临床论著

肿瘤间质比及联合免疫评分对预测脊柱脊索瘤患者生存预后的意义

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【摘要】目的: 分析脊柱脊索瘤中肿瘤间质比(tumor-stroma ratio, TSR)、免疫评分(immunescore, IS)与患者预后之间的关系, 探讨 TSR 及其联合 IS 在预测患者预后中的临床价值。**方法**: 回顾性分析 77 例脊柱脊索瘤患者的临床资料, 其中男性 54 例, 女性 23 例。由 2 位病理科医师对病理切片中的 TSR 进行独立评估, 利用 X-tile 软件获得局部无复发生存期(local relapse-free survival, LRFS)及总体生存时间(overall survival, OS)具有最小对数秩 *P* 值的点, 利用该点将患者分为高 TSR 组和低 TSR 组; 应用免疫组化法对 77 例脊索瘤标本进行 CD3+和 CD8+肿瘤浸润性淋巴细胞(tumor-infiltrating lymphocytes, TILs)子集的检测, 再对其进行自动图像分析, 得出 IS, 并将患者分为高 IS 组和低 IS 组。采用 Kaplan-Meier 方法对临床和病理参数(年龄、性别、肿瘤大小、位置、术前复发、周围组织浸润、级别、分期、切除方式、出血和坏死情况、TSR 和 IS)与患者结局(LRFS、OS)的关系进行单因素生存分析; 纳入单因素分析有显著统计学意义的变量, 使用 Cox 比例风险模型分析患者 LRFS 和 OS 的独立危险因素; Pearson′s 相关性分析两个连续变量之间的关系。应用受试者工作特征 (receiver operating characteristic, ROC)曲线比较 TSR 联合 IS 和 TSR 或 IS 单独使用时的预测能力。应用 Bland-Altman 一致性分析评估两位评估者之间 TSR 测量的一致性。**结果**: 两位评估者在 TSR 评估方面存在很强的相关性(r=0.924, P<0.001); Bland-Altman 证实两位评估者之间 TSR 数据的平均差异较小, 有良好的一致性(P=0.292)。单变量分析显示 TSR、IS、年龄、周围肌肉浸润、手术切除方式与 LRFS 存在相关性(P<0.05)。TSR、IS、周围肌肉浸润、肿瘤分期、手术切除方式与 OS 存在相关性(P<0.05)。TSR 与 IS 呈正相关(P<0.05), 高 IS 预示着良好的临床预后, 而低 TSR 和低 IS 患者存活率最低。LRFS 的多变量 Cox 分析显示周围肌肉浸润、TSR 和 IS 可独立预测预后 (P<0.05), OS 的多变量 Cox 分析显示 TSR 是 OS 的唯一预测因素(P=0.011)。ROC 分析显示 TSR 在预测 LRFS 和 OS 方面的能力与 IS 相当 [LRFS: AUC(TSR)=0.565, AUC(IS)=0.630; OS: AUC(TSR)=0.632, AUC(IS)=0.648]; 将 TSR 纳入 IS 系统中可提高 TSR 对疾病复发和生存率预测的准确性 [LRFS: AUC(TSR+IS)=0.709; OS: AUC(TSR+IS)=0.727]。**结论**: TSR 与患者的生存率相关, 且是 LRFS 和 OS 的预测因素。在生存分析中纳入 TSR 可提高其预测预后的能力, 将 TSR 纳入 IS 系统中可提高 IS 对疾病复发和生存率预测的准确性。

【关键词】 脊索瘤; 肿瘤间质比; 生存分析; 预测因素; 免疫评分

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Significance of tumor-stroma ratio and tumor-stroma ratio combined with immunescore in predicting the survival and prognosis of spinal chordoma patients/ZHENG Bowen, ZOU Mingxiang, LIU Fusheng, et al//Chinese Journal of Spine and Spinal Cord, 2021, 31(2): 134-144

【Abstract】 Objectives: By analyzing the relationship between tumor-stroma ratio(TSR), immunescore(IS), and patient prognosis in spinal chordoma, we aimed to determine the clinical significance of TSR and further investigate the predictive ability of TSR combined with IS. **Methods:** The clinical data of 77 patients with spinal chordoma were retrospectively analyzed, including 54 men and 23 women. All the spinal cord tumor cases fell into the class of classic pathology. TSR was evaluated on pathology slides by 2 independent pathologists, the local relapse-free survival(LRFS) and overall survival(OS) point with the smallest log rank P-value was obtained using X-tile software, and then the patients were divided it into high TSR and low TSR groups.

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Immunohistochemistry was applied to 77 tumor specimens for CD3+ and CD8+ tumor-infiltrating lymphocytes subset(TILs), automated image analysis was performed to derive IS, and the patients were classified into two groups: high and low on the basis of IS. A univariate Kaplan-Meier curve by log-rank test was used to explore the relationship between clinicopathological factors and patient outcomes. A multivariate Cox proportional hazards model was used to assess independent prognostic factors of LRFS and OS after adjusting for other clinical predictors that were significant in our univariate survival analysis. Pearson′s correlation test was used to observe the relationship between two continuous variables. Receiver operating characteristic (ROC) curves were used to compare the predictive power of TSR in combination with IS or TSR or IS alone. And Bland-Altman consistency analysis was used to assess the consistency of TSR measures between two assessors. All tests were two-sided, and $P<0.05$ was considered to be statistically significant. **Results:** There was a strong correlation between the two assessors for TSR assessment($r=0.924$, $P<0.001$); Bland-Altman confirmed a small mean difference in TSR data between the two assessors with good agreement ($P=0.292$). Univariate analysis showed that TSR, IS, age, surrounding muscle invasion, type of surgery were correlated with LRFS($P<0.05$). TSR, IS, surrounding muscle invasion, tumor stage, and type of surgerywere related to OS($P<0.05$). TSR was positively correlated with IS($P<0.05$), high IS indicated a good clinical prognosis, patients with low TSR combined with low IS had the lowest survival rates. Multivariate Cox analysis of LRFS showed that surrounding muscle invasion, TSR, and IS could independently predict prognosis($P<0.05$), and multivariate Cox analysis of OS shows that TSR was the only predictor of OS($P=0.011$). ROC analysis showed that incorporating TSR into the IS system improved the accuracy of the IS in predicting disease recurrence and survival. **Conclusions:** TSR is associated with patient survival and is a predictor of LRFS and OS. Inclusion of TSR in survival analysis improves its ability to predict prognosis, and inclusion of TSR in the IS system improves the accuracy of IS in predicting disease recurrence and survival.

【Key words】 Chordoma; Tumor-stroma ratio; Survival analysis; Prognostic biomarker; Immunescore

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脊索瘤起源于胚胎时期残存的脊索组织,是一种罕见的且生长缓慢的间叶组织来源性恶性肿瘤[1,2]。临床上,脊索瘤最多见于骶骨和颅底,发病率低于百万分之一[3,4]。由于脊索瘤对传统的放化疗不敏感[2,5],目前理想的治疗方法是初次手术时最大范围地切除肿瘤再联合术后放疗[2,6-9]。然而,即使做到切除边缘干净无瘤,脊索瘤仍有很高的复发风险,40%~50%的患者可发生远处转移[10,11]。由于脊索瘤的预后较差,迫切需要更好的治疗策略来提高患者的生存率。有研究发现许多与脊索瘤预后相关的分子标记物[12,13],但对这些标记物的研究仅局限于脊索瘤细胞的分子特征,并未考虑肿瘤间质成分对脊索瘤生物学的影响,这可能会导致其预后信息不够准确。肿瘤间质由细胞外基质、巨噬细胞、内皮细胞及肿瘤相关性成纤维细胞等构成。以往的研究证明肿瘤细胞和微环境下的间质细胞是一个整体,肿瘤间质在肿瘤生成、发展、侵袭和转移中起着重要作用[14-16]。此外,有文献证实间质基因的表达是人类某些肿瘤预后的重要决定因素[17-20]。近年来,越来越多的研究表明,低肿瘤间质比(tumor-stroma ratio,TSR)与肿瘤患者预后不良显著相关[21],但目前尚缺乏关于脊柱脊索瘤 TSR 的相关临床数据。免疫评分(immunescore,IS)[22] 是脊索瘤预后的独立预测指标,其在预测生存率方面甚至优于 Enneking 分级系统[23]。已有文献报道肿瘤间质可以抑制肿瘤的免疫反应[24],但脊索瘤微环境中间质含量与免疫参数之间的关系研究较少。我们推测高间质成分和低 IS 同时存在时脊索瘤将可能表现出更具侵袭性的生物学行为和更差的临床预后。本研究通过分析脊柱脊索瘤中 TSR、IS 与患者预后之间的关系,旨在最终确定 TSR 的临床意义,并进一步探究 TSR 联合 IS 在预测患者预后中的临床应用价值。

1 资料与方法

1.1 一般资料

收集我院 2002 年 6 月~2018 年 9 月接受手

术治疗的 77 例脊柱脊索瘤患者的资料，患者的基本特征、治疗史和临床结果数据从患者的病历记录中获得，包括 54 例男性和 23 例女性。77 例脊索瘤标本均从我院病理科获得，经福尔马林固定石蜡包埋，4μm 厚组织切片。根据脊索瘤诊断标准[2]，对其进行组织学评估并加以诊断。所有标本均属于经典病理类型。其中，手术切除类型由两名病理科医师根据术后标本分析评估，并依照标准记录为 Enneking 建议的手术切缘 [Enneking appropriate(EA)，简称为恰当切除]或 Enneking 不建议的手术切缘[Enneking inappropriate(EI)，简称为不恰当切除][25]。肿瘤分级及分期均根据用于指导恶性骨与软组织肿瘤手术分期的 Enneking 分期系统来完成：肿瘤分级根据细胞结构和核异型性来评估[26]；肿瘤分期则根据 Enneking 分期中组织学分级(G)、解剖部位(T)和是否存在转移灶(M)的标准进行分类[27]。

1.2 随访

对 77 例患者定期随访至 2019 年 12 月。根据临床和影像学结果评判肿瘤是否复发，对复发且行手术治疗的患者，再次通过病理检查加以证实。随访的主要终点为局部无复发生存期(local relapse-free survival，LRFS)，定义为手术切除肿瘤到第一次局部复发的时间[28]；次要终点为总生存期(overall survival，OS)，定义为肿瘤切除至患者死亡的时间。

1.3 TSR 的组织学评估

根据之前文献介绍的方法对 HE 染色的脊索瘤组织切片进行 TSR 的评估[29-31]。首先用光学显微镜观察整个切片，用 4 倍物镜选择肿瘤浸润最明显的区域，然后根据肿瘤的异质性，在该区域内换用 10 倍物镜，选择间质最丰富的区域，最终对包括肿瘤细胞及其周围间质成分的图像区域完成间质百分比的评估[29,30]。TSR 评定时排除直视下的肿瘤坏死和出血。由两位经验丰富的病理科医师在对患者资料不了解的情况下独立完成。若有结果的不一致，通过两者协商或与第三位病理科医师协商后决定。计算两位评估者 TSR 数据的平均值并用于分析。脊索瘤标本中 TSR 高水平和低水平的代表性图像见图 1。

1.4 IS 自动图像分析

应用免疫组化法对 77 例标本进行 CD3+和 CD8+肿瘤浸润性淋巴细胞 (tumor-infiltrating lymphocytes，TILs)子集进行检测，再根据文献报道[31-34]，对 CD3+和 CD8+TILs 子集进行自动图像分析。即使用 Eclipse Ti 微型示波器观察 TILs 密度较高区域的截面，使用 NIS-Elements 图像分析软件来获取肿瘤内部(tumor interior，TI)和肿瘤边缘 (invasive margin，IM) 中 CD3+和 CD8+TILs 的图像。然后，使用计算机辅助图像分析方法，在 5 个热点(20×)中对 TILs 子集的数量进行计数。最后，将每个组织表面单位的阳性染色细胞的平均数以平方毫米(mm^2)为单位记录为测量值。根据文献报道的标准[22]，通过 TI 和 IM 区域中 CD3+和 CD8+淋巴细胞密度的计数来建立 IS，即把 TI 和 IM 区域中的 CD3+和 CD8+TILs 密度进行分割(低记为 0 分，高记为 1 分)，随后，通过将四个二进制得分值相加获得 IS 的总分，总分值记为 0~4 分[22,35,36]，0~4 分的代表性图像如图 2 所示。由于患者数量较少，为便于分析，将患者分为高 IS 组(3~4 分)和低 IS 组(0~2 分)。

1.5 统计分析

使用 SPSS 26.0 进行统计分析，定量数据以平均值±标准差($\bar{x}\pm s$)表示，统计分析采用独立样本 t 检验；计数资料以频率或构成比表示，统计分析采用卡方检验。X-tile 软件用于确定生存分析的阈值，即校正后的对数秩检验最小 P 值所对应的点[37]。采用 Kaplan-Meier 方法对患者临床病理参数(年龄、性别、肿瘤大小、位置、术前复发、周围组织浸润、级别、分期、切除方式、出血和坏死情况、TSR 和 IS)与患者结局(LRFS、OS)进行单因素生存分析，探讨临床病理参数与患者结局的关系；使用 Cox 比例风险模型分析患者 LRFS 和 OS 的独立危险因素，分析时仅纳入单因素分析有显著

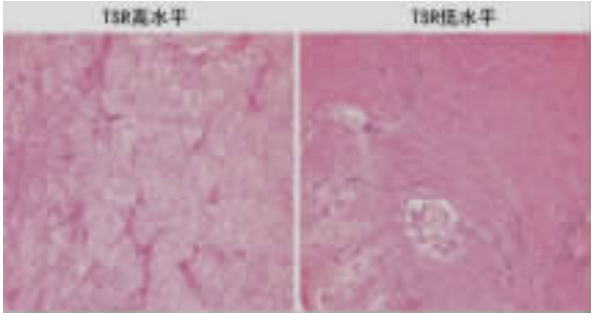


图 1 脊索瘤标本中肿瘤间质比高水平和低水平的代表性图像(HE 染色，×400)

Figure 1 Representative sections showing high and low TSR levels in chordoma tissues(HE, ×400)

统计学意义的变量。Pearson′s 相关性分析两个连续变量之间的关系。应用受试者工作特征(receiver operating characteristic, ROC) 曲线比较 TSR 联合 IS 与 TSR 或 IS 单独使用时的预测能力。采用 Bland-Altman 一致性分析评估两位评估者之间 TSR 测量的一致性[38]。$P \leqslant 0.05$ 为差异有统计学意义。

2　结果

2.1　脊索瘤组织中的 TSR

77 例脊索瘤患者的临床资料见表 1。脊索瘤组织中 TSR 的平均值为 0.53±0.27。Pearson′s 相关性分析显示两位评估者在 TSR 评估方面存在很强的相关性(r=0.924, P<0.001, 图 3a)。Bland-Altman 一致性分析结果显示两位评估者之间 TSR 数据的平均差异较小, 有良好的一致性(P=0.292, 图 3b)。在 LRFS 和 OS 的预测分析中, TSR 的临界值分别为 0.2 和 0.6(图 4), 根据此数值将患者分为低 TSR 组和高 TSR 组, 用于随后的预后分析。

2.2　单因素分析

对数秩检验的单变量分析发现 TSR、IS、年龄、周围肌肉浸润、手术切除方式是 LRFS 的重要预测指标 (P 值分别为: <0.001、0.008、0.010、<0.001、<0.001, 表 2)。TSR、IS、周围肌肉浸润、肿瘤分期、手术切除方式可预测 OS (P 值分别为: <0.001、<0.001、0.009、<0.001、0.015, 表 3)。TSR 与 IS 呈正相关(P<0.001, 图 5)。

Kaplan-Meier 生存曲线显示, 高 IS 也预示着良好的临床预后(P=0.008, 图 6a、b), 高 TSR 患者 LRFS 和 OS 明显优于低 TSR 的患者 (P 值分别为: <0.001 和<0.001, 图 6c、d)。和其他脊索瘤表型相比, 低 TSR 合并低 IS 的患者存活率最低(P<0.001, 图 6e、f)。

2.3　多因素分析

将单因素分析中有统计学意义的变量纳入多

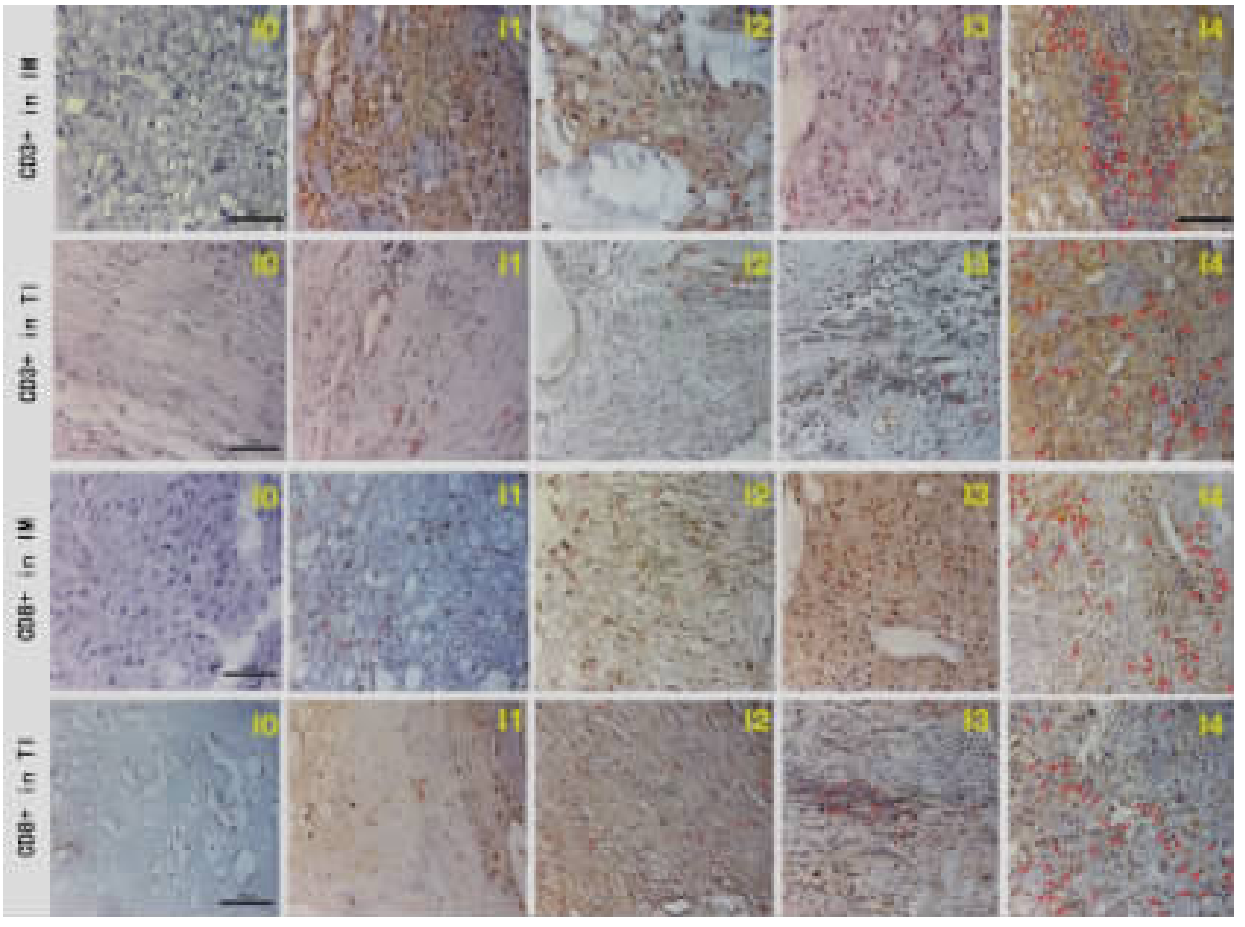


图 2　肿瘤内部(TI)和肿瘤边缘(IM)CD3+TILs 和 CD8+TILs 分级代表性图像(HE, ×400)

Figure 2　Representative grading images of CD3 + TILs and CD8 + TILs in chordoma specimens(HE, ×400)

因素分析，LRFS 的多变量 Cox 分析显示周围肌肉浸润、TSR 和 IS 可独立预测预后（*P* 值分别为：0.010、0.006、0.011，表 2、3）。TSR 是 OS 的独立预测因素（*P*=0.011，表 3）。

表 1　77 例患者的临床资料数据

Table 1　Summary of patient characteristics

项目 Item	患者数量(%)/$\bar{x}\pm s$ Number of patients(%)/$\bar{x}\pm s$
年龄（岁） Age(years)	57.4(23~88)
性别（男/女） Gender(male/female)	54(70.1)/23(29.9)
肿瘤大小（cm） Tumor size	7.14(3~18)
肿瘤部位 Tumor location	
骶尾椎 Sacrococcyx vertebra	58(75.3)
颈椎 Cervical vertebra	9(11.7)
胸椎 Thoracic vertebra	6(7.8)
腰椎 Lumbar vertebra	4(5.2)
周围肌肉浸润（是/否） Surrounding muscle invasion(Yes/No)	51(66.2)/26(33.8)
术前复发（是/否） Preoperative recurrence(Yes/No)	18(23.4)/59(76.6)
肿瘤等级（高/低） Tumor grade(High/Low)	53(68.8)/24(31.2)
肿瘤分期 Tumor stage	
ⅠA/ⅠB	19(24.7)/9(11.7)
ⅡA/ⅡB	7(9.1)/37(48.1)
Ⅲ	5(6.4)
切除方式（不恰当切除/恰当切除） Type of resection(EI/EA)	29(37.7)/48(62.3)
肿瘤出血（否/是） Tumor hemorrhage(No/Yes)	16（20.8)/61(79.2)
肿瘤坏死 Tumor necrosis	
无 Absent	18(23.4)
轻微 Mild	26(33.8)
中等 Moderate	22(28.6)
严重 Severe	11(14.2)
肿瘤内部 CD3+淋巴细胞数 CD3+TILs in TI	192.7±181.4
肿瘤浸润边缘 CD3+淋巴细胞数 CD3+TILs in IM	188.9±150.6
肿瘤内部 CD8+淋巴细胞数 CD8+TILs in TI	178.8±135.3
肿瘤浸润边缘 CD8+淋巴细胞数 CD8+TILs in IM	183.1±179.0
肿瘤间质比 Tumor-stroma ratio	0.53±0.27
免疫评分（高组/低组） Immunoscore(High/Low)	29(37.7)/48(62.3)
随访时期生存情况（死亡/存活） Survival during follow-up(Death/Alive)	31(40.3)/46(59.7)
随访时期复发（是/否） Relapse during follow-up(Yes/No)	51(66.2)/26(33.8)

注：TILs，肿瘤浸润性淋巴细胞；PD-1，程序性死亡受体 1；PD-L1，程序性死亡受体-配体 1；TI，肿瘤内部；IM，肿瘤边缘

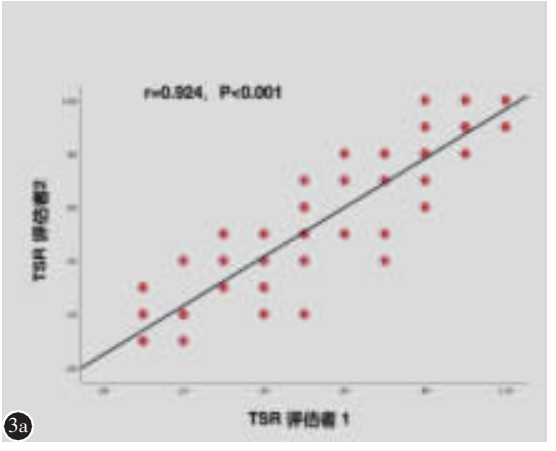
Note: EI, Enneking Inappropriate; EA, Enneking Appropriate; TILs, tumor-infiltrating lymphocytes; PD-1, programmed cell death 1; PD-L1, programmed cell death-1 ligand 1; TI, tumor interior; IM, invasive margin

2.4　TSR、IS 和 TSR+IS 的预测能力比较

ROC 分析显示 TSR 在预测 LRFS 和 OS 方面的能力与 IS 相当 [LRFS：AUC(TSR)=0.565，AUC(IS)=0.630；OS：AUC（TSR)=0.632，AUC（IS)=0.648。图 7a、b]。将 TSR 纳入 IS 系统中可提高对脊索瘤患者 LRFS 和 OS 预测的准确性 [LRFS: AUC(TSR+IS)=0.709；OS: AUC(TSR+IS)=0.727。图 7a、b]。

3　讨论

在本研究中，我们对脊柱脊索瘤的 TSR 进行了描述，并研究了其与患者临床数据的相关性，低 TSR 独立预测了患者更差的 LRFS 和 OS；TSR 和 IS 联合应用优于单独 TSR 或 IS 对预后的预测能



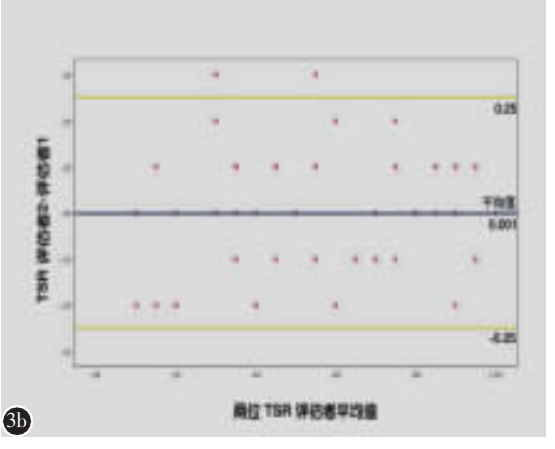


图 3　**a** 两位评估者肿瘤间质比数据的 Pearson′s 相关性测试 **b** 两位评估者肿瘤间质比数据的 Bland-Altman 一致性分析

Figure 3　**a** Pearson′s correlation test of TSR data from two reviewers **b** The Bland-Altman consistency analysis of TSR data between the two reviewers

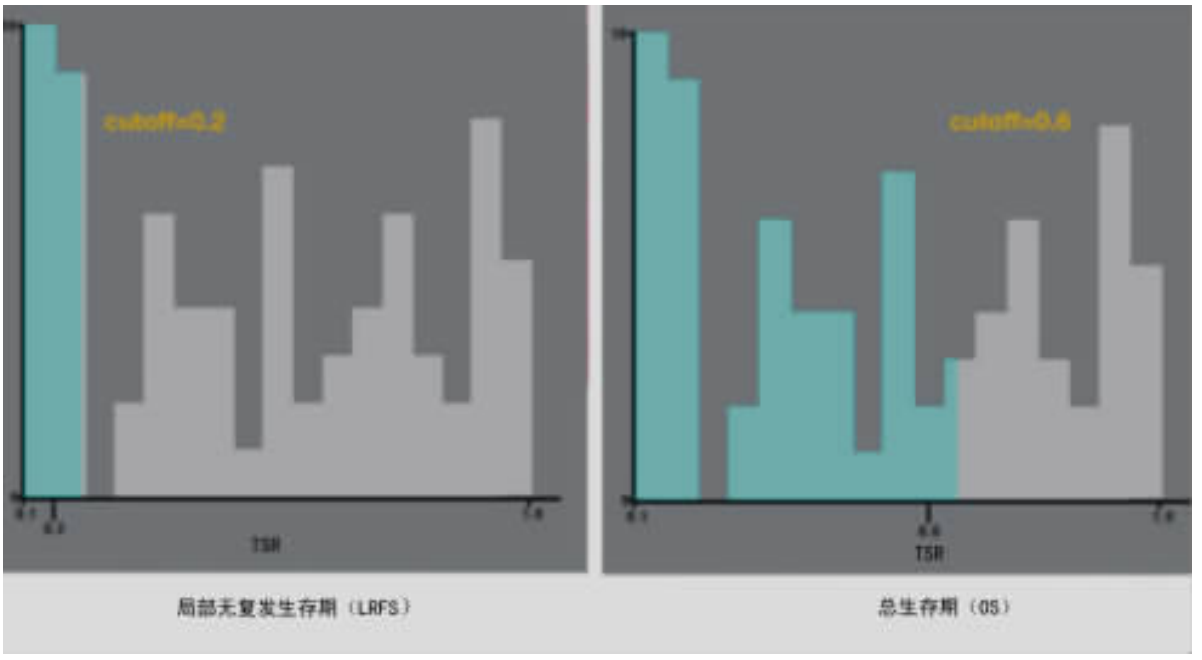


图 4 LRFS、OS 预后分析中肿瘤间质比的临界值

Figure 4 The cutoff values for TSR in prognosis analysis of LRFS and OS

表 2 临床病理参数与局部无复发生存期的关系

Table 2 Association between LRFS and clinicopathological features of chordoma patients

因素 Factors	类别 Categories	单变量分析 Univariate analysis		多变量分析 Multivariate analysis		
		方差 χ^2	*P*值 *P* value	*P*值 *P* value	风险比 HR	95%可信区间 95%CI
性别 Sex	男/女 Male/Female	2.934	0.086			
年龄 Age	≤50/>50	6.561	0.010	0.957	0.966	0.275~3.381
肿瘤大小 Tumor size	≤5cm/>5cm	0279	0.592			
肿瘤位置 Tumor location	骶尾椎/颈椎或胸椎或腰椎 Sacrococcyx/Cervical or thoracic or lumbar vertebra	0.004	0.951			
术前复发 Preoperative recurrence	是/否 Yes/No	0.955	0.322			
周围组织浸润 Surrounding muscle invasion	是/否 Yes/No	24.586	<0.001	0.010	2.995	1.301~6.863
肿瘤级别 Grade	高/低 High/Low	0.232	0.631			
肿瘤分期 Stage	ⅠA/ⅠB/ⅡA/ⅡB/Ⅲ	0.961	0.916			
切除方式 Type of resection	不合适切除/合适切除 EI/EA	16.471	<0.001	0.131	2.075	0.581~5.374
肿瘤出血 Tumor hemorrhage	是/否 Yes/No	4.030	0.045	0.469	1.483	0.509~4.338
肿瘤坏死 Tumor necrosis	无/轻微/中等/严重 Absent/mild/moderate/severe	0.190	0.970			
肿瘤间质比 TSR	高/低 High/Low	19.157	<0.001	0.006	3.662	1.421~9.434
免疫评分 Immunoscore	高/低 High/Low	7.040	0.008	0.011	3.316	1.287~7.631

注：EI，不恰当切除；EA，恰当切除；TSR，肿瘤间质比

Note: EI, Enneking inappropriate; EA, Enneking appropriate; TSR, tumor-stroma ratio

表 3 临床病理参数与总生存期的关系

Table 3 Association between OS and clinicopathological features of chordoma patients

因素 Factors	类别 Categories	单变量分析 Univariate analysis		多变量分析 Multivariate analysis		
		方差 χ^2	*P*值 *P* value	*P*值 *P* value	风险比 HR	95%可信区间 95%CI
性别 Sex	男/女 Male/Female	1.540	0.212			
年龄 Age	≤50/>50	1.459	0.224			
肿瘤大小 Tumor size	≤5cm/>5cm	0.127	0.591			
肿瘤位置 Tumor location	骶尾椎/颈椎或胸椎或腰椎 Sacrococcyx/Cervical or thoracic or lumbar vertebra	0.132	0.722			
术前复发 Preoperative recurrence	是/否 Yes/No	0.546	0.713			
周围组织浸润 Surrounding muscle invasion	是/否 Yes/No	6.793	0.009	0.772	1.172	0.396~3.460
肿瘤级别 Grade	高/低 High/Low	0.641	0.428			
肿瘤分期 Stage	ⅠA/ⅠB/ⅡA/ⅡB/Ⅲ	22.303	<0.001	0.395	1.212	0.777~1.890
切除方式 Type of resection	EI/EA	5.898	0.015	0.522	1.416	0.489~4.116
肿瘤出血 Tumor hemorrhage	是/否 Yes/No	0.319	0.575			
肿瘤坏死 Tumor necrosis	无/轻微/中等/严重 Absent/mild/moderate/severe	4.032	0.254			
肿瘤间质比 TSR	高/低 High/Low	28.425	<0.001	0.011	3.316	1.287~7.631
免疫评分 Immunoscore	高/低 High/Low	24.481	<0.001	0.062	0.238	0.054~1.08

注：EI，不恰当切除；EA，恰当切除；TSR，肿瘤间质比

Note: EI, Enneking inappropriate; EA, Enneking appropriate; TSR, tumor-stroma ratio

力，低 TSR 合并低 IS 的患者预后最差。这些结果提示 TSR 对脊柱脊索瘤的进展和患者的免疫应答有显著影响，为今后针对肿瘤间质的靶向药物治疗脊索瘤提供了一种新思路。

近年来，为了评估肿瘤微环境对肿瘤进展的潜在影响，学者们已进行了大量的研究。其中，TSR 越来越受到关注。迄今为止，尽管 TSR 在肿瘤预后中的确切作用还存在着争议[14,21]，但已有大量证据表明 TSR 是肿瘤患者预后的独立危险因素[21]，这也与我们的研究结果相似。此外，还有研究表明，在人类多种肿瘤中，肿瘤的低 TSR 表现出了更高的侵袭性[21,39-41]。除上述结果外，已有的研究表明，使用针对肿瘤间质的药物在不同类型的肿瘤中可产生临床疗效[42-44]。针对并作用于肿瘤间质相关的药物可能为脊索瘤的治疗提供新的思路。

目前，间质成分是如何影响脊索瘤的进展仍未知。脊索瘤在组织学上的典型特征是黏液样间

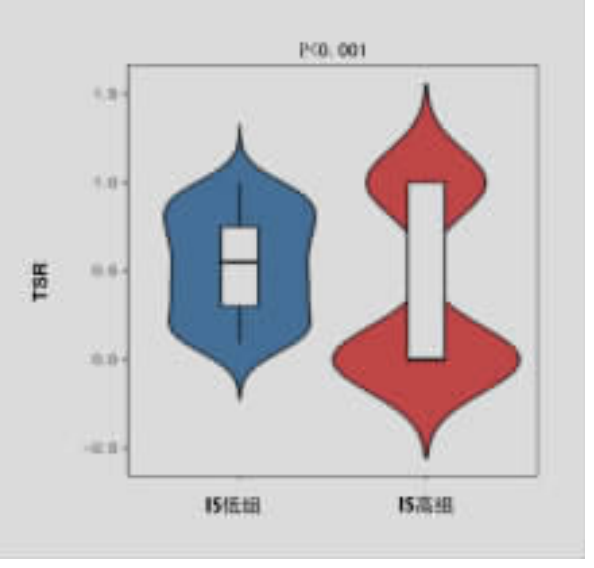


图 5 肿瘤间质比(TSR)与免疫评分(IS)之间存在相关性，且为正相关

Figure 5 Association between TSR and IS. There was a positive correlation between TSR and IS

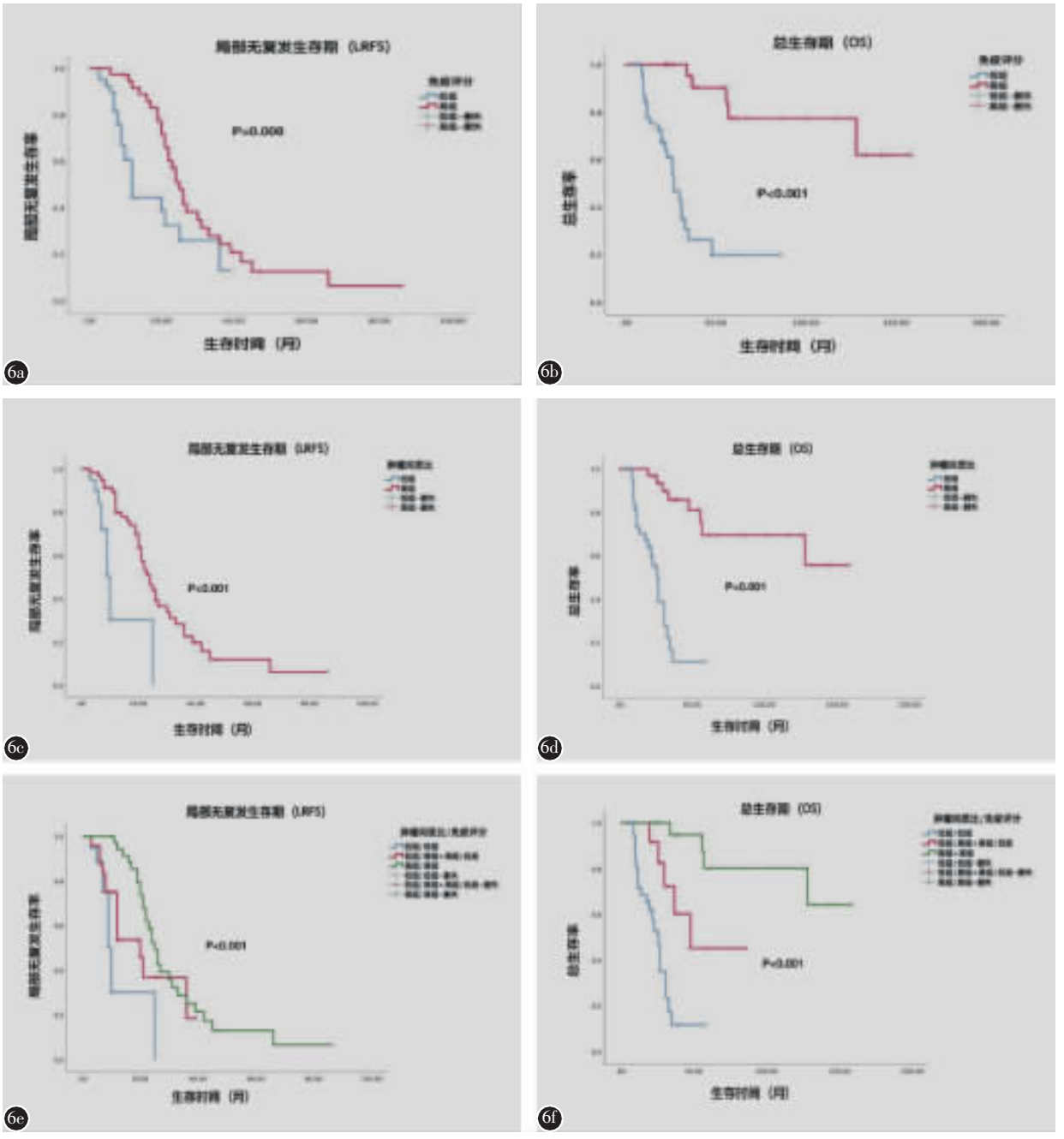


图 6 **a** IS 局部无复发生存期的 Kaplan–Meier 生存曲线：低 IS 的患者局部无复发生存时间短 **b** IS 总生存期的 Kaplan–Meier 生存曲线：低 IS 的患者总生存时间短 **c** TSR 局部无复发生存期的 Kaplan–Meier 生存曲线：低 TSR 的患者局部无复发生存时间短 **d** TSR 总生存期的 Kaplan–Meier 生存曲线：低 TSR 的患者总存时间短 **e** TSR+IS，TSR 和 IS 局部无复发生存期的 Kaplan–Meier 生存曲线：低 TSR+低 IS 的患者局部无复发生存时间短 **f** TSR+IS，TSR 和 IS 总生存期的 Kaplan–Meier 生存曲线 低 TSR+低 IS 的患者总存时间短

Figure 6 **a** Kaplan–Meier curves of LRFS stratified by the IS: patients with low IS were closely related to a worse LRFS **b** Kaplan–Meier curves of OS stratified by the IS: patients with low IS were closely related to a worse OS **c** Kaplan–Meier curves of LRFS stratified by the TSR: patients with low TSR were closely related to a worse LRFS **d** Kaplan–Meier curves of OS stratified by the TSR: patients with low TSR were closely related to a worse OS **e** Kaplan–Meier curves of LRFS stratified by TSR+IS, TSR and IS: patients with low TSR+IS were closely related to a worse LRFS **f** Kaplan–Meier curves of OS stratified by TSR+IS, TSR and IS: patients with low TSR+IS were closely related to a worse OS

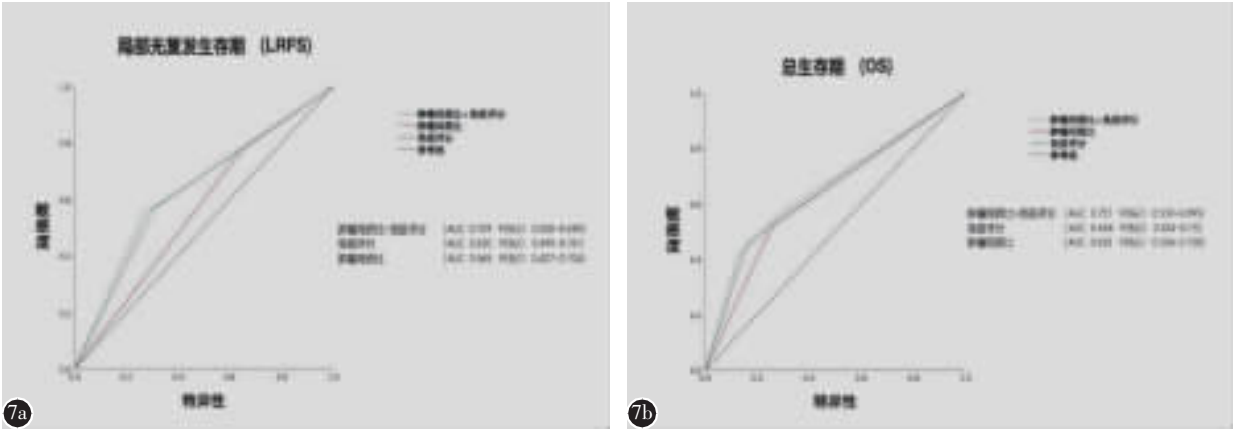


图 7 TSR+IS, TSR 和 IS 对预测局部无复发生存期(**a**)和总生存期(**b**)敏感性和特异性的比较:TSR 联合 IS 的预测能力优于单独使用 TSR 或 IS

Figure 7 Comparison of the sensitivity and specificity between TSR+IS, TSR and IS for LRFS(**a**) and OS(**b**) prediction: the predictive ability of TSR combined with IS is better than using TSR or IS alone

质中含有空泡细胞[45]。鉴于此,间质含量高的脊索瘤病变可能产生丰富的粘液或粘蛋白成分,其可通过多种生物学机制对化疗药物产生耐药[46、47],从而导致不良的预后。此外,已有资料显示,微环境中非免疫细胞可影响骨巨细胞瘤、乳腺癌和结直肠癌的预后[34,48~50]。因此,间质成分是否可通过调节此类型细胞的定植和迁移来影响脊索瘤的预后尚不得知,还需进一步研究。

已有的研究表明,间质含量与淋巴细胞的密度有关[51,52]。也有研究证实,CD3+淋巴细胞对包括脊索瘤在内的人类肿瘤的预后有积极影响[53~55],肿瘤内间质成分可以抑制肿瘤微环境中的免疫应答[24,56,57]。IS 是根据 TI 和 IM 区域 CD3+和 CD8+淋巴细胞密度的计数所建立的[22]。本研究也发现,TSR 与 IS 成正相关。这些数据表明肿瘤间质可能通过抑制免疫效应细胞浸润和促进调节性 T 细胞向肿瘤处聚集来影响脊索瘤的进展[53~55]。受限于回顾性研究的特点和患者数量较少,未来还需要大样本的前瞻性研究来证实我们的观点。

4 结论

本研究探究了 TSR、IS 以及临床变量与脊柱脊索瘤患者生存预后的关系,我们发现 TSR 与患者生存率相关,且是 LRFS 和 OS 的独立预测因素。在生存分析中纳入 TSR 可以提高预测预后的能力,即:将 TSR 纳入 IS 系统中可提高 IS 对疾病复发和生存率预测的准确性。但还需要更进一步的研究来确认脊索瘤间质成分与预后的相关性,以及这些间质成分如何影响患者的临床预后。

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