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Expression of fibroblast growth factor receptor substrate 2 (FRS2) in primary retroperitoneal liposarcoma and its clinical implications

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Abstract. – OBJECTIVE: The aim of this study was to investigate the expression level of fibroblast growth factor receptor substrate 2 (FRS2) in tissues of patients with primary retroperitoneal liposarcoma (PRPLS) and its correlation with recurrence and prognosis.

PATIENTS AND METHODS: The pathological specimens, medical records, and follow-up information of patients with PRPLS who underwent radical surgery for the first time in our hospital from January 2013 to December 2016 were retrospectively analyzed. FRS2 protein expression in tissues was determined by immunohistochemistry staining, and the FRS2 protein positive rates in patients with different clinicopathological features were compared. Factors influencing patients' recurrence and survival were determined using the multivariate Cox stepwise regression model.

RESULTS: This research enrolled 87 patients with PRPLS, with the number of cases presenting FRS2 protein positive rate and positive rate in pathological tissues accounting for 62.07% (54/87) and 37.93% (33/87), respectively. The positive expression of FRS2 protein varied markedly among patients with different pathological types, FNCC, LCC grade, number of tumors, positive margin, and recurrence and metastasis (with *vs.* without) (all $p<0.05$). The 87 patients were followed up for 3.5-102 months (median, 27.5 months), with a postoperative 5-year overall disease-free survival (DFS) rate of 17.24% [median progression-free survival (PFS): 24.7 months] and a 5-year overall survival (OS) rate of 44.83% (median OS: 47.3 months). Kaplan-Meier survival curves revealed significantly shorter PFS and OS in patients with positive FRS2 protein expression vs. those with negative FRS2 protein expression ($\chi^2=6.396$, 5.032, $p<0.05$). According to the univariate analysis, the 5-year overall DFS rate varied significantly among patients with different pathological types, Fédération Nationale des Centres De Lutte Contre le Cancer (FNCLCC) grades, number of tumors, positive margin, and FRS2 protein expression (all $p<0.05$). Pathological type, FNCLCC grading, tumor number, recurrence and metastasis, positive margin, and FRS2 protein expression were significantly correlated with the 5-year OS rate of patients (all $p<0.05$). Furthermore, pathological type, FNCLCC grading, multiple tumors, positive margin, and FRS2 protein expression were identified by multivariate Cox regression analysis to be independent factors that affected patients' 5-year DFS and OS rates (all $p<0.05$), and that relapsed and metastasized patients had a 4.586-fold risk of death than those without recurrence and metastasis.

CONCLUSIONS: FRS2 shows a high positive rate in the tissues of PRPLS patients and is significantly related to the prognostic recurrence and survival of patients, with potential value in judging the prognosis of patients.

Key Words:

Fibroblast growth factor receptor substrate 2, Primary retroperitoneal liposarcoma, Recurrence, prognosis, Cancer progression, Metastasis.

Introduction

Liposarcomas are one of the most common malignant soft tissue sarcomas in adults, accounting for 16%-18% of soft tissue sarcomas[1]. According to relevant reports[2,3], liposarcomas tend to occur in the limbs, retroperitoneal space, groin, and other parts of the human body that are rich in adipose tissue. Of them, retroperitoneal liposarcoma is deep-seated with a hidden onset and no typical clinical presentations, resulting in the fact that it has always oppressed and invaded the surrounding organs when diagnosed. Therefore, the recurrence rate remains high even after complete resection[4], which seriously affects the survival and prognosis of patients. Fibroblast growth factor receptor substrate 2 (FRS2) is a key adaptor protein in the fibroblast growth factor receptor (FGFR) signaling pathway, with its gene located in the chromosomal region 12q13-15[5]. Previous studies[6,7] have shown that atypical lipoma/well-dif-

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ferentiated and dedifferentiated liposarcomas are mainly characterized by abnormal and significant amplification of the chromosomal segment 12q13-15. FRS2, which is co-located in this chromosomal region, and other oncogenes, such as murine double minute 2 (MDM2) and cyclin-dependent kinase 4 (CDK4), have been shown to be significantly over-expressed in liposarcomas and are strongly associated with the malignancy degree of liposarcomas. Therefore, this study analyzed FRS2 expression in primary retroperitoneal liposarcoma (PRPLS) and discussed its influence on patients' prognostic recurrence and survival, to improve the reference value for clinical PRPLS treatment and prognosis evaluation.

Patients and Methods

General Information

The clinical data of patients with PRPLS who underwent radical surgery for the first time in the Peking University International Hospital from January 2013 to December 2016 were retrospectively analyzed, as well as their follow-up data. Criteria for patient enrollment: 1) PRPLS confirmed by postoperative pathology and immunohistochemistry (IHC); 2) treatment-naive patients without any prior adjuvant radiotherapy nor chemotherapy and who received radical resection in our hospital as the first treatment; 3) complete clinical data. Criteria for patient exclusion: 1) no surgery or palliative surgery; 2) perioperative death; 3) other malignant tumors or serious concomitant diseases; 4) death due to other diseases or reasons during postoperative follow-up. The Hospital Ethics Committee gave its approval for conducting this research after careful review. Clinical data, including sex, age, treatment modality, combined organ resection, tumor size and number, histopathological type, histological grading, etc., were collected. According to the World Health Organization (WHO)[8] classification of soft tissue and bone neoplasms, the pathological types were classified as atypical lipoma/well-differentiated, dedifferentiated, myxoid/round cell, and pleomorphic liposarcomas. The PRPLS was graded based on the Fédération Nationale des Centres De Lutte Contre le Cancer (FNCLCC) grading[9].

IHC

IHC staining was performed on paraffin-embedded pathological specimens obtained from the first radical operation. After paraffin sectioning, the pathological tissues were dewaxed and dehydrated using xylene and gradient alcohol, respectively. Following the blocking of the endogenous peroxidase activity of the slices using the peroxidase method, tissues were processed by the EnVision detection system (Dako, Carpinteria, CA, USA). The treated slices were then incubated with an FRS2 monoclonal antibody (Dako, Carpinteria, CA, USA) at an ambient temperature for 1 h, followed by color development with diaminobidine and counterstaining with hematoxylin. Positive slices and phosphate buffered saline (PBS) were used as negative controls of the primary antibody as directed. Two pathologists and two surgical pathologists with extensive experience in soft tissue tumor pathology independently reviewed the immune sections of tumor tissues. Five high-power visual fields were stochastically selected, and 100 tumor cells were examined microscopically to avoid bleeding and necrotic areas as much as possible. The IHC staining intensity was scored as either 0 (colorless), 1 (light yellow), 2 (pale brown), or 3 (tan). The number of positive stained cells <5%, 5-25%, >25-50%, >50% was scored as 0, 1, 2, and 3 points, respectively. The final score was based on the staining intensity × the number of positive cells, and the score of 0-3 was considered negative (-), while ≥4 was considered positive (+)[10].

Postoperative Reexamination and Follow-Up

As for the postoperative review of patients, two doctors experienced in imaging diagnostics at our hospital made the diagnosis of recurrence based on the results of the abdominal CT examination. Postoperative reexamination was conducted every 3 months or half a year postoperatively. Recurrence was indicated by the appearance of new tumor lesions or lymphatic metastasis during re-examination, as compared to abdominal CT findings before discharge. Follow-up was carried out *via* telephone, outpatient review, and follow-up, mainly recording the recurrence and survival of patients. The starting point of each patient's follow-up was the day of the first operation, and the endpoint was the first recurrence or death. The follow-up deadline for all patients was December 2016.

Statistical Analysis

The database was established with EpiData for data processing by SPSS v. 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables that con-

formed to a normal distribution were represented by and analyzed using the independent samples *t*-test; non-normally distributed ones were represented by median (minimum-maximum), and a nonparametric test was performed. Sex, pathological type, FRS2+, and other enumeration data were expressed by the number of cases and percentages (%), and the χ^2 test and Fisher exact probability method were used. Patient survival was visualized using the Kaplan-Meier method, and differences between groups were identified by the Log-rank test. Independent prognostic indicators were identified using the Cox regression model. Differences with $p<0.05$ were statistically significant.

Results

Correlation of FRS2 Protein Expression with Clinicopathological Features

Of the 87 patients with PRPLS, 48 were male (56.32%), and 38 were female (43.68%), with a median age of 53.4 (31-78) years. Among the 87 patients who underwent radical surgical treatment, postoperative pathological results showed that 16 of them had positive surgical margins. Classified by pathological types, well-differentiated, dedifferentiated, myxoid/round cell, polymorphic, and mixed-type liposarcomas were found in 21 cases (24.14%), 36 cases (41.38%), 15 cases (17.24%), 13 cases (14.94%), and 2 cases (2.3%), respectively. Following FNCLCC grading, grade I was found in 44 cases (50.57%), grade II in 25 cases (28.74%), and grade III in 18 cases (20.69%). The median tumor size was 16.4 (3.7-33.0) cm. There were 50 cases (57.47%) of single tumor and 37 cases (42.53%) of multiple tumors. Among the treatment methods, radical operation was performed in 50 cases (57.47%), operation plus hyperthermic antiblastic perfusion in 50 cases (57.47%), and operation plus chemotherapy in 50 cases (57.47%), with intraoperative peripheral organ resection performed in 41 cases (47.13%). The results of immunostaining showed FRS2+ in 54 cases (62.07%) and FRS2- in 33 cases (37.93%) of PRPLS. There was no significant difference in FRS2+ among patients with differences in age, sex, tumor size, and treatment modalities (all $p>0.05$). However, FRS2+ was significantly different, depending on pathological type, FNCLCC grading, number of tumors, positive margin, and recurrence and metastasis (all $p<0.05$). See Table I for details.

Correlation of FRS2 Protein Expression with Prognostic Survival

The 87 patients were followed up for 3.5-102 months, with a median of 27.5 months. Within 5 years after surgery, 68 cases experienced disease recurrence and 4 developed metastases (3 cases of lung metastasis and 1 case of liver metastasis), with a median progression-free survival (PFS) of 24.7 months and a 5-year overall disease-free survival (DFS) rate of 17.24%. In addition, 48 cases died of tumor recurrence or metastasis within 5 years, with a median OS of 47.3 months and a 5-year OS of 44.83%. The median PFS of 16 patients with positive margins was 6.3 months, and the median OS was 8.1 months. The Log-rank χ^2 test was used to compare the survival curves of patients in the FRS2+ and FRS2- groups. The results showed that FRS2 protein was closely related to the 5-year recurrence and metastasis rate ($\chi^2=6.396$, $p<0.05$) and OS rate ($\chi^2=5.032$, $p<0.05$) of PRPLS patients. See Figure 1 for details.

Prognostic Survival Analysis of Patients with Different Clinicopathological Features

Patients with different pathological types, FNCLCC grading, number of tumors, positive margin, and FRS2 protein expression showed significantly different 5-year disease-free OS rates (all $p<0.05$). However, the pathological features of patients, such as sex, age, tumor size, and treatment modalities, had nothing to do with the overall 5-year DFS rate (all $p>0.05$), while pathological type, FNCLCC grading, number of tumors, recurrence and metastasis, positive margin, and FRS2 protein expression were identified to be related factors influencing the overall 5-year survival rate of patients with PRPLS (all $p<0.05$). See Table II for details.

Analysis of Influencing Factors of Prognostic Survival

The above-mentioned related factors with statistical significance ($p<0.05$) in the univariate analysis were incorporated into the multivariate Cox stepwise regression model. The results showed that pathological type (HR=3.593, 95% CI=2.108-6.123), FNCLCC grading (HR=2.489, 95% CI=1.646-3.764), multiple tumors (HR=1.766, 95% CI=1.063-2.935), positive margin (HR=2.793, 95% CI=1.560-4.998), and FRS2 protein expression (HR=2.085, 95% CI=1.263-3.444) were independent influencing factors for the 5-year DFS rate of PRPLS patients (all $p<0.05$). See Table III for details.

Table I. Correlation of positive expression of FRS2 protein with clinicopathological features in patients with primary retroperitoneal liposarcoma (n=87).

Pathological factors		n (%)	FRS2 positive [n (%)]	χ^2 value	*p*-value
Sex				0.499	0.48
	Male	49 (56.32)	32 (65.31)		
	Female	38 (43.68)	22 (57.89)		
Age (years old)				1.052	0.305
	<60	52 (59.77)	30 (57.69)		
	≥60	35 (40.23)	24 (68.57)		
Pathological type				12.244	0.016
	Well-differentiated liposarcoma	21 (24.14)	8 (38.10)		
	Dedifferentiated liposarcoma	36 (41.38)	26 (72.22)		
	Myxoid/round cell liposarcoma	15 (17.24)	7 (46.67)		
	Pleomorphic liposarcoma	13 (14.94)	11 (84.62)		
	Mixed-type liposarcoma	2 (2.30)	2 (100.00)		
FNCLCC grading				9.717	0.008
	I	44 (50.57)	21 (47.73)		
	II	25 (28.74)	17 (68.00)		
	III	18 (20.69)	16 (88.89)		
Tumor size (cm)				0.960	0.327
	≤20	55 (63.22)	32 (58.18)		
	>20	32 (36.78)	22 (68.75)		
Number of tumors				9.884	0.002
	Single	50 (57.47)	24 (48.00)		
	Multiple	37 (42.53)	30 (81.08)		
Treatment method				1.707	0.426
	Surgery	45 (51.72)	25 (55.56)		
	Surgery+hyperthermic antiblastic perfusion	33 (37.93)	23 (69.70)		
	Surgery+chemotherapy	9 (10.34)	6 (66.67)		
Combined organ resection				0.472	0.492
	Yes	41 (47.13)	27 (65.85)		
	No	46 (52.87)	27 (58.70)		
Recurrence and metastasis				6.357	0.012
	Yes	72 (82.76)	49 (68.06)		
	No	15 (17.24)	5 (33.33)		
Positive margin				8.358	0.004
	Yes	16 (18.39)	15 (93.75)		
	No	71 (81.61)	39 (54.93)		

Multivariate analysis of patients with PRPLS was performed using the Cox proportional hazards model with 5-year OS as the boundary. It showed that pathological type (HR=2.641, 95% CI=2.249-3.101), FNCLCC grading (HR=1.752, 95% CI=1.337-2.230), multiple tumors (HR=1.346, 95% CI=1.155-1.568), recurrence and metastasis (HR=4.586, 95% CI=1.917-10.970), positive margin (HR=3.370, 95% CI=1.786-6.360), and FRS2 protein expression (HR=1.881, 95% CI=1.225-2.890) were factors independently influencing the prognostic survival of patients with PRPLS (all $p<0.05$). See Table IV for details.

Discussion

In recent years, the incidence of liposarcomas has increased year by year, with the predilection sites being extremities and deep tissues such as retroperitoneal space[11]. PRPLS is a malignant adipocyte tumor with various degrees of differentiation and pathological aberrations. Despite the clearly improved complete resection rate, the postoperative recurrence rate of PRPLS is still high (41-71%), with local recurrence as the predominant[12,13]. In addition, the difficulty of reoper-

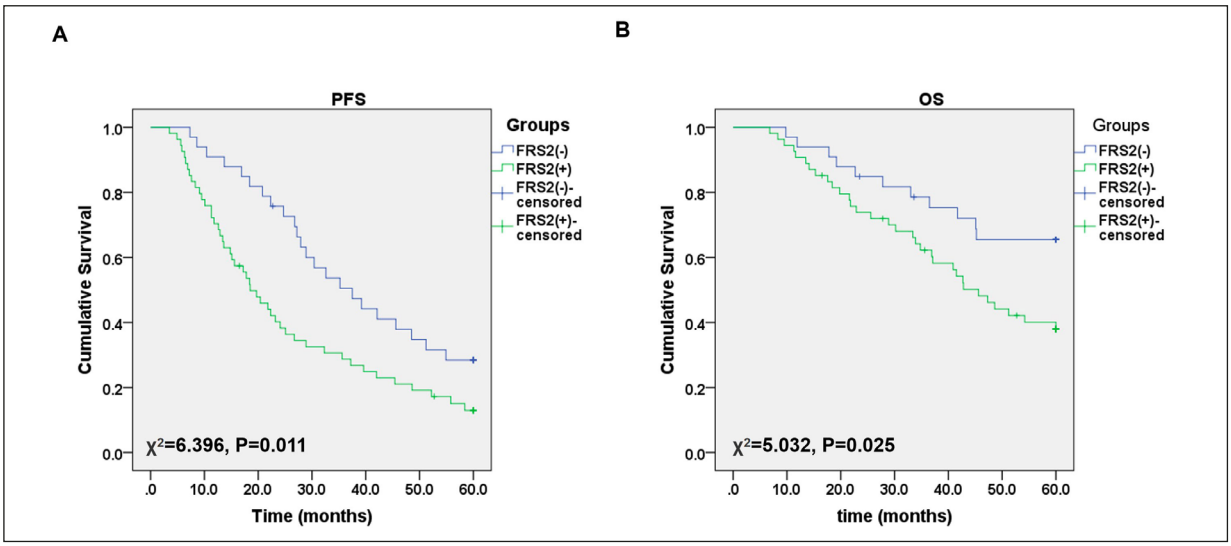

Figure 1. Kaplan-Meier survival curves of PFS (**A**) and OS (**B**) in primary retroperitoneal liposarcoma patients with positive and negative FRS2 protein expression.

ation and the risk of postoperative complications are further increased due to the increased degree of tumor malignancy caused by abdominal adhesion and tissue subtype transformation during the recurrence process of liposarcomas. This study found a 5-year DFS rate as low as 17.24% in patients with PRPLS, and a postoperative recurrence and metastasis rate as high as 82.76%, with a 5-year OS rate of barely 44.83%. The prognosis varies in liposarcoma patients with different pathological types, and lower tumor differentiation is associated with a worse prognosis[14]. Moreover, poorly differentiated liposarcomas are more invasive, which means that the possibility of combined resection of peripheral organs is increased, and the expected recurrence time after the operation is shorter. Earlier, complete resection or palliative surgery was shown[15] to effectively prolong the OS of patients with recurrent liposarcomas. However, for patients with liposarcoma with a high malignant degree, surgery can only improve their clinical symptoms but not their survival time.

As a docking/scaffold adaptor protein in the FGFR signaling pathway, FRS2 plays an important "signal connection center" role in FGF ligand and receptor signaling[16]. In addition, FRS2 can act as a connexin of other receptor tyrosine kinases (RTKs) to activate multiple RTK carcinogenic signal transduction pathways; moreover, it is abnormally activated or amplified in osteosarcoma, glioma, high-grade ovarian cancer, and other cancers[17-19]. *FRS2* gene is located in the chromosome 12q13-15 region, while abnormal amplification and overexpression of the 12q13-15 region are common in liposarcomas. Aberrant amplification or strong protein expression of oncogenes such as MDM2 and CDK4 located in this region play an important auxiliary role in the diagnosis of liposarcomas[20]. Wang et al[21] showed that compared with normal adipose tissue and lipoma, well-differentiated and dedifferentiated liposarcomas and other malignant tumors showed significantly abnormal amplification. Combined with the important role of FRS2 in the FGFR signaling pathway, it is inferred that FRS2 signaling may serve as a potential therapeutic target for liposarcomas. The research of Jing et al[22] indicated that the abnormal amplification rate of FRS2 was as high as 93.2% in well-differentiated and dedifferentiated liposarcomas. It presents a higher abnormal amplification rate in more malignant dedifferentiated liposarcoma than in well-differentiated liposarcoma. This suggests a close connection between FRS2 and clinicopathological features such as malignancy degree and pathological classification of liposarcomas. Studies in literature found that the IHC staining results of FRS2 in well-differentiated and dedifferentiated liposarcomas were highly consistent with the abnormal amplification of FRS2. The IHC staining results of FRS2 in pathological tissues can effectively diagnose well-differentiated and dedifferentiated liposarcomas, and the diagnostic specificity of FRS2 is slightly higher than the diagnostic "gold standard" indexes such as MDM2 and CDK4[23]. In

Table II. Univariate analysis of prognostic survival of patients with primary retroperitoneal liposarcoma.

Pathological factors	n	5-year overall disease-free survival rate (%)	χ^2 value	*p*-value	5-year overall survival rate (%)	χ^2 value	*p*-value
Sex			0.687	0.829		0.782	0.377
Male	49	14.29			48.98		
Female	38	21.05			39.47		
Age (years old)			0.359	0.549		0.332	0.565
<60	52	19.23			42.31		
≥60	35	14.29			48.57		
Pathological type			17.164	0.002		22.044	<0.001
Well-differentiated liposarcoma	21	42.86			76.19		
Dedifferentiated liposarcoma	36	5.56			33.00		
Myxoid/round cell liposarcoma	15	26.67			66.67		
Pleomorphic liposarcoma	13	0.00			7.69		
Mixed-type liposarcoma	2	0.00			0.00		
Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading			7.344	0.026		13.732	0.001
I	44	27.27			63.64		
II	25	12.00			32.00		
III	18	0.00			16.67		
Tumor size (cm)			0.762	0.383		1.099	0.295
≤20	55	14.55			49.09		
>20	32	21.88			37.50		
Number of tumors			6.321	0.012		5.934	0.015
Single	50	26.00			56.00		
Multiple	37	5.41			29.73		
Treatment modality			2.475	0.29		2.165	0.339
Surgery	45	11.11			37.78		
Surgery+hyperthermic antiblastic perfusion	33	24.24			54.55		
Surgery+chemotherapy	9	22.22			44.44		
Combined organ resection			0.369	0.543		0.463	0.496
Yes	41	14.63			46.34		
No	46	19.57			43.48		
Recurrence and metastasis						22.308	<0.001
Yes	72	-	-	-	33.33		
No	15	-			100.00		
Positive margin			4.085	0.043		8.284	0.004
Yes	16	0.00			12.50		
No	71	21.13			52.11		
FRS2 protein expression			3.749	0.049		8.795	0.003
Positive	54	11.11			29.63		
Negative	33	27.27			69.70		

Table III. Cox multivariate analysis of postoperative 5-year tumor-free survival in patients with primary retroperitoneal liposarcoma.

Factors	β	SE	Wald χ^2	*p*-value	HR (95% CI)
Pathological type (pleomorphic *vs.* well-differentiated liposarcoma)	1.279	0.272	22.111	0.000	3.593 (2.108-6.123)
FNCLCC grading (Grade III *vs.* Grade II *vs.* Grade I)	0.912	0.211	18.682	0.000	2.489 (1.646-3.764)
Multiple tumors (multiple *vs.* single)	0.569	0.259	4.826	0.028	1.766 (1.063-2.935)
Surgical margins (positive *vs.* negative)	1.027	0.297	11.957	0.001	2.793 (1.560-4.998)
FRS2 protein expression (positive *vs.* negative)	0.735	0.256	8.243	0.004	2.085 (1.263-3.444)

Table IV. Cox multivariate analysis of postoperative 5-year overall survival in patients with primary retroperitoneal liposarcoma.

Factors	β	SE	Wald χ^2	*p*-value	HR (95% CI)
Pathological type (pleomorphic *vs.* well-differentiated liposarcoma)	0.971	0.082	140.220	0.000	2.641 (2.249-3.101)
FNCLCC grading (Grade III *vs.* Grade II *vs.* Grade I)	0.561	0.123	20.802	0.000	1.752 (1.337-2.230)
Number of tumors (multiple *vs.* single)	0.297	0.078	14.499	0.000	1.346 (1.155-1.568)
Recurrence and metastasis (yes *vs.* no)	1.523	0.445	11.713	0.001	4.586 (1.917-10.970)
Surgical margins (positive *vs.* negative)	1.215	0.324	14.063	0.000	3.370 (1.786-6.360)
FRS2 protein expression (positive *vs.* negative)	0.632	0.219	8.328	0.004	1.881 (1.225-2.890)

this study, IHC staining results showed that the FRS2+ rate in the tissues of patients with PRPLS was closely related to pathological type, FNCLCC grade, number of tumors, recurrence, metastasis, etc. Patients with FRS2+ had a higher probability of multiple tumors, lower tissue differentiation, higher tissue grading, worse malignancy degree, and higher risk of recurrence and metastasis. FRS2+ patients also presented significantly lower OS and PFS than those with FRS2-, suggesting that the expression of FRS2 protein is closely related to the recurrence and survival of patients with PRPLS. Zhang et al[24] also believe that FRS2 combined with CDK4 and MDM2 can more accurately reflect the pathological features of high-grade pleomorphic liposarcomas. Besides, the activated FGFR/FRS2 signaling plays a key role in pleomorphic liposarcoma progression. Moreover, this research identified that FRS2+, pathological type, FNCLCC grading, and multiple tumors were independent influencing factors for the recurrence and survival of patients with PRPLS.

Conclusions

FRS2 shows a high positive protein expression rate in the tissues of patients with PRPLS, with its positive expression level closely related to pathological type, FNCLCC grade, number of tumors, and recurrence and metastasis. FRS2+ patients are associated with significantly shorter PFS and OS. And the expression of FRS2 protein is an independent imaging factor that affects patients' recurrence and survival, suggesting poor prognosis in PRPLS patients with FRS2+. With the continuous breakthrough of molecular targeted therapy technology, research targeting FRS2 protein provides a certain reference value for the treatment of PRPLS patients.

Availability of Data and Materials

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Conflict of Interest
The authors declare that they have no competing interests.

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Authors' Contributions
Weida Chen conceived the study design and the content concept; Chengli Miao performed the data collection, extraction and analyzed the data. Weida Chen, Chengli Miao interpreted and reviewed the data and drafts. Chengli Miao reviewed the final draft.

Informed Consent
Patients gave informed consent for this study and signed the informed consent form.

Ethics Approval
This study was approved by the Ethics Committee of Peking University International Hospital (No. 2023-0004-01).

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