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The Prognostic Value of Immunonutritional Indexes in Pineal Region Tumor

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Abstract

Background Recent studies have identified immunonutritional indexes such as hemoglobin–albumin–lymphocyte–platelet (HALP) score, prognostic nutritional index (PNI), and neutrophil-to-lymphocyte ratio (NLR) in various malignancies. However, there is a lack of studies to indicate whether the immune-nutritional indexes can predict the prognosis of patients with pineal region tumors. The objective was to estimate the prognostication of immune-nutritional indexes in patients with pineal region tumors.

Methods A retrospective cohort investigation involving 51 patients with pineal region tumors was conducted. Therefore, the HALP score, PNI, and NLR were measured for each patient before surgery. The association between the immune-nutritional indexes and prognosis was analyzed using Cox hazard regression.

Results For the total cohort, 1-, 2-, and 5-year survival probabilities were 92% (95% confidence interval [CI] 85–99.8), 92% (95% CI 85–99.8), and 81% (95% CI 70–94.1), respectively. HALP scores were positively associated with survival benefits. At the cutoff threshold of 22.6, the high-HALP group had a significantly longer survival time than the low-HALP group (hazard ratio 0.25, 95% CI 0.06–1.00, *p*-value 0.05).

Conclusion The preoperative HALP score is an independent prognostic factor for patients diagnosed with pineal region tumors. Furthermore, prospective multicenter studies ought to be performed in the future to externally validate the immunonutritional indexes' prognostication.

Keywords
- hemoglobin–albumin–lymphocyte–platelet score
- germinoma
- germ cell tumor
- pineal tumor
- neutrophil-to-lymphocyte ratio
- prognosis
- prognostic nutritional index

Introduction

Pineal tumors are rare, comprising approximately 0.4 to 1% of all malignant brain tumors. These tumors account for 1 to 4% of brain tumors in adults and 10% of brain tumors in children.[1,2] The pineal region contains a wide variety of histoanatomical structures, leading to the appearance of various malignancies in this location, including germ cell tumors, pineal parenchymal tumors, gliomas, miscellaneous tumors, and cysts.[3] Therefore, the management of malignancies in the pineal region is determined by the specific histological subtypes.[4]

Prognostic factors for tumors of the pineal region have been identified through a review of the relevant literature. According to Valsechi et al, the predictor of a poor prognosis in germinoma was female gender, whereas male was associated with an unfavorable prognosis in pineoblastoma.[5] Additionally, Cavalheiro et al found that entire resection was a potential predictor of outcome in pediatric patients with pineal area tumors.[6] In a population-based study, older age, male gender, nongerm cell tumor, and receiving chemotherapy were significantly associated with prognosis.[7]

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In recent studies, several immunonutritional indexes that function as prognostic factors for a wide range of malignancies have been identified.[8,9] Preoperative hemoglobin–albumin–lymphocyte–platelet (HALP) score of more than 24 was associated with disease recurrence and mortality in univariate analysis, while the prognostic nutritional index (PNI) of more than 45 was found to be substantially associated with mortality in endometrial cancer, according to Njoku et al.[10] Additionally, Leetanaporn and Hanprasertpong discovered that patients with locally advanced cervical cancer who had a HALP score of more than 22.2 had a longer progressive-free survival and overall survival time.[11] Shen et al discovered that HALP scores of more than 25.8 were substantially associated with recurrence-free survival in elderly patients with gastric cancer or small-cell lung cancer.[12] Furthermore, as a prognostic factor, the neutrophil-to-lymphocyte ratio (NLR) is among the immune-inflammatory biomarkers that have been investigated. In univariate analysis, Garrett et al demonstrated that NLR less than 5.07 and PNI more than 46.97 were significantly associated with prolonged survival time in univariate analysis; however, in multivariate analysis, these biomarkers were not significantly associated with survival.[13] Various immunonutritional indexes associated with long survival time that are potentially explained by the indexes can represent patient status, both nutritional and inflammatory status, and reflect the severity of the disease.[14,15]

According to a study of the literature, a few studies have been conducted on the prognostic value of immunonutritional indexes in patients with intracranial tumors, particularly pineal region tumors. In response to this knowledge gap, the authors aimed to assess the prognostic value of HALP score, PNI, and NLR in patients with pineal region tumors.

Methods

Study Design and Study Population

After institutional ethics board approval (REC.65-431-10-1), a retrospective cohort study of patients with pineal tumors who had confirmed diagnoses from tissue specimens by a pathologist between January 2010 and December 2022 was conducted. Patients who lacked complete medical records or histological slides for diagnosis confirmation, or who could not identify their current state, were eliminated. Baseline patient information, clinicopathological data, and preoperative laboratories were gathered such as age, gender, extent of resection, tumor size, preoperative hydrocephalus, pathological result, complete blood count, and tumor markers.

Before the review of the medical records, the operational definition was made. Based on the research conducted by previous studies,[16,17] the evaluation of residual tumor and the extent of resection were performed utilizing postoperative T1-weighted with contrast imaging. In detail, a postoperative residual tumor of no more than 5% was referred to as gross total resection (GTR). Subtotal resection was defined as a very small and usually strongly adhesive remnant portion adhered to the venous walls or infiltrating important structures. Partial resection was defined as the resection of less than 95% of the residual tumor that was visible on postoperative imaging. Moreover, the biopsy was just used for diagnostic purposes and not for tumor removal.[16–18]

The preoperative hematological measures comprised hemoglobin, leukocyte, neutrophil, lymphocyte, platelet counts, and albumin that were used to determine HALP score, PNI, and NLR. The HALP score was calculated using the following formula: hemoglobin (g/L) $\times$ albumin (g/L) $\times$ lymphocyte (/L)/platelet (/L).[15] The PNI was determined as $10 \times$ serum albumin (g/dL) $+ 0.005 \times$ total lymphocyte count (per mm^3), while the ratio of neutrophil to lymphocyte counts was used to calculate NLR.[19]

For outcome evaluation, follow-up data were gathered until December 2023, which included status information (death or staying alive). Follow-up data were gathered during patients' visits to outpatient clinics or through information obtained from the death records by the local municipality.

Statistical Analysis

Descriptive statistics were utilized to determine clinical characteristics and imaging results. Mean and standard deviation were utilized for continuous variables, and percentages were used for categorical data. For survival analysis, the median overall survival time was estimated. Using maximum selected rank statistical techniques, the cutoff threshold for each immunonutritional indicator was determined. The Cox proportional hazard regression model was used to explore prognosis in both univariate and multivariable analysis. Candidate variables with a p-value of 0.1 or less in the univariate analysis were examined in a multivariable model using backward stepwise selection in order to finalize the final model. Therefore, the model that obtained the lowest Akaike information criterion (AIC) value was selected as the final model.

Thus, a Kaplan–Meier survival curve was established, and log-rank tests were utilized to evaluate each predictor in the final model. Statistical analyses were performed by the Jamovi version 2.3.28 software (The Jamovi project, Sydney, Australia).

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). A human research ethics committee of the Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand approved the present study (REC.65-431-10-1). Because it was a retrospective analysis, the current study did not require patients' informed consent. However, the identity numbers of patients were encoded before analysis.

Results

Characteristics of Patients in the Present Cohort

The clinical characteristics of the 51 patients with pineal region tumors are shown in ►**Table 1**. The majority of patients were males, with an average age of 20.3 ± 16.2 years. Typical symptoms included worsening headache, alteration of consciousness, and ataxia resulting from

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Table 1 Baseline clinical characteristics

Factor	*N* (%)
Gender	
Male	40 (78.4)
Female	11 (21.6)
Mean age, y (SD)	20.3 (16.2)
Age group, y	
≤ 24	36 (70.6)
> 24	15 (29.4)
Preoperative symptoms	
Headache	36 (70.6)
Alteration of consciousness	18 (35.3)
Ataxia	15 (29.4)
Weakness	11 (21.6)
Seizure	8 (15.7)
Behavior change	2 (3.9)
Glasgow Coma Score	
< 13	5 (9.8)
≥ 13	46 (90.2)
Extent of resection	
Gross total resection	5 (9.8)
Subtotal resection	7 (13.7)
Partial resection	15 (29.4)
Biopsy	24 (47.1)
Pathological result	
Germinoma	17 (33.3)
Germ cell tumor (nongerminoma)	8 (15.7)
Nongerm cell tumor	26 (51.0)
Pilocytic astrocytoma	1 (2.0)
Diffuse astrocytoma	2 (3.9)
Anaplastic astrocytoma	4 (7.8)
Ependymoma	1 (2.0)
Subependymal giant cell astrocytoma	1 (2.0)
Pineal parenchymal tumor	4 (7.8)
Meningioma	3 (5.9)
Craniopharyngioma	1 (2.0)
Metastasis	1 (2.0)
Neuroblastoma	1 (2.0)
Other	7 (13.6)

Abbreviation: SD, standard deviation.

hydrocephalus before surgery. Additionally, preoperative hydrocephalus was found in 84.3% of cases. Germinoma is the most common tumor in the pineal region, accounting for 33.3% of cases, while pineal parenchymal tumors occurred in 7.8% of cases. The study found an average preoperative tumor diameter of 3.64 ± 1.35 cm and a mean tumor volume of 31.3 ± 33.5 mL.

Table 2 Imaging findings and preoperative laboratory results

Factor	*N* (%)
Imaging finding	
Preoperative hydrocephalus	43 (84.3)
Number of tumor	
Single	44 (86.3)
Multiple	7 (13.7)
Mean midline shift, mm (SD)	0.412 (1.88)
Mean tumor diameter, cm (SD)	3.64 (1.35)
Mean tumor volume, mL^3 (SD)	31.3 (33.5)
Preoperative laboratory	
Mean hemoglobin, mg% (SD)	12.9 (1.98)
Mean lymphocyte count, cell/uL (SD)	2,586 (1612)
Mean platelet count, cell/uL (SD)	358,137 (115,309)
Mean albumin, g/dL (SD)	4.31 (0.457)
Biomarkers	
Mean serum alpha-fetoprotein, ng/mL	215.00 (594.66)
Mean CSF alpha-fetoprotein, ng/mL	183.39 (632.72)
Mean serum beta hCG, mIU/mL	74.12 (233.65)
Mean CSF beta hCG, mIU/mL	36.59 (87.04)
Immune-nutritional indexes	
Mean hemoglobin, albumin, lymphocyte, and platelet score (SD)	42.1 (29.6)
Mean neutrophil-to-lymphocyte ratio (SD)	49.9 (54.7)
Mean prognostic nutritional index (SD)	68.9 (16.4)

Abbreviations: CSF, cerebrospinal fluid; hCG, human chorionic gonadotropin; SD, standard deviation.

Preoperative laboratories, biomarkers, and immunonutritional indexes are shown in ►**Table 2**. The mean serum alpha-fetoprotein was 215.00 ± 594.66 ng/mL, while the mean alpha-fetoprotein in cerebrospinal fluid (CSF) was 183.39 ± 632.72 ng/mL. Additionally, human chorionic gonadotropin (hCG) levels in the serum were mean of 74.12 ± 233.65 mIU/mL, while hCG levels in the CSF were mean of 36.59 ± 87.04 mIU/mL. Additionally, the average HALP score was 42.1 ± 29.6, and the mean PNI was 68.9 ± 16.4.

Survival Analysis

Average follow-up time was 64.84 ± 45.00 months and 1-, 2-, and 5-year survival probabilities were 92% (95% confidence interval [CI] 85–99.8), 92% (95% CI 85–99.8), and 81% (95% CI 70–94.1), respectively. Moreover, the median overall survival time was determined but the estimated median survival was not reached, as shown in ►**Fig. 1**. The extent of resection was

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Table 3 Univariate analysis by Cox regression analysis

Factor	Hazard ratio (95% CI)	*p*-Value
Age, y	0.96 (0.89–1.02)	0.18
Age group, y		
≤ 24	Ref	
> 24	0.57 (0.17–4.87)	0.99
Gender		
Female	Ref	
Male	31.09 (0.02–4853.10)	0.35
Weakness		
No	Ref	
Yes	0.46 (0.06–3.79)	0.47
Headache		
No	Ref	
Yes	3.30 (0.41–26.84)	0.26
Seizure		
No	Ref	
Yes	3.27 (0.78–13.72)	0.10
Behavior change		
No	Ref	
Yes	0.67 (0.28–3.73)	0.98
Ataxia		
No	Ref	
Yes	0.95 (0.19–4.74)	0.95
Alteration of consciousness		
No	Ref	
Yes	3.04 (0.73–12.72)	0.12
Blurred vision		
No	Ref	
Yes	3.08 (0.74–12.93)	0.12
Extraocular movement deficit		
No	Ref	
Yes	3.31 (0.67–16.47)	0.14
Glasgow Coma Score		
≥ 13	Ref	
< 13	2.65 (0.53–13.20)	0.23
Extent of resection		
Gross total resection	Ref	
Nontotal resection	0.04 (0.01–887.68)	0.53
Pathological result		
Germinoma	Ref	
Nongerminoma	0.71 (0.17–2.98)	0.64
Preoperative hydrocephalus		
No	Ref	
Yes	0.59 (0.12–2.93)	0.51
Number of tumors		
Multiple	Ref	
Single	0.96 (0.12–7.85)	0.97
Tumor volume, mL^3		
≤ 20.16	Ref	
> 20.16	0.34 (0.07–1.69)	0.18
Serum alpha-fetoprotein, ng/mL		
≤ 1.68	Ref	
> 1.68	1.10 (0.97–1.17)	0.58
CSF alpha-fetoprotein, ng/mL		
≤ 0.60	Ref	
> 0.60	1.07 (0.84–1.27)	0.87
Serum beta hCG, mIU/mL		
≤ 50.0	Ref	
> 50.0	1.17 (0.89–1.24)	0.95
CSF beta hCG, mIU/mL		
≤ 5	Ref	
> 5	1.01 (0.99–1.11)	0.59
HALP score		
≤ 22.6	Ref	
> 22.6	0.25 (0.06–1.00)	0.05
PNI		
≤ 56.08	Ref	
> 56.08	0.31 (0.08–1.25)	0.10
NLR		
≤ 45.9	Ref	
> 45.9	0.75 (0.15–3.75)	0.72

Abbreviation: CI, confidence interval; CSF, cerebrospinal fluid; HALP, hemoglobin–albumin–lymphocyte–platelet score; hCG, human chorionic gonadotropin; NLR, neutrophil lymphocyte ratio; PNI, prognostic nutritional index.

estimated for association with prognosis, and we found that the GTR group was not significantly associated with a favorable prognosis compared with the non-GTR group ($p = 0.33$), as shown in ►**Fig. 2A**. Furthermore, ►**Fig. 2B** shows that the prognosis of patients with germinoma was not substantially different from that of the nongerminoma group ($p = 0.64$). Additionally, 1-, 2-, and 5-year survival probabilities of germinoma were 88.2% (95% CI 74.2–100), 88.2% (95% CI 74.2–100), and 80.8% (95% CI 63.4–100), respectively.

In immunonutritional indexes, the maximum selected rank statistical method was used to examine the HALP score, PNI, and NLP cutoff thresholds. These values were 22.6, 56.08, and 45.9, respectively. The Cox proportional hazard

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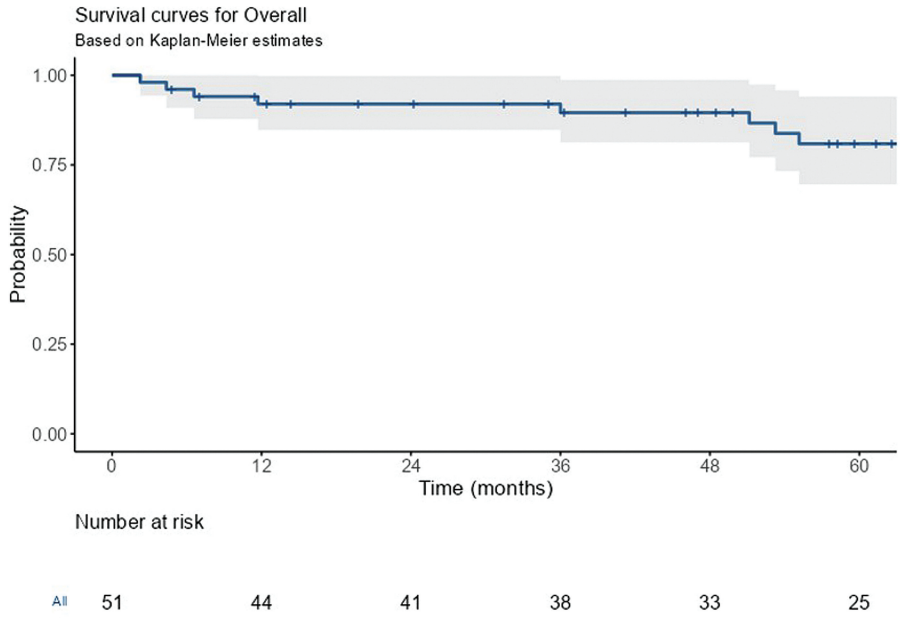

Fig. 1 Kaplan–Meier survival curve of overall survival.

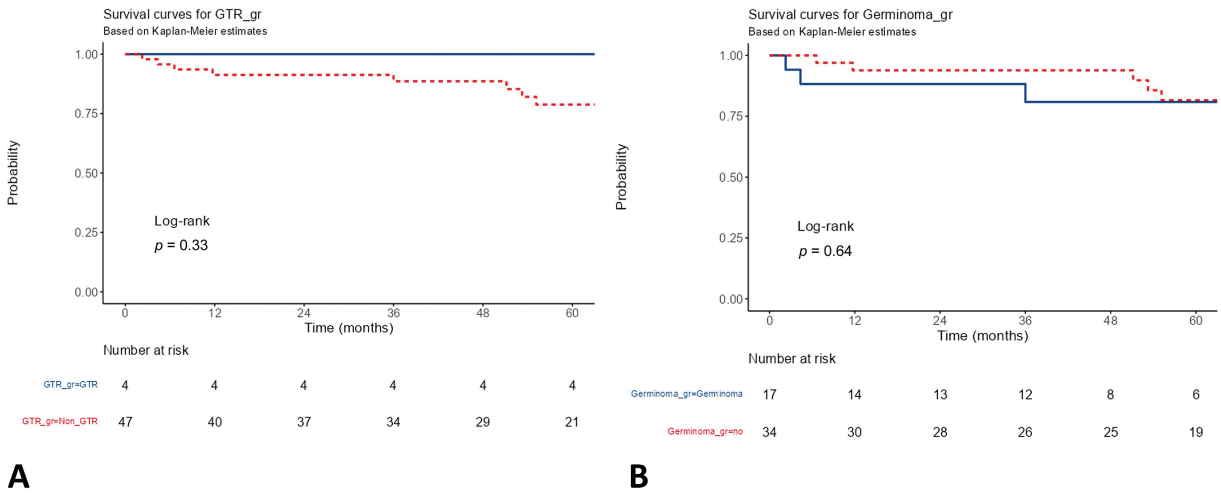

Fig. 2 Kaplan–Meier survival curves of the extent of resection and histological types of tumor. (**A**) Gross total resection (GTR) group and non-GTR group. (**B**) Germinoma group and nongerminoma group.

regression was performed to explore factors associated with prognosis. Seizure symptom, HALP score, and PNI were candidate variables in univariate analysis, as shown in ►**Table 3**. Kaplan–Meier survival curves of immunonutritional indexes and candidate variables are demonstrated in ►**Fig. 3A–D**. Thus, these candidates were analyzed in multivariable analysis using a backward stepwise procedure with the lowest AIC value. The HALP score was the only predictor included in the final model (hazard ratio 0.25, 95% CI 0.06–1.00, $p = 0.05$). In addition, there was a significant difference in prognosis between the high and low HALP score group by log-rank test ($p = 0.035$).

Discussion

The present study revealed a favorable prognosis for the pineal tumor region. The 5-year survival probability was 81%, which was marginally higher than the prognosis from previous research. From 1973 to 2005, Al-Hussaini et al analyzed the prognosis of 633 patients with pineal tumors using the Surveillance, Epidemiology, and End Results (SEER) database. They discovered that the overall 5-year survival rate was 65%.[20] Additionally, Vuong et al used the SEER database from 1975 to 2016 to analyze the survival of pineal tumors and the separated cases diagnosed between 1975 and 2016 into four groups for survival trend analysis: 1975 to 1984, 1985 to 1994, 1995 to 2004, and 2005 to 2016. Consequently, there has been a rise in the survival rate of pineal gland tumors over time, which may be attributed to notable advancements in technology and health care.[7] For pineal germinoma, the 5-year survival of germinoma in the present study was 80.8% which is consistent with prior studies. Cavalheiro et al reported that the overall survival rate for patients with germinomas at 1, 2, and 5 years was

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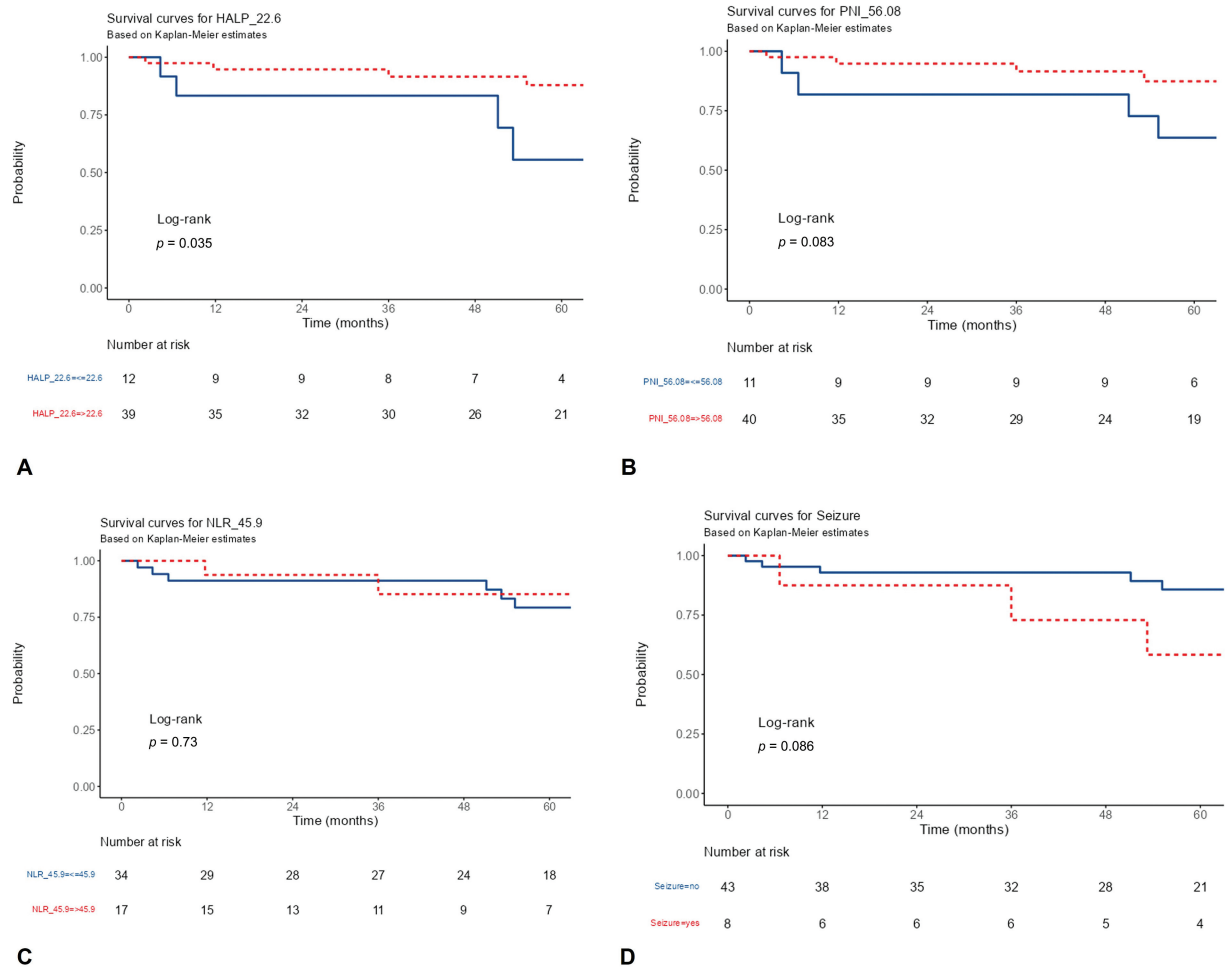

Fig. 3 Kaplan–Meier survival curves of immune-nutritional indexes and candidate variables. (**A**) Hemoglobin–albumin–lymphocyte–platelet (HALP) score. (**B**) Prognostic nutritional index (PNI). (**C**) Neutrophil-to-lymphocyte ratio (NLR). (**D**) Preoperative seizure.

93.7, 93.7, and 88%, respectively, whereas Valsechi et al determined that the 5-year survival rate for germinomas was 88%.[5,6]

Previous studies have identified prognostic factors for pineal tumors, including gender, age, and the extent of resection. In the present study, the HALP score is strongly associated with prognosis. In detail, a high HALP score demonstrated a significant survival benefit compared to low HALP scores. This might be explained by the fact that the score measures both the patient's immune system and nutritional status.[21] Because the HALP score had never been reported in the pineal tumor region in previous research, and there was no standard cutoff value for the HAP score based on a literature review, we utilized a statistical method to identify an optimal cutoff value that could be validated in the future.[22] From literature review, a limited number of previous studies have revealed that HALP serves as a prognostic factor.

Tunthanathip and Oearsakul studied various immune-nutritional indexes for prognostication in glioblastoma and found that HALP score of more than 32 was significantly associated with prolong survival time.[23] Wang et al reported that the HALP cutoff threshold for endometrial cancer was 33.8 and that the group with lower HALP had worse survival outcomes compared to the group with higher HALP.[24] In gastrointestinal stromal tumors, HALP was a prognostic factor with a threshold value of 31.5.[25] Furthermore, the result of the present study tended to utilize PNI as a predictor due to the biomarker's statistical significance in univariate analysis. Nevertheless, there was no significant correlation between PNI and prognosis in the multivariable analysis. Immunonutritional indicators, which require regular laboratory tests that are often performed on patients, can serve as straightforward and adjustable predictors to help clinicians enhance the prognosis of patients with immunonutritional deficiencies.[8]

To the best of the authors' knowledge, this was the first study to show a significant relationship between HALP and the prognosis of patients diagnosed with pineal region tumors. However, it was noted that the present study had certain limitations. First, the authors considered a limited number of patients for survival analysis. This limitation could be resolved through multicenter research, which could boost the number of study population and solve the overfitting problem of the predictive model by validation with unseen data.[26,27] Therefore, the study's retrospective design introduced biases in both selection and information. However, the authors attempted to address the limitation

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through the creation of an operational definition, inclusion, and exclusion criteria before the assessment.[28,29] Furthermore, the present study just assessed immunonutritional indexes in the preoperative phase. In the future, a longitudinal study with a repeated-measures design should be conducted to investigate the association between immunonutritional indexes and prognosis.[30]

Conclusion

The preoperative HALP score is an independent prognostic factor for patients diagnosed with pineal region tumors. The prognostication of the immunonutritional indexes requires to be validated in the future.

Declarations

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). A human research ethics committee approved the present study (REC.65-431-10-1). Because it was a retrospective analysis, the current study did not require patients' informed consent. However, the identity numbers of patients were encoded before analysis.

Authors' Contributions

S.S. and T.T. conceived the study and designed the method. T.T. supervised the completion of the data collection. S.S., A.K., and T.T. undertook the recruitment of participating centers and patients and managed the data, including quality control. A.K. and T.T. provided statistical advice on the study design and analyzed the data, while S.S. drafted the manuscript, and all authors contributed substantially to its revision. T.T. takes responsibility for the paper as a whole.

Conflict of Interest

None declared.

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