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Research Article

Prognostic Values of the De Ritis Ratio and Other Inflammatory Markers in Patients with Extensive-Stage Small Cell Lung Cancer

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Abstract

Objectives: We aimed to evaluate the prognostic significances of the aspartate aminotransferase-to-alanine aminotransferase ratio (the De Ritis ratio) and other some inflammatory markers on survival in extensive-stage small cell lung cancer (ES-SCLC).

Methods: A total of 135 patients diagnosed with ES-SCLC in between 2017 and 2020 were included. The pre-treatment values of the De Ritis ratio, the neutrophil-lymphocyte ratio (NLR), the platelet-lymphocyte ratio (PLR), and the pre-treatment levels of gamma-glutamyl transferase (GGT) and lactate dehydrogenase (LDH) were analyzed for their relationship with overall survival (OS). Optimal cutoff values were determined through receiver operating characteristic curves and survival probabilities were analyzed through the Kaplan–Meier method. Multivariate analyses were performed to investigate the prognostic significance of these parameters for ES-SCLC.

Results: The median age of the patients at diagnosis was 62.2 (min: 42.5–max: 86.6). The median follow-up time was 8.94±8.02 months. The most common sites of metastasis at admission were bones (33%), followed by the liver (27%), the brain (23%), and the adrenal glands (17%). Median OS was 7.52 months (min: 0.2–max: 50.6). The De Ritis ratio and other inflammatory markers (NLR, PLR, and GGT) were not statistically significantly related with OS (p=0.40; 0.06; 0.29; and 0.49, respectively). Multivariate analyses indicated that only LDH (HR=1.001; p=0.012) was an independent prognostic factor.

Conclusion: The De Ritis ratio and other systemic inflammatory markers are not predictive for prognosis in ES-SCLC patients. There is a need for larger prospective studies to investigate the roles of potential biomarker candidates in predicting prognosis in ES-SCLC.

Keywords: De Ritis, extensive stage, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, prognosis, small cell lung cancer

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Lung cancer is one of the three leading types of cancer with high incidence rates globally but with mortality rates significantly ahead of the others. Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers and is the most aggressive subtype. It is characterized by rapid tumor proliferation, metastatic potential, and frequent relapses despite the dramatic first-line treatment response.[1] Classically, SCLC is evaluated in two stages as a limited disease and an extensive disease.[2] Median survival in extensive-stage SCLC (ES-SCLC) is around 8–13 months, even when the patient receives treatment. The clinical parameters, which have been determined to be predictive of

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prognosis so far, include age, the disease stage at the time of diagnosis, gender, poor performance status, weight loss, and the serum levels of carcinoembryonic antigen and lactate dehydrogenase (LDH).[3,4]

Aminotransferases that include aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are the serum biomarkers of liver functions. The ratio of the serum concentrations of AST to ALT was defined by De Ritis in 1957 and is now known as the De Ritis ratio. Besides the recent emphasis on the De Ritis ratio in liver diseases, particularly in hepatitis, it has also been shown that the De Ritis ratio may have a prognostic role in some types of cancer including cancers of the pancreas and esophagus.[5,6] Another parameter is gamma-glutamyl transferase (GGT), which is a critical enzyme in glutathione metabolism, acting as one of the primary antioxidant enzymes of the cell. It neutralizes reactive oxygen species and free radicals by catalyzing the degradation of extracellular glutathione. Some previous studies have shown that serum GGT levels may be associated with an increased risk of cancer and increased mortality in cancer.[7,8]

Inflammation has important effects on the tumor microenvironment. It is effective at many points in tumor development from the emergence and survival of tumor cells to angiogenesis and metastasis. Furthermore, inflammation may reduce the response to treatment agents.[9] Increased levels of the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR), as indicators of systemic inflammation, have been shown to be poor prognostic factors in many different types of cancer.[10-12]

In this study, we primarily aimed to examine the prognostic values of the De Ritis ratio and GGT for the 1st time in ES-SCLC, which is a divergent cancer type characterized by an aggressive clinical course compared to other types of cancer. In addition, we aimed to reveal whether NLR and PLR act on the clinical course and overall survival (OS) in ES-SCLC as easily tested parameters in blood and attracting attention as inflammatory markers.

Methods

The data of the patients, who were followed up with a diagnosis of ES-SCLC in the period between February 2017 and September 2020 in our center, were analyzed retrospectively. The study was approved by the Institutional Review Board of the Namık Kemal University. Information on the clinicopathological characteristics of the included patients was retrieved from patient medical records. Patients with a previously diagnosed chronic disease or drug use that could affect liver function, hematologic diseases, active infections, or patients using a drug that might affect serum hematological parameters, including steroids for brain metastasis, were excluded from the study. The patients whose laboratory values were related with adrenal insufficiency were also excluded from the study. Age, gender, and other demographic data of the patients, stages at diagnosis, clinicopathological features, and the dates of death were recorded. The De Ritis ratio and the NLR and PLR ratios were calculated using the serum levels of respective parameters tested before the treatment. GGT and LDH levels were recorded, too. NLR was calculated by dividing the total neutrophil count by the absolute lymphocyte count. Similarly, PLR was calculated by dividing the total platelet count by the lymphocyte count.

The receiver operating characteristic (ROC) curve was used to determine the cutoff values because no optimal cutoff values have been determined for the markers listed to predict OS in ES-SCLC (Fig. 1). OS was defined as the time from the diagnosis to the date of all-cause mortality. The variables acting on OS were analyzed by the Kaplan–Meier method and were compared by the log-rank test. Univariate and multivariate analyses were performed using the Cox regression hazard models. Factors found as significant in univariate analyses were selected as covariates for a multivariate Cox model. The statistical software package SPSS for Windows, version 23, was used to perform statistical analyses. All P-values were two sided and $p<0.05$ was considered to be statistically significant.

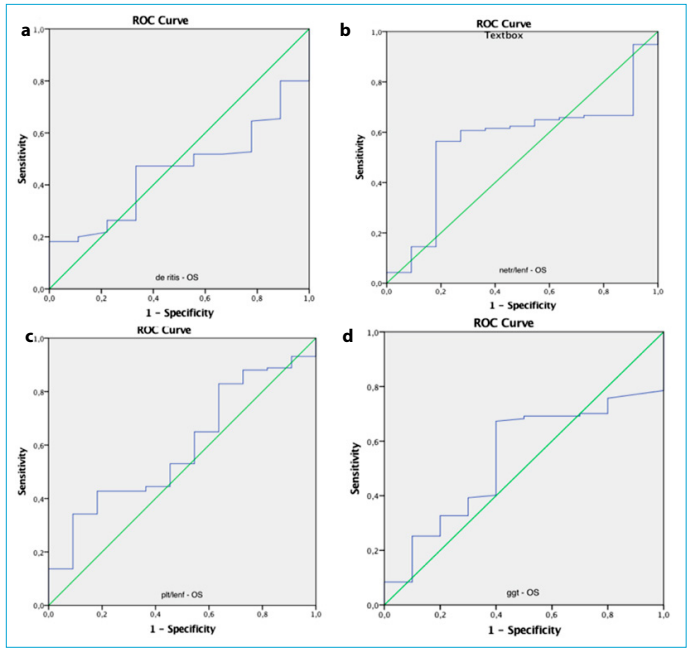

Figure 1. Receiver operating characteristic analysis for overall survival according to the pretreatment De Ritis ratio and neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and gamma-glutamyl transferase values.

Results

Data of a total of 1783 lung cancer patients were retrieved from patient medical records. Of these patients, 241 (7.3%) were SCLC and 181 were in the extensive stage. After excluding the patients per the exclusion criteria, 135 (78%) patients were included in the study and data of these patients were analyzed. The median follow-up time of the patients was 7.56 months (min: 0.2–max: 50.93). Of the patients included in the study, 126 (93.3%) were men. The median age at diagnosis was 62.2 (min: 42.5–max: 86.6). At the time of the retrospective patient data review for the study, it was found out that 119 (88.1%) patients had died. Median OS was 7.49 months (min: 0.2–max: 42.12). The most common site of metastasis at diagnosis was bones in 45 patients (33%), followed by the liver in 37 (27%), the brain in 31 (23%), adrenal glands in 23 (17%), and the contralateral lung in 12 (9%) patients. Prophylactic cranial irradiation (PCI) was applied to 24 (18%) patients. Second-line chemotherapy was administered to 112 (83%) patients, who progressed after first-line therapy. Demographic and clinical data of the study patients are summarized in Table 1.

ROC analysis was performed to determine whether the pre-treatment De Ritis ratio and the values of NLR, PLR, and GGT had a diagnostic value for the patient's clinical prognosis and to determine cutoff values for these parameters predictive for OS. The ROC analysis revealed the optimal cutoff points for the De Ritis ratio, NLR, PLR, and GGT as 1.23, 2.86, 203.3, and 32.5, respectively (Fig. 1). Figure 2 shows that the prognosis of the patients with a high De Ritis ratio and high values of NLR, PLR, and GGT was similar to that of patients having lower values of these parameters (log-rank tests: p=0.40, p=0.06, p=0.29, and p=0.49, respectively).

Table 1. Demographic and clinical data of the study patients

Variables	n (%) or median (±IQR)
Age	62.6±8.69
Gender, male	126 (93.3)
De Ritis ratio	1.09±0.66
GGT	47.5±63.3
NLR	3.45±2.95
PLR	178.72±164.41
LDH	293±234.8
PCI (yes)	24 (18)
Second-line chemotherapy	112 (83)
Metastatic site at the time of diagnosis	Liver 36 (27)
Brain	31 (23)
Bone	44 (33)
OS	7.49±8.23

IQR: Interquartile range; PCI: Prophylactic cranial irradiation; GGT: Gamma-glutamyl transferase; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; LDH: Lactate dehydrogenase; OS: Overall survival.

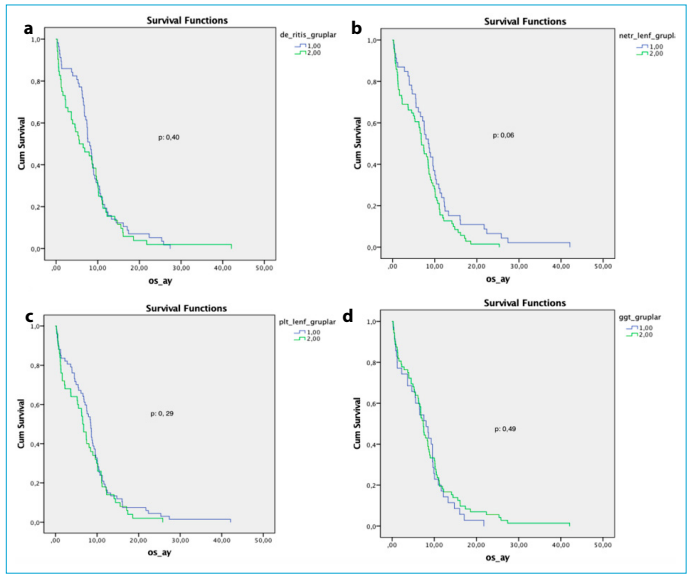

Figure 2. Kaplan–Meier analysis of overall survival according to the pre-treatment De Ritis ratio and neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and gamma-glutamyl transferase values.

On univariate analyses to predict OS, GGT (HR 1.002, 95% CI 1.001–1.003, p=0.002), liver metastases (HR 1.64, 95% CI 1–2.70, p=0.04), and LDH (HR 1.001, CI 1.001–1.002, p=0.000) were found as significant predictors but the De Ritis ratio (HR 1.07, 95% CI 0.69–1.68, p=0.73), NLR (HR 1.43, 95% CI 0.97–2.09, p= 0.068), PLR (HR 1.23 95% CI 0.80–1.88, p=0.342), GGT >32.5 versus <32.5 (HR 1.22, 95% CI 0.72–2.06, p=0.444), and LDH >250 versus <250 (HR 1.31, 95% CI 0.85–2, p=0.216) were not significant. On multivariate Cox regression models of clinicopathological parameters to predict OS, only LDH (HR 1.001, 95% CI 1.000–1.002) was found out to be an independent prognostic factor. Although the GGT level and liver metastases were found significant in the results of the univariate analyses (HR 0.1.002, 95% CI 1.001–1.1003, p=0.002 and HR 1.64 95% CI 1.00–2.70, p=0.04, respectively), this association was not confirmed in the results of multivariate analyses (Table 2).

Discussion

In this study, we have investigated for the 1st time whether the De Ritis ratio and GGT have prognostic effects in ES-SCLC. The optimal cutoff value for the De Ritis ratio was determined as 1.23; however, the De Ritis ratio was found out to be insufficient to predict OS in ES-SCLC. To date, studies in the literature have shown that the De Ritis ratio can predict survival in some tumor types.[5,6] Different mechanisms of action have been proposed to explain correlations between the De Ritis ratio and survival. One of these explanations proposes that although AST is widely expressed in dif-

Table 2. Univariate and multivariate cox proportional hazard models for survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Age >65 versus <65	1.51 (0.98–2.34)	0.06		
De Ritis ratio >1.23 versus <1.23	1.07 (0.69–1.68)	0.73		
NLR >2.86 versus <2.86	1.43 (0.97–2.09)	0.068		
PLR >203.3 versus <203.3	1.23 (0.80–1.88)	0.342		
GGT >32.5 versus >32.5	1.22 (0.72–2.06	0.444		
GGT	1.002 (1.001–1.003)	0.002	1.000 (0.997–1.002)	0.724
LDH >250 versus <250	1.31 (0.85–2.00)	0.216		
LDH	1.001 (1.001–1.002)	0.000	1.001 (1.000–1.002)	0.012
Metastasis to the liver yes/no	1.64 (1.00–2.70)	0.04	1.655 (0.901–3.041)	0.104
Metastasis to the brain yes/no	1.083 (0.661–1.774)	0.751		
Metastasis to bones yes/no	1.317 (0.834–2.080)	0.238		

HR: Hazard ratio; CI: Confidence interval; GGT: Gamma-glutamyl transferase; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; LDH: Lactate dehydrogenase.

ferent tissue types, ALT is liver specific or abundantly found in the liver.[13] Therefore, assuming that AST elevations will be higher compared to ALT in cases of tissue damage and high tumor cell turnover, one may suggest that the De Ritis ratio could be an interesting potential biomarker. Glucose metabolism is another hypothesis proposed in the previous literature. According to Warburg's theory, cancer tissue shows a higher rate of aerobic glycolysis than normal tissue.[14] AST plays an important role in aerobic glycolysis by relocating the generated cytoplasmic nicotinamide adenine dinucleotide hydrogen into mitochondria through the malate-aspartate shuttle pathway.[13,14] SCLC is a high-grade neuroendocrine tumor and patients usually have metastatic disease at the time of presentation. Most patients relapse within the first 2 years after treatment and the 2-year survival rate is <10% in metastatic patients. SCLC has distinct morphologic features on hematoxylin and eosin-stained sections showing a high mitotic rate, usually more than 10 mitoses per 2 mm^2. Furthermore, an increased apoptotic rate and a frequent presence of extensive tumor necrosis are observed.[15] A potential reason to explain the lack of the prognostic value of the De Ritis ratio in ES-SCLC may be the progression toward a different inflammatory cascade due to the rapid cell proliferation and turnover in ES-SCLC.

Although GGT is most abundant in the liver and kidneys, it is found in almost all epithelial tissues.[16] GGT plays a key role in the synthesis and catabolism of glutathione, the most essential extracellular non-protein antioxidant.[16] Therefore, changes in GGT reflect the change in the oxidative stress state. It has been suggested that it may be a potential marker for increased oxidative stress conditions such as Type-2 diabetes[17] and cancer.[18] A systematic review of the literature reveals that GGT might be associated with cancer-related mortality.[7] In a population-based study in which patients with endometrial cancer were followed for a median of 12 years, Edlinger et al.[19] reported that increased GGT was one of the extensively effective risk factors for cancer-related mortality (HR=3.35, 95% CI 1.12–10.03). Consistent with the information in the literature, the results of the univariate analysis in our study revealed that GGT was one of the effective factors on OS but this finding was not confirmed in the multivariate analysis. In addition, an optimal cutoff value for GGT was not found out.

Besides the De Ritis ratio and GGT, we investigated some other potentially interesting serum markers such as NLR, PLR, and LDH. While LDH was significant in predicting OS in both univariate and multivariate analyses, NLR and PLR were not found out to be significant. To date, NLR and PLR have been studied in many different types of cancer as markers of increased systemic inflammation and studies have shown that they may be of prognostic value. In one of the previous studies about SCLC, Kang et al. examined the prognostic effect of NLR and PLR in SCLC patients. Similar to our study findings, NLR was detected as a prognostic factor for OS in subgroup analyzes of extensive-stage patients in that study but PLR did not reach significance in the multivariate analysis.[20] In other studies, while NLR showed a significant prognostic effect in ES-SCLC, PLR was not significant.[21,22] P-value we obtained for NLR in our study (p=0.06) suggests that NLR could show a statistically significant prognostic value similar to other studies if the number of patients included in the study was higher. Significant results have also been obtained in studies examining the ratios between albumin and inflammatory markers

in the literature.[23,24] We did not examine albumin levels in our study. Studies involving the integration of albumin to inflammatory markers in ES-SCLC may be more useful in further studies.

As a classic inflammatory marker, LDH is correlated with tumor burden and released by rapidly growing tumors. LDH has been reported to be a marker for OS and tumor load in patients with various malignancies, including SCLC.[25,26] Similar to the previous studies, we have found that LDH has a prognostic effect on OS in ES-SCLC patients. This has been demonstrated in both univariate and multivariate analyses in our study.

This study is the first in its field but it has some limitations. One of the limitations is the retrospective design of the study, which prevented us from controlling potential confounding factors such as drug interactions that might have influenced liver functions or the presence of liver diseases or other disease states that could affect the levels of serum AST or ALT. Another limitation is the low number of patients included in the study. Furthermore, absolute lymphocyte count was used in the parameters requiring a lymphocyte count. Identification of lymphocyte subpopulations would be useful for more comprehensive analyses.

Conclusion

The De Ritis ratio and systemic inflammatory markers, which are reported to have prognostic significance in some different types of cancer, are insufficient to predict prognosis in ES-SCLC. The most distinctive feature of ES-SCLC is its aggressive nature that distinguishes it from other cancers. We believe that new biomarkers associated with the disease's pathophysiology should be identified to predict prognosis in ES-SCLC.

Disclosures

Ethics Committee Approval: Institution: Tekirdağ: Namık Kemal University, Approval Date: 28.07.2020 Approval Number: 2020.176.07.09.

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Authorship Contributions: Concept – O.A.; Design – O.A.; Supervision – E.S.S.; Materials – C.O.U.; Data Collection &/ or processing – C.O.U.; Analysis and/or interpretation – O.A.; Literature Search – O.A.; Writing – O.A.; Critical review – A.Y.

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