Research Article

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Area of Expertise: Immunology, Internal Diseases, Clinical Sciences

Title: The impact of SARS-CoV-2 infection on the survival in NSCLC patients undergoing immunotherapy.

Short title: Effect of SARS-CoV-2 in NSCLC patients treated with immunotherapy.

Abstract

Purpose: The impact of immune checkpoint inhibitor (ICI) utilisation on prognosis and the prognostic value of inflammatory markers (neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), systemic immune inflammation score (SII), prognostic nutrition index (PNI)) in patients with advanced non-small cell lung cancer (NSCLC) were evaluated in the context of the ongoing pandemic. The cut-off values of the prognostic markers were obtained from clinical studies in the literature.

Materials and methods: A non-probability sequential sampling technique ensured the study included 104 patients who had received ICI at any stage. Laboratory tests taken at the outset of ICI treatment were recorded, and NLR, PLR, PNI and SII were calculated and 2-year median overall survival (mOS) was then evaluated.

Results: The median age of the cohort was 63.99 years, with 98% of patients being male. Infection with SARS-CoV-2 virus was documented in 29 patients (27.9%). The survival results were similar in both groups when the cut-off values were applied for inflamatuar markers. The two-year mOS was 22 months (44.1%). The two-year survival rate of patients who developed a SARS-CoV-2 infection following the administration of an ICI at any stage of treatment was inferior to that of ICI recipients who did not develop the infection (14.3 months vs. 53.6 months; p=0.001). In contrast with previous studies, 57.1% of patients with a PD-L1 level of 0 survived for two years, while only 10% with levels of 1-49 did so (p=0.010).

Conclusion: This study revealed a significantly lower two-year survival rate in patients with a positive diagnosis for SARS-CoV-2 during ICI use compared to those without a positive diagnosis (14.3 months; 53.6 months; p=0.001). In the course of our research, we were unsuccessful in identifying a prognostic marker that could be useful in predicting survival in NSCLC patients using ICI in the context of the pandemic. This investigation

yielded findings that differed from the conclusions of previous studies. It demonstrated that, contrary to the prevailing view, the two-year survival rate was higher in patients exhibiting PD-L1 '0' than in those with PD-L1:1-49 (57.1%; 10%, *p*=0.010).
Keywords: NSCLC, COVID-19, immunotherapy.

Makale başlığı: İmmünoterapi uygulanan NSCLC hastalarında SARS-CoV-2 enfeksiyonunun sağkalım üzerine etkisi.

Kısa başlık: İmmünoterapi ile tedavi edilen NSCLC hastalarında SARS-CoV-2'nin etkisi.

Öz

Amaç: İleri evre küçük hücreli dışı akciğer kanserli (NSCLC) hastalarda immün kontrol noktası inhibitörü (ICI) kullanımının prognoz üzerindeki etkisi ve inflamatuar belirteçlerin (nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR), sistemik immün inflamasyon skoru (SII), prognostik beslenme indeksi (PNI)) prognostik değeri devam eden pandemi bağlamında değerlendirildi.

Gereç ve yöntemler: Olasılıksız sıralı örnekleme tekniği ile belirlenen tedavinin herhangi bir basamağında ICI almış 104 hastanın çalışmaya dahil edildi. ICI tedavisinin başlangıcında alınan laboratuvar testleri kaydedilerek; NLR, PLR, PNI ve SII hesaplandı. Ardından 2 yıllık medyan genel sağkalım (mOS) değerlendirildi. Prognostik belirteçlerin cut-off değerleri literatürde yer alan klinik çalışmalardan elde edildi.

Bulgular: Ortalama tanı yaşı 63,99 yıl olup hastaların %98'i erkekti. SARS-CoV-2 virüsü ile enfekte olan 29 hasta (%27,9) vardı. Enflamatuar belirteçler için kesme değerler uygulandığında sağkalım sonuçları her iki grupta da benzerdi. İki yıllık mOS 22 aydı (%44,1). Tedavinin herhangi bir aşamasında ICI uygulanmasını takiben SARS-CoV-2 enfeksiyonu gelişen hastaların iki yıllık sağkalım oranı, enfeksiyon gelişmeyen ICI alıcılarınınkinden daha düşüktü (14,3 ay; 53,6 ay; *p*=0,001). Önceki çalışmaların aksine, PD-L1 düzeyi 0 olan hastaların %57,1'i iki yıl boyunca hayatta kalırken, 1-49 düzeyine sahip hastaların yalnızca %10'u hayatta kalmıştır (*p*=0,010).

Sonuç: Bu çalışma, ICI kullanımı sırasında SARS-CoV-2 için pozitif tanı alan hastalarda, pozitif tanı almayanlara kıyasla iki yıllık sağkalım oranının anlamlı derecede düşük olduğunu ortaya koymuştur (14,3 ay; 53,6 ay; *p*=0,001). Araştırmamızda, pandemi döneminde ICI kullanan NSCLC hastalarında sağkalımı tahmin etmede yararlı olabilecek bir prognostik belirteç tanımlayamadık. Bu araştırma, önceki çalışmaların sonuçlarından farklı olarak, iki yıllık sağkalım oranının PD-L1:'0' olan hastalarda PD-L1:1-49 gösterenlere göre daha yüksek olduğunu göstermiştir (%57,1; %10, *p*=0,010).

Anahtar kelimeler: NSCLC, COVID-19, immünoterapi.

Introduction

In alignment with the data disseminated by the International Agency for Research on Cancer (IARC) in 2022, lung cancer represents the most commonly diagnosed malignant neoplasm of the solid organs. Lung cancer is the most frequent cause of mortality from cancer among both men and women (18.7%), with 2.5 million new cases and 1.8 million deaths related to lung cancer on a global scale [1].

All treatments for advanced non-small cell lung cancer (NSCLC) are palliative. They are designed to minimise treatment-related adverse effects and enhance survival without compromising quality of life. The treatment options available include cytotoxic chemotherapy, the targeting of specific mutations (EGFR, ALK, KRAS, ROS1, HER2, MET, RET, BRAF, NTRK) and immune checkpoint inhibitors (ICI)s (pembrolizumab, atezolizumab and nivolumab). It has been demonstrated that ICI therapies targeting programmed cell death ligand (PD-L1) and programmed cell death protein 1 (PD-1) are effective at improving survival outcomes in NSCLC patients without driver mutations. In advanced NSCLC patients with driver mutations other than KRAS, BRAF and MET mutations, no sensitivity to ICI has been observed. Therefore, a driver mutation analysis is performed before treatment decisions are taken [2, 3].

Treatment decisions should be based on a comprehensive assessment of the patient, including factors such as the ECOG PS, age, height and weight. They should also account for factors outside the patient's control. The 2019-nCoV severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a significant environmental factor with a global impact. It is the third human coronavirus infection to result in significant morbidity and mortality, following SARS-CoV and MERS [4-6]. The first case of infection with the novel coronavirus, designated SARS-CoV-2, was identified in Wuhan, China, in December 2019. The case presented with pneumonia of unknown aetiology. By 1 July 2020, SARS-CoV-2 had affected more than 200 countries, with over 10 million identified cases and 508.000 confirmed deaths. The global pandemic of Coronavirus disease (COVID-19), caused by SARS-CoV-2, has resulted in a significant increase in hospitalisations for pneumonia, leading to multiple organ failure and mortality. The typical incubation period for the disease is approximately five days, with onset of symptoms occurring within 11.5 days of initial exposure. The median duration of hospitalization is seven days, with a range of three to nine days. The most commonly observed symptoms are a dry cough, dyspnoea and fever. Despite the non-specific nature of the disease, laboratory abnormalities, such as lymphopenia and elevated LDH, are commonly observed. In addition to the asymptomatic course of the disease, some patients present

with a fulminant disease process and acute respiratory failure. The primary management strategy for the disease is the administration of supportive treatments for hypoxia and multiorgan failure. Despite the recommendation of supportive therapies, there remains significant concern among clinicians regarding the risk of mortality associated with infection [7, 8]. Following the determination of the treatment plan, further research is warranted to elucidate the potential impact of SARS-CoV-2 infection on the prognosis of advanced NSCLC patients undergoing ICI, as well as the prognostic value of available inflammatory markers.

Materials and methods

Patient characteristics and data collection

Included in this study were all patients with NSCLC aged 18 years and older who received immunotherapy (ICI) at any stage of their treatment between January 2020 and June 2024 in the medical oncology clinic of xxxxxxxxxx University, Faculty of Medicine. The selection process was conducted using a non-probability sequential sampling technique. Clinical and demographic data pertaining to the patients were sourced from the medical oncology file records, while haematological and biochemical parameters were derived from the hospital database. A principal focus of the study was to examine the impact of a patient's history with COVID-19, both preceding and occurring concurrently with ICI treatment, on survival and treatment response. In the present study, we sought to examine the prognostic value of prior or current infection with SARS-CoV-2 in patients undergoing ICI treatment. The role of the inflammatory response in oncopathogenesis, which sustains the survival of cancer cells, has been well-documented in the literature. This has led to the definition of specific inflammatory markers that reflect this phenomenon in clinical and laboratory data used in patient follow-up [9-12]. In the patient cohort included in this study, prognostic markers that could predict the course of SARS-CoV-2 infection were subjected to analysis. The objective was to examine the relationship between the neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), systemic immune-inflammation score (SII), and prognostic nutritional index (PNI) and median overall survival (mOS) and median progression-free survival (mPFS). This was accomplished by documenting the patient's haematological and biochemical values, which were then input into the formulas.

Objectives and calculationof prognostic markers

Neutrophil-to-lymphocyte ratio (NLR): It is a prognostic marker indicating the inflammatory response calculated by the ‘neutrophil-to-lymphocyte’ formula [9].

Platelet-lymphocyte ratio (PLR): It is a prognostic marker indicating the inflammatory response calculated with the formula ‘platelet÷lymphocyte’ [10].

Systemic immune inflammation score (SII): It is a prognostic marker that indicates the extent of the inflammatory response, calculated by the formula 'platelet*neutrophil/lymphocyte' [11].

Prognostic nutritional index (PNI): It is a prognostic marker showing the immunonutrition status of the patient calculated with the formula ‘albumin(g/L)+5*lymphocyte(109/L)’ [12].

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows. Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)'. Descriptive statistics were presented as n and % for categorical variables and median for continuous variables. In order to ascertain the optimal cut-off value for prognostic scoring, receiver operating characteristic (ROC) analysis was employed. Survival analyses of prognostic markers were performed using cut-off values found to be significant in clinical studies in the literature since statistical significance was not found by ROC analysis of prognostic markers. Kaplan-Meier method was utilised for survival (mOS, mPFS) analyses. The prognostic value of the results falling below and above the cut-off value for two-year mOS was analysed. PFS is defined as the period of time between the diagnosis date and the first documented instance of disease progression. OS was defined as the time elapsed between the date of diagnosis and either the date of death or the last follow-up. Univariate analysis was conducted. Subsequently, a univariate Cox proportional-hazards regression analysis was performed in order to evaluate which of the aforementioned parameters were significant in the context of a survival analysis. Statistically significant results (p<0.05) are indicated with a (*) sign next to the pvalue.

xxxxxxxxxx University Faculty of Medicine, xxxxxxxxxx Ethics Committee approval was obtained (approval dated 12.06.2024 and approval number: E-60116787-020-540043, board meeting).

Results

Clinical and demographic data of NSCLC patients who received ICI at any stage of their treatment during the COVID-19 pandemic affecting the whole world are presented in Table 1. The median age of the participants was 63.99 years, and 98% of the sample was male. A total of 29 participants (27.9%) reported a history of infection with SARS-CoV-2. Those who had COVID-19 infection after receiving a diagnosis of ‘lung cancer’

accounted for 69% (n:20 patients). ECOG performance was ‘0’ in 67.3% (n:70) of the patients. There were 10 patients (9.6%) who were never smoker. Active smokers were excluded from the study. The majority of patients with a smoking history smoked less than 43 pack/year (n:38;30.8%). The location of the primary tumour, tumour pathological subtype, stage at diagnosis, operation history and PDL1 level were recorded. Most patients (n=22) received immunotherapy after COVID-19 diagnosis. Median follow up was 22 months and mPFS after COVID-19 was 19.79 months (Table 1). Clinical and demographic data of NSCLC patients who received ICI with and without a history of COVID-19 are shown in Table 2. There were 29 patients with a history of COVID-19 and 75 patients without a history of COVID-19. The median BMI of those with a history of COVID-19 was significantly higher (26.0;24.0; *p*=0.016). More patients with a history of COVID-19 received immunotherapy at the third line. Without a history of COVID-19 received immunotherapy were mostly in the first and second line (*p*=<0.001). In Both groups, there was no difference in median age, gender, smoking history, ECOG PS, primary tumour localisation, pathological subtype, stage, PDL1 level, progression after ICI treatment and follow-up periods (Table 2).

Table 3 presents the calculated cut-off values of prognostic parameters for overall survival, as determined through ROC curve analysis. The survival outcomes observed in both groups, formed as previously described, were comparable regardless of whether the cut-off values were above or below (NLR (*p*=0.415), PLR (*p*=0.666), PNI (*p*=0.270) and SII (*p*=0.737)). As the ROC analysis of prognostic markers did not show statistical significance, survival analyses were performed using the cut-off values of prognostic markers (NLR (9), PLR (10), SII (11) and PNI (12)) found to be significant in clinical studies in the literatüre. The survival results were similar in both groups (NLR (*p*=0.815), PLR (*p*=0.648), PNI (*p*=0.992) and SII (*p*=0.875)) (Table 4) (Figure 1).

The impact of prognostic markers on two-year survival in patients with NSCLC receiving ICIs during the period of the SARS-CoV-2 pandemic was evaluated. OS was determined to have a median value of 22 months for the total patient cohort (44.1%; minimum-maximum: 15.37-28.62). The two-year survival of patients who developed a SARS-CoV-2 infection following the administration of ICIs at any stage of treatment was found to be inferior to that of ICI recipients who did not develop a SARS-CoV-2 infection (14.3 months vs. 53.6 months; *p*=0.001). In contrast with the findings of previous studies, the two-year survival rate for patients with a PD-L1 level of 0 was 57.1%. In comparison, the rate was 10% for the group with a PD-L1 level of 1-49. These findings reached a statistically significant level (*p*=0.010). No significant correlation was identified between age (*p*=0.689), gender (*p*=0.797), smoking history (*p*=0.849), ECOG PS (*p*=0.476),

primary tumour localisation (p=0.629), pathological subtype (p=0.321) and BMI value (p=0.687) (Table 5).

In NSCLC patients receiving ICI, the effect of clinical and demographic data on 2-year survival was evaluated in grouping according to COVID-19 history. In patients with a history of COVID-19, although it did not reach statistical significance, two-year survival was longer in patients aged <65 years, male and BMI<25 (p>0.05). In patients without a history of COVID-19, two-year survival was longer in patients aged <65 years, female, BMI<25 (p>0.05). As a result of this analysis, it was concluded that the evaluation of clinical and demographic variables together with COVID-19 history had no prognostic value (Table 6).

Discussion

Our study aimed to investigate the safety of ICI use in NSCLC patients during the ongoing pandemic and its impact on prognosis in systemic treatment. Patients with a positive test for the SARS-CoV-2 who received ICI in systemic therapy had a shorter two-year survival rate. This study found that, contrary to the literature, two-year survival was 57.1% in patients with PD-L1 level '0', while it was 10% in the group with PD-L1: 1-49. Therefore, the survival analysis was performed using values from clinical trials with significant cut-off values (NLR, PLR, PNI and SII). Similar survival results were found in both groups. The same survival results were obtained in the groupings formed below and above the cut-off values of the prognostic markers. These were obtained by placing the laboratory parameters of the patients into formulae obtained from the literature. We found no useful prognostic marker to predict survival of NSCLC patients who used ICI during the pandemic. We can state with confidence that age, gender, smoking history, ECOG PS, primary tumour localisation, pathological subtype (squamous cell carcinoma and non-squamous carcinoma) and BMI were not significantly associated with two-year mOS. In patients with a history of COVID-19, two-year survival was longer in patients aged under 65, male and BMI <25 (p>0.05). Two-year survival was longer in patients under 65 with BMI under 25 (p>0.05) without a history of COVID-19. This analysis shows that evaluating clinical and demographic variables together with history of COVID-19 has no prognostic value.

The immunosuppressive microenvironment, comprising peritumoural lymphopenia and neutrophilia, is the mechanism that prevents the immune system from responding to the life cycle of the cancer cell. In the event of the immune system failing to inhibit this process at this stage, it will result in uncontrolled proliferation and metastasis. The use of

ICI therapies reorganises and activates this peritumoural immunosuppressive environment [13].

Lymphocytes represent the most significant cellular defence mechanism in the inhibition of tumour cell proliferation. Consequently, a reduction in lymphocyte count, regardless of the underlying cause, has been linked to an unfavourable prognosis. Similarly, as with other respiratory viral infections, It has been established that SARS-CoV-2 is capable of inducing apoptosis in lymphocytes, which can lead to significant lymphopenia [14]. T cells play a crucial role in immune protection against lethal COVID-19. In this study, the frequencies and functions of CD4+/CD8+ T cells were investigated using combined single-cell methodologies and flow cytometry. Furthermore, an increase in the simultaneous expression of inhibitory receptors, such as PD-1 and T-cell immunoglobulin and mucin domain-3 (TIM-3), was observed in individuals who had previously been infected. The results of our study also lend support to this conclusion. Following the administration of ICI, patients with a positive diagnosis of SARS-CoV-2 infection exhibited a significantly shorter survival rate (14.3 months; 53.6 months; p=0.001) [15].

With regard to the SARS-CoV-2 pathogen, an impairment in epithelial endothelial integrity is observed, concomitant with an increase in viral replication. An elevated inflammatory response gives rise to the migration of monocytes and neutrophils. In autopsy studies, the inflammatory response results in the formation of hyaline membranes, which are characterised by inflammatory infiltrates and intercellular oedema. The occurrence of angioedema due to an increase in bradykinin contributes to an unfavourable prognosis. An inevitable consequence of infection with SARS-CoV-2 is the subsequent development of acute respiratory distress syndrome (ARDS), which in turn gives rise to a reduction of oxygen delivery to both the alveolar and capillary vessels. Impairment of the endothelial barrier function is the underlying cause of the observed reduction in oxygen delivery. This results in the formation of ground-glass opacities within the lung parenchyma, as observed on computed tomography scans [16]. Another mechanism that determines prognosis is the formation of microthrombi with fulminant activation of coagulation (myocardial infarction, pulmonary embolism, deep vein thrombosis, ischaemic stroke, diffuse intravascular coagulation) [17]. Based on the aforementioned pathogenesis, it can be posited that supportive treatment management of acute hypoxic respiratory failure and ARDS should be applied in the treatment plan of patients.

In a study evaluating the impact of SARS-CoV-2 infection on systemic treatment, Jung et al. [18] identified 452 patients with metastatic and recurrent disease following

surgery and definitive radiotherapy among 1.127 patients diagnosed with NSCLC and SARS-CoV-2. Among the 387 individuals who received palliative systemic therapy during the course of their infection with the novel coronavirus, 95.3% (369 of 387) continued their systemic therapy within one month of the onset of their infection. Only one patient discontinued treatment as a consequence of complications arising from the infection, while 18 patients modified their systemic therapy regimen as a result of disease progression. In this study, 63 patients contracted the SARS-CoV-2 virus while undergoing treatment with a programmed cell death 1/programmed cell death 1 ligand (PD-1/PD-L1) inhibitor as monotherapy (n=37) or in combination with chemotherapy (n=25). Three patients terminated treatment due to disease progression, whereas sixty patients continued treatment following the diagnosis of SARS-CoV-2 infection. This study, which employs a machine learning model, elucidates the case fatality rate and risk factors associated with COVID-19 in patients with NSCLC. It was confirmed by the findings that the risk factors for case fatality rates included palliative chemotherapy (especially cytotoxic chemotherapy), advanced age, male gender, diabetes, a history of smoking, a history of lung radiotherapy, hypertension, and COPD.

At the outset of the global pandemic caused by the SARS-CoV-2 virus, there was a paucity of guidance on the treatment of systemic disease. The cessation of systemic therapy in advanced cancers may result in disease progression and an increased risk of cancer-related mortality. The findings of this study indicate that there was no impact of the SARS-CoV-2 infection on the continuation of systemic therapy. They were more likely to receive combined palliative treatments.

A study of 1.547 NSCLC patients. A total of 1.329 patients were included in the study before the pandemic (Nov 2015 to Dec 2020) and 218 during the pandemic. The two groups exhibited comparable age distributions and prevalence of comorbidities. In contrast with the anticipated outcome, the incidence of NSCLC screening via low-dose computed tomography exhibited a 25% decline during the pandemic period. During the period of the global pandemic caused by the novel coronavirus, a greater number of patients were diagnosed with advanced stages of the disease, and the mortality rate six months after diagnosis was higher than in the period preceding the pandemic (28% compared to 22%, p=0.04). The SARS-CoV-2 pandemic has reduced the anticipated median survival rate due to more advanced disease stages being identified. This, in turn, resulted in a decline in the number of admissions and surgical procedures conducted for the purpose of early diagnosis, as evidenced by reference to the literature [19].

Yang et al. [20] analysed 860 NSCLC patients. The vaccination rate was 71.11% in early-stage and 19.48% in those with advanced disease. The majority of patients (86.5%)

had received the inactivated SARS-CoV-2 vaccine (Coronavac; Sinovac), produced using Vero cells. The most frequently reported systemic adverse effect was weakness. The primary rationale for declining the vaccine among unvaccinated patients was concern about its safety in the context of tumour presence and ongoing treatment (56.9% and 53.4%, respectively). The findings were similar to those of the previous study. There was no statistically significant difference in PFS or OS for vaccinated and unvaccinated patients, regardless of stage (p=0.478). It was concluded that vaccination did not affect OS in NSCLC patients.

A review of the literature indicates an unfavourable prognosis for patients undergoing immunotherapy for COVID-19 who are receiving ≥10 mg prednisone daily or equivalent doses of steroids. It is therefore recommended that steroids be used in a controlled manner for patients with NSCLC who are receiving immunotherapy, except in cases where there is a presence of symptomatic brain metastasis. In comparison to the general population, the occurrence of complications associated with COVID-19 is more prevalent among patients with immunosuppression. While the 30-day mortality rate for patients with cancer is 13-33%, a mortality rate of 0.1-2% has been observed in the general population [21].

Patients with NSCLC are particularly susceptible to complications due to the inherent fragility of their pulmonary and alveolar structures, which can be further compromised by a history of surgical procedures, radiation therapy, and underlying lung disease. The objective of managing patients with NSCLC during the ongoing pandemic is to minimise the risk of exposure and complications in the event that the patient contracts the virus while undergoing treatment for a condition with a high mortality rate. In light of the aforementioned considerations, the proliferation of studies pertaining to the selection and monitoring of treatment regimens is likely to prove beneficial for medical oncologists engaged in decision-making processes during the ongoing pandemic.

The limitations of this study include the analysis of single-centre data, the insufficient patients number, and retrospective data analysis. It is therefore proposed that a prospective study with a higher number of patients would yield stronger statistical significance and provide a more robust basis for evaluation of the hypothesis. It should be noted that similar limitations are inherent to all retrospective studies. The field of cancer and tumour microenvironment remains a prominent area of research.

In conclusion, this study evaluated the use of ICIs in patients with NSCLC during the ongoing pandemic and its effect on prognosis. Two-year mOS rate for patients with SARS-CoV-2 test positive during ICI treatment is significantly lower than for patients with negative results (14.3 vs. 53.6 months, p=0.001). This study found that the two-year

mOS rate was 57.1% in patients with PD-L1 expression levels of 0 and 10% in those with levels of 1-49 (p=0.010). Our research found no markers for predicting NSCLC patient survival using ICI during the pandemic. Given the current evidence, patients with a history of COVID-19 should have at least a 15-day interval before resuming systemic therapy. It is recommended that, in the case of NSCLC patients, controlled steroid use is employed, with the exception of those presenting with symptomatic brain metastasis. Ultimately, the findings indicated that the administration of the SARS-CoV-2 vaccine did not influence the survival outcomes of NSCLC patients, irrespective of their disease stage. The results of this study may be strengthened by the inclusion of a larger patient cohort in future prospective studies.

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Authors contributions: M.O. and G.G.D. constructed the main idea and hypothesis of the study. M.O. and G.G.D. developed the theory and arranged/edited the material and method section. M.O. and G.G.D. has done the evaluation of the data in the results section. The discussion section of the article was written by M.O. and G.G.D. and reviewed, corrected, and approved by A.G.D., S.D., B.Y.T. and A.Y. In addition, all authors discussed the entire study and approved the final version.

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Table 1. Demographic and clinical properties of nsclc patients who received ımmune checkpoint ınhibitors for systemic treatment during the COVID-19 pandemic period

Variables	**Total n=104**
Age, Median±SD	63.99±8.46
Gender, n (%)	
Male	98 (94.2%)
Female	6 (5.8%)
COVID-19	
-	75 (72.1%)
+	29 (27.9%)
NSCLC diagnosis date and COVID-19 timing	
Had COVID-19 before diagnosis	9 (31%)
Had COVID-19 after diagnosis	20 (69%)
Immune checkpoint inhibitor	
Used before COVID-19	7 (24.1%)
Used after COVID-19	22 (75.9%)
Smoking history, n (%)	
Never smoker	10 (9.6%)
Ex smoker <43 packs/year	38 (30.8%)
Ex smoker >43 packs/year	2 (1.9%)
ECOG PS, n (%)	
0-1	70 (67.3%)
2	34 (32.7%)

Localization of primary tumor, n (%)	
Right lung	63 (60.6%)
Left lung	39 (37.5%)
Bilateral	2 (1.9%)
Tumor pathological subtype	
Nonsquamous carcinoma	45 (43.3%)
Squamous carcinoma	59 (56.7%)
Stage at diagnosis (%)	
1	1 (1.0%)
2	7 (6.7%)
3	47 (45.2%)
4	49 (47.1%)
PDL1, n (%)	
0	22 (21.2%)
1-49	40 (38.5%)
≥50	42 (40.4%)
Surgery, n (%)	
-	99 (95.2%)
+	5 (4.8%)
Progression after immunotherapy, n (%)	
-	2 (1.9%)
+	102 (98.1%)
Mortality, n (%)	
Alive	35 (33.7%)
Exitus	69 (66.3%)
Mortality after COVID-19, n (%)	
Alive	11 (37.9%)
Exitus	18 (62.1%)
Follow-up period (months), Median±SD	22.12±10.52
PFS after Covid-19 (months), Median±SD	19.79±12.59

Descriptive statistics are presented as Median for continuous variables, n and % for categorical variables

Table 2. Distribution of data on clinical and sociodemographic characteristics according to Covid-19 history

Variables total n=104	**Without a history of COVID-19 n=75**	**With a history of COVID-19 n=29**	***p***
Age, Median	63.0 (44.0-87.0)	66.0 (42.0-77.0)	0.241[c]
BMI, Median	24.0 (18.0-42.0)	26.0 (15.0-42.0)	0.016[c]
<25	44 (58.7)	11 (37.9)	0.057[a]
≥25	31 (41.3)	18 (62.1)	
Gender, n (%)			
Male	70 (93.3)	28 (96.6)	0.463[b]
Female	5 (6.7)	1 (3.4)	
Smoking history, n (%)			COVID-19 öyküsü ile
Never smoker	8 (10.7)	2 (6.9)	0.769[a]
Ex smoker <43 packs/year	28 (37.3)	10 (34.5)	
Ex smoker >43 packs/year	39 (52)	17 (58.6)	

ECOG PS, n (%)			
0	51 (68)	19 (65.5)	0.809[a]
1-2	24 (32)	10 (34.5)	
Localization of primary tumor, n (%)			
Right lung	47 (62.7)	16 (55.2)	0.534[b]
Left lung	27 (36)	12 (41.4)	
Bilateral	1 (1.3)	1 (3.4)	
Tumor pathological subtype, n (%)			
Nonsquamous carcinoma	35 (46.7)	10 (34.5)	0.261[a]
Squamous carcinoma	40 (53.3)	19 (65.5)	
Stage at diagnosis, n (%)			
1	1 (1.3)	0 (0)	0.846[a]
2	6 (8)	1 (3.4)	
3	34 (45.3)	13 (44.8)	
4	34 (45.3)	15 (51.7)	
Metastasis, n (%)			
Denova Metastasis	33 (70.2)	15 (65.2)	0.672[a]
Metachron Metastasis	14 (29.8)	8 (34.8)	
PDL1, n (%)			
0	15 (20)	7 (24.1)	0.842[a]
1-49	30 (40)	10 (34.5)	
≥50	30 (40)	12 (41.4)	
Treatment step of immunotherapy			
1	6 (8)	0 (0)	<0.001[b]
2	54 (72)	8 (27.6)	
3	15 (20)	21 (72.4)	
Progression after immunotherapy, n (%)			
-	17 (22.7)	8 (27.6)	0.599[a]
+	58 (77.3)	21 (72.4)	
Median PFS after immunotherapy	13.8 (4.0-41.0)	13.0 (5.0-27.0)	0.885[c]
Mortality, n (%)			
Alive	24 (32)	11 (37.9)	0.566[a]
Exitus	51 (68)	18 (62.1)	
Follow-up period (months), Median	21.0 (4.0-41.0)	21.0 (7.0-51.0)	0.344[c]

Descriptive statistics are presented as median for continuous variables n and % for categorical variables

a: Pearson Chi Square test, b: Fisher's Exact test, c: Mann Whitney U test, $p<0.05$ is statistically significant

Table 3. ROC curve analysis results of cut-off values of prognostic parameters

Variable	AUC	95% CI	Cut off	Sensitivity (%)	Specificity (%)	*p*
NLR	0.594	0.378-0.811	≥3.90	50.0	50.0	0.415
PLR	0.550	0.239-0.771	≥177.0	50.0	50.0	0.666
PNI	0.628	0.419-0.837	≤408.50	61.1	60.0	0.270
SII	0.539	0.318-0.759	≥1000.0	61.1	60.0	0.737

AUC: Area under the curve, 95%CI: Confidence interval, NLR: neutrophil lymphocyte ratio
PLR: platelet lymphocyte ratio, PNI: prognostic nutritional index, SII: Systemic immune inflammation score, Receiver Operating Characteristic (ROC) analysis was employed

Table 4. Statistical value of prognostic markers in predicting two-year survival in NSCLC patients with a history of Covid-19 receiving immune checkpoint inhibitors

OS Variables	With a history of Covid-19 n=29		*p*
	2-year mOS%	Median (95% CI)	
NLR			
<6.39	47.4	24.00 (17.40-30.59)	0.815
>6.39	40.0	24.00 (11.18-36.88)	
PLR			
<125.78	44.4	21.00 (15.15-26.84)	0.648
>125.78	46.3	24.00 (18.98-29.02)	
PNI			
>442.5	50,0	17.00 (0.19-33.80)	0.992
≤442.5	44.6	24.00 (18.45-29.54)	
SII			
<550.0	37.5	19.00 (6.52-31.47)	0.875
>550.0	49.1	24.00 (18.77-29.22)	

Kaplan Meier curve, NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio
PNI: prognostic nutritional index, SII: Systemic immune inflammation score
p<0.05 is statistically significant

Table 5. Statistical value of prognostic markers in predicting 2-year survival in NSCLC patients under treatment with immune checkpoint inhibitors during the Covid-19 pandemic period

OS (months)	**2-year mOS%**	**Median (95%CI)**	***p***
Overall survival	44.1	22.0 (15.37-28.62)	
Covid-19			
Before NSCLC diagnosis	88.9	32.00 (-)	0.067
After NSCLC diagnosis	35.0	13.00 (10.82-15.18)	
Immunotherapy before **Covid**-19			
+	14.3	4.00 (1.43-6.56)	0.001*
-	53.6	32.00 (21.69-42.30)	
Age			
≤65	36.9	18.00 (10.45-25.541)	0.689
>65	50.0	22.00 (6.04-37.96)	
Gender			
Male	32.8	21.00 (6.47-35.52)	0.797
Female	-	22.00 (-)	
Smoking history, n (%)			
Never smoker	50.0	22.00 (-)	0.849
Ex smoker <43 packs/year	50.0	13.00 (0.00-40.54)	
Ex smoker >43 packs/year	39.7	21.00 (9.68-32.32)	
ECOG PS			
0-1	56.6	22.00 (0.00-45.15)	0.476
2	40.0	21.00 (8.95-33.05)	
Primary tumor localization			
Right lung	50.0	27.00 (0.00-50.64)	0.629
Left lung	40.0	18.00 (0.00-38.06)	
Bilateral	-	22.00 (-)	
Tumor pathological subtype			
Squamous carcinoma	50.0	22.00 (-)	0.321
Nonsquamous carcinoma	41.4	13.00 (3.69-22.30)	
PDL1			
0	57.1	32.00 (16.72-47.27)	0.010*
1-49	10.0	8.00 (0.00-17.29)	
≥50	66.7		
BMI			
<25	45.5	21.00 (3.73-38.26)	0.687
≥25	43.2	22.00 (14.42-29.57)	

BMI: body mass index, Kaplan Meier curve, Long rank test, Statistically significant results ($p<0.05$) are indicated with a (*) sign next to the *p* value

Table 6. Statistical value of Covid-19 and prognostic markers in predicting two-year survival in NSCLC patients receiving immune checkpoint inhibitors

OS Variables	Without a history of Covid-19 n=75			With a history of Covid-19 n=29		
	2-year mOS%	Median (95% CI)	*p*	2-year mOS%	Median (95% CI)	*p*
Age						
<65	49.8	22.00 (13.00-30.99)	0.281	51.9	25.00 (18.93-31.06)	0.976
≥65	33.9	21.00 (14.00-27.99)		42.9	21.00 (11.85-30.14)	
BMI						
<25	47.0	23.00 (15.91-30.09)	0.328	54.5	25.00 (14.38-35.61)	0.934
≥25	38.7	18.00 (12.54-23.45)		43.2	24.00 (18.31-29.68)	
Gender, n (%)						
Male	43.9	21.00 (15.01-26.98)	0.997	48.6	24.00 (17.94-30.05)	0.201
Female	40.0	24.00 (11.11-36.88)		-	16.00 (-)	
Smoking history, n (%)						
Never smoker	37.5	18.00 (4.14-31.85)	0.718	50.0	16.00 (-)	0.928
Ex smoker <43 packs/year	45.9	21.00 (9.58-32.41)		60.0	30.00 (0.39-59.60)	
Ex smoker >43 packs/year	43.6	22.00 (12.21-31.78)		41.2	24.00 (19.02-28.97)	
ECOG PS, n (%)						
0	52.6	26.00 (12.88-39.11)	0.030	46.8	24.00 (10.79-37.20)	0.792
1-2	25.0	16.00 (10.39-21.60)		46.7	24.00 (18.43-29.57)	
Tumor pathological subtype, n (%)						
Nonsquamous carcinoma	42.4	18.00 (9.50-26.49)	0.704	43.8	24.00 (16.95-31.04)	0.472
Squamous carcinoma	44.4	22.00 (16.03-27.96)		47.4	24.00 (15.81-32.19)	
Metastasis, n (%)						
Denova Metastasis	39.4	17.00 (11.37-22.62)	0.908	44.4	24.00 (16.98-31.01)	0.777
Metachron Metastasis	26.8	18.00 (8.83-27.16)		50.0	24.00 (15.68-32.31)	

PDL1, n (%)						
0	46.7	24.00 (10.11-37.88)	0.452	38.1	24.00 (7.59-40.41)	0.007
1-49	32.5	18.00 (14.77-21.22)		20.0	18.00 (9.73-26.26)	
≥50	53.3	26.00 (17.81-34.18)		75.0	- (-)	
Treatment step of immunotherapy						
1	50.0	14.00 (0.00-31.60)	0.242			0.012
2	36.2	18.00 (13.56-22.43)		87.5	- (-)	
3	66.7	37.00 (23.33-50.66)		33.3	21.00 (15.07-26.92)	

BMI: body mass index, Kaplan Meier curve, Long rank test, statistically significant results (p<0.05) are indicated with a (*) sign next to the p value

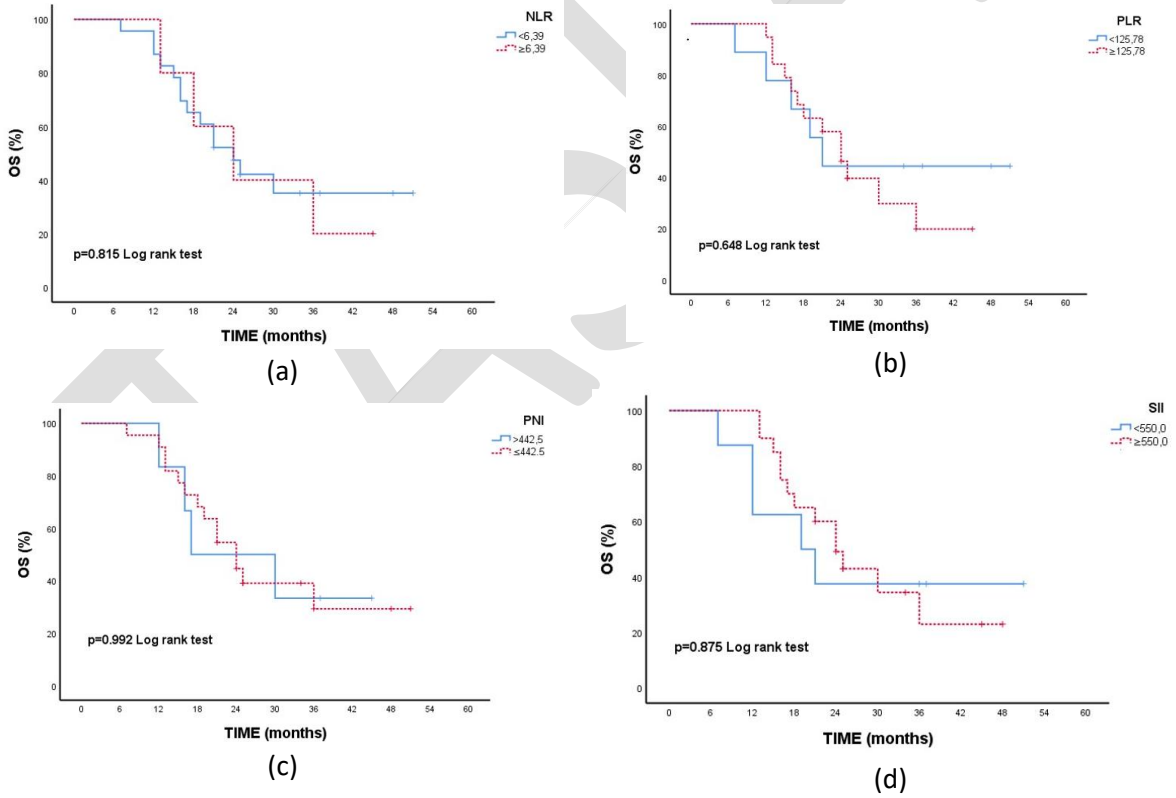

Figure 1. Kaplan-Meier overall survival prediction with prognostic markers for those with a history of COVID-19

NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio, PNI: prognostic nutritional index, SII: Systemic immune inflammation score; NLR(a), PLR(b), PNI(c), SII(d).

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