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Predictive importance of systemic inflammation response index in de novo brain metastatic small cell lung cancer patients

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ABSTRACT

Aims: The subtype of lung cancer, known as small cell lung cancer (SCLC), tends to have a highly fatal course, especially in advanced stages. In particular, the overall survival durations further decrease in cases of brain metastases in SCLC. There is increasing evidence for the role of systemic inflammation parameters in predicting cancer prognosis, and they appear likely to become potential target markers for clinical treatments in the future. We aimed to evaluate the systemic inflammation response index (SIRI), a novel inflammatory laboratory marker that could predict long-term survival and serve as a potential target marker for clinical treatment, in patients with de novo brain metastatic small cell lung carcinoma (DNBM SCLC)."

Methods: Clinicopathological features of adult patients diagnosed with DNBM SCLC were recorded from the patient registry of the hospital. Patients without medical records were not included in the study. Investigations were carried out to assess the prognostic effect of the SIRI parameter in predicting the 12-month overall survival (OS12) in DNBM SCLC patients, by determining a cut-off value and conducting appropriate statistical analyses, considering p-values (<0.05) as statistically significant.

Results: In this study 256 SCLC patients screened from the hospital database and detected 42 patients with de novo brain metastases (DNBM) were included in the study.The median age of patients was 61; 85.7% of the sample was male while 14.3% was female. When the SIRI marker was 1.79 or below, OS12 in patients was statistically significantly better predicted than in those with values above 1.79 (Cut off ≤ 1.79 AUC: 0.751, sensitivity: 66.7%, specificity: 66.7%; p=0.022). Also, SIRI ≤ 1.79 was found to be an independent variable predicting OS12 in DNBM SCLC patients.

Conclusion: Our study is important in terms of the short overall survival durations observed in DNBM SCLC patients and the identification of conventional laboratory parameters that can be used to predict longer survival durations in these patients.

Keywords: Small cell lung cancer, systemic inflammation, 12-month overall survival, brain metastasis

INTRODUCTION

Lung cancer is one of the most commonly diagnosed cancer types worldwide, with approximately 2 million new cases and 1.79 million deaths annually, making it the leading cause of cancer-related mortality.[1] Furthermore, lung cancer (LC) is a highly heterogeneous group of diseases, classified into two categories: small cell and non-small cell. Small cell lung cancer (SCLC) constitutes approximately 15% of all lung cancers, and it is highly associated with cigarette smoking. Also SCLC is observed at a higher rate in men compared to women and associated with rapid growth, a high tendency for metastasis, and poor survival.[2-3] Timely diagnosis of early-stage cancers is a key factor in improving the prognosis of cancer patients. In this regard, low-dose computer tomography scans can screen for early-stage NSCLC but do not assist in the early diagnosis of SCLC due to its aggressive nature.[4] Therefore, patients with SCLC are generally diagnosed when advanced stage metastatic symptoms occur. Among the common metastatic sites of SCLC are the brain, bones, adrenal glands, liver, colorectum, and lymph nodes. Due to the presence of neuroendocrine cells, SCLC has a higher tendency to metastasize to the liver and brain compared to NSCLC.[5] Brain metastases (BM) are among the common metastatic sites in LC patients, being present in approximately 10% of patients at the time of diagnosis and observed in over 80% of patients during autopsy.[6] Median OS in advanced stage SCLC patients is approximately 12 months, while in those with BM, median OS is around 5 months and the 2-year survival rate in patients with BM is only below 2%.[7,8] Local and systemic inflammation can influence tumor progression and response to treatment. BM consist of various cellular structures, including LC cells, tumor-associated

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fibroblasts, brain parenchymal cells, circulating blood dendritic cells, macrophages, and immune system cells such as B and T lymphocytes.[9] In BM, reactive astrocytes in the tumor microenvironment, along with cells of the innate and adaptive immune systems, play a significant role in inducing tumor proliferation.[10] Furthermore, circulating inflammatory cells (macrophage subtypes, mast cells, neutrophils, T and B lymphocyte subsets) secrete various signaling molecules that facilitate tumor angiogenesis, proliferation, and metastasis.[11,12] SIRI is a parameter that reflects the host's immune and inflammatory status quite effectively. It has been reported to predict survival in various malignancies, such as pancreatic cancer, gallbladder cancer, oral squamous cell carcinoma, and cervical cancer. However, data regarding the prognostic role of SIRI in lung cancer are quite limited.[13]

This study aims to predict the patient group with a 12-month survival using the SIRI parameter in DNBM SLCL patients who have a median survival of less than 6 months, as reported in the literature.

METHODS

The study was carried out with the permission of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Clinical Researches Ethics Committee (Date: 21.12.2022, Decision No: 2022-12/2203). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Between December 2014 and August 2021, patients aged 18 and over who were diagnosed with DNBM SCLC in the Medical Oncology Unit of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital were included. The study was prepared in accordance with the Helsinki Declaration. Patient information was retrospectively scanned and recorded from the hospital database. Patients who did not meet the inclusion criteria were excluded.

SIRI was calculated from pre-treatment laboratory parameters in the included patients using the method of monocyte count x neutrophil count / lymphocyte count. The analyses evaluated the impact of the SIRI variable on the prognosis of DNBM SCLC patients.

All patients underwent staging evaluations with brain MRI and PET-CT. All causes, apart from malignancies that could affect the SIRI value, were excluded from the patients.

Statistical analyses were conducted using SPSS version 24.0. Survival analyses were compared using the Kaplan-Meier test. The role of the SIRI variable in predicting OS12 in DNBM SCLC patients was assessed using the Receiver Operating Characteristic (ROC) curve. In univariate analyses, variables with a p-value <0.250, which could contribute to survival clinically, were evaluated in multivariate logistic regression analysis. A significance level of $p<0.05$ was considered statistically significant in all statistical tests.

RESULTS

Out of the 256 registered SCLC patients in the database, 42 patients diagnosed as DNBM were included in the study. Among the patients, 36 were male (85.7%), and 6 were female (14.3%), with age of 19 patients (45.2%) were 60 years or younger, while 23 (54.8%) were over 60 years old.

Cases were evaluated according to the Eastern Cooperative Oncology Group (ECOG) performance score, with 1 patient (2.4%) having a score of 0, 27 patients (64.3%) having a score of 1, and 14 patients (33.3%) having a score of 2.

Out of the patients, 34 (80.9%) had metastases in distant organs in addition to brain metastasis either at the time of diagnosis or during follow-up. In 8 patients (19.1%), de novo brain metastasis was the only distant organ metastasis observed.

Among the patients, 32 (%76.2) received only first-line platinum-etoposide combination chemotherapy (CT) , while 10 (%23.8) patients received 2 or more lines of systemic CT after progression based on their treatment history. Additionally, all 42 (100%) patients received whole-brain radiotherapy (WBRT) before CT.

SVCS was observed in 3 patients (7.1%) at the time of diagnosis, and hyponatremia was observed in 11 patients (26.2%).The median OS of the patients included in the study was determined to be 5.6 months. Demographic and clinical characteristics of the patients are summarized in **Table 1**.

In the survival analysis conducted based on age, no statistically significant difference was observed between patients aged 60 and below compared to those aged over 60 (6.5 months vs. 5.3 months; p = 0.32) (**Figure 1.**).

At the time of diagnosis, SIRI values were calculated for each patient before initiating any treatment based on the laboratory parameters obtained. ROC analysis demonstrated that when the SIRI marker was ≤ 1.79, the OS12 of the patients was statistically significantly predicted (AUC: 0.751, sensitivity: 66.7%, specificity: 66.7%; p=0.022) (**Figure 2**).

Table 1. Clinicopathological features of the patients Total n:42/(%)	
Gender	
Female	6 (14.3)
Male	36 (85.7)
Age median (min-max)	61 (39-81)
≤60	19 (45.2)
>60	23 (54.8)
Ecog	
0	1 (2.4)
1	27 (64.3)
2	14 (33.3)
Smoking	
No	1 (2.4)
Yes	41 (97.6)
Presence of other distant organ metastases at diagnosis or during follow-up	
No	8 (19.1)
Yes	34 (80.9)
Superior vena cava syndrome (SVCS) at diagnosis	
No	39 (92.9)
Yes	3 (7.1)
Number of lines of chemotherapy	
<2	32 (76.2)
≥2	10 (23.8)
Palliative WBRT	
No	0 (0.0)
Yes	42(%100)
Hyponatremia	
No	31 (73.8)
Yes	11 (26.2)
*Median OS (Overall Survival)	
≤60 years	6.5 months
>60 years	5.3 months
Total	5.6 months
*Kaplan-Meier survival analysis	

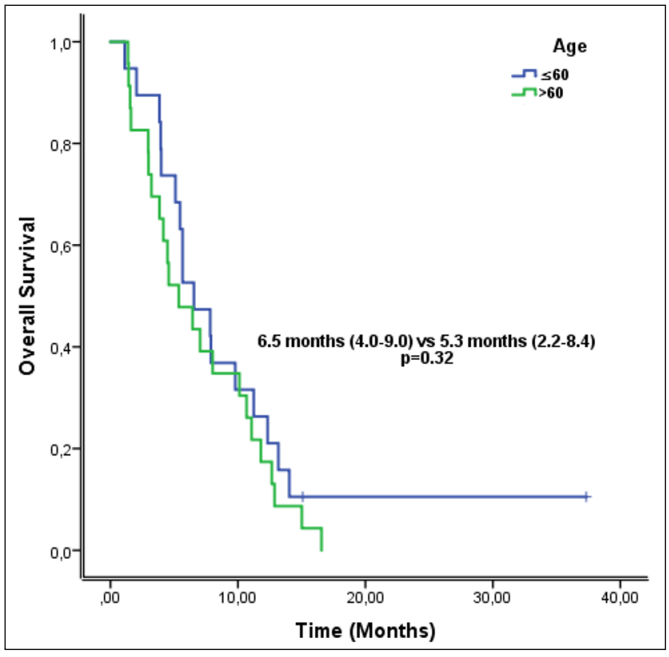

Figure 1. Overall survival by age

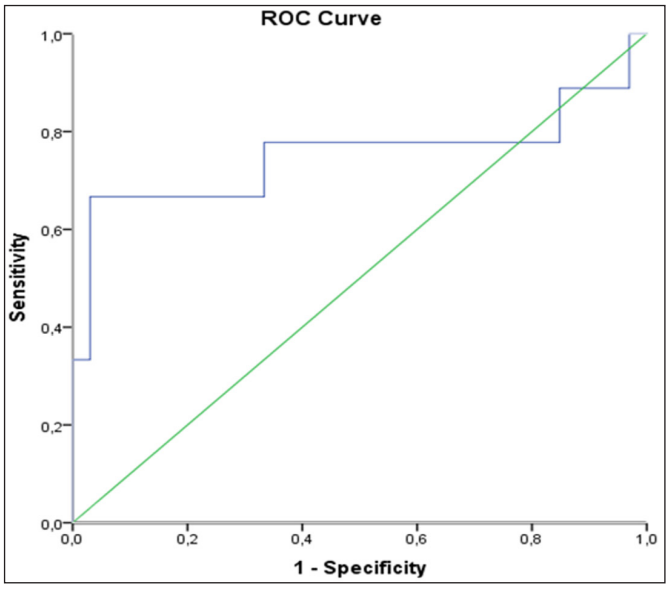

Figure 2. Evaluation of SIRI variable with the ROC curve in DNBM SCLC patients for predicting OS12

OS 12-month	AUC	95% CI	Cut-Off	Sensitivity (%)	Specificity (%)	p
SIRI	0.751	0.507-0.995	≤1.79	66.7	66.7	0.022

In the univariate analysis, among the laboratory factors, hemoglobin (Hb), Total Bilirubin (T.bil.), Calcium (Ca), and SIRI were found to be effective on OS12 in DNBM SCLC patients. Multivariate logistic regression analysis indicated that having SIRI ≤ 1.79 was a statistically significant positive independent predictor for OS12 compared to SIRI >1.79 (odds ratio: 8.00, 95% confidence interval: 1.08-58.90, p=0.04) (Table 2).

Table 2. 12-month overall survival*	univariate logistic regression		multivariate logistic regression	
	or (CI 95%)	p value	or (CI 95%)	p value
Hb	0.60 (0.36-1.01)	0.05	0.69 (0.40-1.19)	0.18
Total bilirubin	0.21 (0.01-2.38)	0.21	0.35 (0.02-5.78)	0.46
Calcium	0.36 (0.10-1.27)	0.11	0.24 (0.04-1.38)	0.11
SIRI >1.79 SIRI ≤1.79	1 4.00 (0.83-19.10)	0.08	1 8.00 (1.08-58.90)	0.04
			r2 = 0.38, -2loglikelihood= 31.57	
*Logistic regression analysis				

DISCUSSION

Treatment delays incancer patients can increase mortality.[14] For predicting the prognosis of SCLC, various factors have been investigated, but the lack of a standardized marker highlights the need for new biomarkers in this regard.[15] Inflamation markes are practical in many solid tumors.[16] Various inflammation and immune-based

prognostic indices such as the neutrophil-lymphocyte ratio (NLR) , monocyte-lymphocyte ratio (MLR) , and platelet-lymphocyte ratio (PLR) have been developed to predict patients' recurrence and survival rates.[17] SIRI is a newly defined index, calculated as the neutrophil count × the monocyte count / the lymphocyte count, which better reflects the host's immune and inflammation balance. Furthermore, it has been reported to predict survival in various cancer types, although studies on its role in lung cancer are rare.[13] The aim of this study is to evaluate the prognostic and predictive significance of the pre-treatment calculated SIRI index in SCLC patients with DNBM who received palliative WBRT and systemic CT in the first-line treatment.

Similar to LC in general, SCLC is more common in men, but the proportion of cases in women has increased worldwide in the last 50 years when compared to men, which also reflects trends in tobacco consumption. Additionally, the elderly population among SCLC patients is on the rise, with the proportion of elderly patients (>70 years old) in the United States increasing from 23% in 1975 to 44% in 2010.18 Of the 42 patients included in our study, 36 were male (85.7%), 23 patients were aged 60 or older (54.8%), and 41 patients (97.6%) had a history of smoking.

Superior vena cava syndrome (SVCS) occurs due to the compression of the mass, tumor invasion, and/or thrombosis of the superior vena cava (SVC). It encompasses a wide clinical spectrum, ranging from asymptomatic cases to life-threatening emergencies.[19] SVCS is observed in approximately 10% of SCLC patients at the time of diagnosis.CT and/or radiotherapy (RT) can alleviate the symptoms of SVCS in these patients.[20] Electrolyte disturbances are common in cancer patients and can worsen the prognosis. Among these disorders, hyponatremia is the most common, with a prevalence of 11% in limited-stage SCLC patients and 24% in extensive-stage patients.[21] In our study, SVCS was observed in 3 patients (7.1%) at the time of diagnosis, and hyponatremia was observed in [11] patients (26.2%). These findings are consistent with the data in the literature, indicating that the patient population in our study is similar to the literature data.

At the time of diagnosis, DNBM is detected in 10% of SCLC patients.[6] The median OS in extensive-stage SCLC is 5 months.[7] In this study, DNBM was detected in 16% of 256 retrospectively scanned SCLC patients, and the mean median OS of the cases was determined to be 5.6 months, showing similarity to the data in the literature.

Cancer-related studies comparing the prognostic capacity of SIRI and NLR in similar cohorts have shown that SIRI is a stronger predictive marker than NLR.[22] In a meta-analysis that included 10,754 cases encompassing all cancer patients conducted by Zhou et al.[23] it was demonstrated that high pre-treatment SIRI levels were associated with a poor prognosis. In the study conducted by Yılmaz et al.[15] SIRI was identified as an independent prognostic factor for both progression free survival (PFS) and OS in extensive-stage SCLC. It was noted that a high SIRI level was significantly associated with shorter PFS and OS. In our study, ROC analysis demonstrated that when the SIRI marker was ≤1.79, it significantly predicted OS12 in patients (AUC: 0.751, sensitivity: 66.7%, specificity: 66.7%; p=0.022). Furthermore, in univariate analysis, among the laboratory parameters effective for OS12 in DNBM SCLC patients, and in multivariate logistic regression analysis, where these parameters were evaluated, it was found that SIRI ≤1.79 was a statistically significant positive independent predictor for OS12 compared to SIRI >1.79 (OR: 8.00, 95% CI: 1.08-58.90, p=0.04).

In a study encompassing patients with advanced-stage melanoma, gastrointestinal, lung, and head-neck cancer who received immunotherapy, it was demonstrated that a high baseline or early increase in the measured NLR, PLR, and MLR markers during treatment were associated with poor clinical outcomes.[24] Furthermore, in another study investigating the relationship between the pretreatment calculated high systemic immune inflammation index (SII) based on circulating blood platelet, neutrophil, and lymphocyte counts (platelet × neutrophil/lymphocyte) and immunotherapy response, it was demonstrated that a high SII value before treatment was independently associated with poor PFS and OS in patients with metastatic renal cell carcinoma treated with nivolumab-ipilimumab in the first-line setting.[25] Adding atezolizumab to platinum-etoposide chemotherapy as shown in the IMpower 133 trial and adding durvalumab to the treatment regimen as shown in the CASPIAN trial were both demonstrated to contribute approximately 2-2.5 months to the statistically significant median OS in extensive stage SCLC, and PD-L1 has no predictive value for immunotherapy in SCLC.[3] Based on the analyses in our study and considering the studies conducted on immunotherapy and inflammatory index parameters, it can be suggested that low SIRI in pre-treatment DNBM SCLC patients predicts longer OS12 when immunotherapy is added to the treatment. Furthermore, there is a need for extensive studies to investigate the independent role of SIRI as a predictor for immunotherapy in extensive-stage SCLC. In the future, parameters based on systemic inflammation may not only identify the risk but also serve as target markers for clinical treatments in cancer patients.[22]

CONCLUSION

The findings of this study, given that the patient group in the study population had clinical and pathological characteristics similar to the literature, are valuable in predicting independently lower SIRI markers for patients with DNBM SCLC who live longer than the expected average overall survival. However, for the practical application of this information in real-world scenarios, further comprehensive research is needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Clinical Researches Ethics Committee (Date: 21.12.2022, Decision No: 2022-12/2203).

Informed consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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