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Research article

Roles of the systemic inflammatory response biomarkers in the diagnosis of cancer patients with solid tumors

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ABSTRACT

Aim: Cancer is still considered as one of the leading causes of mortality worldwide. Various tumor factors have been used for the diagnosis and follow-up of solid tumors; however, their clinical features remains controversial in terms of their diagnostic, prognostic, and predictive values. In this study, we aimed to investigate the use of the systemic inflammatory response biomarkers, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), in the diagnosis of solid tumors.

Method: We retrospectively analyzed the records of 256 patients with solid tumors, including lung, breast, liver, and pancreatic cancers, who were diagnosed at the outpatient clinics of our institution between January 2017 and July 2018. The neutrophil, lymphocyte, monocyte, and platelet counts were measured using a hematology analyzer and the results were analyzed statistically.

Results: The results of the receiver operating characteristic analysis showed that the NLR and LMR could be statistically reliable biomarkers, with area under the curve (AUC) values of 0.574 ($p = 0.017$) and 0.596 ($p = 0.002$). However, the PLR statistically failed to discriminate the patients and the control subjects, with AUC values of 0.545 ($p = 0.148$).

Conclusions: Certain systemic inflammatory response biomarkers, such as the NLR and LMR, can play roles in the clinical diagnosis of patients with solid tumors.

Keywords: Solid tumors; systemic inflammatory response; diagnosis, neutrophil-to-lymphocyte ratio.

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Introduction

One of the highest worldwide mortality rate is still caused by cancer, which is estimated to be responsible for approximately 9.6 million deaths in 2018 [1]. Moreover, recent evidence shows that one in three people will develop cancer in their lifetimes, and among them, one

in four will die from it [2]. Globally, the most common cause of cancer-related death is resulted from lung cancer that is followed by lung, breast, liver, and pancreatic cancers, which account for approximately one half of all new cases and deaths [1,3–5].

Various tumor biomarkers have been used in the diagnosis and follow-up of solid tumors, including the carcinoembryonic antigen, carbohydrate antigen 125 (CA 125), CA 19-9, α-fetoprotein, and tumor-specific growth factor. However, their clinical usefulness is controversial in terms of their diagnostic, prognostic, and predictive values [6–9]. In the literature, it has been explicitly showed that carcinogenesis and tumor growth are directly linked with chronic inflammation and the host's immune system response [10]. A direct correlation has been shown between systemic inflammation and poor outcomes in many types of solid tumors. However, inflammation has been linked to both the development and progression of cancer [11]. Tumor-associated neutrophils, macrophages, and platelets found in the tumor microenvironment is responsible for the growth of tumors and the spread of metastases, leading to poor outcomes in a variety of malignancies [3,12–14]. The biochemical and hematological biomarkers, such as an elevated C-reactive protein concentration and increased white blood cell, neutrophil, and platelet counts are the most commonly preferred methods for the clinical measure of systemic inflammatory response in cancer patients [15]. The peripheral blood-based parameters have been evaluated as factors that might be linked to a host's immune response. The results has suggested that an increase in the circulating white blood cells might be responsible for the alterations of the neutrophil, lymphocyte, and monocyte proportions. As a results, this may be associated with the systemic inflammatory response. Therefore, the relationships between cancer prognoses and the absolute monocyte count, absolute lymphocyte count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) have been evaluated in various types of cancer [15–17]. Moreover, the chronic systemic inflammatory response has been evaluated in terms of the progression and prognosis of lung, breast, liver, and pancreatic cancers [3,5,16,18,19].

In the present study, it was aimed to investigate the use of the NLR, PLR, and LMR as systemic inflammatory response biomarkers for the diagnosis of solid tumors with the goal of using laboratory tests more effectively in these cancer types. The results of our study will be important in terms of the clinical relevancy of these new peripheral blood parameter indices.

Methods

We retrospectively analyzed the records of patients with lung, breast, liver, and pancreatic cancer solid tumors, who were diagnosed at the outpatient clinics of our institution between January 2017 and July 2018, following an approval from the institutional ethics board (2018/224). Those patients without detailed laboratory data were excluded from the research. In total, 256 patients were enrolled in the present study. Additionally, 132 control subjects, who were healthy individuals presenting for routine check-ups at our institution, were enrolled. Each participant's clinical data, including their age, sex, and first laboratory results after the cancer diagnosis (in the cancer patient group), was obtained from their medical records. Those patients who were with infectious diseases and hematological malignancies, who were suspected of having an infection and who had inconsistent

information were excluded. The neutrophil, lymphocyte, monocyte, and platelet counts were measured using a CELL-DYN 3700 hematology analyzer (Abbott Diagnostics, Abbott Park, Illinois, USA).

Statistical analysis

The statistical analyses were performed using IBM SPSS for Windows version 21 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the patient demographics and biomarkers. The continuous variables were presented as the mean, standard deviation, median, and minimum–maximum. Moreover, the categorical variables were presented as the frequency and percentage. The chi-squared test, independent samples t-test, and Mann-Whitney U test were used to evaluate the categorical, normal, and skewed continuous variables, respectively. A receiver operating characteristic (ROC) analysis was used to evaluate the performances of the biomarkers in discriminating the cases from the controls. The significance level was considered as 0.05 for all of the analyses.

Results

In this retrospective study, 388 subjects were analyzed: 65.9% were cases and 34.1% were control subjects. The distribution of genders within the groups were similar to each other (Pearson chi-squared analysis, p = 0.784). The female percentages in the patient and control groups were 51.6% and 53.0%, respectively.

The results of the comparisons of the ages and biomarkers between the case and control groups are shown in Table 1. The mean age was similar between the cases and controls (p =0,390). Although the platelet, lymphocyte, and monocyte values were not significantly different between the cases and controls, there was a significant difference in the NLRs and LMRs (p=0.017 and p=0.002). In the patient group, the mean NLR value was higher, however, the mean LMR value was lower. Moreover, the mean PLR value was similar between the groups (p = 0.148).

Table 2 shows the results of the ROC analysis used to measure the performance of

Table 1. Comparison of age and biomarker values among the patient and control groups.

Parameters	Groups		*P*
	Patients (n=256)	Control (n=132)	
Gender, Female n(mean) Male	132 (51.6) 124 (48.4)	70 (53.0) 62 (47.0)	0.784
Age	62 (30 – 86)	65 (35 – 92)	0.390
Platelet 10^9/L	251 (38.5 – 571)	249 (111 – 634)	0.942
Lymphocyte 10^9/L	1.76 (0.17 – 4.94)	1.99 (0.27 – 4.11)	***0.037***
Monocyte 10^9/L	0.53 (0.20 – 1.44)	0.50 (0.08 – 1.20)	0.186
Neutrophil 10^9/L	4.52 (0.07 – 14.1)	4.28 (2.14 – 7.74)	0.106
NLR	2.35 (0.05 – 51.2)	2.17 (0.84 – 20.29)	***0.017***
LMR	3.12 (0.49 – 14.5)	4.09 (0.81 – 21.08)	***0.002***
PLR	133 (42.4– 771)	129 (46– 704)	0.148

The values were presented as median(min–max). NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio.

biomarkers in differentiating the cases from the controls. The ROC analysis results showed that the NLR and LMR were significant biomarkers with area under the curve (AUC) values of 0.574 (p = 0.017) and 0.596 (p = 0.002). However, the PLR was not a significant biomarker for discriminating the cases from the controls (p = 0.148). Figure 1 shows the ROC curves of the biomarkers. Based on the results, the LMR curve was below the reference line because the lower LMRs indicated disease states. Therefore, we subtracted the estimated LMR AUC value from one in order to obtain the true AUC value in those cases in which the lower values indicated the disease.

Tablo 2. ROC analysis results for biomarkers.

Biomarker	AUC	95% Confidence Interval	*P*
NLR	0.574	0.515 – 0.632	***0.017***
LMR*	0.596	0.538 – 0.655	***0.002***
PLR	0.545	0.486 – 0.603	0.148

ROC: Receiver operating characteristic analysis, AUC: Area under the curve values, NLR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, PLR: Platelet-to-lymphocyte ratio.

Discussion

Because cancer is one of the leading causes of mortality, a prompt diagnostic evaluation is vital when cancer is suspected. The systemic inflammatory response values could represent new biomarkers for a cancer diagnosis. The systemic inflammatory response is a complex reaction involving changes in the protein and energy metabolism, hematopoietic systems (including the neutrophils, macrophages, and

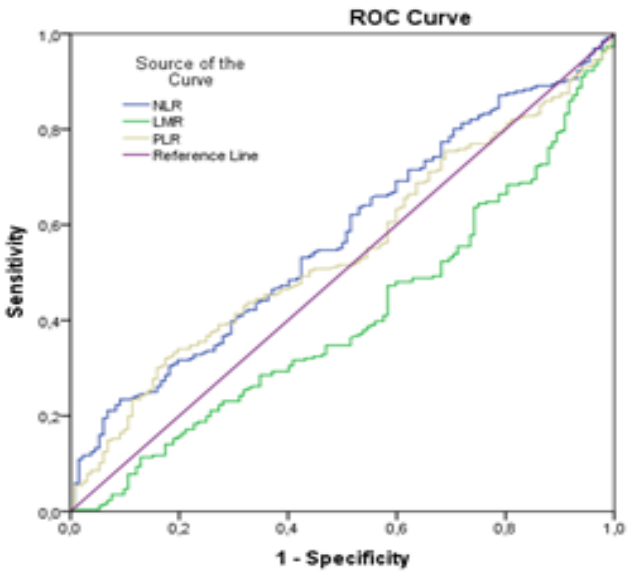

Figure 1. ROC Curves for selected biomarkers.

platelets), and acute phase proteins (including the albumin and C-reactive protein, that albumin is a negative acute phase reactant). Previous studies have shown that the systemic inflammatory response biomarkers play important roles in the preoperative clinical evaluation of patients with solid tumors [2,20,21]. Therefore, we investigated the diagnostic values of the NLR, PLR, and LMR in lung, liver, breast, and pancreatic solid tumor cancer cases. Our results showed that the NLR and LMR can be used as a reliable diagnostic biomarkers.

In their study of 442 patients diagnosed with primary breast cancer, Noh et al. reported that the pretreatment with NLR had prognostic value in breast cancer cases with regard to the disease-specific survival rate and the intrinsic subtype [22]. Gomez et al. also evaluated the preoperative NLR in hepatocellular carcinoma cases, and they reported that, along with the hepatic margin involvement, the NLR was an independent predictor of a poorer cancer-specific survival rate [23]. In the current study, there was a significant difference between the two groups with regard to the NLR (Table 1). Moreover, the results of our ROC analysis of

the discrimination performance showed that the NLR was a significant biomarker with an AUC value of 0.574 (p = 0.017). However, this value displayed a weak performance.

Zhang et al. reported that the preoperative PLR and NLR had prognostic value in 400 lung cancer patients [24]. In their study of 110 patients, who underwent potentially curative resections for pancreatic head cancer, Smith et al. reported that the preoperative PLR had prognostic value regardless of the tumor size and lymph node ratio [25]. In our study, there was not any statistically significant difference between the two groups with regard to the PLR (Table 1). Moreover, the results of the ROC analysis of the differentiation performance showed that the PLR was not considered a reliable biomarker with an AUC value of 0.545 (p = 0.148).

In their study of 145 invasive ductal breast cancer patients, who underwent surgery, Lee et al. reported that the LMR had prognostic value with regard to breast cancer [16]. In our study, there was a significant difference in the LMRs between the two groups (Table 1). Moreover, the results of the ROC analysis of the differentiation performance showed that the LMR was a significant biomarker with an AUC value of 0.596 (p = 0.002). However, this value did suggest weak performance.

The abovementioned studies support the prognostic and predictive values of the preoperative systemic inflammatory response biomarker levels. The aim of our study was to determine the roles of the systemic inflammatory response biomarkers in the diagnosis of cancer. However, in cancer cases, the systemic inflammatory response may simply reflect a nonspecific inflammatory response, secondary to tumor hypoxia and necrosis or local tissue damage [21]. Moreover, the systemic inflammatory response may not happen at earlier stages of cancer, which may explain the low diagnostic value of the biomarkers in the present study.

The actual mechanism of change of laboratory indices in solid tumors is not precise. Elevated neutrophils and monocytes values, decreasing lymphocyte values are changes showing a systemic inflammatory response. These changes are thought to be pathologies secondary to subclinical inflammation of the patients [20].

Our study did have several limitations due to its retrospective study design. In addition, the liver is central to the amplification of the systemic inflammatory response. Upon stimulation, hepatocytes synthesize and release a variety of acute-phase proteins in to the systemic circulation that initiate, sustain, or curtail the systemic inflammatory response [21]. However, the acute-phase proteins, such as albumin and the C-reactive protein, were not included in our study. Finally, this study included a relatively small number of patients. Therefore, further prospective studies using larger sample sizes are required to verify our results.

Conclusions

Systemic inflammatory response biomarkers, such as the NLR and LMR, can play important roles for the clinical diagnosis of patients with solid tumors. The techniques used to measure these biomarkers are widely available and inexpensive; therefore, they can be measured routinely in the diagnosis of cancer patients with minimal additional costs.

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