signal of potential cancer, which remains to be clarified in the future researches.

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Declaration of Interest:
The authors declare that there is no conflict of interest regarding the publication of this paper.

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