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ORIGINAL ARTICLE

Prognostic role of De Ritis and basal neutrophil to lymphocyte ratio in patients with advanced stage pancreatic cancer [Izmir Oncology Group (IZOG) Study]

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Summary

Purpose: *We aimed to investigate the prognostic significance of neutrophil/lymphocyte ratio (NLR), an indirect indicator for the immune response and AST/ALT ratio (De Ritis), liver enzymes that are commonly used in various clinical fields, in patients with advanced-stage pancreatic cancer.*

Methods: *NLR and De Ritis of the patients with diagnosis of locally advanced and metastatic pancreatic cancer between the 2010-2017 were evaluated retrospectively. All patients were divided into two groups as high and low according to NLR and De Ritis cut-off values which were 2.4 and 0.75, respectively.*

Results: *A total of 191 patients were evaluated. The mean overall survival (OS) in patients with NLR<2.4 at the time of diagnosis was 10±0.8 months, while it was 4±0.49 months in patients with NLR>2.4 (p<0.0001). The mean OS of the patients with a De Ritis <0.75 was 8±1.2 months, whereas the survival of those with De Ritis >0.75 was 6±0.74 months (p=0.024). The mean progression free survival (PFS) in patients with NLR<2.4 and De Ritis <0.75 at diagnosis were 5±0.76 months and 6±0.87 months respectively, whilst it was 3±0.37 months in patients with NLR>2.4 (p=0.017) and 4±0.3 months in patients with De Ritis >0.75 (p=0.14).*

Conclusions: *The NLR and De Ritis are associated with prognosis in many cancers and have been found to be associated with survival outcome in advanced-stage pancreatic cancer patients.*

Key words: *pancreatic cancer, advanced stage, neutrophil/lymphocyte ratio, De Ritis, prognosis*

Introduction

Pancreatic ductal adenocarcinoma is one of the most aggressive solid malignancies. Despite a low incidence, it remains the fourth leading cause of cancer-related deaths [1,2]. Only 20% of patients diagnosed with pancreatic cancer (PC) are eligible for surgical resection, and a significant proportion of patients present with local and distant spread at the time of diagnosis with a very poor 5-year survival [3,4]. Thus, identifying advanced stage PC patients with a high possibility of early progression is important for improving their prognosis. So, it is important to use reliable prognostic markers that are especially easy to measure using non-invasive techniques [5].

The importance of inflammation and biomarkers reflecting the inflammatory state in malignant diseases is known. During the inflammatory response, the rates of circulating leukocytes may

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change. The physiological response of leukocytes to stress is increased neutrophil count and a corresponding decrease in the relative lymphocyte count. Therefore, it has been suggested that neutrophil/lymphocyte ratio (NLR) can be used as a simple indicator of inflammation linked to cancer, and is even compatible with the severity and prognosis of the disease [6-8]. A recent meta-analysis suggested that NLR may be a simple and noninvasive blood biomarker for identifying patients with poor prognosis in colorectal cancer [9]. The relationship between NLR and survival in patients with metastatic breast cancer was evaluated in a meta-analysis and found that it could be used as a prognostic factor [10]. In the same way, several studies have been conducted with many malignancies such as lung, gastric, bladder, ovarian and also prostate cancer [11-16].

The rate of serum activities of aspartataminotransferase (AST) and alaninaminotransferase (ALT) was first defined by Fernando De Ritis in 1957 and since then the ratio between AST and ALT activities (AST/ALT) is known as De Ritis ratio [17]. AST and ALT are enzymes released from the liver into the blood, but are also secreted from both malignant and non-malignant cells, and in some studies, it has been proved to be of value for inferences from some cancer types (urothelial carcinoma, renal cell carcinoma, cholangiocarcinoma, gastric adenocarcinoma and head and neck cancers) [18-23].

One of our aims in this study was to investigate whether NLR is a prognostic factor in pancreatic cancer cases and its relationship with the course of the disease. Another research subject was to investigate whether the De Ritis, which can be easily assessed from peripheral blood such as NLR, has prognostic significance in advanced-stage pancreatic cancer patients.

Methods

The patients who applied to the medical oncology clinic of Izmir Katip Celebi University Ataturk Research and Training Hospital between 2010-2017 were retrospectively enrolled. The patients who were followed with the diagnosis of locally advanced or metastatic pancreatic cancer were analyzed. Informed consent was obtained from all the participants and the institution's ethics committee approved the study.

All haematological parameters including neutrophil, lymphocyte, and AST, ALT values were determined at the time of diagnosis before any treatment. Patients who had chronic diseases such as diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, hematologic diseases, rheumatic diseases, renal and hepatic failure, infection, or use of a drug which might affect serum haematological and hepatic values, were excluded from the study. Age, gender and other demographic data of the patients, TNM stages, clinicopathological features, and death dates were recorded. In addition, chemotherapy regimens of patients were evaluated in detail as first and subsequent treatments.

The ratio of neutrophil count to lymphocyte count was calculated based on the hemogram of the patients at the time of diagnosis. The number of white blood cells and the percentage of particular types of cells were determined with hemocytometer 'Sysmex'. Cut-off value was calculated according to receiver operating characteristics (ROC) curve. All patients were divided into two groups as high and low according to NLR ratio 2.4 as the cut off value.

The ratio of AST to ALT was calculated at the time of diagnosis and these hepatic enzymes were determined with biochemistry analyzer 'Architect'. The cut-off value was also calculated according to the ROC curve. All patients were divided into two groups as high and low according to De Ritis ratio 0.75 as the cut-off value.

Statistics

Statistical evaluation of the data was performed using the SPSS 24.0 for Windows package program. Descriptive analyses were evaluated based on frequencies, means and standard deviations for the variables. Overall survival (OS) was defined as the time of diagnosis to the last oncological follow-up or until death. Progression-free survival (PFS) was defined as the time from pathological diagnosis until disease progression or death by any cause before disease progression. Kaplan-Meier method was used in survival analysis and the survival of the groups was compared with the log-rank. P value <0.05 was considered statistically significant.

Table 1. Demographic characteristics of the patients

Characteristics	*n (%)*
Gender	
Female	78 (40.8)
Male	113 (59.2)
Disease status	
Locally advanced	43 (22.5)
Metastatic	148 (77.5)
Chemotherapy receiving status	
Chemotherpy not received	43 (22.5)
First-line chemotherapy	148 (77.5)
Second-line chemotherapy	57 (29.8)
Third-line chemotherapy	17 (8.9)
Surgical procedures	
Paliative surgery	11 (5.8)
Surgical exploration	6 (3.1)
Surgery not performed	174 (91.1)
Survival status	
Survivors	9 (4.7)
Deceased	182 (95.3)

Results

191 patients with locally advanced and metastatic pancreatic cancer were evaluated. The mean age of the patients was 61.5 (31-84). Seventy eight (40.8%) of the patients were female and 113 (59.2%) male. Forty-three of these patients (22.5%) were with locally advanced disease and 148 (77.5%) had metastatic disease at diagnosis. Eighteen patients (8.9%) had surgical operation; 7 patients (3.1%) had surgical exploration with biopsy only, 11 (5.8%) had palliative surgery. Most of the patients (n=173, 91.1%) were considered inoperable and had no surgical operation. During the follow-up, 182 patients (95.3%) died. Demographic characteristics of the patients are given in Table 1.

Forty-three (22.5%) of the 191 patients did not undergo chemotherapy because of comobidities, poor performance status or patient denial, while 148 (77.5%) had received first-line chemotherapy. Almost half (n=76) of these 148 patients were given single-agent gemcitabine as a first-line treatment; 54 patients were treated with the combination of cisplatin or carboplatin/gemcitabine, 9 patients

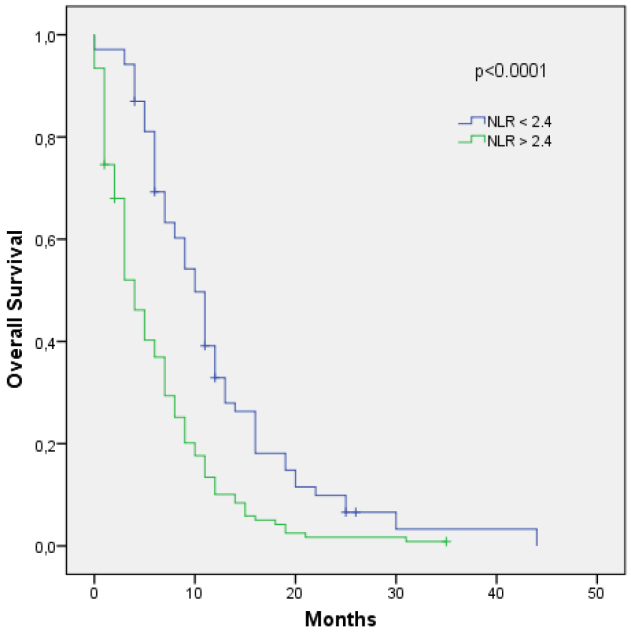

Figure 1. The effect of NLR on overall survival.

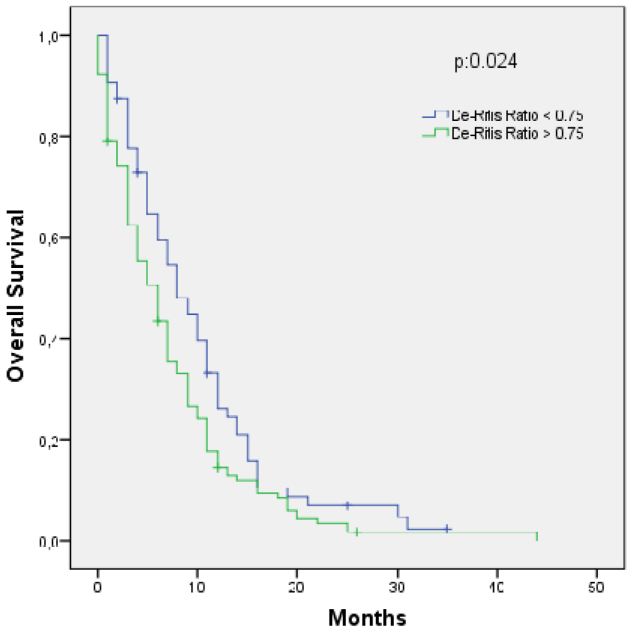

Figure 2. The effect of De Ritis on overall survival.

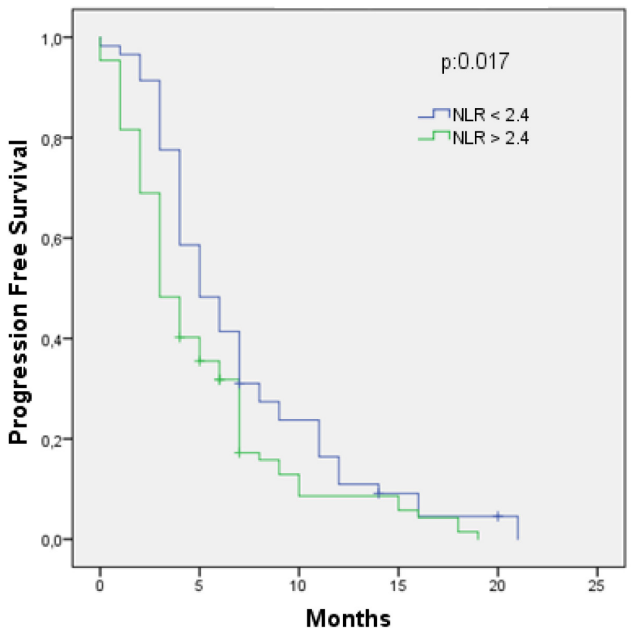

Figure 3. The effect of NLR on progression free survival.

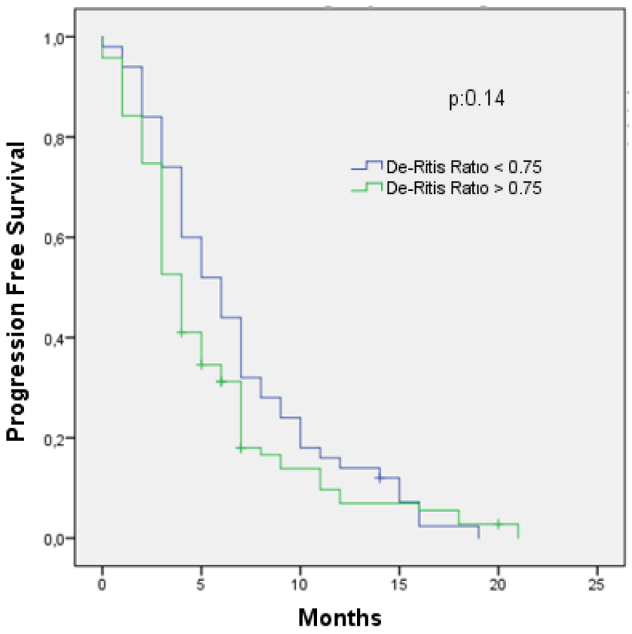

Figure 4. The effect of De Ritis on progression free survival.

Table 2. Survival rates of patients according to NLR and De Ritis

NLR	*n*	*Mean OS (months)*	*p*	*Mean PFS (months)*	*p*
NLR <2.4	49	10±0.8	p<0.0001	5±0.76	0.017
NLR >2.4	142	4±0.49	p<0.0001	3±0.37	0.017
De Ritis	*n*	*Mean OS (months)*	*p*	*Mean PFS (months)*	*p*
De Ritis <0.75	63	8±1.2	0.024	6 ±0.87	0.14
De Ritis >0.75	128	6±0.74	0.024	4 ±0.3	0.14

with 5-florouracil (5-FU)/oxaliplatin/irinotecan combination, 3 with gemcitabine/capecitabine combination, 3 with 5-FU or capecitabine/oxaliplatin combination and 3 with single-agent chemotherapy other than gemcitabine. Of 148 patients who received first-line chemotherapy, 57 (38.5%) received second-line chemotherapy and 91 (61.5%) patients were unable to continue chemotherapy. Twenty-four of 57 patients receiving chemotherapy were treated with capecitabine plus oxaliplatin, 6 were treated with single-agent capecitabine and 4 were treated with single-agent gemcitabine. Only 17 (29.8%) of the 57 patients who received second-line chemotherapy received a third-line chemotherapy regimen, and 40 (70.2%) patients were unable to continue treatment.

The mean OS of the patients with NLR ratio below 2.4 (n=49) was 10±0.8 months, while the mean OS rate was 4±0.49 months in patients with NLR ratio over 2.4 (n=142) (p<0.0001) (Figure 1). The mean OS was 8±1.2 months in patients with De Ritis ratio below 0.75 (n=63) and the mean OS in patients with Ritis ratio over 0.75 (n=128) was 6±0.74 months (p=0.024) (Figure 2) (Table 2).

The mean PFS of the patients with a NLR ratio with less than 2.4 was 5±0.76 months, while the mean PFS for those over 2.4 was 3±0.37 months (p=0.017) (Figure 3). The mean PFS of the patients with De Ritis below 0.75 was 6±0.87 months, and the mean PFS for those over 0.75 was 4±0.3 months (p=0.14) (Figure 4). Although the mean survival rate was higher in patients with low de Ritis, it was not statistically significant (Table 2).

Discussion

NLR is a cheap, repeatable and widely used marker and it has been found to be an important prognostic marker for a number of malignant tumors [11-16] and recent studies have shown that the AST/ALT ratio can be a potential biomarker to identify patients with poor prognosis for certain types of malignancies [18-23]. In our study, advanced stage pancreatic cancer patients with a high NLR at the time of diagnosis had significantly worse survival time than those with a normal NLR. Similarly, De Ritis over 0.75 was found to be associated with a shorter OS when compared with De Ritis below 0.75 for the same patient population.

It is well known that inflammation contributes to the development and progression of cancer and the high neutrophil count is an indicator of systemic inflammation. Increasing in neutrophil number can induce the development and progression of the neoplasm, providing an adequate environment for tumor growth [24]. In particular, neutrophils and vascular secretion of inflammatory cytokines including interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor alpha (TNF-α) and proangiogenic endothelial growth factors provide a tumor microenvironment suitable for cancer progression. In addition, increased levels of IL-10 and TNF-α result in a reduction in the number of lymphocytes, an important component of the natural and adaptive immune response, and play an important role in the immune surveillance process against cancer cells. Thus, both the neutrophil-dependent inflammatory reaction and the lymphocyte-mediated immune response are associated with tumor progression [25].

Several studies have potentially demonstrated the relationship between NLR values and its prognostic impact in patients with pancreatic cancer. Engelken et al found that leukocytosis was an independent predictor of poor survival for patients with unresectable pancreatic cancer treated with palliative care [26]. In a study conducted by Fogar et al total lymphocyte counts in blood in pancreatic cancer patients were found to be lower than those with benign pancreatic disease. Furthermore, lymphocytes were found to be lower in advanced-stage (IIB-IV) patients compared to patients with early stage (0-IIA) disease. In conclusion, the number of circulating lymphocytes can negatively predict the survival of patients with pancreatic cancer independent of the tumor stage [27]. Ong et al reported a high NLR level as a surrogate marker in potentially resectable pancreatic adenocarcinoma patients [28]. In a Chinese study, preoperative NLR and circulating regulatory T cells were found as

independent prognostic factors for OS in early-stage pancreatic cancer patients. High NLR levels in combination with the presence of regulatory T cells, which is a reflection of decreased immune status, are associated with a poor prognosis [29]. Similarly, in operable pancreatic head cancer patients, serum NLR and CA19-9 measured before pancreatectomy provided significant prognostic information associated with OS [30]. In the setting of metastatic pancreatic cancer patients both Guo and Piciucchi et al [31,32] concluded that pretreatment higher NLR values were significantly associated with poor survival. The results of these studies are consistent with the results of our study.

Mechanisms lying under the relationship of AST and ALT in cancer metabolism are not fully understood. While AST is widely expressed in different tissue types, it is likely that the prognostic significance of this ratio in malignancies is not yet sufficiently elucidated as ALT is considered to be more specific for the liver [33]. Glucose metabolism is one of the hypotheses put forward in previous publications. Aerobic glycolysis generally occurs in actively proliferating cancer cells and AST seems to be more active than ALT [34,35]. AST plays an important role in aerobic glycolysis through nicotinamide adenine dinucleotide hydrogen (NADH) generated in the cytoplasm into the mitochondria by malat-aspartate shuttle [36]. It is noteworthy that ALT is mainly present in the cytoplasm of the cell while AST may be found both in the cytoplasm and mitochondria. The increased De Ritis ratio may indicate dysfunction at the mitochondrial level, which may cause increased oxidative stress [37-39].

De Ritis was defined as an appropriate prognostic marker for cholangiocarcinoma and was associated with poor prognosis [18]. Recently, studies on prostate cancer, renal cell carcinoma and upper tract urothelial carcinoma have revealed the prognostic role of AST/ALT ratio in urological malignancies [19-21]. The AST/ALT ratio was also demonstrated to be a prognostic factor of head and neck squamous cell carcinoma and gastric adenocarcinoma [22,23]. In addition, De Ritis has proven to be a biomarker with a prognostic role in non-malignant diseases, including cardiovascular-related death in diabetic patients [40]. We could not find any study in the literature evaluating the prognostic impact of De Ritis in advanced-stage pancreatic cancer patients. Serum AST was determined in a multifactorial prognostic model including albumin, CA 19-9, alkaline phosphatase, lactate dehydrogenase, leucocytes and blood urea nitrogen in order to stratify individual pancreatic cancer patient risk and improve the prediction of their survival [41]. Both serum AST and ALT were used together with neutrophil, lymphocyte, platelet, CA19-9, total bilirubin, albumin and alkaline phosphatase in a systemic immune-inflammation index to evaluate their prognostic significance and found them as independent prognostic markers for patients with advanced pancreatic cancer [42].

Although this was a retrospective analysis with limited number of sample size, an important feature of this study is that all patients were selected from a homogeneous group, including only patients with locally advanced and metastatic pancreatic cancer. In summary, we found an association between increased NLR and De Ritis with decreased OS in patients with advanced-stage pancreatic cancer. In daily clinical practice, the measurement of NLR and De Ritis at the time of diagnosis which is a simple method to determine can be widely applied to identify patients at risk of poor outcome.

Conflict of interests

The authors declare no conflict of interests.

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