What are the predictors of delirium for patients with lung cancer?

Akciğer kanseri olan hastalarda deliryum prediktörleri nelerdir?

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ABSTRACT

Objective: Delirium is a common psychiatric disorder in advanced cancer but there are a few reports about delirium in patients with lung cancer. We aimed to investigate the predictors of delirium occurring in patients with lung cancer regardless of surgery.

Methods: A total of 212 patients over the age of 18 hospitalized with lung cancer for any reason between 2013-2019 were retrospectively investigated in this research. Patients diagnosed with delirium between these dates were determined and patients with concurrent lung cancer diagnosis were selected for this study. A similar number of patients over the age of 18 diagnosed with lung cancer but not diagnosed with delirium in the same period were also defined as the control group. Patients were diagnosed with delirium by the criterias of the Diagnostic and Statistical Manual of Mental Disorders V. criterias during their hospitalization by psychiatrist consultant physician. Age, gender, comorbidities, durations of hospital stay, laboratory parameters at the time of diagnosis (biochemistry, hemogram), the type of lung cancer and existing organ metastases of the patients were recorded from the patient files and hospital information system. Neutrophil to lymphocyte ratio and paletelet to lymphocyte ratio were calculated and recorded. The patients with lung cancer were divided

ÖZET

Amaç: Deliryum, ilerlemiş kanserde yaygın bir psikiyatrik bozukluktur ancak akciğer kanseri olan hastalarda deliryum hakkında çok az sayıda çalışma mevcuttur. Bu çalışmada, akciğer kanseri olan hastalarda gelişen deliryum prediktörlerinin, cerrahiden bağımsız olarak araştırılması amaçlanmıştır.

Yöntem: Bu çalışmada, 2013-2019 yılları arasında 18 yaş üstü, akciğer kanseri tanısı alan ve herhangi bir sebeple hastaneye yatışı sırasında deliryum tanısı konulan ve aynı dönemlerde benzer sayıda 18 yaş üstü olup akciğer kanseri olan ancak deliryum tanısı olmayan toplam 212 hasta retrospektif olarak incelenmiştir. Hastaların deliryum tanısı yatışları sırasında psikiyatri konsültasyonu ile Ruhsal Bozuklukların Teşhis ve İstatistik El Kitabı V. Kriterlerine göre konulmuştur. Hastaların yaş, cinsiyet, hastanede kalış süresi, komorbiditeleri, tanı anındaki laboratuar parametreleri (hemogram, biyokimya), akciğer kanseri tipi ve mevcut organ metastazları hasta dosyalarından ve hastane bilgi sisteminden kaydedilmiştir. Hastaların nötrofil / lenfosit oranı (NLR) ve platelet / lenfosit oranları (PLR) hesaplanmış ve kaydedilmiştir. Hastalar, deliryum tanısı alan ve deliryum tanısı almayan akciğer kanseri tanısı olan hastalar olarak iki gruba ayrılarak karşılaştırılmıştır.

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into two groups as patients diagnosed with delirium and without delirium and they were compared.

Results: Of the 212 patients, 93.9% of the were male and the average age of the patients was 63.45 ± 8.68 (38-91) years in our study. The number of the patients with delirium was 126 and the median diagnostic age of the patients with delirium was determined to be 64.00 (59.00-71.00) years. Although the median levels of white blood cell (WBC), neutrophil, neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were higher, the median level of lymphocyte was found to be lower in the group with delirium ($p < 0.05$). According to the logistic regression analysis, it was determined that the absence of accompanying chronic obstructive lung diseases (COPD), metastasis, pneumonia and heart disease as well as being a male, increased the delirium risk.

Conclusion: NLR and PLR which are systematic inflammatory markers, are associated with delirium and lung cancer. Increased NLR and PLR are significant risk factors for delirium in hospitalized patients with lung cancer and maintaining a low level of an inflammation may help prevent delirium. Male gender and acute illnesses requiring hospitalization may also increase the risk of delirium.

Key Words: Lung cancer, delirium, neutrophil, platelet, lymphocyte

Bulgular: Çalışmamızda 212 hastanın %93,9'u erkek ve yaş ortalaması 63,4 ± 8,7 (38-91) yıldır. Deliryum tanılı hasta sayısı 126 olup deliryumu olmayan hastaların tanı yaşı medyan 64,0 (59,0-71,0) olarak belirlenmiştir. Deliryum olan grupta ortalama beyaz kan hücresi (WBC), nötrofil, nötrofil/lenfosit oranı (NLR) ve trombosit/lenfosit oranı (PLR) seviyeleri daha yüksek olmasına rağmen ortalama lenfosit düzeyi daha düşük bulunmuştur ($p < 0,05$). Lojistik regresyon analizine göre erkek olmanın yanı sıra eşlik eden kronik obstrüktif akciğer hastalığı (KOAH), metastaz, pnömoni ve kalp hastalığının olmamasının deliryum riskini artırdığı tespit edilmiştir.

Sonuç: Sistematik inflamatuar belirteçler olan NLR ve PLR, deliryum ve akciğer kanseri ile ilişkilidir. Artmış NLR ve PLR, hastanede yatan akciğer kanserli hastalarda deliryum için önemli risk faktörleridir ve düşük düzeyde bir inflamasyonun sürdürülmesi deliryumu önlemeye yardımcı olabilir. Erkek cinsiyet ve hastaneye yatış gerektiren akut hastalıklar da deliryum riskini artırabilir.

Anahtar Kelimeler: Akciğer kanseri, deliryum, nötrofil, platelet, lenfosit

INTRODUCTION

Delirium identified as an acute and temporary unstable mental condition, is associated with psychotic symptoms, involving inattention, varying degrees of consciousness, hallucinations and delusions (1). It is the second most frequent psychiatric condition seen in 14-55% of hospitalized with cancer patients, and it is also seen in 90% of cancer patients in the last period of their lives (2). Delirium may develop from structional problems or metabolic problems and reported to be associated with increased mortality and prolonged hospitalization (3,4). Several studies have investigated the risk factors for developing delirium in many diseases but there is no report which has evaluated the risk factors of delirium in lung cancer patients.

Delirium is a relatively frequent postoperative complication of lung cancer and advanced age is generally recognized as a major risk factor for the occurance of postoperative delirium (5,6). Its usage as a measure of health care quality is arising for older

patients.

The early diagnosis of delirium, which causes an increase in costs by raising the duration of hospital stay and long term care, is critical because it can be avoided by a one-third rate of identification of high risk patients with appropriate intervention (7). In this study we aimed to investigate the predictors of delirium occurring in patients with lung cancer regardless of surgery.

MATERIAL and METHOD

We performed a single centre, retrospective study on patients, over the age of 18, hospitalized with lung cancer for any reason between January 2013 and January 2019. A total of 212 patients were included in this study. First of all, patients diagnosed with delirium between these dates were determined and patients with concurrent lung cancer diagnosis were selected for this study. A similar number of patients over the age of 18 diagnosed with lung cancer but not diagnosed with delirium in the same period were also defined as the control group. Patients with an accompanying secondary malignancy, whose data could not be reached, and patients who were referred to another center were excluded from the study. The patient groups were heterogeneous according to diagnosis and follow up time. Informed consents couldn't be taken from the patients due to the retrospective nature of research. Approval for the study was granted by the medical training board of a chest diseases and chest surgery education and training hospital in Ankara, Turkey. Approval for the study was granted by the medical training board of our hospital. (Approval number and date: 663/20.02.2020). Patients were diagnosed with delirium by the Diagnostic and Statistical Manual of Mental Disorders V criterias during their hospitalization by psychiatrist consultant physician. Age, comorbidities, duration of hospital stay, laboratory parameters at the time of diagnosis (biochemistry, hemogram), the type of lung cancer and existing organ metastases of the patients

were recorded from the patient files and hospital information system. The patients with lung cancer were divided into two groups as patients diagnosed with delirium and without delirium and they were compared.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 25 was used for the statistical analyses. Frequency, percentage values, median and quartile values of 25 and 75 percent were used in the presentation of the descriptive data of the study. Chi-square test was used to evaluate the statistical differences of categorical variables. After evaluating the suitability of the measurement data to normal distribution, the Mann Whitney U test was used to test the difference between individuals with and without delirium, since the values did not show a normal distribution. To determine the predictive factors of delirium, a multivariate logistic regression analyses was applied with variables whose p value was <0.02 in univariant analyses. The presence of correlation among these variables was analyzed using a Spearman test, and in each pair, the variable that detected correlation with the other variable was excluded from the regression model. To assess the model's goodness of fit, the Hosmer-Lemeshow test was performed. The 95% confidence intervals (95% CIs) were calculated whenever appropriate, and a two-tailed p-value <0.05 was considered statistically significant.

RESULTS

Of the 212 patients, 93.9% (n= 199) of the were male and the average age of the patients was 63.4 ± 8.7 (38-91) years in our study. The number of the patients with delirium was 126 and the median diagnostic age of the patients with delirium was determined to be 64.0 (59.0-71.0) years. The patients' average duration of stay at the hospital was 19.44 ± 12.71 (1-77) days. Patients diagnosed with small cell lung

cancer comprised 41.0% (n=87) of all patients. While delirium was more common in men, no relationship was found with age, duration of hospitalization and type of cancer. Sociodemographic characteristics of the patients according to the presence of delirium are given in Table 1.

While the median levels of WBC, neutrophil count, NLR and PLR were higher, the median level of lymphocyte was found to be lower in the group with delirium (p <0.05). Some laboratory parameters of the patients according to the existence of delirium are given in Table 2.

Table 1. Sociodemographic characteristics of the patients according to the presence of delirium

			Delirium (+)	Delirium (-)	p	Crude OR (95% Cl)
Gender	Female	n (%)	4 (3.1)	9 (10.4)	0.03	1
	Male	n (%)	122 (96.8)	77 (89.5)		3.56 (1.06-11.97)
Age - Median (IQR25-75)			64.0 (60.0-71.0)	63.0 (56.0-68.0)	0.05	1.02 (0.99-1.04)
Duration of hospitalization (d) - Median (IQR25 75)			17.00 (10.0-26.0)	16.0 (10.0-23.0)	0.31	1.01 (0.99-1.04)
Type of cancer	NSCLL	n (%)	78 (61.9)	47 (54.7)	0.29	1
	SCLL	n (%)	48 (38.1)	39 (45.3)		0.77 (0.42-1.29)

OR: Odds Ratio; IQR: The interquartile range; NSCLL: Non small cell lung cancer; SCLL: Small cell lung cancer

Table 2. Laboratory parameters of the patients according to the existence of delirium

	Delirium (+)	Delirium (-)	p
	Median (IQR25-75)	Median (IQR25-75)	
Hb (g/dL)	10.8 (9.6-12.5)	11.6 (10.2-12.7)	0.08
WBC (10^3/mm³)	12.6 (8.5-17)	8.7 (.0-13.2)	**<0.001**
Lymphocyte (10^3/mm³)	0.7 (0.4-1)	0.8 (0.5-1.5)	**0.04**
Neutrophil (10^3/mm³)	10.9 (6.6-16.2)	6.8 (4.3-11.3)	**<0.001**
Plt (10^3/mm³)	223 (163-325)	228 (165-310)	0.52
MPV (µm³)	8.2 (7.5-9.7)	8.2 (7.0-9.1)	0.19
Sodium (mEq/L)	137 (134-140)	136 (134-139)	0.11
Creatinin(mg%)	0.7 (0.5-1)	0.8 (0.6-1)	0.15
AST (IU/L)	22 (15-34)	21 (15-33)	0.62
ALT (IU/L)	23 (16-36)	22 (13-37)	0.85
NLR	14.6 (7.9-25.1)	8.8 (3.3-18.2)	**<0.001**
PLR	332.7 (211.5-494.1)	225.6 (129.1-406.4)	**0.003**

Bold values denote statistical signifcance at the p<0.05
Hb: Hemoglobine; WBC: White blood cell; Plt: Platelet; MPV: Mean platelet volume; AST: Aspartat aminotransferase; ALT: Alanine aminotransferase; NLR: Neutrophil lymphocyte rate; PLR: Platelet lymphocyte rate

COPD, metastasis, pneumonia, respiratory failure, pulmonary thromboembolism (PTE), cardiac diseases were found to be less common in the group with delirium (p <0.05). The distribution of comorbid diseases according to the existence of delirium is presented in Table 3.

Table 3. The distribution of comorbid diseases according to the existence of delirium

		Delirium (+)		Delirium (-)		p	Crude OR (%95 CI)
		n	%	n	%		
COPD	(+)	42	48.8	14	11.1	**<0.001**	1
	(-)	44	51.2	112	88.9		**7.63 (3.79-15.35**
Metastasis	(+)	66	76.7	58	46.0	**<0.001**	1
	(-)	20	23.3	68	54.0		**3.86 (2.10-7.12)**
Brain metastasis	(+)	35	40.7	39	31.0	0.144	1
	(-)	51	59.3	87	69.0		1.53(0.86-2.71)
Tuberculosis	(+)	3	2.4	0	0	0.164*	1
	(-)	83	97.6	126	100		NA
Pneumonia	(+)	34	39.5	11	8.7	**<0.001**	1
	(-)	52	60.5	115	91.3		**6.83 (3.21-14.53)**
Respiratory failure	(+)	15	17.4	5	4	**0.001**	1
	(-)	71	82.6	120	96		**5.07 (1.6-14.54)**
PTE	(+)	12	14	3	2.4	**0.001**	1
	(-)	74	86	123	97.6		**6.64 (1.81-24.33)**
ILD	(+)	1	1.2	0	0	0.406*	1
	(-)	85	98.8	126	100		NA
Asthma	(+)	2	2.3	0	0	0.163*	1
	(-)	84	97.7	126	100		NA
Cardiac diseases	(+)	20	23.3	10	7.9	**0.002**	1
	(-)	66	76.7	116	92.1		**3.51 (1.55-7.95)**
OSAS	(+)	0	0	1	0.8	0.594*	1
	(-)	86	100	126	99.2		NA
Neurological diseases	(+)	0	0	4	3.2	0.148*	1
	(-)	86	100	122	96.8		NA

Fisher's Exact Test, Bold values denote statistical significance at the p<0.05
OSAS: Obstructive Sleep Apne Syndrome; ILD:Interstititel Lung Disease; NA: Not analysed; OR: Odds Ratio; Cl: Confidence Interval

When performed multivariate logistic regression analysis, it was determined that the absence of accompanying COPD, metastasis, pneumonia and cardiac diseases as well as being a male, increased the risk of delirium. The logistic regression carried out to determine the variables affecting delirium are given in Table 4.

DISCUSSION

Lung cancer is characterized by shorter survival times than other cancers (8) and delirium is the most common neuropsychiatric symptom in advanced stage lung cancer (9). The risk of developing organic psychiatric disorders is greater in elderly cancer patients than younger patients. Older age, cognitive impairment, hypoalbuminemia, bone metastasis, and hematologic malignancy were identified as risk factors for delirium in the study of Ljubisavljevic and Kelly (10). Delirium was reported as 25% in patients over 60 years of age and 10% in younger patients (11) and Suzuki et. al (4) found that delirium is a common psychiatric complication in elderly patients during hospitalization independent of the existence of cancer. In our study, the mean age of our patients with delirium was 64, and it was not significantly different from patients without delirium. This was due to the fact that the patients in the control group were in the similar age group, but the average age> 60 years supported that advanced age was a risk factor for delirium. This made it easier to reveal age-independent risk factors.

Non-small cell lung cancer (NSCLC) accounts for more than 80% of lung cancers (12). NSCLS was diagnosed in 59% of our patients and we detected more delirium in NSCLC patients. In our study, the higher rate of delirium in patients with NSCLC may be due to the higher rate of NSCLC compared to SCLC and the occurence of NSCLC in older patients compared

Table 4. Logistic regression analysis of variables affecting delirium

Parameter	OR	(95%CL)
Gender (Reference:Female)	8.64	(1.36-54.76)
Age	1.04	(0.99-1.09)
WBC	1.06	(0.88-1.27)
Lymphocyte	1.00	(0.93-1.08)
Neutrophile	1.01	(0.85-1.20)
NLR	0.99	(0.97-1.02)
PLR	1.00	(0.99-1.00)
COPD (Reference: +)	6.01	(2.39-15.09)
Metastasis (Reference: +)	8.45	(3.47-20.61)
Pneumonia (Reference: +)	4.98	(1.78-13.88)
Respiratory Failure (Reference: +)	2.06	(0.50-8.46)
PTE (Reference: +)	2.78	(0.45-17.21)
Cardiac Diseases (Reference: +)	4.26	(1.21-14.89)

to SCLC. It is obvious that in the coming years, with the increasing elderly population, we will encounter more with both the number of elderly patients with NSCLC and patients with organic mental disorders.

In the study conducted by Riquelme et al.(13); 101 patients over 65 years of age with pneumonia and a control group consisting of different diseases matched with suitable age and gender were compared and delirium was found to be higher in the pneumonia group. Pneumonia was reported as a major risk factor for the development of delirium in patients with advanced lung cancer in Suzuki et al.'s (4) study. These findings indicate that pneumonia may play a considerable role in causing delirium among older patients. However, accompanying pneumonia was found to be less frequent in the group with delirium in our research. This may be due to the fact that pneumonia is not a single risk factor in the development of delirium and it plays a role as a risk factor with age. Similarly, the presence of COPD, metastasis, respiratory failure, pulmonary thromboembolism and heart diseases were found to be less common in the group with delirium in our study. Delirium may develop more frequently in acute conditions compared to chronic diseases.

Inflammation and oxidative stress have been documented to play a crucial role in the occurrence of delirium (14,15). Systemic inflammation can lead to neuro-inflammation and subsequent delirium by stimulating parenchymal cells and expressing cytokines in the brain (16). The white blood cell count, neutrophil count, NLR and PLR which were known to be markers of inflammation were high, and the lymphocyte count was low in patients with delirium in our study in accordance with the literature. These parameters are conducted regularly at no extra expense in most hospitalized patients. In various research settings, both NLR and PLR are identified readily available indicators of generalized inflammation (17,18). Inoue et al., (19) defined a higher probability of developing delirium in intensive care patients with reduced lymphocyte levels. The possible association between impaired NLR and delirium in the older population was remarked in a research by Egberts et al. (15). In several researchs, increased neutrophil count and NLR in lung cancer patients before treatment, were also found to be associated with poor prognosis (20,21). Increased NLR, which develops according to the degree of neuroinflammation as a result of increased neutrophil count and decreased lymphocyte count, can be used as a simple and useful test to predict delirium.

In varied diseases, containing coronary artery disease, acute kidney injury, and various cancers, the PLR has been identified as a marker for inflammatory reply. Jiang et al., (22) found that PLR in lung cancer patients with delirium was substantially higher. Platelets may have a major impact on inflammatory modulation by faciliating the release of inflammatory cytokines that trigger the inflammatory process and lymphocytes are also an important inflammatory factor in various diseases. The PLR was therefore suggested as a new marker for inflammation in different disorders. It can be a useful predictor of delirium too and it ensures the implementation of early interventions.

There were some limitations and advantages in our study. It was a retrospective analysis and the size of the sample was relatively small. The stages of the patients with lung cancer weren't defined and there was no information about the follow-up of the patients after delirium. To the best of our knowledge, no study has evaluated the predictors of delirium in lung cancer patients. Our study will contribute to the literature.

In conclusion, NLR and PLR which are systematic inflammatory markers, are associated with delirium and lung cancer. Increased NLR and PLR are significant risk factors for delirium in hospitalized patients with lung cancer and maintaining a low level of an inflammation may help prevent delirium. Male gender and acute illnesses requiring hospitalization may also increase the risk of delirium.

ETHICS COMITTEE APPROVAL

* The study was approved by the University of Health Sciences Medical Training Board (Date: 20.02.2020 and Number: 683).

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