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Analysis of the Relationship between the Levels of Carcinoembryonic Antigen and Lactate Dehydrogenase, and the Neutrophil/Lymphocyte Ratio in Colorectal Cancer

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Abstract

Background: Tumor markers and inflammatory markers by themselves are associated with prognostic and clinicopathological factors in colorectal cancers. The objective of this study was to explore the relationship between the levels of carcinoembryonic antigen (CEA) and lactate dehydrogenase (LDH), and the neutrophil-lymphocyte ratio (NLR) in colorectal cancer.

Methods: We conducted a retrospective clinical study of 145 patients diagnosed with colon or rectal cancer between January 1, 2013 and December 30, 2014 in two hospitals in Turkey. Only patients whose records contained demographic information (age, gender), pathology reports, and radiology reports were included in the study. The levels of CEA and LDH as well as the LNR were noted.

Results: Of the 145 patients, 87 (60%) patients had colon cancer and 58 (40%) patients had rectal cancer. Over half of all the patients (55.8%) had stage 3 or stage 4 cancer. The median levels of CEA and LDH were in the normal clinical range while the NLR was 2.9. In both colon and rectal tumors, there was a weak positive but statistically significant relationship between CEA, LDH and NLR ($r<25$ and $p<0.05$ in all comparisons). In analyzing the correlation in terms of tumor stage, there was no good correlation. The strongest relationship ($r=0.424$, $p=0.022$) was between CEA and LDH in stage 1 tumors. In all other tumor stages there was no correlation.

Conclusion: In colorectal cancers; CEA, LDH and NLR may be important individually, but no relation appears between them.

Keywords: Colorectal cancer; Tumor markers; Inflammatory mediators

Introduction

Tumors create an inflammation within their own microenvironment and within the host [1,2]. Circulating C-Reactive Protein (CRP) is independently associated with both overall and cancer-specific survival in colorectal cancer [3]. During tumor progression, a huge number of different cytokines and other inflammatory mediators are released into the tumor microenvironment and circulation. As a result of these complex interactions between mediators, host and the tumor, it has been observed that there is an increase in the neutrophil count and a decrease in the lymphocyte count in multiple different cancers including colorectal cancers [4,5].

Carcinoembryonic antigen (CEA) is a widely used tumor marker used clinically to monitor colorectal carcinoma after surgical resection [6,7]. Despite the lack of knowledge about the precise mechanism and role of CEA in normal human physiology and in cancerous tissues, there is strong evidence for the relationship between CEA and the immune system [8-10].

Another important feature of tumors is the alteration in metabolic pathways [11]. Total serum lactate dehydrogenase (LDH) levels are often increased in cancers as a result of an increased energy demand (compensated for by an increase in anaerobic glycolysis) and /or cellular destruction [12,13].

When we considered the Neutrophil/Lymphocyte Ratio (NLR) and the possible behaviors that are a consequence of the tumor-host interaction, we asked if CEA could be a tumor-derived reaction to the host and whether LDH could be a metabolic marker of these immune based interactions. In this study we hypothesized that there should be a strong positive correlation between NLR, CEA and LDH in colorectal cancers which is compatible with tumor stage.

Materials and Methods

Study design and setting

The study took place in two discrete university hospitals. One of the hospital (Yüzüncü Yıl University) is in the east part of Turkey and the other one (Adnan Menderes University) is in the west part of Turkey. Files of patients diagnosed with colon or rectal cancer between January 01, 2013 and December 30, 2014 were searched retrospectively for previously established parameters. Reliable data of a total of 145 cases were further analyzed in this study.

Patients

Patients who had had a biopsy and a proven diagnosis of colon or rectal cancer were included in the study. We included cases that had histopathological colon or rectal adenocarcinoma diagnoses and cases with tumor staging done radiologically or pathologically (postoperative

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specimen based). We excluded cases that had a diagnosis of any kind of an infection that could affect the study parameters. Cases that had been given neoadjuvant therapy were also excluded from the study (due to the probable effects of chemo- or radio-therapy on neutrophil and lymphocyte counts). Cases that had a different concomitant cancer were excluded.

Data collection

All data were collected from patient files registered to a hospital computer system. Patients' demographic (age, gender) information, pathology reports, and radiology reports were recorded routinely in both hospitals. Tumor staging was performed according to the American Joint Committee on Cancer (AJCC 7th edition) TNM staging system. Tumor locations were divided into colon and rectum categories. Pre-treatment serum levels of total LDH were measured from peripheral blood samples taken from the patients. A 4 mL blood sample without hemolysis was analyzed 1 to 2 hours after being drawn from the patient. LDH levels were measured using spectrophotometric methods with an auto-analyzer (C8000 Architect, Abbott, Abbott Park, IL, USA) and the normal range was designated as 125-220 U/L. As a routine pre-treatment work-up, Complete Blood Count (CBC) was studied from peripheral blood samples. Neutrophil and lymphocyte counts were collected from these CBC results. The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. An initial CEA test was typically ordered prior to treatment as a "baseline" value in both hospitals. Measurement of the CEA level was measured by enzyme-linked immunosorbent assay (ELISA) using an auto-analyzer (C8000 Architect, Abbott, Abbott Park, IL, USA) and the normal range was designated as 0.0-5.0 ng/mL.

Statistical analyses

Once all nominal, categorical and continuous (gender, tumor site, tumor stage, CEA, NLR and LDH) variables were entered into the computer, analyses were performed using SPSS version 20 (SPSS, Chicago, ILL) statistical analysis software. Descriptive analyses were presented using frequencies for ordinal variables, using median and minimum-maxımum for non-normally distributed variables, using mean and standard deviation for normally distributed variables. For categorical and nominal variables comparisons were done by χ^2 or Fisher's exact test where appropriate. The Mann-Whitney U test was used to compare CEA, NLR and LDH levels between tumor locations and the Kruskal-Wallis test was conducted to compare these parameters with the tumor stage. While investigating the associations between non-normally distributed (CEA, NLR, LDH) and/or ordinal variables (tumor stage and location), the correlation coefficients and their significance were calculated using the Spearman test. A 5% type 1 error was used to infer statistical significance.

Results

Out of 145 cases, the majority of the patients were male with a mean age of 63.5 (Table 1). Most of the cases had colon cancer (60%) rather than rectal cancer and over half of the cases (55.8%) were stage 3 or stage 4 cancers. There was a significant difference between tumor location and cancer stage (p=0.032); 65.5% of colon tumors were stage 3 or over, whereas 58.6% of rectal tumors were stage 2 or stage 1.

Levels of CEA and LDH and the NLR according tumor location and stage

As seen in Table 2, the mean levels of CEA and LDH and the NLR exceeded the normal range, while the median values were in the normal range. Because the values of these three variables were not normally distributed, we used the median values for all subsequent analyses.

As shown in Table 3, the median value of CEA was within the normal range although it was higher in colon tumors rather than rectal tumors which may be because a higher proportion of the colon tumors are more advanced in stage. Like the CEA values, the median value of the NLR was higher in colon tumors than in rectal tumors, but the difference was not statistically significant (Table 3). The median LDH level was also higher in colon tumors but not significantly so.

The NLR and LDH levels were not significantly different based on tumor stage (p=0.656 and 0.727, respectively) while, the CEA level was significantly different based on tumor stage (p=0,001). The median and minimum-maximum levels of the CEA were: 2,30 (0,74-327) for stage 1, 3,00 (0,58-23,11) for stage 2, 3,23 (0,60-106,30) for stage 3, and 6,53 (1,09- 852,98) for stage 4.

The association between the levels of CEA and LDH and the NLR

First, we performed the correlation of CEA, LDH and the NLR for both colon and rectal tumors (Table 4). In both tumor locations, there was a weak positive but statistically significant relationship between CEA, LDH and NLR (Figure 1).

When we analyzed the relationship between the CEA and LDH levels and the NLR separately according to tumor location, we observed that the CEA, LDH and NLR values in rectal tumors had no significant correlation while in colon tumors there was a low but significant correlation between the CEA level and the NLR (Table 5).

There was no good correlation between tumor stage and the CEA and LDH levels and the NLR. The strongest relation (r=0.424 p=0.022) was between the CEA and LDH levels in stage 1 tumors. In all other stage tumors there was no correlation.

Over all, we observed that there was no relationship between the following important tumor biomarkers: CEA and LDH levels and the NLR.

Gender (Female/Male)		62/83
Age (mean ± standard deviation)		63.5 ± 12.5
Stage (Frequency, Percent)	**1**	29 (20%)
	2	35 (24.1%)
	3	46 (31.7%)
	4	35 (24.1%)
Side (Frequency, Percent)	**Colon**	87 (60%)
	Rectum	58 (40%)

Table 1: Characteristics of patients and tumors.

		CEA (ng/ml)	NLR	LDH (U/L)
N		**145**	**145**	**145**
Mean		**24.9096**	**5.0531**	**239.63**
Median		**3.3200**	**2.8500**	**210.00**
Std. Deviation		**91.34354**	**8.21684**	**101.785**
Range		**852.40**	**82.76**	**504**
Percentiles	**25**	**1.9650**	**2.0200**	**178.00**
	50	**3.3200**	**2.8500**	**210.00**
	75	**7.8750**	**5.0600**	**278.00**

CEA: Carcinoembryonic antigen, NLR: Neutrophil-lymphocyte ratio, LDH: Lactate dehydrogenase

Table 2: Descriptive values of the levels of CEA and LDH and the NLR for all cases.

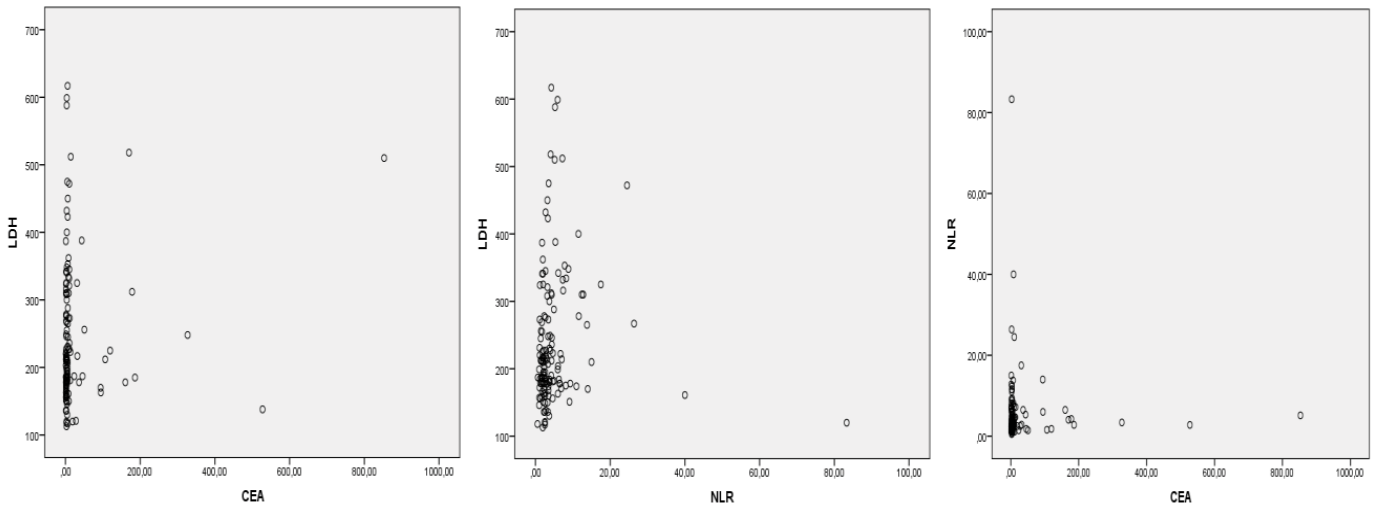

Figure 1: Scatter plot of the relationship between the levels of CEA and LDH and the NLR in all cases (CEA: Carcinoembryonic antigen, NLR: Neutrophil-lymphocyte ratio, LDH: Lactate).

	Colon	Rectum	Total	P
CEA ng/mL	3.6	3.1	3.32	0.302
Median	5.96	6.26	6.1	
Interquartile range				
NLR (Median)	3.2	2.8	2.85	0.750
Interquartile range	3.45	2.65	3.03	
LDH U/L (Median)	212	206	210	0.832
Interquartile range	104	103	100	
CEA: carcinoembryonic antigen, NLR: Neutrophil-lymphocyte ratio, LDH: Lactate dehydrogenase, MW-U: Mann Whitney U.				

Table 3: The significance of CEA, LDH and the NLR levels according tumor location.

	Spearman's rho	p
CEA-NLR	0.18	0.034
CEA-LDH	0.20	0.022
LDH-NLR	0.22	0.009
CEA: carcinoembryonic antigen, NLR: Neutrophil-lymphocyte ratio, LDH: Lactate dehydrogenase.		

Table 4: Correlation between the levels of CEA and LDH and the NLR in all cases.

	Colon		Rectum	
	Spearman's rho	**p**	**Spearman's rho**	**p**
CEA-NLR	0.226	0.036	0.105	0.431
CEA-LDH	0.152	0.160	0.236	0.074
LDH-NLR	0.198	0.66	0.203	0.126
CEA: Carcinoembryonic antigen, NLR: Neutrophil-lymphocyte ratio, LDH: Lactate dehydrogenase				

Table 5: Correlation between the levels of CEA and LDH and the NLR according to tumor location.

Discussion

After the discovery of the CEA as a tumor associated antigen in human serum nearly five decades ago, it has been used as a tumor marker, especially in monitoring the progress of colorectal cancer following surgery [6,14]. Despite wide clinical use of CEA, preoperative levels of CEA may be in the normal range, as observed in our study. Lee et al. [15] reported that the preoperative CEA level in 66% of cases was less than 5 ng/ml, which is considered within the normal range. In our study, CEA levels increased with tumor stage; the median CEA value in stage 1 tumors was 2.3 and 6,53 in stage 4 tumors.

Increased levels of LDH have been found in many malignancies and a precise relationship between LDH expression and tumor growth has been assessed [12,13]. Scartozzi et al. reported that the preoperative LDH level was a good predictive factor in assessing chemotherapy efficacy [16]. Interestingly, the median level of LDH was in the normal range in our study. In a recent study, Caputo et al. reported that the LDH level was in the normal range in 56.2% of non-metastatic colorectal cancer patients [17]. In the same study, the authors concluded that, "Preoperative serum levels of LDH alone failed to demonstrate a prognostic role in a selected series of colorectal cancer patients". Similar to the results of our study, Caputo et al. did not find a statistically significant difference between the LDH level and tumor stage. The relation between the LDH level and colorectal cancer is controversial in the literature and is still being investigated.

The relationship between malignancy and inflammation has been investigated and speculated for a long time [1,2]. In recent years, the NLR gained exaggerated fame in the field of inflammation and cancer [4]. Since the NLR can be easily measured and calculated from a blood sample, and since it is a cheap method, it has been investigated and accepted as a prognostic factor in many malignancies [5,18-21]. In a systematic review of all these studies, Guthrie et al. reported that only four of eleven colorectal cancer studies reported the NLR as an independent prognostic factor with a weighted average hazard ratio of 1.4 [4]. Moreover, the authors concluded that the NLR is more consistently an independent prognostic factor in patients with upper gastrointestinal malignancies. The heterogeneity in the threshold level of the NLR in the reported studies is another important problem [18-21]. The threshold level for the NLR range is between 2 to 5 [4]. Accordingly, if we assume the threshold as 2 or 3 we could say that, in our study, an elevated NLR was associated with clinicopathological factors. But, like most studies in the literature, we considered an NLR threshold of five. That is, we did not observe any relation between tumor stage and the NLR.

The main objective of this study was to clarify the probable relation between the levels of CEA and LDH and the NLR, which has not been investigated to date. Our results showed that there was no overall correlation. In stage 1 tumors, the correlation between the levels of CEA and LDH (r=0.424 p=0.022), which is moderate to weak, was the strongest relation in the study. Therefore, the level of CEA, that appeared to be associated with tumor stage in this study and in other studies, was not related to the NLR. We found that there was a low but significant positive correlation between these variables (Table 4). As a consequence of the discrepancies between the p value' and the correlation coefficient, we concluded that the p value may be an artifact of a large sample size (n=145) or the low correlation coefficient (r<0, 30 in most comparisons) may be the result of some extreme values in the study.

The main drawbacks of this study were the retrospective design and lack of ability to control for potential confounding factors, such as medications and cigarette use.

Consequently, we think that the relationship between the NLR and levels of LDH and CEA is not linear and needs to be investigated further.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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