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ORIGINAL ARTICLE

Six-month prognosis of acute ischemic stroke in patients with cancer: A prospective study

Hasan Hüseyin Kozak[1], Murat Araz[2], Ayşenur İnce[1], Ahmet Buğrul[1]

[1]Department of Neurology, Necmettin Erbakan University Faculty of Medicine, Konya, Türkiye
[2]Department of Internal Medicine, Division of Oncology, Necmettin Erbakan University Faculty of Medicine, Konya, Türkiye

ABSTRACT

Objectives: This study aimed to investigate factors associated with six-month survival in patients with a history of cancer diagnosis.

Patients and methods: This prospective study included 66 patients (37 males, 29 females; median age: 67 years; range, 60 to 73 years) who were admitted to a tertiary hospital with acute ischemic stroke and a history of cancer between July 2020 and October 2022.

Results: At six months, 39 (59.1%) patients had died. Multivariable Cox regression analysis identified three factors significantly associated with six-month mortality. Each 1-point increase in the platelet distribution width (hazard ratio [HR] = 1.280, p = 0.008) and neutrophil-to-lymphocyte ratio (HR = 1.040, p < 0.001) were associated with increased mortality. By contrast, each 1-point increase in body mass index was associated with a 10% lower risk of death (HR = 0.899, p = 0.023).

Conclusion: Higher neutrophil-to-lymphocyte ratio and platelet distribution width, and lower body mass index were independently associated with six-month mortality in patients with acute ischemic stroke and a history of cancer. These findings highlight the need for careful prognostic assessment, although they should be interpreted with caution given the study's limited sample size.

Keywords: Body mass index, cancer, neutrophil-to-lymphocyte ratio, platelet distribution width, stroke.

Stroke and cancer are among the leading causes of death worldwide. The association between ischemic stroke and cancer is well recognized. Previous research found that 4.4% of patients hospitalized for ischemic stroke had cancer as a comorbidity,[1] and 2.1 to 4.3% of patients with ischemic stroke and no prior cancer diagnosis were subsequently diagnosed with cancer during follow-up.[2,3]

Ischemic stroke in patients with cancer is a complex condition influenced by several mechanisms. Procoagulant factors secreted by tumor cells increase the risk of thrombosis by enhancing platelet activation and fibrin formation.[4] Chemotherapy and radiotherapy can also cause vascular damage, thereby triggering thrombotic events. Moreover, conditions commonly observed in patients with cancer, including immobility, infections, and associated comorbidities, contribute to the pathogenesis of ischemic stroke.[5,6]

Predicting ischemic stroke prognosis in patients with cancer may guide long-term management. This study aimed to investigate factors associated with six-month survival in this group.

PATIENTS AND METHODS

This prospective study involved 66 patients (37 males, 29 females; median age: 67 years; range, 60 to 73 years) with acute ischemic stroke and a history of cancer who were admitted to the Necmettin Erbakan University Faculty of Medicine between July 2020 and October 2022. Patients younger than 18 years were excluded. To ensure a homogeneous study population and minimize potential confounding, patients with hematological

Correspondence: Ahmet Buğrul, MD. Necmettin Erbakan Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı, 42080 Selçuklu, Konya, Türkiye.
E-mail: ahmet.bugrul@gmail.com
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malignancies or primary brain tumors were also excluded, as these cancer types involve distinct stroke mechanisms (e.g., leukostasis, coagulopathy, and direct vascular compression) that differ from those associated with systemic solid tumors.[7,8] Written informed consent was obtained from all patients. The study protocol was approved by the Necmettin Erbakan University Faculty of Medicine Ethics Committee (Date: 03.07.2020, Approval number: 2020/2663). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Active cancer was defined as meeting one of the following criteria: (1) diagnosis within six months before or during enrollment; (2) treatment with radiotherapy, chemotherapy, or surgery within the previous six months; or (3) recurrent or metastatic cancer.

Patients were classified as having acute ischemic stroke if they presented within 24 h of symptom onset with focal neurological deficits and showed diffusion restriction on diffusion-weighted imaging (DWI) consistent with acute infarction and corresponding to the clinical findings. Blood was collected within the first 24 h of hospitalization. Enrolled patients were prospectively followed for six months at the same clinic where they received care through scheduled outpatient visits or telephone interviews conducted by neurologists and oncologists.

The following data were obtained from patients' medical records: demographic and clinical characteristics, cancer type and histology, cancer activity status, presence of systemic metastases, history of chemotherapy or radiotherapy, medical history, baseline and follow-up modified Rankin Scale (mRS) scores, National Institutes of Health Stroke Scale score at admission, acute ischemic stroke patterns on DWI, and stroke treatments.

Statistical analysis

Statistical analyses were performed using IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were reported as medians (interquartile ranges) and compared between groups using the Mann-Whitney U test. Categorical variables were reported as percentages and compared between groups using the chi-square test. Univariable and multivariable Cox proportional hazards regression models were used to identify predictors of six-month survival. Variables with clinical relevance and those with a p-value < 0.1 in the univariable analyses were considered for inclusion in the multivariable model. To preserve statistical power, variables with a high proportion of missing data were excluded. For pairs of highly correlated variables (Pearson's $r > 0.7$), only one variable was retained based on clinical relevance or statistical significance to reduce collinearity. The variance inflation factor (VIF) was calculated; all variables had a VIF < 1.5, indicating acceptable collinearity. The final model was tested using 1000 bootstrap resamples, and variables that were not significant were excluded. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. A two-sided p-value < 0.05 was considered statistically significant.

RESULTS

The most common cancer types were gastrointestinal (28.8%) and genitourinary (25.8%), and adenocarcinoma was the predominant histological subtype (56.1%). Most patients had

TABLE 1
Index of cancer (n = 66)

Cancer site	n	%
Gastrointestinal malignancies	19 (13*)	28.8
Colorectal	10 (9*)	15.2
Pancreas	4 (3*)	6.1
Gastric	3 (1*)	4.5
Esophageal	1 (0*)	1.5
Cholangiocarcinoma	1 (0*)	1.5
Genitourinary malignancies	17 (8*)	25.8
Bladder	5 (0*)	7.6
Ovarian	4 (3*)	6.1
Prostate	4 (2*)	6.1
Cervical	2 (1*)	3
Kidney	2 (2*)	3
Thoracic malignancies	16 (12*)	24.2
Lung	16	24.2
Head and neck malignancies	7 (3*)	10.6
Nasopharyngeal	4 (2*)	6.1
Thyroid	1 (0*)	1.5
Laryngeal	1 (0*)	1.5
Salivary gland	1 (1*)	1.5
Breast malignancies	5 (3*)	7.6
Breast	5	7.6
Others	2 (2*)	3
Cancer of unknown primary	1 (1*)	1.5
Gestational trophoblastic tumors	1 (1*)	1.5
Histological type		
Adenocarcinoma	37	56.1
Non-adenocarcinoma	29	43.9
Active cancer	61	92.4
Metastasis	41	62.1

* It refers to metastatic cancers.

active cancer (92.4%), and 62.1% presented with metastatic disease (Table 1).

At six months, 27 (40.9%) patients were alive, and 39 (59.1%) died. Distributions of age, sex, and comorbidity were similar between survivors and nonsurvivors. Nonsurvivors were more likely to have multiple ischemic infarcts, a lower body mass index (BMI), and a shorter interval between cancer diagnosis and stroke onset. Neurological impairment was more severe among nonsurvivors,

TABLE 2
Clinical characteristics of patients according to outcomes 180 days after admission

	Survivor (n = 27)				Non-survivor (n = 39)				
	n	%	Median	25th-75th percentile	n	%	Median	25th-75th percentile	*p*
Age (year)			66	60-72			68	60-73	0.845†
Sex									0.945‡
Female	12	44.4			17	43.6			
Male	15	55.6			22	56.4			
Body mass index (kg/m²)			27	24-30			24.5	22-26	**0.011**†
Body surface area (m²)			1.8	1.6-1.96			1.71	1.57-1.84	0.135†
Comorbidity									
Diabetes	9	33.3			8	20.5			0.242‡
Hypertension	15	55.6			15	38.5			0.170‡
Coronary artery disease	6	22.2			9	23.1			0.935‡
Atrial fibrillation	7	25.9			7	17.9			0.436‡
Ischemic stroke history	2	7.4			8	20.5			0.144‡
Chronic obstructive pulmonary disease	2	7.4			3	7.7			0.966‡
Febrile neutropenia	9	33.3			11	28.2			0.656‡
Site of cancer									0.218‡
Lung	4	14.8			12	30.8			
Gastrointestinal	6	22.2			13	33.3			
Genitourinary	9	33.3			8	20.5			
Breast	2	7.4			3	7.7			
Head and neck	4	14.8			3	7.7			
Others	2	7.4			0	0			
Histological type									0.114‡
Adenocarcinoma	12	44.4			25	64.1			
Non-adenocarcinoma	15	55.6			14	35.9			
Time between cancer diagnosis and ischemic stroke (days)			730	210-2190			210	40-600	**0.009**†
Time to hospital admission (h)			6	3-12			10	6-19	**0.037**†
Active cancer	24	88.9			37	94.9			0.366‡
Metastasis	14	51.9			27	69.2			0.152‡
Radiotherapy history	11	40.7			12	30.0			0.403‡
Chemotherapy history	20	74.1			31	79.5			0.564‡
Fu-containing chemotherapy	3	11.1			7	17.9			0.446‡
Platinum-containing chemotherapy	13	48.1			18	46.2			0.873‡
VEGF-containing chemotherapy	3	11.1			5	12.8			0.834‡
Others	16	59.3			22	56.4			0.818‡
Multiple infarcts	8	29.6			23	59			**0.019**‡
mRS score			1	1-2			2	2-4	**< 0.001**†
mRS score at day 30			2	1-2			6	4-6	**< 0.001**†
mRS score at day 90			2	1-2			6	6-6	**< 0.001**†
NIHSS score on admission			3	2-5			5	3-9	**0.009**†
GCS score on admission			15	14-15			14	14-15	0.053†

VEGF, vascular endothelial growth factor; mRS, Modified Rankin Scale; NIHSS, National Institute of Health stroke scale; GCS: Glasgow Coma Scale; †, Mann-Whitney U test was used; ‡, Chi square test was used.

who had significantly higher median mRS scores at admission, 30 days, and 90 days (Table 2).

Comparisons of laboratory parameters showed that nonsurvivors had lower platelet counts and albumin levels, and higher mean platelet volume, platelet distribution width (PDW), C-reactive protein, and urea levels, indicating a greater inflammatory burden and nutritional deficit (Table 3).

TABLE 3
Comparison of laboratory data of the groups

	Survivor (n = 27)		Non-survivor (n = 39)		
	Median	25th-75th percentile	Median	25th-75th percentile	*p*†
WBC (*10⁹/L)	8	5-12	11	6-15	0.327
Neutrophil (*10⁹/L)	6	4-10	7	4.6-11	0.239
Lymphocyte (*10⁹/L)	1.05	0.8-1.4	0.9	0.44-1.48	0.267
Hemoglobin (g/L)	12	10-15	11	10-13	0.167
Platelets (*10⁹/L)	253	181-316	175	84-263	**0.010**
PDW (fL)	15	11-16	16	16-17	**0.001**
MPV (fL)	10	9-10	11	9-12	**0.028**
NLR	5	2-11	6	4-13	0.156
PLR	251	141-283	140	67-244	0.053
Urea (mg/dL)	42	29-57	56	35-82	**0.047**
Creatine (mmol/L)	0.95	0.80-1.30	1	0.70-1.3	0.901
AST (U/L)	16	10-22	12	[8-23	0.315
ALT (U/L)	19	14-26	22	16-33	0.120
Sodium (mmol/L)	137	136-139	136	135-138	0.121
Potassium (mmol/L)	4.1	3.8-4.4	4.3	3.8-5	0.170
Albumin (g/dL)	37	31.2-40.7	31.5	[29.2-36	**0.004**
CRP (mg/dL)	16	5-104	67	20-126	**0.036**
Lactate (mmol/L)	1.7	1.1-2.7	2.6	1.7-4.2	0.051
Fibrinogen (mg/dL)	373	325-591	329	239-451	0.071
D-dimer (ng/mL)	1335	04-3917	2450	936-9082	0.133

WBC, white blood cell; PDW, platelet distribution width; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet lymphocyte ratio; AST, aspartate transaminase; ALT, alanine transaminase; CRP, C-reactive protein; † Mann-Whitney U test was used.

TABLE 4
Prognostic factors for six-month survival in cancer patients with acute ischemic stroke

	Multivariable analysis*							
	Model 1				Model 2			
			95% CI				95% CI	
	p	HR	Lower	Upper	*p*	HR	Lower	Upper
Body mass index	**0.005**	0.779	0.654	0.929	**0.023**	0.899	0.820	0.986
Platelet distribution width	**0.015**	1.437	1.072	1.927	**0.008**	1.280	1.065	1.538
Neutrophil-to-lymphocyte ratio	**0.037**	1.133	1.007	1.274	**< 0.001**	1.040	1.018	1.063
Modified Rankin Scale	**< 0.001**	2.260	1.434	3.562	-	-	-	-

CI, confidence interval; HR, Hazard ratio; * Univariable analysis was performed using Cox proportional hazards regression to evaluate the association of each variable with six-month mortality. Variables with $p < 0.10$ in the univariable analysis and those deemed clinically relevant were included in the multivariable Cox regression model using backward stepwise elimination. Variables showing high collinearity (variance inflation factor ≥ 1.5) or strong correlation ($r > 0.7$) were excluded from the multivariable model. Given the conceptual overlap between functional disability and mortality, an additional sensitivity analysis was conducted excluding modified Rankin Scale scores from the multivariable model to avoid potential circularity bias, and the modified Rankin Scale-excluded model was considered the primary analytical model. Considering the limited number of events (n = 39), the number of covariates in the final multivariable model was restricted to minimize the risk of overfitting. Bootstrap testing (1000 number of samples) was performed on the final model, and variables that lost statistical significance were excluded. In addition, the stability and robustness of the final model were further evaluated through bootstrap resampling. Hazard ratios and 95% confidence intervals were reported. Statistical significance was set at $p < 0.05$.

In Model 1, which included both clinical and laboratory variables, multivariable Cox regression analysis identified higher mRS scores (HR = 2.260, $p < 0.001$), lower BMI (HR = 0.779, $p = 0.005$), increased PDW (HR = 1.437, $p = 0.015$), and increased neutrophil-to-lymphocyte ratio (NLR; HR = 1.133, $p = 0.037$) as independent predictors of six-month mortality (Table 4).

In Model 2, constructed as a sensitivity analysis excluding mRS scores to avoid potential circularity, each 1-point increase in PDW (HR = 1.280, $p = 0.008$) and NLR (HR = 1.040, $p < 0.001$) was associated with increased mortality, whereas each 1-point increase in BMI was associated with a lower risk of death (HR = 0.899, $p = 0.023$). These findings indicated that nutritional status (BMI) and systemic inflammatory markers (PDW and NLR) remained independently associated with six-month mortality even after excluding functional disability from the model (Table 4).

DISCUSSION

This study investigated predictors of six-month prognosis in patients with cancer and acute ischemic stroke. Higher NLR and PDW, and lower BMI were identified as independent predictors of six-month mortality in multivariable Cox regression analysis.

Ischemic stroke is most frequently associated with lung, pancreatic, colorectal, breast, prostate, gastric, and genitourinary cancers, with adenocarcinoma being the predominant histological subtype in cancers related to ischemic stroke.[9] Ischemic strokes in patients with cancer can be classified into three main etiological categories: cancer related, treatment related, and diagnosis related. The key underlying mechanisms include hypercoagulability, tumor embolism, vascular invasion, radiation-induced vasculopathy, and treatment-related immunosuppression leading to infection. Additionally, environmental factors such as smoking, which increase the risk of both cancer and ischemic stroke, also contribute to pathogenesis. These factors appear to be particularly prominent in certain cancer types, such as adenocarcinomas.[10] In our study, the most common cancer types were gastrointestinal, genitourinary, and lung cancer, with adenocarcinoma being the predominant histological type. Among nonsurvivors, the most common cancer types were gastrointestinal, lung, and genitourinary cancer, with adenocarcinoma being the dominant histological type. However, cancer type and histological distribution did not significantly affect prognosis.

The presence of metastases is a well-established critical prognostic factor in patients with cancer. Metastases not only increase the risk of ischemic stroke but also significantly increase the risk of poststroke mortality. Yoo et al.[11] compared patients with inactive cancer, nonmetastatic active cancer, and metastatic cancer and identified metastasis as the sole poor prognostic factor for survival. In our study, metastasis was not statistically significant, potentially due to heterogeneity among cancer types, metastatic patterns, and treatment modalities analyzed together. Since our sample size was small, subgroup analysis was not feasible, which may have further limited the statistical power. Therefore, the lack of significance for metastasis should not be interpreted as a true absence of effect. However, future studies should evaluate whether specific metastatic cancers are more frequently associated with ischemic stroke to improve homogeneity and interpretation.

In patients with cancer, elevated D-dimer levels are considered a marker of fibrin turnover within the coagulation system, suggesting the propagation of microthrombi in small vessels. This process is believed to result in multiple ischemic lesions accompanied by an inflammatory response. Multiple infarct regions and elevated D-dimer levels have been strongly linked to an underlying malignancy, particularly in cryptogenic strokes.[12,13] Additionally, bilateral hemispheric infarction in patients without comorbidities may be a warning sign of possible malignancy.[14] Multiple infarcts have also been independently associated with poor prognosis.[15] Although D-dimer is a crucial prognostic variable in many studies, it was not significant in our study. This finding may be due to the lack of cancer staging and the heterogeneity of the cancer population.

During cancer development, a storm of proinflammatory cytokines and chemokines initiates cancer-induced inflammation, leading to the activation of immune cells. Increased neutrophil numbers are involved in the remodeling of the extracellular matrix, which promotes angiogenesis and contributes to tumor development.[16] Lymphocytes are a key component of the host immune system, playing a crucial role in attacking cancer cells. The infiltration of lymphocytes into the tumor is considered an antineoplastic immune response that improves survival. Lymphopenia is usually observed in advanced stages of cancer

and indicates an inadequate immune response.[17] The NLR has emerged as a potential biomarker for cancer prognosis owing to its accessibility and ease of calculation.[18,19] After ischemic stroke, neutrophils are rapidly activated, contributing to endothelial damage, oxidative stress, and disruption of the blood-brain barrier, while lymphocytes undergo stress-induced suppression and apoptosis. This imbalance increases the risk of both inflammation-related deterioration and infection risk due to immunosuppression.[20] The NLR has been reported not only as a poor prognostic indicator but also as an independent risk factor for both ischemic stroke and patients with cancer.[19,21,22] In an umbrella review of 204 meta-analyses, Cupp et al.[19] reported that an elevated NLR was associated with increased mortality across various malignancies, including solid tumors and hematologic cancers. However, they emphasized that defining a universal cutoff is difficult due to disease-specific and methodological heterogeneity. Neutrophil-to-lymphocyte ratio was independently associated with six-month mortality in the multivariable Cox regression model, suggesting that, despite its limited discriminative performance, the NLR may still have prognostic value in cancer-related ischemic stroke.

Several cytokines regulate megakaryocyte maturation, platelet production, and platelet size, including IL-6, colony-stimulating factor 3 (CSF3, formerly called granulocyte colony-stimulating factor), and colony-stimulating factor 1 (CSF1, formerly called macrophage colony-stimulating factor). These cytokines, released by cancer cells and dysfunctional bone marrow cells, are believed to influence PDW.[23-26] In a meta-analysis of 1,903 patients with solid tumors, increased PDW was significantly associated with poor overall survival.[27] Although some individual studies have suggested a prognostic role for PDW in acute ischemic stroke, a meta-analysis involving 2,390 patients did not show a significant association between PDW and clinical outcomes, suggesting that its prognostic value may vary by disease context.[28] This discrepancy is possibly due to differences in the kinetics of platelet parameter alterations across disease states. In cancer, systemic inflammation and bone marrow-driven thrombopoiesis occur chronically, allowing time for PDW to increase. In contrast, the acute nature of ischemic stroke may not allow sufficient time for detectable changes in platelet morphology, particularly within the first 24 h, limiting the immediate prognostic utility of PDW in this setting. In our study, PDW was significantly associated with six-month mortality in patients with acute ischemic stroke and cancer, which may reflect the influence of underlying malignancy on PDW rather than an effect of the acute ischemic event itself. Further research is required to elucidate the disease-specific mechanisms underlying this association.

Excess body weight increases the overall risk of mortality and the risk of developing many different malignancies in the general population.[29] However, paradoxical associations were reported, in which a higher BMI appeared to be associated with a lower risk of mortality in populations with chronic diseases; this phenomenon was termed the "obesity paradox."[30] This paradox may be explained by the increased fat reserves in individuals who are obese, which can contribute to better physiological tolerance against catabolic stress caused by treatments such as chemotherapy. Hormonal and immunological alterations associated with obesity, such as differences in adipokine levels (e.g., leptin and adiponectin) and changes in cytokine profiles, were also suggested to exert regulatory effects on the tumor microenvironment and immune response, potentially improving survival.[31] Although studies reporting conflicting findings across different cancer types support the obesity paradox in patients with cancer, it is important to note that these studies often reflect selected BMI categories rather than encompassing the full range of obesity. In a cohort study involving 114,430 patients, Tu et al.[32] reported that mortality rates decreased with increasing BMI for 23 of 24 cancer types. A BMI above 22.5 kg/m^2 was associated with decreased all-cause mortality, with the lowest risk found in the range of 29.6 to 34.2 kg/m^2. In a meta-analysis of 6.3 million patients, Petrelli et al.[33] found that obesity (BMI > 30 kg/m^2) was associated with higher mortality in patients with cancer. However, they found that mortality was lower in patients with obesity with lung cancer, renal cell carcinoma, and melanoma. Li et al.[34] investigated the relationship between BMI and survival outcomes in patients with colorectal cancer. Their meta-analysis examined data from 16 studies encompassing over 55,000 patients and found that individuals who were overweight (BMI 25-29.9 kg/m^2) had better overall and cancer-specific survival compared to those with a normal weight. However, despite the protective association observed in overweight individuals, morbid obesity (BMI ≥ 35 kg/m^2) was associated with worse overall and disease-free survival.

In a recent meta-analysis of 32 cohort studies encompassing 330,353 patients with acute ischemic stroke, being overweight (BMI 25-29.9 kg/m^2) and having class I obesity (BMI 30-34.9 kg/m^2) were associated with better functional outcomes and reduced mortality compared to having a normal weight.[35] However, this beneficial association was not observed in individuals with morbid obesity (BMI ≥ 35 kg/m^2) or those who were underweight (BMI < 18.5 kg/m^2), supporting a U-shaped relationship between BMI and clinical outcomes in acute ischemic stroke.[36] The support for the obesity paradox observed in our study may be explained by the absence of patients who were morbidly obese (BMI ≥ 35 kg/m^2) and the predominance of cancer types, such as lung and colorectal cancer, in which the obesity paradox has been frequently reported. In addition, BMI was analyzed as a continuous variable due to the limited sample size and imbalance across BMI categories, which precluded reliable categorical subgroup analyses. Therefore, the obesity paradox should be interpreted cautiously.

Zhang et al.[37] found that mRS scores at admission and during follow-up were similar in patients with ischemic stroke with and without cancer. Gon et al.[38] reported that prestroke mRS scores were significantly higher in ischemic strokes of unknown etiology than in strokes of known etiology in patients with active cancer, but this did not affect prognosis. Our findings demonstrated that nonsurvivors had significantly higher mRS scores at admission.

In our prospective study, patients who survived had a significantly longer interval between cancer diagnosis and the occurrence of ischemic stroke than those who died within six months. This finding suggests that stroke occurring earlier in the cancer trajectory may reflect a more aggressive or hypercoagulable disease state, consistent with cancer-related coagulopathy and systemic inflammation. However, Göçmen et al.[39] found no significant association between the timing of cancer diagnosis and survival. Additionally, a shorter time to hospital admission was associated with improved survival, suggesting that prompt medical attention facilitates earlier stroke intervention and more effective supportive care. It is also possible that patients with delayed hospital admission had a lower socioeconomic status, limiting their access to timely care and comprehensive cancer treatment. However, our study did not collect data on socioeconomic or educational background.

Patients with hematologic malignancies were excluded from our study due to their distinct pathophysiological features compared to solid tumors. Unlike solid tumors, which primarily exert systemic effects such as chronic inflammation, cachexia, or tumor-associated coagulopathy over time, hematologic cancers (e.g., leukemias and lymphomas) can cause stroke via different mechanisms, including leukostasis, hyperviscosity, disseminated intravascular coagulation, and direct bone marrow suppression.[7,8] These patients are also more likely to experience profound cytopenias, receive intensive chemotherapy with myelosuppressive regimens, and require frequent transfusions, which may directly alter platelet indices, such as PDW, and confound their prognostic interpretation. We excluded hematologic malignancies to reduce biological variability and better evaluate associations of PDW and NLR with mortality in patients with ischemic stroke. Nevertheless, this exclusion restricts the generalizability of our findings to patients with hematologic cancers. Further dedicated research is needed in this subgroup to clarify the prognostic significance of these parameters.

Our study had several limitations that should be considered when interpreting its findings. First, the relatively small sample size and single-center design may limit the generalizability of the results. Second, the exclusion of patients with hematologic cancers, primary brain cancers, and patients younger than 18 years may limit the generalizability of the findings to a broader cancer population. Third, while the focus on six-month survival outcomes provides valuable insights, longer-term studies are needed to assess sustained effects. Fourth, while multivariable regression analyses were performed, unmeasured confounders, such as socioeconomic status or detailed nutritional status, may have influenced the outcomes. Fifth, all-cause mortality was used as the primary outcome, and cause-specific mortality (stroke related *vs.* cancer related) could not be reliably distinguished. This limitation may reduce the precision of the clinical interpretation of the identified predictors. Sixth, optimal cutoff values for continuous biomarkers, including PDW and NLR, were not calculated due to limited sample size, as receiver operating characteristic-based threshold estimation and precise performance measures require larger samples and a sufficient number of events, which may have limited the clinical interpretability of these findings. Finally, the inclusion of various cancer types and treatment modalities introduced

heterogeneity, which may have obscured the identification of cancer-specific prognostic factors related to ischemic stroke. Therefore, future studies should consider stratifying analyses by cancer type and treatment characteristics to better delineate these associations.

In conclusion, this study identified NLR, PDW, and BMI as key determinants of six-month mortality in patients with acute ischemic stroke and cancer. These findings may help estimate patient prognosis and support risk stratification. However, due to the study's small sample size and single-center design, the generalizability of these findings is limited. Further multicenter studies with larger cohorts and longer follow-up periods are warranted to confirm these results and to better clarify their clinical applicability in cancer-related ischemic stroke.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: H.H.K., A.B., M.A.: Idea/concept, design, data collection and/or processing; H.H.K., M.A.: Control/supervision; A.B.: Analysis and/or interpretation; A.B., A.İ.: Literature review, writing the article, materials; A.B., A.İ., H.H.K., M.A.: Critical review; A.B., A.İ., H.H.K., M.A.: References and fundings

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