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Relationship between prognostic nutritional index and mortality in cancer patients treated with immunotherapy

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Abstract

Immunotherapy, in addition to surgery, chemotherapy, radiotherapy, and targeted therapies in cancer treatment, has emerged over the last decade as a significant contributor to improving patient survival. The prognostic nutritional index (PNI), which is a simple and useful tool that provides information about the general health status of patients and helps the treatment process, is used for many different types of cancer. This study aimed to evaluate the prognostic importance of PNI on mortality in cancer patients treated with immunotherapy. A total of 100 patients who were treated with immune checkpoint blockade in the oncology outpatient clinic were included retrospectively. According to our findings, only 23% of patients responded to immunotherapy, while 72% progressed. When PNI values were compared according to mortality status, it was determined that PNI values at baseline, first, third, sixth, and twelfth months were statistically significantly lower in patients who died during their follow-up. We also determined 44 as the cut-off value for the PNI in our study. The mortality rate was 76.7% in patients with PNI>44 and 43.5% in patients with PNI≤44. PNI appears to be a simple and useful tool for predicting mortality in cancer patients treated with immunotherapy.

Keywords: Prognostic nutritional index, cancer, mortality, immunotherapy

Introduction

Based on the information released by the International Agency for Research on Cancer, which excludes non-melanoma skin cancer, the number of cancer diagnoses reached 19.3 million people in 2020, and about 10 million people died from cancer [1]. Cancer treatment includes surgery, radiotherapy and systemic treatments, including chemotherapy, molecularly targeted therapies, hormone therapy, and immunotherapy. It usually consists of different combinations of these methods, which are personalized by evaluating the patient individually [2]. Immunotherapy is one of these therapeutic approaches and has become the leading treatment approach for many types of cancer in the last decade [3]. The use of immune checkpoint inhibitors has led to better outcomes in terms of progression-free and overall survival compared to standard chemotherapy treatments [4,5].

Many variables affect the response to treatment and mortality in cancer, such as the stage and type of the disease, age, general health status, tumor burden, biological characteristics, genetic factors, and the patient's nutritional status [6,7]. In recent years, prognostic indicators that can help develop a more personalized and effective approach to treatment and predict treatment response and mortality have been investigated [8,9]. Conventional prognostic methods such as medical imaging, pathology, demographics, and laboratory tests have limitations such as invasiveness, high cost, special training requirement, and subjectivity, and are not sufficient alone to predict patient outcomes [10]. Noninvasive, cost-effective, and easy-to-use

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markers such as the prognostic nutritional index (PNI), modified Glasgow prognostic score (mGPS), inflammatory prognostic index (IPI), and controlling nutritional status (CONUT) are promising tools for predicting prognosis and mortality in cancer patients [11-13].

The PNI was initially proposed in 1980 with a formula involving four factors (serum albumin and transferrin levels, triceps skinfold thickness, and skin test reactivity) [14]. However, due to subjectivity in the measurement of triceps skinfold thickness and skin test reactivity, its clinical use was limited. Therefore, in 1984, the PNI formula was modified as follows: PNI=serum albumin (g/L)+5 x total lymphocyte counts (10^9/L) [15], which is more cost-effective, easier to perform, and standardized. PNI is commonly used to estimate the prognosis of cancer patients because it reflects their nutritional status, which is often compromised in cancer [10]. In a systematic review and meta-analysis, low PNI was associated with a higher risk of poor overall survival and cancer-specific survival, regardless of cancer type, site, surgery type, cutoff value, and sample size [16]. Accordingly, many studies have been conducted targeting different cancer patients and treatment methods, questioning the prognostic importance of PNI, but the findings obtained so far are not consistent [11,12,17,18]. Hence, we examined the prognostic importance of PNI on mortality in cancer patients treated with immune checkpoint blockade in this study.

Material and Methods

Study design

Cancer patients who applied to Çukurova University Faculty of Medicine Hospital between January 2018 and June 2023 were examined retrospectively. A total of 100 cancer patients over the age of 18 who received immunotherapy treatment at the advanced stage were included in the study.

The criteria for exclusion of patients were as follows: i) liver and kidney transplant patients, ii) patients with autoimmune disease, heart disease, or stage 3-4 heart failure iii) using steroids more than 20 mg per day, iv) receiving immunosuppressive treatment v) severe liver and kidney failure, vi) immunodeficiency or neuropsychiatric disorders that interfere with immunotherapy treatment.

Biochemical findings and clinical information of the patients including age, gender, diagnosis, microsatellite instability (MSI), allergy, and medicine were collected from the medical records. In this study, we calculated the PNI scores of the patients at 3, 6, 9, and 12 months according to the following formula; PNI=serum albumin (g/L)+5 x total lymphocyte counts (109/L) [15].

Patient follow-up

The follow-up period for our patients was 12 months. We recorded the PNI scores of the patients at 3, 6, 9, and 12 months. Data from 11 of the 100 included patients were lost to follow-up and could not be included in the analyses regarding PNI values during the one-year follow-up period.

Ethical approval

Ethical approval was received from the Cukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee with decision number 55 on 07.04.2023. In addition, informed consent was obtained from all subjects involved in the study.

Statistical analysis

Using 80% power and 95% confidence interval d=0.5 as a reference, the minimum sample size to be reached was determined as 100. A total of 100 patients were included in the study. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY), with data presented in numerical, percentage, arithmetic mean, standard deviation, and median formats. The Kolmogorov-Smirnov test was used as a normality test. Parametric tests were used for normally distributed data, and non-parametric tests were used for data that did not meet parametric assumptions. Paired t-test, Wilcoxon test, Chi-square test, and binary logistic regression analysis were used for statistical analysis. A p-value of less than 0.05 was considered statistically significant. The optimal cut-off values for PNI were determined by the receiver operating characteristic (ROC) curve and the area under the curve (AUC).

Results

The sample of the research consisted of 100 cancer patients and Table 1 provides a summary of the clinical characteristics of these patients. The average age of patients was 58.54±13.82 years and 73% were male. The majority of patients were diagnosed with malignant melanoma (32%) or lung cancer (23%). The most used immunotherapy drugs were Nivolumab (69%) and Pembrolizumab (12%). The majority of patients received anti-PD-1 immune-checkpoint blockade therapy (81%). When the response of the patients to immunotherapy was examined, it was found that 72% of them had progressed and 23% had a response (Table 1).

We performed the ROC analysis performed to examine whether PNI is an important test tool in the diagnosis of mortality in patients receiving immunotherapy, the area under the curve (Figure 1) was found to be important, and the PNI score was an important but weak diagnostic test (Table 2).

According to the results of our study, the optimum cut-off value for the PNI index in the prediction of mortality was found to be 44. Values below this value should be interpreted in favor of mortality. For the 44-value, the sensitivity is 62.3% and the specificity is 72.2% (Table 3).

According to the logistic regression analysis created to estimate the mortality risk for the optimum PNI cut-off value (omnibus test p=0.001) was found to be important. PNI explained 15% of the variation in mortality, and 15% of the variation in the

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dependent variable was explained by the independent variables. The mortality risk was found to be a 4.29-fold increase in immunotherapy patients with a PNI value<44 during the 1-year follow-up period (Table 4).

When the PNI indexes were compared according to the mortality status of the patients during the follow-up periods, it was found that the PNI values of the patients who died during the follow-ups were statistically significantly lower at the beginning, first, third, sixth, and twelfth months (Table 5).

It was found that the mortality rates in patients with a PNI score below and above the cut-off value were statistically significantly different, and the mortality rate in patients below 44 was 76.7%, and in patients above 43.5% (Table 6).

Table 1. Clinical characteristics of the patients

Clinical factor	n	%
Gender		
Male	73	73.0
Female	27	27.0
Cancer		
Lung	23	23.0
Hepatocellular carcinoma	8	8.0
Hodgkin's lymphoma	9	9.0
Malignant melanoma	32	32.0
Mesothelioma	6	6.0
Non-Hodgkin's lymphoma	4	4.0
Renal cell carcinoma	8	8.0
Others	10	10.0
Drug groups		
Atezolumab	9	9.0
İpilimumab	7	7.0
Nivolumab	69	69.0
Pembrolizumab	12	12.0
Nivolumab and İpilimumab	3	3.0
Treatment		
Anti-PD-1	81	81.0
Anti-PDL-1	9	9.0
Anti-CTLA-4	7	7.0
IO/IO combination	3	3.0
Immunotherapy responses		
Response	23	23.0
Progressive disease	72	72.0
Stable disease	5	5.0
Total	100	100

Anti-PD-1: anti-programmed cell death-1, Anti-PDL-1: programmed death ligand-1, Anti-CTLA-4: anti cytotoxic-T-lymphocyte-associated antigen-4, IO/IO combination: combined immune-oncology (IO) agents

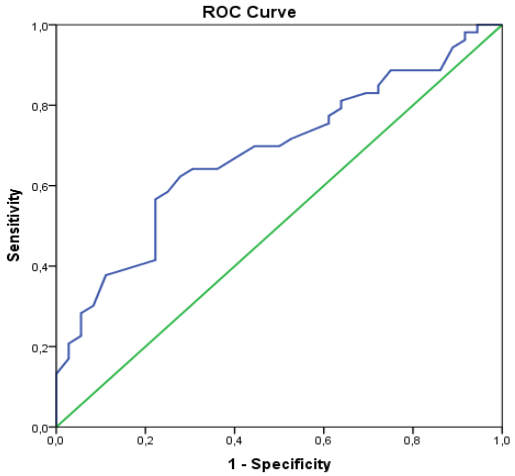

Figure 1. Areas under the curve for PNI

Table 2. Areas under the curve for PNI

Test result variable: Primary preoperative PNI value				
Area	**Std. Error**	**p-value**	**Asymptotic 95% CI**	
			Lower Bound	**Upper Bound**
0.681	0.056	0.004	0.571	0.792

PNI: prognostic nutritional index, Cl: confidence interval

Table 3. Validity results for PNI

Positive if less than or equal to	Sensitivity (%)	Specificity (%)	Youden's index	LR (+)	LR (-)
44	62.3	72.2	0.345	2.24	0.52

LR (+): Positive likelihood ratio; LR (-): negative likelihood ratio

Table 4. Logistic regression analysis to determine the independent risk factors for mortality according to the PNI cut-off value

	B	p	OR	95% CI for OR	
				Lower	Upper
Constant	0.466	**0.046**	1.593		
PNI Ref. >44 Risk <44	1.456	**0.002**	4.290	1.715	10.730

PNI: prognostic nutritional index, B: beta coefficients, OR: odds ratio, Cl: confidence interval

Table 5. PNI values between survivors and non-survivors

PNI values	Survivors (n=36)			Non-survivors (n=53)			
	Mean	SD	Median	Mean	SD	Median	p
Baseline	47.67	7.75	46.75	41.54	9.81	41.25	**0.002**
1st month	48.20	8.24	47.50	36.32	11.82	34.50	**<0.001**
3rd month	45.98	7.23	46.75	40.28	11.27	41.00	**0.028**
6th month	46.59	8.43	47.00	40.54	10.31	40.00	**0.031**
12th month	48.87	8.86	47.00	39.00	9.91	43.00	**0.005**

PNI: prognostic nutritional index, SD: standard deviation
Due to a lack of data in calculating PNI values, 89 patients were included in the analyses regarding PNI values during the one-year follow-up period

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Table 6. Comparison of survival rates according to PNI cut-off value

		PNI Group		
		>44	0-44	p
Survivors (n=36)	n	26	10	**0.003**
	%	56.5	23.3	
Non-survivors (n=53)	n	20	33	
	%	43.5	76.7	
Total (n=89)	n	46	43	
	%	100.0	100.0	

Due to a lack of data in calculating PNI values, 89 patients were included in the analyses regarding PNI values during the one-year follow-up period

Discussion

In this study, we investigated the association between PNI and mortality in cancer patients treated with immune checkpoint inhibitors. The majority of our patients had malignant melanoma and lung cancer and received anti-programmed death 1 (PD-1) blockade therapy. Our findings evinced that PNI was an independent predictive factor of mortality in cancer patients who were treated with immunotherapy.

Low PNI has been predominantly associated with worse outcomes in various cancers [19-23]. The finding that the PNI score explains 15% of the variation in mortality highlights the potential of this immunonutritional index to predict the health status of patients and their response to treatment (Table 4). Our findings support the adoption of a more customized approach to the evaluation of patients in clinical practice. However, the molecular mechanisms responsible for the prognostic impact of PNI on cancer are still unclear. PNI is an indicator for assessing both the nutritional and immunological status of cancer patients. A low PNI signifies reduced levels of albumin and/or lymphocytes. Albumin not only reflects nutritional status but also plays a role in cellular growth, DNA stability, and hormonal regulation against cancer. Low serum albumin is associated with worse prognosis and survival in cancer patients [24]. Furthermore, low lymphocyte levels are associated with an inadequate immune response, which can contribute to a poor prognosis [25]. Altogether, these findings suggest that malnutrition and lymphocytopenia can signal a persistent impairment in the immune system of cancer patients [26].

Malnutrition is the foremost cause of poor prognosis in cancer patients. A meta-analysis investigating the association between markers of malnutrition and clinical outcomes in older adults with cancer found that PNI was associated with overall survival [27]. The authors pointed out that PNI components, albumin and total lymphocyte count, might indicate inflammation more than nutritional status. Also, an association between a very low body mass index (<18 kg/m^2) and poor clinical outcomes was reported especially in lung cancer [27]. Most previous studies evaluated only pretreatment PNI values [28-30]. In our study, we evaluated PNI not only before treatment but also in the first, third, sixth, and twelfth months during treatment. Our findings revealed that the PNI values of patients who died during the follow-up period were significantly lower at baseline, first, third, sixth, and twelfth months. Consequently, maintaining a healthy nutritional status during treatment may provide potential benefits in improving cancer patient outcomes.

Although numerous studies have investigated the prognostic impact of PNI in different types of cancer, there is no established normal PNI value. Therefore, we determined 44 as the cut-off value for the PNI in our study, as a result of logistic regression analysis created to estimate the mortality risk for the optimal PNI cut-off value. PNI has recently received great attention and has been investigated in terms of prognostic prediction, especially in cancer patients. This immunonutritional index has been suggested as a useful technique that reliably and comprehensively evaluates patients' nutritional profiles by combining serum albumin with total lymphocyte count, reflecting the importance of inflammation and nutritional status on cancer metabolism [31]. Previous studies using a range of PNI cutoff values revealed that PNI had a prognostic impact on long-term outcomes in different cancer patients [32]. Nozoe et al. [33] found that PNI was an independent prognostic factor. While Sakurai et al.[34] found an association between preoperative PNI and long-term prognosis, Migita et al. [32] suggested that PNI should be incorporated in the routine evaluation of patients. In a study conducted on cancer patients consisting mostly of, melanoma, renal cell carcinoma, and non-small cell lung cancer in Turkey, it has been reported that higher PNI levels were associated with longer survival [35]. Consistent with the literature, our current study demonstrated that cancer patients treated with immunotherapy and lower pretreatment PNI (≤44) experienced poorer survival than those with elevated pretreatment PNI (>44). In our study, unlike previous studies, we showed that PNI scores during treatment have prognostic importance like pretreatment PNI. Our findings suggest that the PNI value can be used as a potential tool in assessing the mortality risk of patients and may be useful in managing patients' treatment plans and follow-ups accordingly.

Limitations of study

Our study has some limitations such as selection and information bias due to its single-center retrospective nature. Apart from this, other limitations include the limited sample size and the failure to evaluate different immunotherapy treatments separately. These results need to be confirmed in larger samples, in different cancer groups, and specific to the treatment received, and potential confounding factors need to be taken into account.

Conclusion

Our current study investigated the critical relationship between PNI and mortality in cancer patients treated with immune checkpoint inhibitors. Our findings elucidated the independent predictive role of pretreatment PNI in determining the mortality risk of cancer patients receiving immunotherapy. Consistent

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with existing literature, we showed that low pretreatment PNI in cancer patients receiving immunotherapy was associated with worse survival compared to those with high pretreatment PNI. In particular, our study also revealed the novel finding that PNI scores during treatment have prognostic significance. In conclusion, we highlight the usefulness of PNI in assessing mortality risk and potentially guiding treatment strategies and follow-up protocols for cancer patients.

Conflict of Interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical Approval

Permission for the study, dated 07/04/2023 and numbered 2023/55, was obtained from the Cukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee.

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