

Prognostic Value of Cumulative Score Based on Preoperative Fibrinogen and Albumin Level in Skull Base Chordoma

This article was published in the following Dove Press journal:
OncoTargets and Therapy

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Objective: Inflammation and malnutrition have been shown to be correlated with tumor progression and a poor prognosis in various cancers. However, the clinical implications of biomarkers of inflammation and malnutrition in chordoma have not been elucidated. We attempted to characterize the fibrinogen and albumin levels in skull base chordoma and investigate their correlations with clinicopathological data and survival.

Methods: The preoperative levels of fibrinogen and albumin were assessed in 183 primary skull base chordoma patients. The cutoff values were determined by X-tile software, and their correlations with patient prognosis were further explored using the Kaplan–Meier curve and Cox proportional hazards regression analysis. In addition, the predictive performances of these markers in survival were evaluated by receiver operating characteristic curves.

Results: The values of fibrinogen and albumin in skull base chordoma patients ranged from 1.73 to 7.40 and 37.6 to 53.0 g/L, respectively. The optimal cutoff values for fibrinogen and albumin were 3.29 and 44.60 g/L, respectively. Fibrinogen and albumin were correlated with the patient age and tumor pathology types. Albumin, but not fibrinogen, was associated with the patients' progression-free survival and overall survival. Importantly, the FA score, which combines fibrinogen and albumin, could independently predict both progression-free survival and overall survival, and enhanced the performance of fibrinogen or albumin in survival prediction in skull base chordoma.

Conclusion: Our data reveal the clinical prognostic role of albumin and suggest that the FA score may be a valuable prognostic grading system in skull base chordoma.

Keywords: skull base chordoma, fibrinogen, albumin, biomarker, prognosis

Introduction

Skull base chordoma is a rare malignancy of the central nervous system originating from residual notochord.¹ Radical surgery and postoperative radiotherapy remain the best treatment for increasing the life span of skull base chordoma patients.² However, because skull base chordoma is adjacent to vital neurovascular tissues, is resistant to conventional radiotherapy and chemotherapy and has a high recurrence rate, the therapy of skull base chordoma has been a difficult challenge in neurosurgery.³⁻⁵ A risk stratification assessment of recurrence and death before therapy could help clinicians identify the optimal choice of treatment and improve the prognosis of patients. However, a dependable preoperative prognostic grading system that can accurately predict the individual clinical outcome of patients is currently lacking.

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An increasing number of studies have demonstrated that systematic inflammation and the nutritional status play significant roles in the tumor initiation, progression and clinical outcomes in various human cancers.^{6–8} In particular, fibrinogen, which is a type of glycoprotein produced by hepatic epithelium cells that is indispensable for the coagulation cascade, plays an important role in the human response to systematic inflammation and may reflect the inflammation status.⁹ Moreover, recent studies show that high levels of preoperative fibrinogen predict a poor prognosis in non-small cell lung cancer, high-grade glioma, colorectal cancer and renal cell carcinoma.^{10–13}

Many studies have shown that malnutrition is closely associated with tumor progression and human immunity and that albumin, which is an acute-phase protein mostly synthesized by the liver and a nutritional indicator regularly used to evaluate the nutritional status, is involved in systemic inflammation.^{14,15} Moreover, low levels of serum albumin have been observed in several cancers compared to healthy controls.¹⁶ Several studies report that a low preoperative albumin level can represent an adverse prognostic factor for patient outcomes and a latent risk factor for postoperative complications in human cancers.^{17,18} Furthermore, considering the prognostic role of fibrinogen and albumin, the FA score, which is a novel scoring system that combines fibrinogen and albumin, has recently been reported, and this score can independently predict outcomes in patients with esophageal cancer and urothelial carcinoma.^{19,20}

To the best of our knowledge, thus far, studies evaluating the prognostic performance of preoperative fibrinogen and/or albumin in skull base chordoma are limited. Therefore, in the current study, we retrospectively characterized the preoperative level of fibrinogen and albumin and investigated the association among fibrinogen, albumin, clinicopathological data and survival in 183 primary skull base chordoma patients who underwent surgery. In addition, the FA score (0 to 2) was generated and the prognostic role of the FA score was further analysed. We also compared the predictive value of fibrinogen, albumin and the FA score in skull base chordoma.

Materials and Methods

Patients

One hundred eighty-three eligible patients with primary skull base chordoma treated with surgical therapy at Beijing Tiantan Hospital, Capital Medical University, between January 2008 and September 2014 were retrospectively

included in the current research. The inclusion criteria in this study were as follows: (a) histologically newly confirmed skull base chordoma; (b) first surgery with no preoperative radiotherapy and/or chemotherapy; (c) patients with complete clinicopathological information and preoperative level of fibrinogen and albumin; and (d) patients with follow-up data. Otherwise, patients were excluded for the following conditions: (a) unclear pathological diagnosis; (b) patients who received a previous treatment such as surgery, radiotherapy or chemotherapy; (c) patients with clinical evidence of chronic or acute infection/inflammation disease, haematological disease or a previous history of other malignancies; (d) without adequate clinical information and/or blood tests; and (e) lost to follow-up.

Data Collection

Basic clinical and laboratory information including age, gender, body mass index (kg/m^2), clinical symptoms, histological type (classical chordoma, chondroid chordoma or dedifferentiated chordoma),⁴ tumor size (mm^3), brainstem involvement, tumor blood supply (abundant or others), tumor texture (soft or others), extent of resection (total resection: no evidence of residual tumor on postoperative magnetic resonance imaging; and non total resection),²¹ and preoperative fibrinogen (g/L) and albumin (g/L) levels were gathered from the medical record system.

FA Score

The optimal cutoff values for albumin and fibrinogen were defined as the values that generate the minimum *p* value via a Log rank test between the groups in the overall survival analysis using X-tile 3.61 software (Yale University, New Haven, CT, USA).²² After identifying these values, the two original continuous variables were divided into categorical variables representing high and low levels. Then, we defined the FA score using a combination of fibrinogen and albumin as follows: score 2, patients with increased fibrinogen and decreased albumin; score 1, patients with either increased fibrinogen or decreased albumin; and score 0, patients with neither increased fibrinogen or decreased albumin.¹⁹

Follow-Up

All patients were regularly followed up via outpatient examinations, e-mail and telephone, and the deadline of our follow-up period was October 2019. Tumor recurrence was diagnosed by evidence of new clinical symptoms and/or imaging findings. Progression-free survival (PFS), the

interval between tumor resection to the firstly tumor recurrence, and overall survival (OS), the time from the date of tumor surgery to death, were identified for patient outcome assessment. For those who were progression-free (PFS) or alive (OS) at the final follow-up, the observations were censored.

Statistical Analysis

All analyses were conducted using IBM SPSS, version 19.0 (IBM Corp., Armonk, NY, USA) and GraphPad prism 7.0 (GraphPad, La Jolla, CA, USA). The quantitative data are shown as the mean \pm standard deviation (SD), and the associations between categorical factors were analysed by the chi-square test or Wilcoxon rank sum test. The Kaplan–Meier method and Log rank test were performed for the PFS and OS analysis. Multivariable Cox proportional hazard regression models that included variables with $p < 0.10$ in the univariable analysis were applied to determine the independent variables affecting PFS and OS. The abilities of fibrinogen, albumin and the FA score to predict PFS and OS were compared by receiver operating characteristic (ROC) analysis. All tests were 2-sided, and a p value < 0.05 was considered statistically significant.

Results

Patients Characteristics

In the current study, 183 skull base chordoma patients were included between January 2008 and September 2014 following inclusive criteria. Of these patients, ninety six patients were men, and 87 patients were women, and the mean age at diagnosis was 40.1 (SD, 15.2) years. The most common symptom was headache (85/183), followed by diplopia (66/183) and blurred vision (59/183). The classical chordoma histopathological subtype was found in 125 patients, and the remaining 58 patients were pathologically diagnosed with chondroid chordoma. The median tumor volume, which was calculated as half of the product of the longest diameters of the coronal, sagittal and axial axes, was 21,000.0 mm³. Patients were followed up until October 2019, and the median follow-up duration was 74 months. The clinicopathological data of the study cohort are described in detail in Table 1.

Description of the Fibrinogen and Albumin Levels in Skull Base Chordoma Patients

The level of fibrinogen ranged from 1.73 to 7.40 g/L (median, 2.93 g/L) and the median serum albumin level

was 45.8 g/L (range, 37.6–53.0 g/L) in 183 skull base chordoma patients (Table 1). Then, we used X-tile software to assess the optimal cut off values, which were 3.29 for fibrinogen (Figure S1) and 44.60 g/L for albumin (Figure S2). Of the 183 patients, 130 (71.0%) patients had a fibrinogen level < 3.29 g/L and an albumin level < 44.60 g/L was found in 55 (30.1%) patients. We further combined the two variables using the FA score as described above. Specifically, 93 (50.8%) patients had an FA score of 0, 72 (39.3%) patients had an FA score of 1 and the remaining 18 patients (9.8%) had an FA score of 2.

Association Among Fibrinogen, Albumin, the FA Score and the Clinicopathological Variables

A higher fibrinogen level was correlated with an older age ($p < 0.001$) and a larger tumor volume ($p = 0.011$). Additionally, a higher fibrinogen level was observed in the classical chordoma type ($p = 0.042$) (Table 2). In contrast, the albumin level was negatively correlated with patients' age ($p = 0.022$), and patients with chondroid chordoma had a higher albumin level ($p = 0.026$). Moreover, a lower level of albumin was associated with a soft tumor texture ($p = 0.023$) (Table 2). Strong associations were observed between a higher FA score and an older age ($p < 0.001$) and the classical chordoma pathological type ($p = 0.005$). Tumors with a soft texture tended to have a lower FA score, although the correlation was not statistically significant ($p = 0.122$). No statistically significant associations were identified between the FA score and other clinical variables, including sex, tumor volume, blood supply and brainstem involvement (Table 2).

Analysis of the Association Between Fibrinogen, Albumin or the FA Score and Patients' Survival

At the final follow-up, 128 (69.9%) patients experienced tumor progression and 72 (39.3%) patients died. The follow-up time ranged from 3 to 141 months (median 74 months), and the median PFS and OS were 30 months and 74 months, respectively. The Kaplan–Meier curve indicated that the median PFS (Figure 1A) and OS (Figure 1B) of the patients with high fibrinogen were shorter than those in the low fibrinogen group (PFS: 25 months vs 36 months; OS: 96 months vs 125 months), although the differences were not significant ($p = 0.056$, 0.059, log rank test, respectively). In contrast, the patients

Table 1 Summary of Clinicopathological Features in 183 Skull Base Chordoma Patients

Characteristic	Number of Patients, (%)
Median age (year, mean \pm SD)	41.0 (40.1 \pm 15.2)
Sex	
Male	96 (52.5)
Female	87 (47.5)
Median tumor volume (mm ³ , mean \pm SD)	21,000.0 (31,700.9 \pm 33,318.2)
Symptom	
Headache	85 (46.4)
Diplopia	66 (36.1)
Blurred vision	59 (32.2)
Vision field defect	42 (23.0)
Dizziness	30 (16.4)
Tumor texture	
Soft	55 (30.1)
Others (hard or moderate)	128 (69.9)
Tumor blood supply	
Rich	107 (58.5)
Others (poor or moderate)	76 (41.5)
Pathology type	
Classical	125 (68.3)
Chondroid	58 (31.7)
Dedifferentiated	0 (0)
Brainstem involvement	
No	68 (37.2)
Yes	115 (62.8)
Median body mass index (kg/m ² , mean \pm SD)	23.0 (23.3 \pm 3.2)
Median fibrinogen (g/L, mean \pm SD)	2.93 (3.00 \pm 0.73)
Median albumin (g/L, mean \pm SD)	45.8 (46.0 \pm 3.1)
Recurrence during follow-up	128 (69.9)
Death during follow-up	72 (39.3)

Abbreviation: SD, standard deviation.

with a high level of albumin had longer PFS than the patients with an albumin level <44.60 g/L (median PFS time: 36 months vs 21 months, $p=0.024$, Log rank test) (Figure 1C). Furthermore, the median OS in the patients with high albumin was 125 months, which was significantly longer than that in the low-albumin patients (median OS, 72 months, $p<0.001$) (Figure 1D). A higher FA score was associated with worse PFS ($p=0.014$, Figure 1E) and OS ($p<0.001$, Figure 1F) according to the Kaplan–Meier analysis. In particular, significant differences in PFS were observed between the patients with an FA score of 0 and those with an FA score of 1 (median PFS time: 42

months vs 24 months, $p=0.012$, Log rank test) or FA score of 2 (median PFS time: 42 months vs 21 months, $p=0.026$, Log rank test). Regarding OS, the Log rank tests showed significant differences in OS between the FA score 2 group and FA score 1 group (median time: 47 months vs 100 months, $p=0.011$) and FA score 0 group (median time: 47 months vs 125 months, $p<0.001$).

We further performed a subgroup analysis of the FA score with different pathology types and tumor volume chordoma. No significant difference in PFS was observed among the different FA score groups in the classical chordoma patients ($p=0.205$) (Figure 2A). However, a high FA score was associated with a shorter PFS in the chondroid chordoma patients ($p=0.041$) (Figure 2B). Moreover, the classical chordoma patients in the high FA score group had a shorter OS ($p=0.001$) (Figure 2C), but this difference was not significant among the chondroid chordoma patients ($p=0.527$) (Figure 2D). A high FA score was still correlated with poor OS among the patients with either tumor volume either $\leq 20,000$ mm³ ($p=0.005$) or $>20,000$ mm³ ($p=0.007$), although the differences in PFS were not significant ($p=0.185$, 0.242, respectively) (Figure 2E–H).

We also performed a Cox survival analysis, and the results indicated that age ($p=0.018$), tumor volume ($p=0.004$), tumor texture ($p=0.013$), blood supply ($p=0.045$), pathology type ($p=0.031$), degree of resection ($p<0.001$), albumin level ($p=0.027$) and FA score ($p=0.017$), but not the fibrinogen level ($p=0.061$), were associated with PFS in the univariable analysis. The multivariable analysis showed that the FA score ($p=0.026$) was an independent predictor of PFS in skull base chordoma (Table 3). Additionally, we analysed the role of fibrinogen, albumin and the FA score in OS. A low albumin level ($p=0.001$) and a high FA score ($p<0.001$) were correlated with a shorter OS, and the FA score ($p<0.001$) was identified as an independent prognostic indicator of OS (Table 4).

Value of Fibrinogen, Albumin and the FA Score in Predicting Patient Outcomes

Next, we compared the ability of fibrinogen, albumin and the FA score to predict patients' survival using ROC curve analysis. The ROC analysis showed that the FA score had more predictive power than fibrinogen or albumin in predicting 3-year (AUC, area under the curve: 0.609, 0.585 and 0.550, respectively) and 5-year (AUC: 0.643, 0.586 and 0.594, respectively) PFS (Figure 3A). Similar results were

Table 2 Association Between Fibrinogen, Albumin, FA Score and Clinicopathological Features in Skull Base Chordoma

Variables	N	Fibrinogen (g/L)			Albumin (g/L)			FA Score			
		<3.29	≥3.29	P value	<44.60	≥44.60	P value	0	1	2	P value
Sex				0.696			0.117				0.632
Male	96	67	29		24	72		52	35	9	
Female	87	63	24		31	56		41	37	9	
Age				<0.001*			0.022*				<0.001*
≤55	151	117	34		40	111		88	52	11	
>55	32	13	19		15	17		5	20	7	
Tumor volume				0.011*			0.935				0.222
≤20,000mm ³	89	71	18		27	62		51	31	7	
>20,000mm ³	94	59	35		28	66		42	41	11	
Texture				0.703			0.023*				0.122
Soft	55	38	17		23	32		24	22	9	
Others (hard or moderate)	128	92	36		32	96		69	50	9	
Blood supply				0.319			0.547				0.438
Abundant	107	73	34		34	73		52	42	13	
Others (poor or moderate)	76	57	19		21	55		41	30	5	
Pathology				0.042*			0.026*				0.005*
Classical	125	83	42		44	81		57	50	18	
Chondroid	58	47	11		11	47		36	22	0	
Brainstem involvement				0.437			0.851				0.178
No	68	46	22		21	47		35	23	10	
Yes	115	84	31		34	81		58	49	8	
Total	183	130	53		55	128		93	72	18	

Note: *Indicate $p < 0.05$.

also found in the OS analysis as follows: the AUC of the FA score in the 3-year and 5-year OS analysis were 0.594 and 0.639, which were larger than those of fibrinogen (0.559 and 0.574) and albumin (0.572 and 0.616) (Figure 3B).

Discussion

In the present study, for the first time, we characterized the level of fibrinogen and albumin, and investigated their associations with clinicopathological data in primary skull base chordoma patients. We found that the fibrinogen level and albumin level were correlated with age and the pathological types, which are potential risk factors for a poor outcome in chordoma patients.^{4,23} Low levels of albumin were associated with a poor PFS and OS. Moreover, the combined analysis of fibrinogen and albumin revealed that the FA score was an independent prognostic factor for PFS and OS. Additionally, the FA score showed better predictive ability than fibrinogen or albumin alone; the patients with an FA score of 2 (high fibrinogen and low albumin)

had the worst prognosis. Our findings reveal that the FA score may be a potential marker for screening high-risk groups and that patients with an FA score of 2 should be more closely monitored. The FA score can be easily acquired from a routine blood test and may help clinicians evaluate personal prognosis. Agents targeting fibrinogen-mediated inflammation and albumin supplements may provide a valuable complementary therapy for the treatment of chordoma patients.

Increasingly, studies show that systemic inflammation and malnutrition play essential roles in tumor progression, therapy resistance and survival of patients with malignancies.^{6,24,25} The identification of preoperative laboratory biomarkers predicting patient outcomes before treatment is of great importance, possibly enabling the guidance of risk stratification and more appropriate allocation of therapeutic schedules. However, to date, knowledge of inflammatory and nutritional prognostic biomarkers in chordoma is limited. Fibrinogen has been considered an important regulator and biomarker of

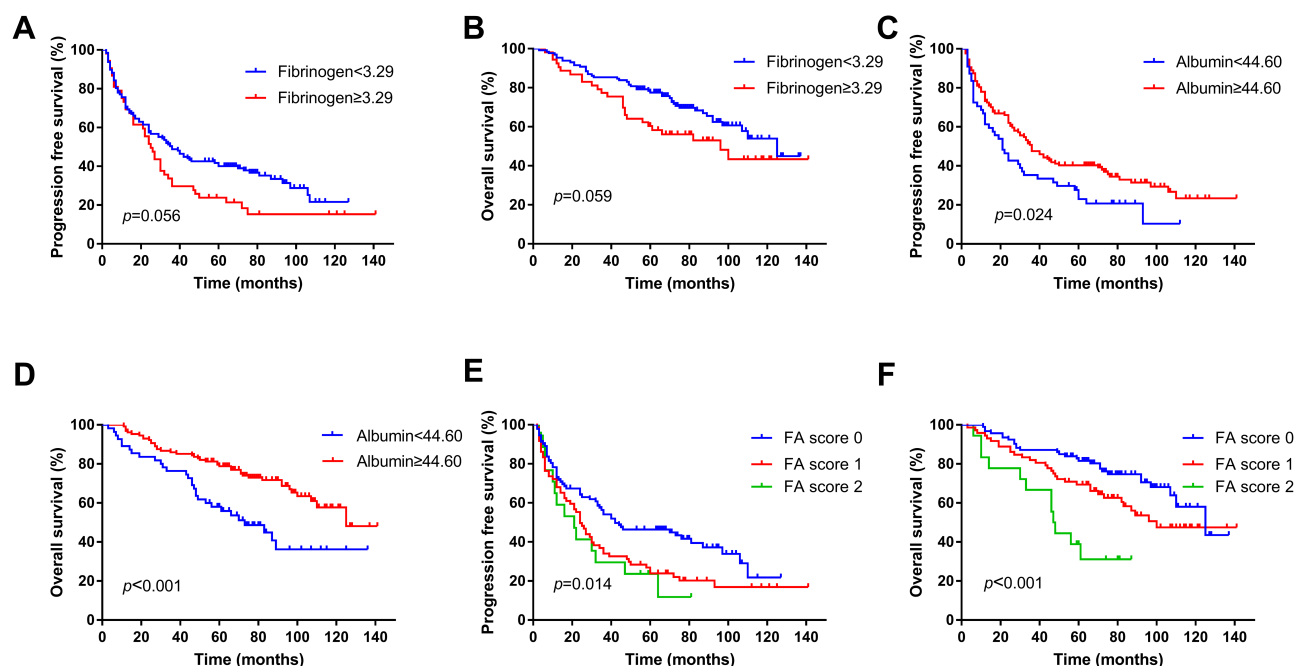


Figure 1 Kaplan-Meier analysis of fibrinogen, albumin and FA score in skull base chordoma. **(A)** Fibrinogen and PFS. **(B)** Fibrinogen and OS. **(C)** Albumin and PFS. **(D)** Albumin and OS. **(E)** FA score and PFS. **(F)** FA score and OS.

Abbreviations: PFS, progression-free survival; OS, overall survival.

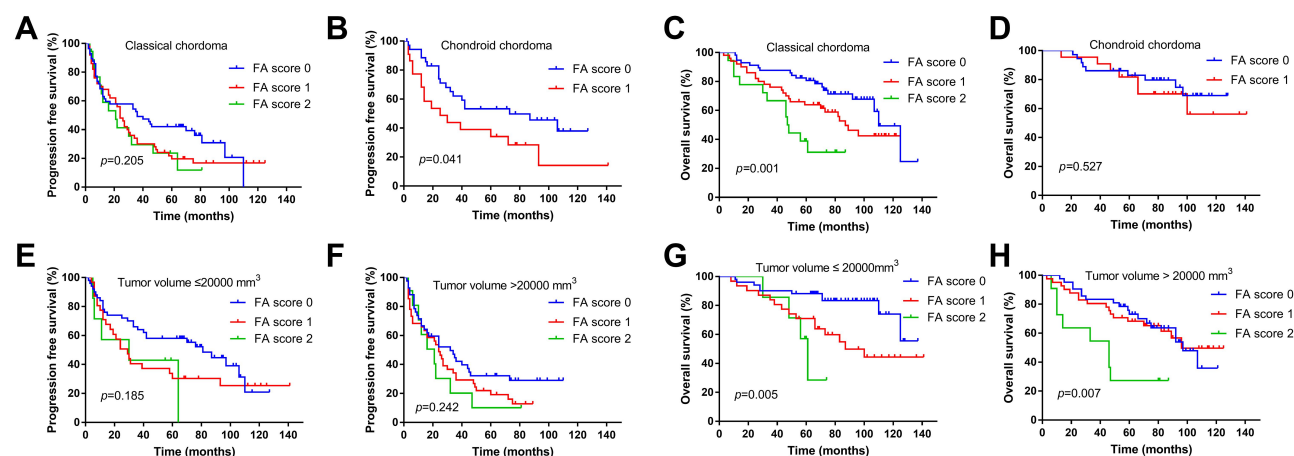


Figure 2 Kaplan-Meier analysis of FA score in different subgroups of skull base chordoma patients. **(A)** PFS analysis of FA score in classical chordoma patients. **(B)** PFS analysis of FA score in chondroid chordoma patients. **(C)** OS analysis of FA score in classical chordoma patients. **(D)** OS analysis of FA score in chondroid chordoma patients. **(E)** PFS analysis of FA score in tumor volume ≤ 20,000 mm³ patients. **(F)** PFS analysis of FA score in tumor volume > 20,000 mm³ patients. **(G)** OS analysis of FA score in tumor volume ≤ 20,000 mm³ patients. **(H)** OS analysis of FA score in tumor volume > 20,000 mm³ patients.

Abbreviations: PFS, progression-free survival; OS, overall survival.

inflammation, and its association with tumor progression and patient prognosis has been identified in several cancers.^{26–29} However, to date, the value of fibrinogen in skull base chordoma patients has been unclear. Our results indicate that patients with high fibrinogen tend to have poor PFS and OS. The detailed mechanisms responsible for the prognostic role of fibrinogen remain poorly understood, and several studies may help explain our findings. Fibrinogen was thought to be

an essential determinant of the metastasis ability of circulating tumor cells via the adhesion effect and survival of tumor cells rather than tumor stroma formation in a mouse model.³⁰ Moreover, previous studies have indicated that fibrinogen could contribute to tumor angiogenesis by interacting with vascular endothelial cells and vascular endothelial growth factor,³¹ and fibrinogen could increase the migration and invasion potential of cancer cells via regulation of the

Table 3 Univariable and Multivariable Cox Analysis of Factors Affecting PFS in Skull Base Chordoma

Variables	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (>55/≤55years)	1.673	1.090–2.566	0.018*	NA	NA	0.099
Sex (female/male)	1.101	0.778–1.558	0.587			
Tumor volume (>20000/≤20000mm ³)	1.678	1.178–2.392	0.004*	NA	NA	0.228
Texture (hard or moderate/soft)	1.674	1.115–2.512	0.013*	2.198	1.392–3.469	0.001*
Blood supply (poor or moderate/abundant)	0.690	0.480–0.992	0.045*	NA	NA	0.190
Pathology (chondroid/classical)	0.651	0.440–0.962	0.031*	0.622	0.401–0.964	0.034*
Brainstem involvement (yes/no)	1.241	0.864–1.782	0.242			
Degree of resection (total/non-total resection)	0.370	0.221–0.620	<0.001*	0.468	0.271–0.807	0.006*
Postoperative radiotherapy (yes/no)	1.423	0.985–2.057	0.060	NA	NA	0.157
Fibrinogen (high/low)	1.427	0.984–2.068	0.061	NA	NA	0.518
Albumin (low/high)	1.516	1.048–2.193	0.027*	NA	NA	0.518
FA score			0.017*			0.026*
0	1	reference		1	reference	
1	1.593	1.101–2.303	0.013*	1.656	1.105–2.482	0.014*
2	1.898	1.053–3.421	0.033*	1.849	0.997–3.427	0.051

Note: *Indicate $p < 0.05$.

Abbreviations: PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; NA, not acquired.

Table 4 Univariable and Multivariable Cox Analysis of Factors Affecting OS in Skull Base Chordoma

Variables	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (>55/≤55years)	1.935	1.120–3.343	0.018*	NA	NA	0.524
Sex (female/male)	0.981	0.617–1.561	0.937			
Tumor volume (>20000/≤20000mm ³)	1.702	1.059–2.737	0.028*	NA	NA	0.540
Texture (hard or moderate/soft)	1.549	0.899–2.670	0.115			
Blood supply (poor or moderate/abundant)	0.527	0.317–0.876	0.014*	NA	NA	0.386
Pathology (chondroid/classical)	0.523	0.300–0.912	0.022*	NA	NA	0.237
Brainstem involvement (yes/no)	1.038	0.645–1.669	0.878			
Degree of resection (total/non-total resection)	0.321	0.147–0.701	0.004*	0.419	0.188–0.930	0.033*
Postoperative radiotherapy (yes/no)	0.769	0.464–1.276	0.309			
Recurrence (yes/no)	9.192	3.352–25.205	<0.001*	7.648	2.773–21.091	<0.001*
Fibrinogen (high/low)	1.583	0.978–2.562	0.062	NA	NA	0.213
Albumin (low/high)	2.218	1.383–3.558	0.001*	NA	NA	0.213
FA score			<0.001*			0.001*
0	1	reference		1	reference	
1	1.633	0.983–2.715	0.058	1.301	0.780–2.170	0.314
2	4.041	2.024–8.068	<0.001*	3.959	1.960–7.995	<0.001*

Note: *Indicate $p < 0.05$.

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; NA, not acquired.

epithelial-mesenchymal transition.³² Additionally, fibrinogen participates in the chronic inflammatory response by regulating the synthesis of interleukin-6 (IL-6) and altering the infiltration of leukocytes and lymphocytes.^{29,33} Another potential mechanism is that fibrinogen seems to block the contact between natural killer cells and tumor cells, thereby

contributing to immune escape and weakening the eradication of tumor cells.³⁴

Serum albumin, which is synthesized by the liver and is involved in inflammation, has been widely considered a useful tool for nutritional status assessment and serves as a valuable prognostic biomarker of disease progression and

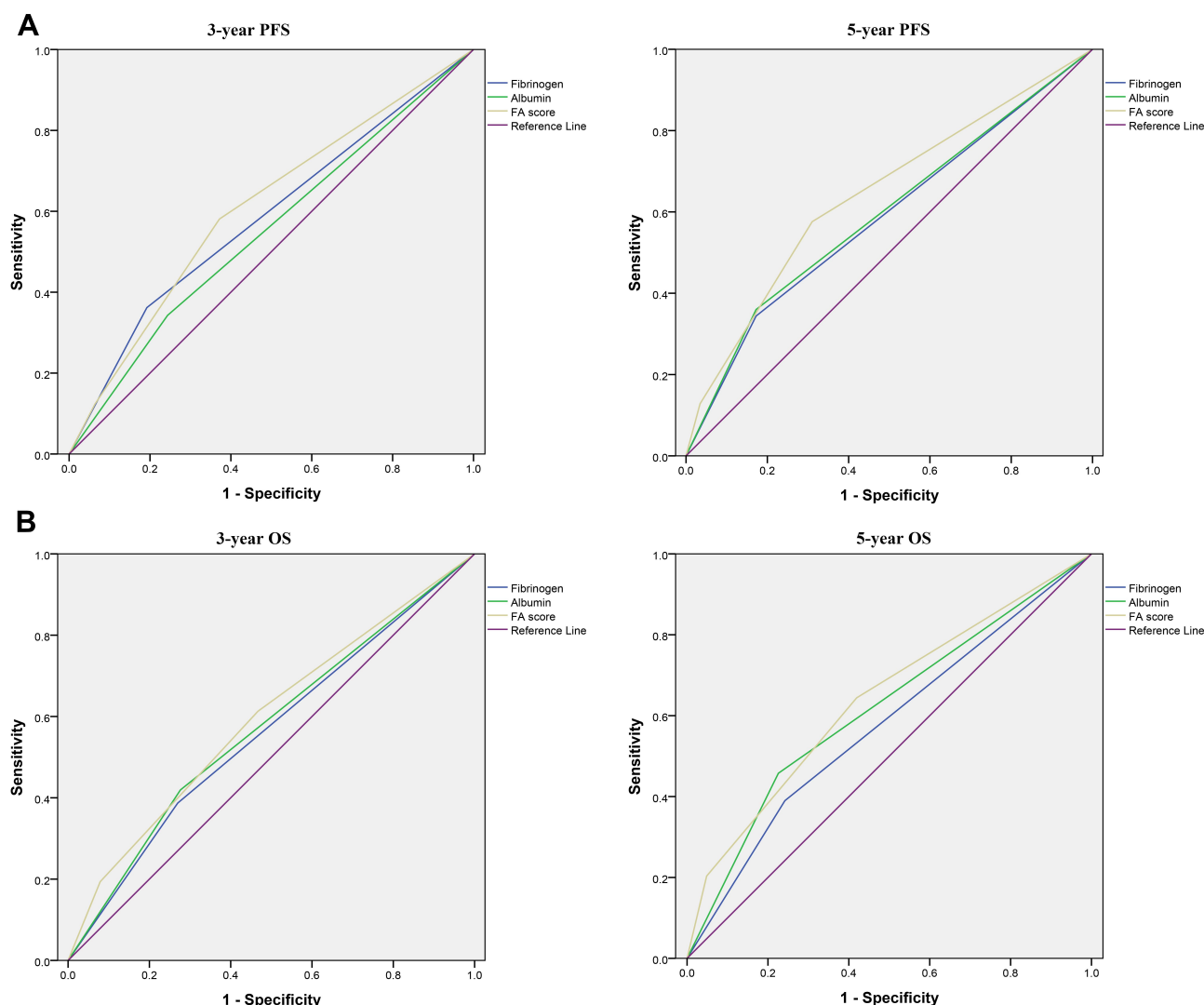


Figure 3 Comparison of the predictive performance of fibrinogen, albumin and FA score for 3-year and 5-year PFS, and 3-year and 5-year OS using ROC analysis. (A) 3-year PFS (left) and 5-year PFS (right). (B) 3-year OS (left) and 5-year OS (right).

Abbreviations: ROC, receiver operating characteristic; PFS, progression-free survival; OS, overall survival.

prognosis in various cancers.¹⁶ Moreover, malnutrition, which could be mirrored by a decreased albumin level, is associated with an increased likelihood of complications, such as infection, a poor human immune defence system, unfavorable response to therapy and a poor quality of life.¹⁵ Similarly, our results reveal that low levels of albumin are associated with a shorter PFS and OS in skull base chordoma patients. However, the reasons why albumin is a prognostic indicator in cancers and the mechanisms causing albumin to decrease remain poorly understood. Previous studies indicate that a low albumin level may be due to the release of several cytokines (such as IL-6 and tumor necrosis factor) by tumor cells during the process of the systemic inflammatory response. Additionally, IL-6 and tumor necrosis factor can be produced by hepatic macrophages in the presence of

micrometastases in the liver.³⁵ These cytokines contribute to the decrease in the serum albumin level by suppressing the hepatocyte synthesis of albumin and increasing the permeability of blood vessels.¹⁶ Considering the crucial relationships among inflammation, immunity and oncogenesis,⁷ exploring the role of albumin in inflammation and immunity may help reveal the deep mechanisms underlying the prognostic value of albumin in cancers. In addition, nutritional therapy aiming to improve cancer patient survival, such as albumin supplementation, merits further research.

The FA score, which is based on preoperative fibrinogen and albumin, was developed as a scoring system to reflect inflammation and the nutrition status by Matsuda and has been recognized as a novel clinical prognostic biomarker in several cancers, showing superior predictive

power in esophageal cancer patients.^{19,20} Consistent with these findings, our results indicate that the FA score is an independent prognostic biomarker of PFS and OS in skull base chordoma patients. The FA score may be a valuable clinical score for the assessment of survival due to its relatively low cost and easy accessibility in daily practice.

Our study also has several limitations. The current study was a retrospective and single-centre research study with a small scale; therefore, selection bias may have played a role. Further prospective, multi-centre studies with large samples are required to confirm the cut-off points and the prognostic values of fibrinogen and albumin found in the current study. Additionally, the prognostic role of postoperative fibrinogen and albumin and the change between the preoperative and postoperative FA score were not analysed in our study. Moreover, further basic and clinical studies identifying how fibrinogen and albumin affect the prognosis of skull base chordoma patients are warranted.

Conclusions

Our data demonstrate that the preoperative level of albumin is associated with clinicopathological features and may predict outcomes in skull base chordoma patients. In particular, the FA score is an independent predictor of PFS and OS and has better predictive ability than fibrinogen or albumin alone. These results suggest that inflammation and nutrition may play crucial roles in the progression of skull base chordoma.

Abbreviations

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ROC, receiver operating characteristic; AUC, area under the curve.

Data Sharing Statement

The datasets analysed during the current study are available from Prof. Zhang on reasonable request.

Ethics Approval and Informed Consent

The current study protocol was approved by the ethics committee of Beijing Tiantan Hospital and carried out according to the 1964 Declaration of Helsinki. In addition, informed consent was obtained from all participants, and we further analysed the data anonymously.

Acknowledgments

We are grateful for the supporting of all patients.

Funding

This study was supported by the National Natural Science Foundation of China (81771489); Supported by Beijing Municipal Science & Technology Commission (Z171100 000117002).

Disclosure

The authors report no conflicts of interest for this work.

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