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# Impact of Prognostic Nutritional Index and Neutrophil-to-Lymphocyte Ratio on Clinical Outcomes of Acute Ischemic Stroke

## Prognostik Nutrisyonel İndeksi ve Nötrofil-Lenfosit Oranının Akut İskemik İnmenin Klinik Sonlanımına Etkisi

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## ABSTRACT

**Objectives:** Acute ischemic stroke (AIS) is a significant cause of death and disability worldwide. Inflammation affects brain damage and prognosis in ischemic stroke, while malnutrition significantly impacts clinical outcomes. The prognostic nutritional index (PNI) and neutrophil-to-lymphocyte ratio (NLR) are used to assess nutritional and inflammatory status, respectively. The aim of our study was to determine the role of PNI and NLR in predicting the prognosis of ischemic stroke.

**Methods:** A total of 215 acute ischemic stroke patients hospitalized in our neurology intensive care unit between September 2020 and November 2021 were retrospectively analyzed. Stroke classifications, vascular risk factors, laboratory parameters, and mortality rates of acute ischemic stroke cases were evaluated. PNI and NLR were calculated, and PNI values were dichotomized into two groups using a cutoff point of 42.5, determined via receiver operating characteristic (ROC) analysis.

**Results:** Over a 60-day period, a multivariable logistic regression analysis for neurological prognosis revealed that coronary artery disease (hazard ratio [HR]:3.9, p=0.021), initial National Institutes of Health Stroke Scale (NIHSS) score (HR:1.16, p<0.001), and PNI (HR:0.022, p<0.001) were significant independent predictors of neurological outcomes. Additionally, Cox regression analysis for overall patient survival indicated that age (HR:1.93, p=0.009), initial NIHSS score (HR:1.04, p=0.008), blood urea nitrogen (BUN) level (HR:1.69, p=0.012), and PNI (HR:0.27, p=0.007) were independent factors influencing mortality.

**Conclusion:** PNI and NLR are accessible and cost-effective biomarkers. These indicators provide insights into patients' inflammatory and nutritional profiles, enabling clinicians to make informed treatment decisions and serving as predictors of prognosis in AIS patients.

**Keywords:** Acute ischemic stroke; Neutrophil-to-lymphocyte ratio; Prognostic nutritional index.

## ÖZET

**Amaç:** Akut iskemik inme (Aİİ), dünya genelinde önemli bir ölüm ve sakatlık nedenidir. İnflamasyon, iskemik inmede beyin hasarını ve prognozu etkilerken; malnütrisyon da klinik sonlanımı önemli ölçüde etkilemektedir. Prognostik nutrisyonel indeks (PNI) ve nötrofil-lenfosit oranı (NLR), sırasıyla beslenme durumu ve inflamatuvar yanıtı değerlendirmek amacıyla kullanılmaktadır. Bu çalışmanın amacı, PNI ve NLR'nin iskemik inme prognozunu belirlemedeki yerini ortaya koymaktır.

**Yöntem:** Eylül 2020 ile Kasım 2021 tarihleri arasında nöroloji yoğun bakım ünitemizde izlenen toplam 215 akut iskemik inme hastası retrospektif olarak analiz edilmiştir. Hastaların etyolojik sınıflamaları, vasküler risk faktörleri,

laboratuvar parametreleri ve mortalite oranları değerlendirilmiştir. PNI ve NLR değerleri hesaplanmış, ROC analizi ile belirlenen 42,5 kesme değeri esas alınarak PNI iki gruba ayrılmıştır.

**Bulgular:** Altmış günlük izlem sonunda yapılan çok değişkenli lojistik regresyon analizinde, koroner arter hastalığı (Risk Oranı [HR]:3,9; p=0,021), giriş Ulusal Sağlık Enstitüsü İnme Ölçeği (NIHSS) skoru (HR:1,16; p<0,001) ve PNI (HR:0,022; p<0,001) nörolojik sonuçların anlamlı bağımsız belirleyicileri olarak bulunmuştur. Ayrıca, genel sağkalımı değerlendiren Cox regresyon analizinde yaş (HR:1,93; p=0,009), giriş NIHSS skoru (HR:1,04; p = 0,008), kan üre azotu (BUN) seviyesi (HR:1,69; p=0,012) ve PNI (HR:0,27; p=0,007) mortaliteyi etkileyen bağımsız faktörler olarak saptanmıştır.

**Sonuç:** PNI ve NLR, kolay ulaşılabilir ve düşük maliyetli biyobelirteçlerdir. Bu belirteçler, hastaların inflamatuvar ve beslenme profilleri hakkında bilgi sağlayarak klinik karar süreçlerini desteklemekte ve Aİİ prognozunun öngörülmesinde kullanılabilmektedir.

**Anahtar sözcükler:** Akut iskemik inme; Nötrofil-lenfosit oranı; Prognostik nutrisyonel indeks.

Acute ischemic stroke (AIS) is a leading cause of morbidity and mortality worldwide.[1] AIS patient prognosis is influenced by age, comorbid conditions, and initial stroke severity. In recent years, there has been a growing focus on the impacts of systemic inflammation and nutritional status on stroke outcomes.[2]

A patient's nutritional status significantly impacts their risk of mortality and morbidity following an ischemic stroke. Prognostic nutritional index (PNI), calculated based on serum albumin levels and lymphocyte count, serves as an indicator of a patient's nutritional and immunological status. Studies have demonstrated that reduced PNI values are associated with unfavorable outcomes in cancer and cardiovascular disorders, indicating PNI's potential usefulness in predicting clinical outcomes for AIS.[3,4] The neutrophil-to-lymphocyte ratio (NLR) is a marker of systemic inflammation. Increased NLR has been associated with unfavorable outcomes in cancer, cardiovascular disorders, sepsis, and ischemic stroke.[5,6] A recent study emphasized the practical utility of these biomarkers in predicting in-hospital mortality associated with AIS.[6] Therefore, we aimed to determine the significance of PNI and NLR in AIS patients' clinical outcomes.

## Methods

### Study Design and Patients

A total of 215 acute ischemic stroke patients, whom we followed in the neurology intensive care unit between September 2020 and November 2021, were retrospectively analyzed. Patients who had recurrent strokes, intracerebral hemorrhaging, a history of infection up to one week before admission, malignancy, and a history of surgery or major trauma in the last month were excluded. The duration of their hospitalization and in-hospital mortality rates were recorded.

### Diagnosis of Ischemic Stroke

Ischemic stroke was diagnosed on the basis of clinical findings and radiological assessments (cranial CT, MRI, and CT angiography). The type of ischemic stroke was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[7] The clinical severity of the stroke was assessed with the National Institute of Health Stroke Scale (NIHSS) at admission and within 24 hours.[8] Stroke progression was defined as a greater than 4-point increase on the NIHSS score. The functional statuses of our cases before and after discharge were measured using the modified Rankin Scale (mRS). A modified Rankin Scale score of less than 3 at the second month was considered a "good prognosis," while a score greater than 3 was considered a "poor prognosis".[9]

### Diagnosis of Nutritional and Immunological Status

Laboratory tests (whole blood cell, biochemistry, coagulation, liver and renal function tests) and C-reactive protein (CRP) were routinely conducted within 24 hours of hospital admission. The laboratory values used in formulas were as follows: platelet (150–450×10³/mL), leukocyte (4–10×10³/mL), neutrophil (1.6–6×10³/mL), lymphocyte (1.2–3.6×10³/mL), albumin (35–52 g/L), blood urea nitrogen (BUN) (8.4–26 mg/dL).

PNI was calculated within the first 24 hours of admission using serum albumin levels (g/dL) and complete blood count for lymphocytes, leukocytes, and neutrophils (10⁹/L). It was computed using the formula=(serum albumin level [g/dL]×10)+(total lymphocyte count [per mm³]×0.005). NLR was calculated as the ratio of neutrophil value to lymphocyte value of complete blood counts at admission. The patients were divided into two groups, "low" and "high," for PNI and NLR values.

### Statistical Analysis

All calculations were performed using IBM SPSS Statistics 22.0 software. A significance level of $p<0.05$ was accepted. Receiver Operating Characteristic (ROC) analysis was performed to achieve optimal sensitivity and specificity for PNI and NLR. The area under the curve (AUC) was calculated for the ROC, and the hypothesis of a value of 0.5 was tested with a 95% confidence interval for AUC. The normal distribution of variables was assessed using visual methods such as histograms and probability plots, and analytical methods such as Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous data were summarized using median and interquartile ranges (IQR). The Chi-square test or Fisher's exact test was preferred for the analysis of categorical variables. Survival over time was calculated using the Kaplan-Meier method. Univariate analyses were applied to identify factors of prognostic importance. Prognostic factors with a p-value<0.05 in univariate analysis were included in multivariable logistic regression (for neurological progression) and Cox proportional hazards regression (for survival analysis) to identify independent predictors. We used "multivariable" models, not "multivariate," as each model included one dependent variable and multiple independent variables.

## Results

The 215 AIS patients' mean age was 68.3±15.0 (21–104). There were 125 (58%) male and 90 (42%) female patients. The median NIHSS score at hospital admission was 10.0, and the median mRS score at the end of the follow-up period was 3. The in-hospital mortality rate was 51.2%. The most common stroke type, according to the TOAST classification, was large-artery atherosclerosis. No statistically significant correlation was observed between stroke etiology and PNI. Table 1 summarizes the relationship between the demographic characteristics and comorbidities of AIS patients and their PNI status.

In laboratory evaluation, the average hemoglobin level was 12.5 g/dL; the median BUN level was 19.0 mg/dL; the median platelet count was $228\times10^3$/L; the median lymphocyte count was $1.48\times10^3$/L; the median leukocyte count was $9.2\times10^3$/L; the average albumin level was 3.3 g/dL; the median PNI was 42.0; and the median NLR was 4.3. The cut-off values obtained for PNI and NLR from ROC analysis were 42.5 and 4.2, respectively. Table 2 details the laboratory findings, and Table 3 summarizes the relationship between the PNI and the laboratory values. Univariate and multivariate analyses revealed significant associations with neurological progression and survival, as demonstrated in Table 4 and Figure 1.

**Table 1.** The relationship between demographic characteristics and comorbidities of AIS patients according to PNI

| | Total | PNI<42.5 | PNI>42.5 | p |
|---|---|---|---|---|
| Number of patients | 215 | 111 | 104 | |
| Age, median [IQR] | 71 [20] | 75 [149] | 63.5 [23] | **<0.001** |
| Male gender (%) | 125 (58.1) | 60 (54.1) | 65 (62.5) | 0.21 |
| Smoking (%) | 47 (21.9) | 25 (19.8) | 22 (19.8) | 0.45 |
| Hypertension (%) | 135 (62.8) | 74 (66.7) | 61 (58.7) | 0.22 |
| Diabetes mellitus (%) | 83 (38.0) | 50 (45.0) | 33 (31.7) | **0.045** |
| Coronary artery diasease (%) | 51(23.0) | 34 (30.6) | 17 (16.3 | **0.014** |
| Atrial fibrillation (%) | 54 (25.5) | 30 (27.0) | 24 (23.8) | 0.58 |
| In-hospital mortality (%) | 110 (51.1) | 87 (78.4) | 23 (22.1) | **<0.001** |
| TOAST classifications (%) | | | | |
| Large-artery atherosclerosis | 117(54.4) | 58(52.3) | 59 (56.7) | 0.90 |
| Small-artery atherosclerosis | 5 (2.3) | 3 (2.7) | 2 (1.9) | 0.65 |
| Cardioembolic | 44 (20.5) | 23(20.7) | 21 (20.2) | 0.74 |
| Other and unknown causes | 49 (22.8) | 27 (24.3) | 22 (21.2) | 0.83 |
| 2nd month mRS | 3.0 (4) | 5.0 (2) | 2.0 (2) | **0.001** |
| NIHSS on admission, median [IQR] | 10 [11] | 11 [10] | 6.0 [10] | **0.001** |

IQR: interquartile range; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; TOAST: Trial of ORG 10172 in Acute Stroke Treatment. High PNI>42.5; Low PNI<42.5.

**Table 2. Laboratory characteristics of AIS patients**

| | Median | Mean | SD | Min. | Max. |
|---|---|---|---|---|---|
| Haemoglobin gr/dL | 12.0 | 12.5 | 1.07 | 6.7 | 17.0 |
| Platelet count ($10^3$/L) | 228 | 240 | 5.00 | 17 | 559 |
| Lymphocyte count ($10^3$/L) | 1.48 | 1.63 | 0.05 | 0.3 | 8.0 |
| Leukocyte count ($10^3$/L) | 9.2 | 10 | 3.9 | 1.1 | 28 |
| Albumin (g/dL) | 3.4 | 3.3 | 0.04 | 1.4 | 4.8 |
| BUN (mg/dL) | 19.0 | 25.9 | 1.40 | 10.0 | 125 |
| PNI | 42.0 | 41.8 | 9.1 | 18.9 | 74 |
| NLR | 4.3 | 6.8 | 6.1 | 0.67 | 30 |

BUN: blood urea nitrogen; Min: minimum; Max: maximum; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; NLR: neutrophil-to-lymphocyte ratio; PNI: prognostic nutritional index; TOAST: Trial of ORG 10172 in Acute Stroke Treatment.

## Discussion

Cerebrovascular diseases are the most prominent causes of morbidity and mortality.[1] While the association between ischemic stroke and elevated inflammatory markers is well established, there is also a correlation between various inflammatory disorders and an increased risk of ischemic stroke incidence. These findings suggest that inflammation may be a major cause of ischemic stroke.[10] Diabetes mellitus (DM) and coronary artery disease (CAD) are also risk factors for stroke, and inflammation acts as a pathogenic factor in the progression of these diseases.

Our study used the PNI and NLR, as simple markers for evaluating nutrition and inflammatory status, to analyze the factors influencing neurological progression and mortality in AIS patients. Low PNI was detected in AIS patients with concurrent comorbidities, including DM and CAD. Significant associations were identified between neurological progression and factors such as age, (male) gender, coronary artery disease, NIHSS score at admission, hemoglobin levels, lymphocyte and leukocyte counts, albumin level, BUN, PNI, and NLR. Similarly, variables significantly associated with mortality included age, CAD, atrial fibrillation, NIHSS score at admission, lymphocyte and leukocyte counts, albumin levels, BUN, and NLR.

NIHSS score at admission, CAD, and PNI were identified as independent predictors of neurological progression. Age, NIHSS value at admission, lymphocyte count, BUN, and PNI were found to be independent predictors of mortality. These findings emphasize the interactions among cardiovascular health, immune function, and nutritional status in defining clinical outcomes for AIS. They are consistent with the literature, which indicates that older patients tend to have poor neurological outcomes.[11] Likewise, the initial NIHSS score is important for evaluating the severity of ischemic stroke and predicting patient outcomes; our study demonstrates a strong correlation between high NIHSS scores at admission and increased rates of morbidity and mortality.[8,12] By contrast, the mortality rate in our study was low in stroke patients with elevated serum albumin levels, which the high-PNI group exhibited.[13]

PNI was initially used as an indicator of nutrition and inflammation in AIS.[14,15] Lower PNI values are linked to higher infection rates and mortality in patients with AIS.[16] These studies confirm that PNI serves as a predictor for assessing AIS clinical outcomes. In our study, the low-PNI group was older and had poor prognoses in the second month following the stroke, high in-hospital mortality rates, and a higher prevalence of DM and CAD. In the laboratory parameters, the low-PNI group had lower hemoglobin, lower lymphocyte counts, higher BUN, and lower serum albumin levels. BUN levels have been recognized as an important prognostic indicator of ischemic stroke; we observed a significant association between elevated BUN levels and increased mortality.[17,18]

**Table 3. Relationship between PNI and laboratory results of AIS patients**

| Laboratory Parameters | | NI< 42.5 | PNI> 42.5 | p |
|---|---|---|---|---|
| Haemoglobin mean ±SD | 12 (4) | 11±4.1 | 13±2 | **<0.001** |
| Platelet count ($10^3$/L), median [IQR] | 228 [98] | 223 [80] | 224 [118] | 0.15 |
| Lymphocyte count ($10^3$/L), median [IQR] | 1.48 [1.1] | 1.1 [0.6] | 2.0 [0.9] | **<0.001** |
| Leukocyte ($10^3$/L), median [IQR] | 9.2 [4.7] | 9.0 [3.1] | 10.0 [6.7] | **0.50** |
| BUN (mg/dL) median [IQR] | 19 [15] | 22 [15] | 10.0 [8] | **<0.001** |
| NLR (<4.2) (n%) | 106 (49.3) | 30 (27.0) | 76 (73.1) | **<0.001** |
| Albumin (g/dL) mean±SD | 3.36±0.04 | 2.8±0.07 | 3.8±0.05 | **<0.001** |

BUN: blood urea nitrogen; PNI: prognostic nutritional index; NLR: neutrophil-to-lymphocyte ratio.

Table 4. Neurological progression and survival parameters of AIS patients.

| | Neurological Progression | | | | Survival | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariable | | Multivariable | | Univariable | | Multivariable | |
| Variables | OR (95% CI) | p | HR (95% CI) | p | OR (95% CI) | p | HR (95% CI) | p |
| Age | 4.27 | <0.001 | | 2.97 | <0.001 | 1.93 | 0.009 | |
| Male Gender | 1.94 | 0.035 | | 1.2 | 0.33 | | | |
| Smoking | 0.96 | 0.93 | | 1.19 | 0.43 | | | |
| Hypertension | 1.2 | 0.58 | | 0.99 | 0.98 | | | |
| Diabetes mellitus | 1.03 | <0.001 | | 1.38 | 0.91 | | | |
| Coronary artery diasease | 4.5 | <0.001 | 3.92 | 0.021 | 1.69 | 0.02 | | |
| Atrial fibrillation | 2.1 | 0.065 | | 1.2 | 0.03 | | | |
| TOAST classifications | | | | | | | | |
| Large-artery atherosclerosis | referance | | | | referance | | | |
| Small-artery atherosclerosis | 2.4 | 0.21 | | 1.19 | 0.45 | | | |
| Cardioembolic | 0.73 | 0.41 | | 0.99 | 0.97 | | | |
| Other and unknown causes | 0.73 | 0.79 | | 1.6 | 0.42 | | | |
| NIHSS on admission | 1.2 | <0.001 | 1.16 | 0.001 | 1.02 | <0.001 | 1.04 | 0.008 |
| Haemoglobin gr/dL | 0.77 | <0.001 | | 0.93 | 0.12 | | | |
| Platelet count ($10^3$/L) | 0.99 | 0.064 | | 0.99 | 0.009 | | | |
| Lymphocyte count ($10^3$/L) | 0.20 | <0.001 | | 0.25 | <0.001 | 1.7 | 0.041 | |
| Leukocyte ($10^3$/L) | 1.085 | 0.041 | | 1.065 | 0.002 | | | |
| Albumin (g/dL) | 0.01 | <0.001 | | 0.25 | <0.001 | | | |
| BUN (mg/dL) | 1.09 | 0.009 | | 1.02 | <0.001 | 1.69 | 0.012 | |
| PNI | 0.013 | <0.001 | 0.022 | <0.001 | 0.16 | <0.001 | 0.27 | 0.007 |
| NLR | 0.17 | <0.001 | | 4.05 | <0.001 | | | |

BUN: blood urea nitrogen; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; NLR: neutrophil-to-lymphocyte ratio; PNI: prognostic nutritional index; TOAST: Trial of ORG 10172 in Acute Stroke Treatment.

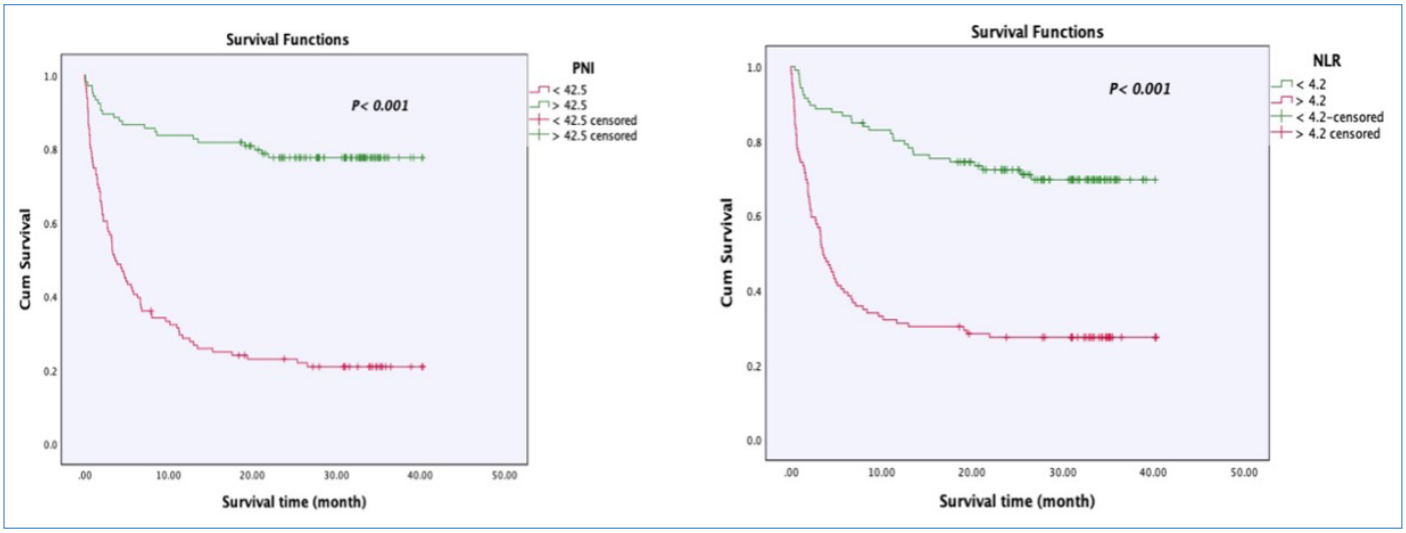


**Figure 1**. Kaplan-Meier survival curves illustrating patients' survival over time, categorized by PNI and NLR. Mortality rates were higher in patients with lower PNI and higher NLR.

PNI: prognostic nutritional index; NLR: neutrophil-to-lymphocyte ratio.

Previous studies have noted that leukocytes play a role in the neurological outcomes and prognoses of AIS patients.[19,20] Lymphocytes are thought to actively contribute to the pathogenesis of ischemic brain damage, although the data regarding their role remains controversial.[20] Numerous data have shown that neutrophil counts and NLR are better indicators of inflammation than leukocyte values for many diseases.[20] The neutrophil-to-lymphocyte ratio (NLR) has been identified as an important indicator of ischemic stroke prognosis.[21-23] Our research found that elevated NLR levels were positively associated with higher mortality and morbidity rates.

Our study has limitations: First, it was conducted in a single center; second, it was retrospective.

Patients identified as high-risk based on low PNI or high NLR values represent a vulnerable subgroup with increased susceptibility to poor outcomes after acute ischemic stroke (AIS). Addressing their specific needs through timely and targeted interventions is critical. Nutritional optimization, especially within the first 48-72 hours of hospitalization, is associated with improved immune response and decreased infection rates in stroke patients. Strategies such as early enteral feeding enriched with protein, omega-3 fatty acids, and micronutrients (zinc, selenium, vitamin D) have shown benefits in neurological recovery and reduction of hospital stay.[24]

Inflammation-modulating strategies such as statins, which have pleiotropic anti-inflammatory effects, have also been linked to better outcomes post-stroke.[25] Furthermore, intensive management of comorbidities like diabetes and coronary artery disease may improve immune-nutritional status and reduce mortality.[26] Given the evidence linking systemic inflammation to stroke severity, emerging anti-inflammatory treatments—such as interleukin-6 inhibitors or NLRP3 inflammasome blockers—are being explored as adjunct therapies. While not yet routine, these therapies could be particularly relevant in patients with persistently elevated NLR.[27] Therefore, identifying patients at risk using PNI and NLR allows for early, personalized intervention strategies that may positively influence short-term and long-term clinical outcomes.

## Conclusion

In conclusion, our findings suggest that AIS patients' pre-hospitalization nutritional status plays a crucial role in determining their short-term outcomes. PNI and NLR are simple markers for predicting stroke prognosis. Low PNI is associated with higher age, worse clinical outcomes, and increased in-hospital mortality rates in AIS patients. Ensuring optimal nutrition both before and after hospitalization can improve prognosis. We suggest that PNI and NLR should be included in the routine assessment of AIS patients' nutritional status. Further prospective studies are needed to determine the relationship of these markers with long-term outcomes.

### Disclosures

**Ethics Committee Approval:** The study was approved by İzmir Katip Çelebi University, Atatürk Training and Research Hospital's ethics committee (Ethics Approval Number: 0491, Date: 26/10/2023).

**Informed Consent:** Written informed consent was obtained from the participants.

**Conflict of Interest:** The authors declare no conflict of interest.

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