Uric Acid and Hemoglobin as Prognostic Factors in Lung Cancer with COVID-19

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Abstract

Background

Cancer patients have an increased risk of COVID-19 compared to the healthy population. Due to increased proinflammatory cytokine excess, unopposed excessive immune response, that is, systemic inflammatory response; is the most important reason that increases the risk of mortality. In this study, we aimed to examine the parameters and inflammatory indices affecting mortality in lung cancer patients with COVID-19.

Methods

This single-center retrospective study included 66 patients diagnosed with lung cancer and treated for COVID-19 between April 2020 and July 2021. Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), prognostic index (PI), modified Glasgow prognostic score (mGPS), and COVID inflammatory score (OIS) were calculated for all patients. Twenty-seven potential prognostic variables were chosen for univariate and multivariate analyses.

Results

A total of 28 variables were analyzed univariable. Seven variables were identified to have prognostic significance: receiving chemotherapy in the last 28 days, hospitalization in the intensive care unit, mechanical ventilation requirement, COVID 19 corticosteroid treatment doses, hemoglobin, platelet count, uric acid. Multivariate analysis by Cox proportional hazard model, including seven prognostic significance factors evident in univariate analysis. In the multivariate logistic regression analysis; hemoglobin, uric acid were independent risk factors for severe COVID-19 in lung cancer.

Conclusion

Serum hemoglobin and uric acid level were identified as important prognostic factors in lung cancer patients with COVID-19. These findings may facilitate the prediction of survival in lung cancer patients with COVID-19. In the literature, there is no previous study on the effect of uric acid on prognosis in patients with COVID-19 and lung cancer. Prospective studies with larger patient populations are needed to confirm this study.

Introduction

COVID-19 emerged at the end of 2019 and has been the most important health problem to date. It is still one of the most important health problems affecting the whole world. Severe inflammation caused by COVID-19 disease causes abnormal responses in the immune system. Those with cardiovascular

disease, diabetes mellitus, chronic lung disease, cancer patients have an increased risk of COVID-19 [1]. Studies have shown that COVID-19 increases overall mortality and complications in cancer patients [1, 2]. The most important factors that increase the severity and mortality of COVID-19 in cancer patients are age, comorbid disease, cancer stage, and smoking [3]. It has been shown that chemotherapy and immunotherapy increase the severity of the disease in COVID-19 patients [4, 5]. However, recent cohort studies have shown that systemic cancer treatments do not increase mortality rates in patients with lung cancer [6].

Unmet immune response due to increased proinflammatory cytokine excess explains the increased death and mortality rates in cancer patients [7–9]. The acute phase response is the first response in systemic inflammation. It causes reactive leukocytosis, peripheral blood neutrophilia, lymphopenia, high C-reactive protein, hypoalbuminemia [10–11]. The prognostic indexes obtained from these values are neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, prognostic nutritional index, prognostic index, modified Glasgow prognostic score and onCOVID inflammatory score may be predictors of morbidity and mortality [12–18].

In this study, we aimed to examine the parameters and inflammatory indices affecting mortality in lung cancer patients with COVID-19.

Materials And Methods

Study Design

This study was conducted in Mersin City Hospital as a single-center, retrospective, and descriptive study. Between April 2020 and July 2021, Mersin City Hospital's electronic information system was scanned and the ICD-10 code was cancer and COVID-19 among 14410 patients diagnosed with cancer and COVID-19. 251 adult cancer patients with COVID-19 disease were identified. 66 patients diagnosed with lung cancer out of 251 cancer patients were included in the study. Demographic characteristics, cancer diagnoses, hemogram, and biochemistry results of the patients included in the study were obtained from the electronic information system.

Prior to the study, ethics committee approval was obtained from Mersin University Ethics Committee, dated 22.09.2021 and numbered 633.

Inflammation-based indices (selected panel of five biomarkers NLR, PLR, OIS, mGPS, and PI) were calculated accordingly in each patient. A previous study was used to calculate inflammatory indices [18].

Statistical Analysis

All analyzes were performed using statistical software program package (SPSS) version 26.0.

Overall survival (OS) was calculated with the log-rank test. The Kaplan–Meier method was used survival curves. The Cox proportional hazards regression model was used to determine statistically significant

variables related to survival. Within the % 95 confidence range $p < 0.05$ was considered statistically significant.

Results

A total of 66 patients were included in this study, including 8 females and 58 males. The median age of patients was 65 years (range 35–85). The patient's baseline characteristics and laboratory parameters are listed in Table 1.

A total of 28 variables were analyzed univariable. Seven variables were identified to have prognostic significance: receiving chemotherapy in the last 28 days ($P = 0.005$), hospitalization in intensive care unit ($P = 0.018$), mechanical ventilation requirement ($P = 0.012$), COVID-19 corticosteroid treatment doses(≤ 1 mg/kg/> 1 mg/kg) ($P = 0.022$), blood uric acid levels ($P = 0.002$), hemoglobin ($P = 0.009$), Platelet count ($P = 0.022$). Univariate analysis results are shown in Table 2.

Multivariate analysis included the seven prognostic significance factors observed to be significant on univariate analysis. Hemoglobin and uric acid were associated with mortality in the multivariate analysis: blood uric acid levels ($P = 0.008$), hemoglobin ($P = 0.047$). The adjusted odds ratios (95 CI) for hemoglobin and üric acid were 3.86 (1.1–14.6) and 28 (2.3–336). The results of multivariate analysis are shown in Table 3.

Discussion

Mortality in COVID-19 is related to the immune response of the host as well as the viral effect. The increase in COVID-19 deaths in cancer patients has yet to be fully explained. In this retrospective study, we analyzed the factors affecting the prognosis of COVID-19 in lung cancer patients.

In univariate analysis, thirty-four possible prognostic factors for survival were analyzed. Seven of thirty-four potential factors were identified as significant prognostic factors for survival: Receiving chemotherapy in the last 28 days, hemoglobin, uric acid, platelet count, hospitalization in the intensive care unit, mechanical ventilation requirement, COVID 19 corticosteroid treatment doses (≤ 1 mg/kg/ >1 mg/ kg).

Hemoglobin and uric acid were associated with mortality in the multivariate analysis. The adjusted odds ratios (95 CI) for hemoglobin and üric acid were 3.86 (1.1–14.6) and 28 (2.3–336).

In cancer patients, the proinflammatory state may be effective in increasing mortality. A recent study found that neutrophil-lymphocyte ratio, on Covid Inflammatory Score, prognostic index, prognostic index, modified Glasgow prognostic score were associated with survival [18]. In our study, however, no statistically significant relationship was found between inflammatory parameters and survival. This result may be due to the small number of patients in our study.

Several previous studies have shown that chemotherapy and immunotherapy increase the severity of the disease in COVID-19 with cancer patients [4, 5]. A recent study showed that systemic cancer treatments do not increase mortality rates in patients with lung cancer [6]. In our study, chemotherapy history in the last 28 days was statistically significant in the univariate analysis($p = 0.005$), but not in the multivariate analysis($p = 0.249$). We think that this result is due to the small number of patients.

Uric acid is one of the anti-oxidants in plasma that protects cells from oxidative damage. Viral invasion causes an immune response, induces the activation of inflammatory factors, and causes the production of a large number of free radicals. These free radicals produce oxidative stress, which can further activate the pathways of inflammatory factors. Oxidative stress plays a crucial role in viral invasion [19]. These suggest that low uric acid levels may indicate a higher inflammatory status and death risk in patients with COVID-19. Previous studies have shown that serum uric acid levels are lower than normal in patients with COVID-19 [20–23]. In our analysis, blood uric acid level was found to be an independent prognostic factor on survival in patients lung cancer with COVID-19 patients ($p = 0.008$). In our patients, favipiravir, which increases the uric acid level, was used in the treatment. However, in our study, uric acid values before starting favipiravir treatment were used. Previous studies on uric acid levels in patients with COVID-19 included patients without cancer [21–22]. Our study was conducted in lung cancer patients, and there is no study on uric acid levels in lung cancer patients. Consumption of uric acid in response to oxidative stress and hyper inflammation may result in decreased uric acid levels in the blood. However, the mechanism was unclear.

Hemoglobin is the most important determinant of the oxygen-carrying capacity of the blood. Hemoglobin levels decrease in hospitalized patients with COVID-19. It is associated with hyper inflammation and cytokine-mediated changes [24]. Huang C et al. study showed that suppression of erythropoiesis and lymphopenia were secondary to the increase in interleukin-10 and interleukin-4 in COVID-19 patients [25]. Omrani-Nava V et al. reported that hemoglobin levels in COVID19 patients were lower than in the control group. However, there was no statistically significant difference [26].

A recent study showed that low hemoglobin level is associated with mortality in cancer patients with COVID-19 [27]. In our study, the results were similar. In our analysis, hemoglobin level was found to be an independent prognostic factor on survival in patients with lung cancer and COVID-19 patients ($p = 0.0047$).

The present study has some limitations which need to be taken into account. Firstly, it is a retrospective study. Secondly, there was a small number of patients.

In conclusıon; serum uric acid and hemoglobin levels were identified as important prognostic factors in lung cancer patients with COVID-19. These findings may also facilitate pretreatment prediction of survival in lung cancer COVID-19 patients. In the literature, there is no previous study on the effect of uric acid on prognosis in patients with COVID-19 and lung cancer. Prospective studies with larger patient populations are needed to confirm this study.

Declarations

Competing interests: The authors declare no competing interests.

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Tables

Table 1
Basic Characteristics and Laboratory Parameters of Patients

Characteristic	n (%)
Age (years)	65 (35–85)
Age ≥ 65 years / Age < 65 years	35 (53) / 31 (47)
Sex	58 (87.9) / 8 (12.1)
Male / Female	
Tumor stage	14 (21.2) / 52 (78.8)
Non-metastatic / Metastatic	
Anticancer treatment history	20 (30.3) / 46 (69.7)
Chemotherapy in the past 28 days	7 (10.6) / 59 (89.4)
Yes / No	
Radiotherapy in the past 28 days	
Yes / No	
Comorbidities	37 (56)
Hypertension	16 (24)
Diabetes mellitus	27 (40)
Cardiovascular disease	18 (27.2)
Chronic pulmonary disease	3 (4.5)
Cerebrovascular disease	
Number of comorbidities	14 (21.2) / 52 (79.8)
0 ≥ 2	
Hospitalization in the intensive care unit	31 (49) / 32 (51)
Yes / No	
Pleural effusion in thorax CT	36 (54.5) / 30 (45.5)
Yes / No	
Additional treatments	38 (62.1)
Mask oxygen	25 (37.9)
Non-invasive/ invasive mechanical ventilation	

Characteristic	n (%)
COVID 19 corticosteroid treatment doses ≤1 mg/kg / > 1 mg/kg	21 (31.8) / 42 (68.2)
Hospitalization result Survivor / Non-survıvor	41 (62.1) / 22 (33.3)
Baseline laboratory parameters	Median(min-max.)
Total white blood cell count (x10^3/uL)	8.8 (0.68-41)
Hemoglobin (g/dL)	11.6(6.2–16)
Platelet count (x10^3/uL)	297 (22–658)
Neutrophil (x10^3/uL)	3.8 (0.2–43)
Lymphocytes (x10^3/uL)	1.46 (0.06-21)
Albümin (g/dL)	3.6 (2.2-5)
C reactive protein (mg/dl)	8.7 (0.3–23)
Uric acid (mg/dl)	5.5 (1.9–13)
Neutrophil:lymphocyte ratio (NLR)	10.4 (0.34-78)
Platelet:lymphocyte ratio (PLR)	548 (2.8–2670)
OnCovid Inflammatory Score (OIS)	44.2 (23–146)
Prognostic nutritional index (PNI)	36.9 (22–50)

Table 2
Univariate Analysis of Survival Time by Categorical Variable

Variable	**Log-rank test value**	***P-value***
Age (< 65 /≥65)	0.062	0.803
Sex (Female/male)	0.087	0,768
Tumor stage	0.704	0.401
Comorbidities (0/≥2)	2.582	0.108
Hypertension	0.117	0.732
Diabetes mellitus	0.021	0.885
Cardiovascular disease	0.010	0.922
Chronic pulmonary disease	0.276	0.599
Cerebrovascular disease	0.383	0.536
Receiving chemotherapy in the last 28 days	7.866	***0.005**
Receiving radiotherapy in the last 28 days	2.254	0.133
Hospitalization in the intensive care unit	5.566	*0.018
Pleural effusion in thorax CT	0.252	0.616
Mechanical ventilation requirement	6.320	*0.012
COVID 19 corticosteroid treatment doses (≤ 1 mg/kg/>1 mg/kg)	5.258	*0.022
Total white blood cell count	1.239	0.255
Hemoglobin	5.280	*0.009
Platelet count	9.353	*0.022
Neutrophil	1.162	0.559
Lymphocytes	1.887	0.389
Albümin	0.561	0.454
C reactive protein	0.475	0.491
Uric acid	12.475	*0.002
Neutrophil:lymphocyte ratio (NLR) < 6/ ≥6	1.762	0.284

**P < 0.05* statistically significant

Variable	Log-rank test value	*P-value*
Platelet:lymphocyte ratio (PLR) < 270/ ≥270	0.497	0.481
OnCovid Inflammatory Score (OIS) > 40/≤40	3.042	0.081
Prognostic Index (PI) 0/2	1.246	0.532
Modified Glasgow prognostic score (mGPS)	0.969	0.616
*$P < 0.05$ statistically significant		

Table 3
Multivariate Analysis of Prognostic Factors

Parameter	p value	OR	%95 CI
Receiving chemotherapy in the last 28 days	0.249	1.95	0.60–6.1
Hospitalization in the intensive care unit	0.746	1.77	0.05-56
Mechanical ventilation requirement	0.617	2.4	0.07-78
COVID-19 corticosteroid treatment doses (≤ 1 mg/kg > 1 mg/kg)	0.934	2.79	0.01–110
Hemoglobin	***0.047**	3.86	1.1–14.6
Platelet count	0.578	0.70	0.2–2.4
Uric acid	***0.008**	28	2.3–336
*$P < 0.05$ statistically significant			