

Prognostic role of pretreatment de ritis and neutrophil to lymphocyte ratio in neuroendocrine carcinoma patients (Izmir oncology group study)

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Abstract

Aim: Neutrophil/lymphocyte ratio (NLR) and AST/ALT ratio (De Ritis) were found to be prognostic in several cancers. So, our aim was to investigate the prognostic importance of these parameters and clinicopathological characteristics in patients with neuroendocrine carcinoma (NEC).

Material and Methods: We retrospectively reviewed 101 NEC patients diagnosed in the last decade. The values of NLR and De Ritis were assessed at the time of diagnosis and their cut-off values were determined as 5 and 1.04 by receiver operating characteristics analysis. The prognostic role of high or low NLR and De Ritis according to these cut-off values and patient or tumor characteristics on clinical outcome was evaluated.

Results: Among 101 patients, 77 were metastatic and 24 were early or locally advanced stage. Almost all patients were death at the time of data analysis (n:90). Twelve patients were treated with adjuvant chemotherapy or radiotherapy while 41 metastatic patients had received first-line chemotherapy. Median overall survival (OS) and progression free survival (PFS) was 7 months and 5 months in NLR low group and 6 months and 4 months in NLR high group (p:0.043, p:0.354), respectively. Median OS was 9 months in De Ritis low group and 5 months in De Ritis high group (p:0.004) while median PFS was 5 and 4 months in De Ritis low and high group of patients (p:0.077).

Conclusion: Low De Ritis showed a strong and low NLR showed a weaker association with improved prognosis in patients with NEC.

Keywords: De Ritis; neuroendocrine carcinoma; neutrophil to lymphocyte ratio; prognosis

INTRODUCTION

Neuroendocrine carcinomas (NECs) are high-grade, poorly differentiated neoplasm which has an aggressive clinical course that is characterized by early and widespread metastases. In patients with loco-regional disease undergoing surgical resection, adjuvant chemotherapy with or without radiotherapy is necessary in most cases. Systemic chemotherapy with cisplatin or carboplatin plus etoposide is recommended for both the adjuvant setting and advanced stage disease. Salvage chemotherapy options for patients with NEC is also very limited and associated with modest response rates. So, they usually relapse and the overall survival is poor (1,2).

The prognostic markers for NEC were unclear and there is limited number of studies about this subject which were usually done in pulmonary large cell neuroendocrine carcinoma. Stromal cells within histological vascular invasion and molecular markers like programmed cell death ligand 1 (PD-L1) and CD8 were investigated only in large cell NEC of the lung (3-8) while laboratory and pathologic markers like Ki67 and epidermal growth factor receptor (EGFR) were investigated in extra-pulmonary NEC (9-13).

Circulating neutrophils have been shown to produce many cytokines and chemokines, and increase in their number may provide an adequate environment for

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tumor progression (14,15). Lymphocytes take an active role in many immune functions and decrease in their number may cause to deteriorate anti-tumor immunity and can worsen cancer prognosis (16). So, neutrophil/lymphocyte ratio (NLR) is an indirect indicator for the immune response and its prognostic role was defined in various cancer types (17-25). In the literature, there is only one study evaluating the relationship between NLR and neuroendocrine carcinomas. Only patients with large cell NEC were included and preoperative NLR was found to be inversely correlated with post-resection survival rates and NLR was concluded as a prognostic marker in this group of patients (26).

Serum activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and their ratio 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 (27). These enzymes are released into the blood from the liver. However, they are also secreted from both non-malignant and malignant cells of several cancer types like urothelial carcinoma, renal cell carcinoma, cholangiocarcinoma, gastric adenocarcinoma and head and neck cancers which have been proved to be a prognostic factor (28-33).

The aim of the study is to investigate whether clinicopathological characteristics, NLR and De Ritis which are easily and routinely detected in clinical practice, has some prognostic significance in patients with NEC.

MATERIAL and METHODS

Patients with the diagnosis of NEC who were treated and followed-up by the medical oncology clinic of Izmir Katip Celebi University Atatürk Research and Training Hospital between the years of 2007 - 2018 were retrospectively analyzed. All stages of NEC patients were included in the study. Patients with any chronic diseases, infection, or drug usage which are metabolized in liver were excluded from the study. Demographic characteristics and clinicopathological features of the patients, TNM stages, their operation details and treatment regimens were all determined.

Neutrophil, lymphocyte, AST and ALT values were recorded at the time of diagnosis before any treatment. The ratio of neutrophil count to lymphocyte count was calculated based on the hemogram which was determined with hemocytometer 'Sysmex'. These hepatic enzymes and their ratio were calculated with biochemistry analyzer 'Architect'. We performed receiver operating characteristics (ROC) analyses to determine the appropriate cut-off values. All patients were divided into two groups as high and low according to NLR ratio 5 and De Ritis ratio 1.04 as the cut off value.

Overall-survival (OS) was defined as the time from the diagnosis to the patient death or last oncological follow-up. Progression free survival (PFS) was defined as the time from pathological diagnosis to the disease progression

or death by any cause before disease progression. Qualitative variables have been presented as frequencies and percentage while quantitative data are presented as means, medians, and ranges. For survival analysis Kaplan-Meier method was used and the survival of the groups was compared with the log-rank. All statistical tests were two-sided, and p value <0.05 was considered statistically significant. SPSS version 20.0 (SPSS Inc., Chicago, IL) was used for all statistical evaluation of the data.

RESULTS

Table 1. Patients' characteristics

Characteristics	Number (n)	%
Gender		
Female	29	29
Male	72	71
Primary Tumor Localization		
Lung	33	32
Esophagogastric	16	16
Colorectal	12	12
Pancreas	12	12
Head and Neck	7	7
Gynecologic	6	6
Gall bladder	2	2
Rare primaries	7	7
Primary Unknown	6	6
Disease status		
Metastatic group	24	24
Non-metastatic group	77	76
Primary tumor (T)		
T1	1	34
T2	5	18
T3	12	42
T4	10	36
Adjuvant Treatment		
Yes	20	20
No	81	80
De Ritis		
High	66	65
Low	35	35
NLR		
High	49	49
Low	52	51
Eksitus		
Yes	90	89
No	11	11

NLR: Neutrophil/lymphocyte Ratio; De Ritis: AST/ALT ratio

Between May 2007 and December 2018, patients with the diagnosis of NEC at the medical oncology department of our hospital were analyzed and those with complete medical records and follow-up dates (n = 101) were included. There were 72 men and 29 women in the study group with a median age of 61 years (interquartile range, 55.5 - 69.5 years). Lung was the most primary tumor localization of the patients (n:33) with decreasing frequencies; esophagogastric (n:16), colorectal (n:12), pancreas (n:12), head and neck (n:7), gynecologic (ovarian, endometrium, cervix and breast; n:6), gall bladder (n:2), other rare primaries (n:7) and primary unknown (n:6). Majority of the patients had small cell NEC (n:21) while the others had large cell (n:18) or undefined (n:62) (Table 1-2).

Only very limited number of patients had the chance to be operated (n:28) because of locally advanced stage

disease or distant metastasis. R0 resection was done in 21 patients and R1 resection in 1 patient. The other operations were either R2 or palliative resections. The median numbers of extracted and positive lymph nodes were 22 and 4. The stage of the patients at diagnosis were; I, II, III and IV in 2, 6, 16 and 77 patients, respectively. Tumor recurrence or metastases were observed in 11 patients during the follow-up period. Although most of the patients developed multiple recurrence and metastatic episodes, the main patterns of recurrence or metastasis were recorded as the first site in which the most common one was liver followed by lymph node, brain, lung, locoregional recurrence and other rare sites (42%, 21%, 16%, 8%, 6% and 7% respectively).

Table 2. Overall survival and progression free survival of patients according to NLR and De Ritis Ratio

	All patients	NLR high	NLR low	p	De Ritis high	De Ritis low	p
Median OS (month)	7	6	7	0.043	5	9	0.004
Median PFS (month)	5	4	5	0.354	4	5	0.077

OS: Overall Survival; PFS: Progression Free Survival

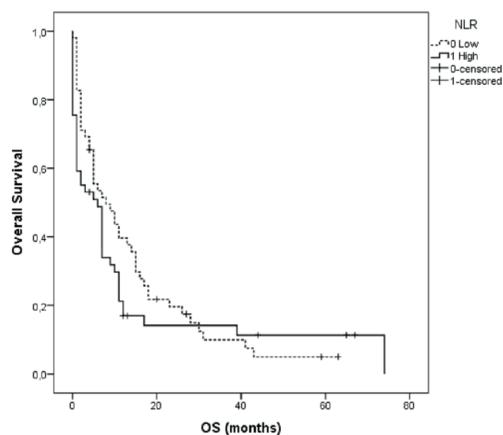


Figure 1. Overall survival curves of all patients stratified by NLR

Ten patients received postoperative adjuvant chemotherapy with a median number of 6 cycles, four patients received adjuvant radiotherapy and six patients received both adjuvant chemotherapy and radiotherapy (cisplatin + etoposide in all of them). Number of the patients who died in the first and second months after diagnosis was 14 (13.8%) and 17 (16.8%) and thus they did not receive any treatment and only 11 patients were alive at the time of data analysis. Forty-seven patients (53%) did not undergo first-line chemotherapy regimen because of death, poor performance status, comorbidities or patient denial; while 41 (47 %) had received first-line chemotherapy. Almost all patients were treated with the combination of cisplatin plus etoposide whereas

the others were treated with either cisplatin or 5-FU based combinations. Only 14 of the 41 patients received a second-line chemotherapy regimen, and 27 (65 %) patients were unable to continue treatment.

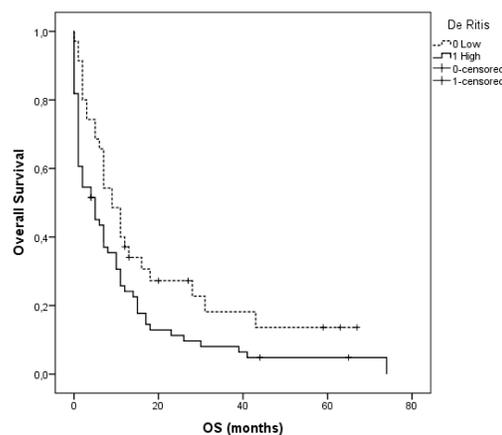


Figure 2. Overall survival curves of patients stratified by De Ritis

Median OS for all patients were 7 months (%95 CI 5.2 - 8.7). The effect of NLR on OS was investigated and median OS was found to be 7 months (%95 CI 3.2 - 10.7) and 6 months (%95 CI 2.6 - 9.3) in low and high NLR group respectively (p:0.043). Median OS was found to be 9 months (%95 CI 5.7 - 12.2) in low De Ritis group and 5 months (%95 CI 0.8 - 7.1) in high De Ritis group (p:0.004). Median PFS of the advanced stage patients who had first line systemic chemotherapy (n:41) were 5 months (%95

CI 3.9 - 6.0). Median PFS was 5 months (%95 CI 3.4 - 6.5) and 4 months (%95 CI 2.1 - 5.8) in NLR low (n:16) and high (n:25) group, respectively (p:0.354). Median PFS was found to be 5 months (%95 CI 2.3 - 7.6) in low De Ritis group (n:25) and 4 months (%95 CI 3.1 - 4.8) in high De Ritis group (n:16) (p:0.077). Although, clinic-pathologic parameters including sex and neuroendocrine type were analyzed in terms of survival, statistically significant difference was found only in stage when divided in two groups as local/ locally advanced stage (18 months %95 CI 5.7 - 30.2) and metastatic (5 months %95 CI 2.4 - 7.5) (p:0.000) (Figure 1-2).

DISCUSSION

We retrospectively reviewed 107 NEC patients with many different primaries who were mostly in advanced stage. According to our results, we clearly showed that NLR and De Ritis at the time of diagnosis were independent prognostic factors for overall survival in NEC patients. To the best of our literature search, this is the first report investigating the prognostic role of De Ritis and the second report for NLR in patients with NEC. This study was conducted by Masayuki et al. Their study consisted of only 26 patients and they examined the prognostic significance of NLR only for patients with large cell pulmonary NEC. In the multivariate analysis of clinically significant overall survival predictors (serum albumin, pathological T stage and preoperative NLR), they demonstrated that preoperative NLR was a prognostic factor in large cell pulmonary NEC patients (26).

Most of the studies about the prognostic factors of neuroendocrine carcinomas were done in pulmonary NEC. In a large population based analysis of pulmonary large cell NEC patients, they concluded that patients with large cell NEC had poorer survival outcomes than other non-small cell lung cancer patients mostly due to isolated liver metastasis or combined invasion to other organs (34). In another study conducted by Asamura et al. they found high grade neuroendocrine histology like large-cell NEC and small-cell lung carcinoma showed poor prognosis when compared to typical and atypical carcinoids. Their multivariate analysis indicated that histologic type, completeness of resection, symptoms, nodal involvement, and age were significantly prognostic (35). Spread through air spaces (STAS) is a newly identified definition for the pattern of tumor invasion and represents tumor cells existing within air spaces in the lung parenchyma beyond the edge of the main tumor. Presence of tumor STAS had prognostic role both in patients with large cell NEC and small cell lung cancer (8).

Many other prognostic factors; PD-L1, nestin, CD8, CD4, CD117 (c-kit), Forkhead box protein P3 (Foxp3) expression and presence of stromal cells within vascular invasion were investigated in high grade neuroendocrine carcinoma of the lung. PD-L1 or CD8 expressions were correlated with superior survival while c-kit or nestin expressions were correlated with poorer survival in patients with pulmonary NEC (5-7). Additionally, Foxp3

positive tumor infiltrating lymphocytes (TILs) were found to be an independent favorable prognostic factor for both OS and recurrence free survival (RFS) and CD4 positive TILs were an independent unfavorable prognostic factor for RFS. However, presence of stromal cells was not found to be a significant predictor for tumor recurrence (3,4).

Extrapulmonary high grade neuroendocrine carcinomas can originate in the genitourinary system, gastrointestinal tract, prostate, head and neck. Like pulmonary NEC, these poorly differentiated carcinomas are usually metastatic or locally advanced at presentation. Sorbye et al. evaluated predictive and prognostic markers for advanced gastrointestinal NEC patients and found poor performance status, colorectal primary, Ki-67>55%, elevated platelets and LDH levels as negative prognostic factors for survival (9). In a retrospective study of 17 gastric neuroendocrine carcinoma patients, Ki-67>60% was correlated with tumor recurrence and together with E-cadherin loss they predicted the aggressiveness of gastric NECs (12).

In small cell and large cell neuroendocrine carcinoma of uterine cervix, patients whose tumors had negative human epidermal growth factor 2 (HER-2) expression tumors survived shorter than those whose tumors were positive and although not significant in patients with EGFR expression there was a trend toward worse survival. The worst survival was shown in the absence of HER-2 expression and presence of EGFR expression (10). In early stage cervical NEC patients, HPV18 DNA viral load may have a prognostic value and low viral load may be correlated with shortened disease-free survival (11). In a Chinese study including 107 breast NEC patients they investigated prognostic factors and demonstrated that higher TNM stage, high Ki67 (>14%) and negative PR expression were prognostic factors for poor OS and distant RFS (13).

CONCLUSION

In our retrospective analysis, we did the ROC analysis and identified an optimal NLR and De Ritis cut-off value of 5 and 1.04. Neuroendocrine carcinoma is not a common disease and it is very difficult to find patients with the same primary organ neuroendocrine carcinoma. For this reason, we selected a heterogeneous group of NEC patients with multiple primaries like most of the other studies. However, the cut-off points for NLR and De Ritis might be influenced from this. Thus, the most appropriate cut-off values have to be validated with further studies. Despite these limitations, we concluded that both NLR and De Ritis at the time of diagnosis were inversely correlated with overall survival in patients with NEC. As a result, the measurement of these parameters which can be easily observed from the peripheral blood may be applied as prognostic markers.

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