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Impact of neutrophil–lymphocyte ratio on long-term outcome in patients with craniopharyngioma

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Abstract

Neutrophil–lymphocyte ratio (NLR) is a poor prognostic factor in many tumors including glioblastoma multiforme (GBM), colorectal, and prostate cancer. The aim of this study was to investigate the prognostic value of preoperative NLR in patients with craniopharyngioma.

Around 149 patients of craniopharyngioma surgically were treated at the Department of Neurosurgery, West China Hospital from January 2008 to December 2010, including 84 males and 65 females aged from 6 to 70 years were retrospectively reviewed, and preoperative NLR was analyzed. Overall survival (OS), progression free survival (PFS), and quality of life (QOL) were evaluated.

The 5-year OS and PFS rates were 81.21% and 75.84%. Preoperative NLR was significantly correlated with OS (HR = 1.44, 95% CI 1.16–1.79, $P = .001$) and PFS (HR = 1.46, 95% CI 1.22–1.74, $P < .001$). The best cut-off value of NLR was found to be 4 based on the receiver operator characteristics (ROC) curve. Patients with NLR ≥4 had a significantly worse QOL ($P = .039$), lower OS rate ($P = .009$), and PFS rate ($P < .001$).

Preoperative NLR may be a simple, readily available, and valid predictor of long-term outcome in craniopharyngioma. We suggest that the NLR can provide effective guidance to neurosurgeons for more information about the tumor and prognostic evaluation.

Abbreviations: ASBS-Q = anterior skull base surgery questionnaire, CP = craniopharyngioma, CT = computed tomography, GBM = glioblastoma multiforme, G-CSF = granulocyte-colony stimulating factor, GTR = gross total resection, HR = hazard ratio, IL-6 = interleukin-6, MRI = magnetic resonance imaging, NLR = neutrophil-lymphocyte ratio, OS = overall survival, PFS = progression free survival, QOL = quality of life, ROC = receiver operator characteristics, TNF = tumor necrosis factor, VEGF = vascular endothelial growth factor.

Keywords: craniopharyngioma, neutrophil–lymphocyte ratio, prognosis, survival

1. Introduction

Craniopharyngioma (CP) is a histologically benign tumor originating from remnants of Rathke's pouch and it is located in the sellar and/or parasellar area.[1,2] It accounts for 2% to 5% of all primary intracranial tumors and 5.6%–13% of intracranial neoplasms in children.[3,4] It consequently ranks as the second most frequent tumor in the hypothalamic-pituitary region regardless of age.[5] Patients may have a variety of manifestations, such as visual, neurological, and hypothalamo-pituitary dysfunction.[6] Surgical resection followed by postoperative radiation, in cases of residual tumor, is the main treatment strategy.[6] Despite its nonmalignant feature, it can be linked with a poor prognosis due to the anatomical involvement and surgical damnification of hypothalamic areas.[7–10] Prognostic predictors including sex, age, tumor size, location, and treatment were considered for possible association with recurrence and quality of life in patients suffering CP.[11] However, it is still very difficult to predict the prognosis of CP, and it is worthwhile to explore new prognostic factors.

It has been demonstrated that chronic inflammation has relationship with tumor in many ways, including cell invasion, promotion of angiogenesis and damage of DNA.[12–14] Recently, Hannahan et al. [15] emphasized the importance of uncontrolled inflammation in driving tumor proliferation. Neutrophil-lymphocyte ratio (NLR) is an easy way to evaluate inflammation that is inexpensive and readily available from the complete blood cell count. Increased pretreatment NLR has recently been shown to be a poor prognostic factor in many tumors including lung cancer, breast cancer, gastrointestinal cancers, urologic cancers, glioblastoma multiforme (GBM), gynecologic cancers, and metastatic disease.[16–20] Besides, elevated NLR has also been reported to be associated with poor outcome in non-neoplastic diseases such as stroke and coronary artery disease.[21,22] Therefore, NLR may be a promising prognostic biomarker in various diseases in clinical work.

As to CP, the histologic findings like degenerative changes and inflammation were common features.[11,23] And inflammation may cause more tumor adhesion and infiltration to adjacent brain. Even worse, this would make gross total resection (GTR) more difficult.[24] We hypothesized the prognostic role of NLR in

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CP, and the impact of NLR on the prognosis in CP has not been reported before. Therefore, to evaluate the prognostic value of NLR on long-term outcome in patients with CP, we retrospectively undertook a preliminary study to analyze overall survival (OS), progression free survival (PFS), weight development, and quality of life (QOL).

2. Materials and methods

2.1. Patient population and data collection

Clinical records of 176 consecutive patients with CP at the Neurosurgery Department, West China Hospital between January 2008 and December 2010 were analyzed. CP was diagnosed by preoperative computed tomography (CT) and enhanced magnetic resonance imaging (MRI) and diagnosis was confirmed by postoperative histological analysis. Patients with other diseases, including other intracranial disease, inflammatory disease, infection within 6 months, trauma, heart disease, diabetes mellitus, metabolic syndrome, severe hepatic or renal dysfunction, blood system diseases and medication usage related to inflammatory conditions that could significantly influence NLR or prognosis or those lacking complete data were excluded. Also all patients underwent craniotomy to remove the tumor under the microscope by experienced neurosurgeons. Eight patients did not accord with the inclusive criteria. In addition, 19 patients were lost at follow-up or not able to cooperate at the follow-up process. In the end, 149 patients were enrolled in this study. This study was approved by the ethics committee of our hospital.

Complete blood count was taken preoperatively before any treatment especially hormone replacement therapy. Blood samples were analyzed within 2 hours after collection using a Sysmex XN-9000 complete blood count analyzer (Sysmex, Japan). We mainly focused on blood neutrophil and lymphocyte. Also NLR was defined as the ratio between neutrophil and lymphocyte count. According to preoperative CT and enhanced MRI results provided by experienced radiologists, we recorded the location and tumor size (cm^2) was calculated using the maximal tumor diameters in 2 dimensions.

Weight and height were expressed as body mass index (BMI = weight [kg]/height^2 [m^2]). In addition, weight development was defined as the difference between BMI at the time of follow-up and before the surgery.

QOL was assessed using the anterior skull base surgery questionnaire (ASBS-Q), and this is a specific instrument that has been validated for use in patients undergoing anterior skull base surgery.[25–28] The ASBS-Q including 35 questions was divided into 6 relevant QOL domains: performance (6 items), physical function (7 items), vitality (7 items), pain (3 items), influence on emotions (5 items), and specific symptoms (7 items). Responses were recorded on a 5-item scale, ranging from 1 to 5 points for each item. In this study we used average score of 35 questions to evaluate QOL of patients, with a higher score representing better QOL. If patient dies, his/her ASBS-Q score was considered as 1 point. Besides, for long-term outcome, we were able to analyze 5-year OS rate and 5-year PFS rate.

2.2. Statistical analysis

We used SPSS 23.0 (SPSS, Inc., Chicago, IL) for Apple's operating system to perform data analysis. Data were expressed as mean ± standard deviation for normally distributed variables and median ± interquartile range for non-normally distributed variables. The distribution of the variables was analyzed with the Kolmogorov–Smirnov test. The difference between 2 groups was tested by Independent Student's *t*-tests for normally distributed variables and Mann–Whitney *U* test for nonparametrically distributed variables. The chi-square test or Fisher exact test was used to compare categorical variables. The bivariate relationship between 2 continuous variables was assessed using the Spearman's correlation coefficient. Univariate and multivariate Cox proportional hazard regression models were constructed to explore the association of NLR and other clinical factors with PFS and OS. OS and PFS were estimated using the Kaplan–Meier method, and differences in PFS and OS were examined with the log-rank test. All tests were 2-sided and P values of $\leq$ .05 were considered as being statistically significant.

3. Results

3.1. Patient characteristics

One hundred and forty-nine patients (female 65, male 84; median age 36, range 6–70) with CP who underwent surgery between January 2008 and December 2010 were finally enrolled in the study. The distributions of clinical and prognostic factors were shown in Table 1. The postoperative stay was 14 ± 17 days. A total of 101 (67.79%) patients achieved gross total resection. Eleven patients died during perioperative period. The tumor size was 4.17 ± 4.01 cm^2. Tumors were mainly located supra- and intrasellar (91) and supra-sellar (51). Patients have different endocrinopathies, such as growth hormone deficiency, hypogonadism, hypothyroidism, hypoadrenalism, and diabetes insipidus. Thirty patients received radiation therapy. The mean NLR was 3.10 ± 1.59.

Thirty-six of 149 (24.16%) had elevated NLR (≥4) at baseline. The distributions of clinical factors and long-term outcome between patients with preoperative NLR ≥4 versus <4 were shown in Table 2. Median follow-up time was 80 months (71.79 ± 27.04, range 1–102). Average increase in BMI was 1.20 ± 0.64 in living individuals. Median ASBS-Q score was 3.34 ± 3. Median progression free survival was 82 months (83.00 ± 9.72, range 66–102). Median overall survival was 83 months (83.00 ± 10.00, range 66–102). Among the entire cohort, 5-year PFS rate was 75.84% while 5-year OS rate was 81.21%, respectively.

3.2. Univariate and multivariate analysis of factors associated with OS and PFS (Table 1)

In the univariate analysis, gross total resection of the tumor (HR = 0.10, 95%CI 0.04–0.26, P < .001), radiation therapy (HR = 0.13, 95%CI 0.02–0.98, P = .047) and NLR (HR = 1.49, 95% CI 1.24–1.78, P < .001) were associated with OS. Also gross total resection of the tumor (HR = 0.12, 95%CI 0.06–0.25, P < .001), radiation therapy (HR = 0.27, 95%CI 0.08–0.88, P = .03), and NLR (HR = 1.50, 95%CI 1.28–1.76, P < .001) were associated with PFS. Other factors were not significantly associated with OS or PFS.

In the multivariate analysis, factors associated with OS were NLR (HR = 1.44, 95%CI 1.16–1.79, P = .001), radiation therapy (HR = 0.05, 95%CI 0.01–0.41, P = .005) and gross total resection (HR = 0.11, 95%CI 0.05–0.29, P < .001). Besides, NLR (HR = 1.46, 95%CI 1.22–1.74, P < .001), radiation therapy (HR = 0.11, 95%CI 0.03–0.37, P < .001) and gross total resection (HR = 0.13, 95%CI 0.06–0.27, P < .001) were associated with PFS.

Table 1

Distribution of clinical and prognostic factors, and univariate and multivariate analysis of their association with 5-year progression free survival and overall survival.

Factor	Distribution (n = 149)	Univariate analysis [HR (95% CI), *P*]		Multivariate analysis [HR (95% CI), *P*]	
		5-year OS	5-year PFS	5-year OS	5-year PFS
Gender (f/m)	65/84	1.01 (0.48–2.14), 0.978	0.86 (0.46–1.61), 0.634		
Age, years	36 ± 39*	1.00 (0.98–1.02), 0.816	0.994 (0.98–1.01), 0.475		
Postoperative stay, days	14 ± 17*	1.00 (0.97–1.03), 0.843	1.01 (0.98–1.03), 0.663		
Gross total resection	101 (67.79%)	0.10 (0.04–0.26), <0.001	0.12 (0.06–0.25), <0.001	0.11 (0.05–0.29), <0.001	0.13 (0.06–0.27), <0.001
Perioperative death (n)	11	—	—		
Tumor size, cm^2	4.17 ± 4.01*	1.29 (0.95–1.58), 0.160	1.45 (0.56–2.38), 0.100		
Tumor location (n)		1.24 (0.81–1.89), 0.319	1.03 (0.75–1.43), 0.846		
Supra-	51				
Intra-	7				
Supra- and Intra-	91				
Endocrinopathy (n)†					
GH deficiency	88	0.94 (0.45–1.99), 0.878	0.90 (0.49–1.67), 0.739		
Hypogonadism	81	0.96 (0.45–2.01), 0.903	0.87 (0.47–1.61), 0.667		
Hypothyroidism	50	0.77 (0.34–1.75), 0.533	0.88 (0.46–1.70), 0.699		
Hypoadrenalism	49	0.95 (0.43–2.09), 0.893	0.96 (0.50–1.85), 0.898		
Diabetes insipidus	17	0.57 (0.14–2.42), 0.450	0.80 (0.29–2.25), 0.673		
Radiation therapy (n)	30	0.13 (0.02–0.98), 0.047	0.27 (0.08–0.88), 0.030	0.05 (0.01–0.41), 0.005	0.11 (0.03–0.37), <0.001
NLR	3.10 ± 1.59‡	1.49 (1.24–1.78), <0.001	1.50 (1.28–1.76), <0.001	1.44 (1.16–1.79), 0.001	1.46 (1.22–1.74), <0.001

ASBS-Q = anterior skull base surgery questionnaire, BMI = body mass index, cm = centimeter, f/m = female/male, HR = hazard ratio, intra- = intrasellar, n = number, NLR = neutrophil-lymphocyte ratio, NS = not significant, OS = overall survival, PFS = progression free survival, supra- = suprasellar, yr = year.

* Described as median ± interquartile range.

† Prior to surgery.

‡ Described as mean ± standard deviation.

3.3. *NLR ≥4 versus <4 of factors and long-term outcome (Table 2)*

Based on the receiver operator characteristics (ROC) curve, the best cut-off value of NLR was found to be 4 (Fig. 1). Moreover, median OS was 77 versus 80 months in patients with NLR ≥4 versus <4 (Fig. 2). The median PFS was 73 versus 78 months in patients with NLR ≥4 versus <4 (Fig. 3).

Tumor size was $5.6 \pm 3.52\,cm^2$ versus $4.07 \pm 1.58\,cm^2$ (*P* = .001) and gross total resection of the tumor was achieved in 15 versus 86 individuals (*P* < .001) in patients with NLR ≥4 versus

Table 2

Distribution of clinical factors and long-term outcome stratified by NLR.

Characteristic	All patients	NLR ≥4	NLR <4	*P*
Patient number (n)	149	36	113	
Gender (f/m)	65/84	21/15	66/47	.994
Age, years*	36 ± 39	37 ± 27	36 ± 32	.843
Tumor size, cm^2*	4.17 ± 4.01	5.6 ± 3.52	4.07 ± 1.58	.001
Gross total resection	101	15	86	<.001
Tumor location (n)				
Supra-	51	16	35	.138
Intra-	7	2	5	.780
Supra- and Intra-	91	18	73	.118
Endocrinopathy (n)†				
GH deficiency	88	21	67	.919
Hypogonadism	81	19	62	.827
Hypothyroidism	50	13	37	.709
Hypoadrenalism	49	7	42	.049
Diabetes insipidus	17	5	12	.591
Increase in BMI (n = 121)‡	1.20 ± 0.64	1.31 ± 0.54	1.17 ± 0.66	.354
ASBS-Q score*	3.34 ± 3	2.70 ± 2.04	3.45 ± 1.60	.039
5-year OS rate	81.21%(121/149)	66.66%(24/36)	85.84%(97/113)	.009
5-yearr PFS rate	75.84%(113/149)	44.44%(16/36)	85.84%(97/113)	<.001

ASBS-Q = anterior skull base surgery questionnaire, BMI = body mass index, cm = centimeter; f/m = female/male, intra- = intrasellar, n = number, NLR = neutrophil-lymphocyte ratio, NS = not significant, OS = overall survival, PFS = progression free survival, supra- = suprasellar, yr = years.

* Described as median ± interquartile range.

† Prior to surgery.

‡ Described as mean ± standard deviation.

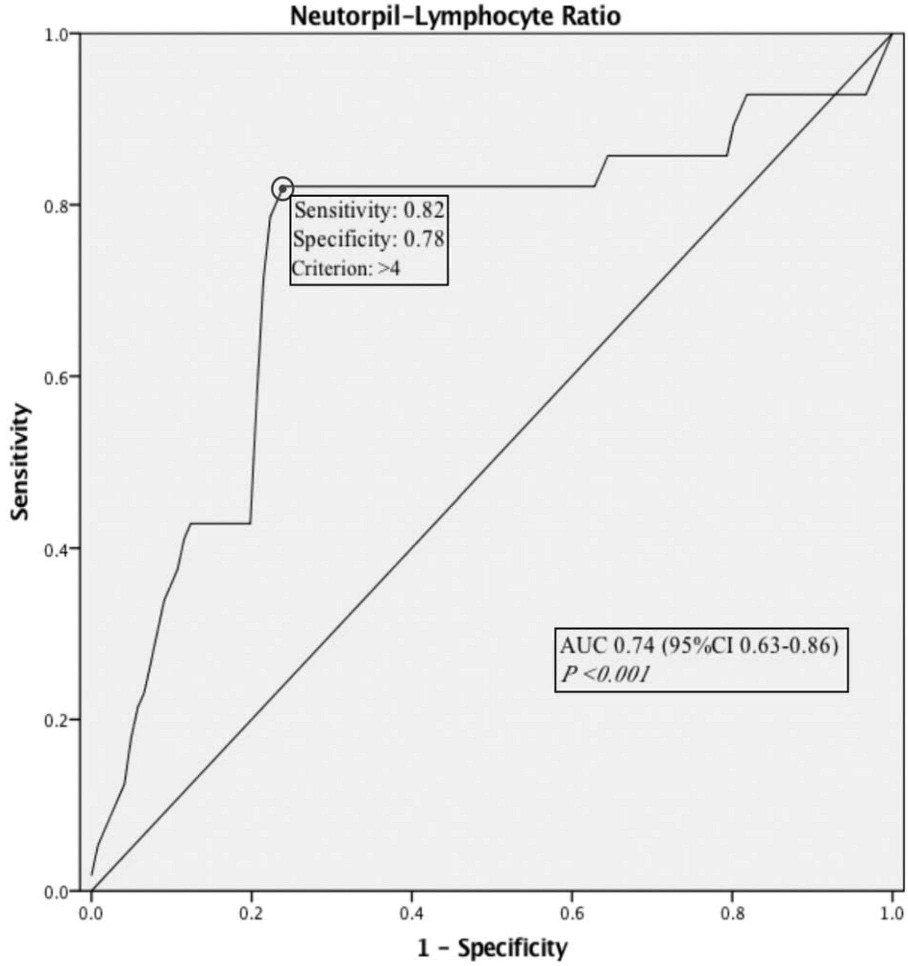

Figure 1. Receiver operator characteristics curve of neutrophil-lymphocyte ratio to predict mortality.

<4. More individuals had hypoadrenalism in patients with NLR <4 (P=.049).

Patients with NLR ≥4 had an average ASBS-Q score of 2.70 ± 2.04, while those with NLR <4 had an average ASBS-Q score of 3.45 ± 1.60 (P=.039). Patients with NLR ≥4 had a 5-year OS rate of 66.66% (24/36) whereas patients with NLR <4 had a 5-year OS rate of 85.84% (97/113) in Kaplan–Meier curve (P=.009) (Fig. 2). The 5-year PFS rate was 44.44% (16/36) versus 85.84% (97/113) in patients with NLR ≥4 versus <4 (P < .001) (Fig. 3). No significant difference was found among other factors between patients with NLR ≥4 and <4.

4. Discussion

Craniopharyngiomas are difficult intracranial lesions to treat due to its deep location and extremely variable growth pattern.[29,30] Although histologically benign, the tumor's potential adhesion to adjacent vital brain structures makes gross total resection and follow-up treatment difficult. In recent studies, about 18% to 84% [3,6,29,31–37] of patients had gross total resection and the 5-year OS rates ranged from 54% to 96%.[29,36–43] In the present study, the 5-year OS rate was 81.21% and 67.79% (101/149) of patients had gross total resection.

The present study assessed the prognostic value of preoperative NLR in surgically treated patients with CP. According to the data we obtained from this study, preoperative NLR may be associated with QOL, OS, and PFS. In addition, NLR value of 4 was determined as cut-off value with a good sensitivity and acceptable specificity. In this retrospective study, patients with preoperative NLR <4 had a better long-term outcome and NLR ≥4 was an alarm signal of increased mortality risk. To our knowledge, this is the first study to assess the prognostic role of preoperative NLR in patients with CP.

Composed of 2 major component of immune system, NLR can be applied to clinical work as marker of a patient's immune state prior to surgery. In the present study, higher NLR (≥4) was associated with larger tumor and worse long-term outcome. Clinical data from recent studies suggest that immune response plays a role in tumorigenesis.[12,13] Tumor and tumor-related neutrophils produce cytokines like vascular endothelial growth factor (VEGF), which promote angiogenesis, provoke tumor cells to proliferate, therefore, to further promote invasive growth, metastasis, and recurrence.[11,44–47] All the above mentioned are associated with worse QOL after surgical treatment and lower PFS rate.[3,33,36,48–51]

In neoplastic processes, neutrophil is consequence of tumor-related inflammatory cytokines including tumor necrosis factor (TNF), interleukin-6 (IL-6), and granulocyte-colony stimulating factor (G-CSF) by tumor cells.[52–57] Thus, a high level of neutrophil in peripheral blood may indicate tumor-associated

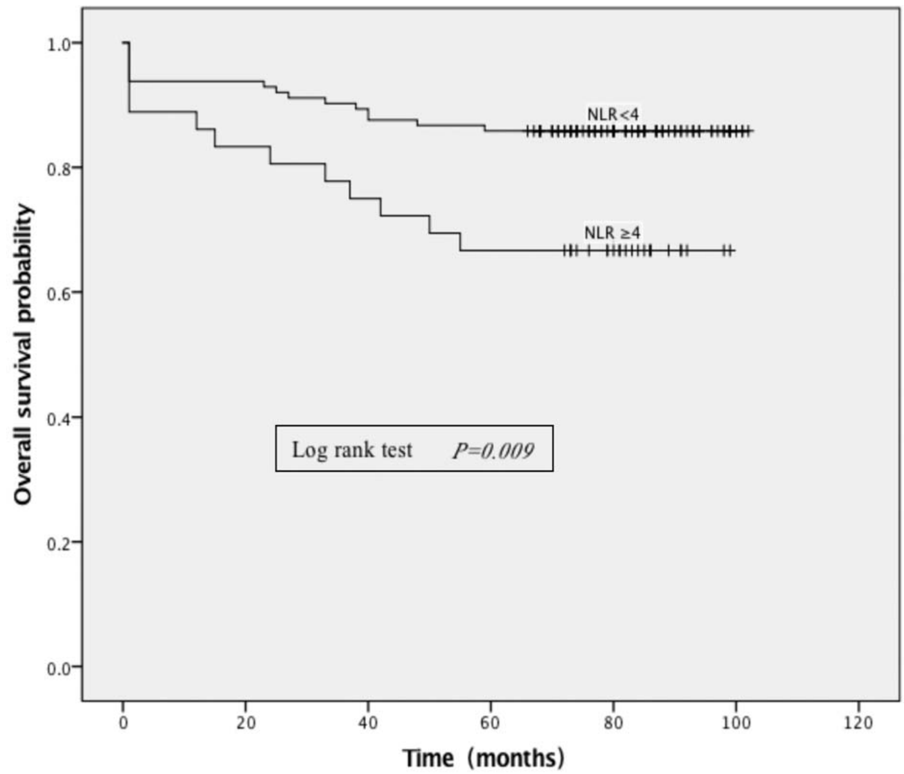

Figure 2. Kaplan–Meier curves showing overall survival, stratified by neutrophil-lymphocyte ratio (NLR). The median OS was 77 versus 80 months in patients with NLR ≥4 versus <4. NLR = neutrophil-lymphocyte ratio.

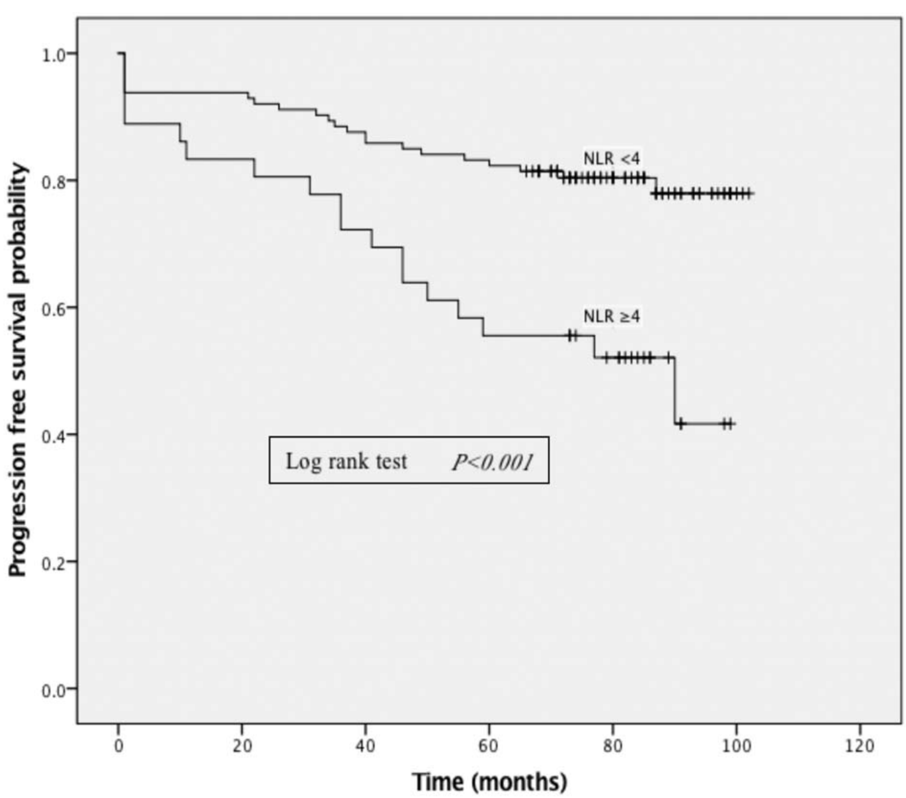

Figure 3. Kaplan–Meier curves showing progression free survival, stratified by neutrophil-lymphocyte ratio (NLR). The median PFS was 73 versus 78 months in patients with NLR ≥4 versus <4. NLR = neutrophil-lymphocyte ratio.

inflammation. In our study, patients with NLR ≥4 had lower gross total resection rate. This phenomenon could be explained by studies indicating a possible involvement of inflammation in the process of cyst formation and adhesion to adjacent brain tissue of craniopharyngioma.[56–58] And as mentioned before, such adhesion could make gross total resection more difficult. Besides, microscopically, craniopharyngioma tissue are closely connected with gliosis area induced by inflammatory in the adjacent brain tissues, which may result in recurrence even the patient had received gross total resection of the tumor.[57,59,60]

Gross total resection is associated with a favorable long progression free survival, better QOL and even cure. About 10%–15% of totally removed CP relapsed and nearly 80% of patients were asymptomatic after total tumor resection during a long follow-up period. In the present study, gross total resection was related to better long-term outcome.

It is controversial whether age at diagnosis is associated with long-term outcome. Previous studies have shown that the younger patients had better outcome.[61] On the contrary, some studies have found longer survival in older patients.[43,62] Our result did not present any difference in long-term outcome with respect to age. The prognostic value of sex has not been conclusively established. Some researchers found a higher mortality in females,[39,62] while the others suggested there were no differences between the sexes.[36,38,63] In the present study, our data did not show any difference between the sexes. Besides, tumor size did not relate to 5-year OS and PFS in our research, and the same finding was reported in an article by Yosef et al.[64].

In some patients, gross total resection cannot be achieved without injury to vital structures of hypothalamus. Subtotal resection and radiation therapy are safe and effective approaches to control the tumor and improve long-term outcome of the patients.[65–67] In our cohort, radiation therapy after subtotal resection was linked to OS and PFS.

The present study had several limitations. The first was that the study was a single-center retrospective study and more reliable findings should be confirmed in multi-center prospective cohort. Secondly, in 48 patients who underwent subtotal resection, only 30 of them received radiation therapy for various reasons, so data from radiation therapy is limited.

5. Conclusion

Preoperative NLR may be a simple, readily available, and valid predictor of long-term outcome in craniopharyngioma. It could not only reflect the local inflammatory information of the tumor and provide effective guidance to neurosurgeons for prognostic evaluation, but also suggest further exploration on tumor therapies based upon modulating host immune response. Patients with NLR ≥4 have worse long-term outcome and they are a more reasonable group to receive radiation therapy. However, more studies are warranted to verify our findings and address the underlying mechanisms.

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