

原发性干燥综合征合并间质性肺病患者临床与高分辨率计算机断层扫描特征观察

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【摘要】 **目的** 探讨原发性干燥综合征合并间质性肺病患者临床特征、高分辨率计算机断层扫描(high-resolution computed tomography, HRCT)特征。**方法** 选取2021年4月—2024年12月在河北中石油中心医院治疗的原发性干燥综合征合并间质性肺病患者50例作为观察组,同时选取原发性干燥综合征未合并间质性肺病患者80例作为对照组,比较2组临床一般资料、实验室指标差异,以及分析观察组HRCT特征。**结果** 观察组和对照组年龄和病程分别为[(58.26±11.06)岁 vs. (49.40±12.25)岁]和[(7.22±1.54)年 vs. (6.03±1.60)年],差异有统计学意义(均 $P=0.002$);观察组干燥综合征疾病活动度评分(European League Against Rheumatism Sjogren's syndrome disease activity index, ESSDAI)评分 ≥ 5 分、咳嗽咳痰、活动后喘憋比例分别为82.00%、76.00%和58.00%,明显高于对照组($P=0.001$, $P<0.001$ 和 $P<0.001$);观察组抗干燥综合征A抗体阳性率和免疫球蛋白G >16 g/L比例分别为86.00%和58.00%,明显高于对照组($P=0.002$ 和 $P=0.009$);观察组和对照组抗核抗体阳性、抗干燥综合征B抗体阳性、类风湿因子 >20 IU/L、免疫球蛋白A >4.0 g/L、免疫球蛋白M >2.3 g/L、补体3 <60.79 g/L和补体4 <0.1 g/L比例比较差异无统计学意义($P>0.05$);观察组中HRCT影像特征主要以肺外带网格影、磨玻璃影、小叶间隔增厚为主;Logistic回归分析显示:年龄、ESSDAI评分、咳嗽咳痰、活动后喘憋、抗核抗体是原发性干燥综合征发生间质性肺病的影响因素($P<0.05$),其预测间质性肺病的受试者工作特征曲线下面积为0.942(95%CI:0.901~0.983),敏感度和特异度分别为91.70%和86.80%。**结论** 年龄增长、ESSDAI评分升高、咳嗽咳痰、活动后喘憋及抗干燥综合征A抗体升高与原发性干燥综合征患者并发间质性肺病的发生风险密切相关,高分辨率计算机断层扫描影像学特征以双肺外带网格状影、磨玻璃样密度影及小叶间隔增厚为主。

【关键词】 干燥综合征;间质性肺病;HRCT特征 doi:10.3969/j.issn.1007-3205.2026.03.006

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Observation of clinical features and high-resolution computed tomography characteristics in patients with primary Sjögren's syndrome complicated with interstitial lung disease

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【Abstract】 **Objective** To investigate the clinical features and high-resolution computed tomography (HRCT) characteristics of patients with primary Sjögren's syndrome (pSS) complicated with interstitial lung disease (ILD). **Methods** A total of 50 patients with pSS complicated with ILD treated in Hebei Petro China Central hospital from April 2021 to December 2024 were selected as the observation group, and 80 patients with pSS but without ILD were selected as the control group. The clinical general data and laboratory indicators of the two groups were compared, and the HRCT characteristics of the observation group were analyzed. **Results** The age and disease duration of the observation group and the control group were [(58.26±11.06) years vs. (49.40±12.25) years] and [(7.22±1.54) years vs. (6.03±1.60) years] respectively, showing significant differences ($P=0.02$). The proportions of patients with European League Against Rheumatism Sjogren's syndrome disease activity index (ESSDAI) score was ≥ 5 points, cough and sputum, and exertional dyspnea in the observation group were 82.00%, 76.00%, and 58.00%,

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respectively, which were significantly higher than those in the control group ($P=0.001$, <0.001 , and <0.001). The positive rate of anti-Sjögren's syndrome A (anti-SSA) antibody and the proportion of immunoglobulin G >16 g/L in the observation group were 86.00% and 58.00%, respectively, which were significantly higher than those in the control group ($P=0.002$ and 0.009). There was no significant difference in the proportion of positive anti-nuclear antibodies (ANA), positive anti Sjögren's syndrome B antibody, rheumatoid factor >20 IU/L, immunoglobulin A >4.0 g/L, immunoglobulin M >2.3 g/L, complement 3 <60.79 g/L, and complement 4 <0.1 g/L between the observation group and the control group ($P>0.05$). The HRCT imaging characteristics in the observation group mainly included peripheral reticular opacities, ground-glass opacities, and thickening of interlobular septa, and logistic regression analysis showed that age, ESSDAI score, cough and sputum, exertional dyspnea, and ANA were the influencing factors for the occurrence of ILD in patients with pSS ($P<0.05$). The area under the receiver operating characteristic curve for predicting ILD was 0.942 (95%CI: 0.901—0.983), with a sensitivity and a specificity of 91.70% and 86.80% respectively. **Conclusion** Increased age, elevated ESSDAI scores, cough and sputum, exertional dyspnea, and elevated anti-SSA antibodies are closely associated with an increased risk of ILD in patients with pSS. The HRCT characteristics predominantly consist of peripheral reticular opacities, ground-glass opacities, and interlobular septal thickening.

[Key words] Sjögren's syndrome; interstitial lung disease; HRCT characteristics

原发性干燥综合征 (primary Sjögren's syndrome, pSS) 的病因较为复杂, 是遗传、环境、感染及免疫异常等多因素共同作用的结果^[1-2]。患者以唾液腺和泪腺受累为特征, 表现为口干和眼干, 严重者可出现全身多器官受累^[3]。肺部内部血管及结缔组织较多, 间质性肺病 (interstitial lung disease, ILD) 是 pSS 的常见并发症, 合并者会出现呼吸障碍, 影响患者生活质量^[4-5]。但是部分 ILD 患者早期没有明显的呼吸道症状, 容易被漏诊, 当出现明显症状时, 患者可能已经出现严重的肺间质纤维化^[6]。pSS 患者并发 ILD 常以一种病理类型为主, 伴多种病理表现共存。临床可通过肺部活检来明确病理特点, 但是活检创伤较大, 不适合广泛推广^[7]。高分辨率计算机断层扫描 (high resolution CT, HRCT) 是诊断和评估结缔组织病相关性肺疾病最常用的检查^[8-9]。本研究分析 pSS 合并 ILD 患者的临床特征及 HRCT 特征, 以期临床诊疗提供依据。

1 资料与方法

1.1 一般资料 选取 2021 年 4 月—2024 年 12 月河北中石油中心医院治疗的 pSS 合并 ILD 患者 50 例作为观察组, 同时按照性别、年龄选匹配取 pSS 未合并 ILD 患者 80 例作为对照组, 纳入标准: ① pSS 诊断符合 2016 年美国风湿病协会与欧洲风湿病联盟颁布的 pSS 的分类标准^[10], ILD 诊断参照美国胸科学会和欧洲呼吸学会制定的特发性间质性肺炎诊断标准^[11]; ② 均接受 HRCT 等检查; ③ 完成血清学检测; ④ 患者及家属知情同意。排除标准:

① 有肺结核、肺气肿、慢性阻塞性肺疾病等其他肺部疾病; ② 继发干燥综合征或其他结缔组织病; ③ 合并有心、肝等其他脏器疾病; ④ 既往接受过肺移植。

本研究经医院伦理委员会的审批通过 (批准文号: KYLL2021-09)。

1.2 HRCT 检查 使用德国西门子 64 排螺旋 CT 机实施检查, 患者仰卧, 双臂上举, 训练患者呼气屏气。在患者深呼气后开始扫描肺尖到肺底范围, 设置层厚 1 mm, 层距 10 mm。获取影像图像, 由 2 名资深影像科医生先单独阅片, 记录 2 组 HRCT 表现 (肺外带网格影、磨玻璃影、小叶间隔增厚、囊性病变、实变影、胸膜下线影、牵拉性支气管扩张、蜂窝影) 及构成比。若 2 位医生意见不一致则由第 3 位医生协助。部分典型 HRCT 检查图见图 1。

1.3 实验室检查 采集所有受试者 3 mL 空腹静脉血, 离心 (2 000 r/min, 10 min) 后留取血清。采用间接免疫荧光法测定抗核抗体 (anti-nuclear antibody, ANA) 水平。采用免疫印迹法检测抗干燥综合征 A (Sjögren's syndrome type A, SSA) 抗体及抗干燥综合征 B (Sjögren's syndrome type B, SSB) 抗体, 使用伯乐 Bio-Rad 公司 ChemiDoc MP Imaging System 凝胶成像系统及赛默飞世尔科技蛋白质印迹试剂盒。实验操作参照试剂盒说明书进行: 将含有预包被 SSA 与 SSB 抗原的膜条与稀释后患者血清共同孵育, 使血清中的抗 SSA 或抗 SSB 抗体与膜上相应抗原结合。充分洗涤后, 加入辣根过氧化物酶标记的山羊抗人 IgG 二抗进行

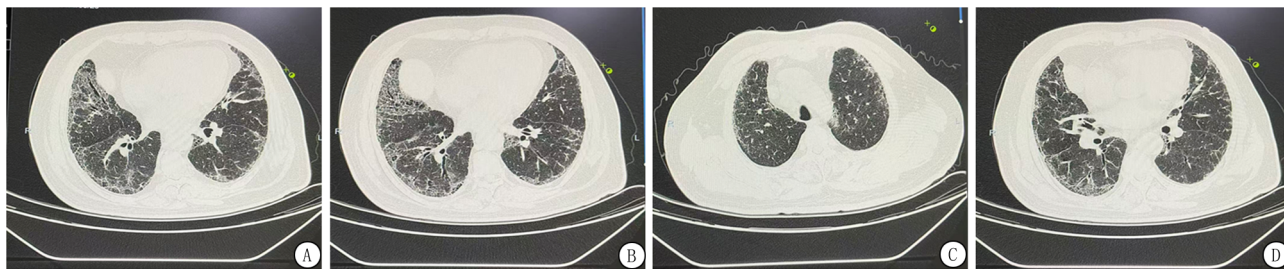


图1 部分典型病例HRCT图像

Figure 1 HRCT images of several typical cases

孵育。再次洗涤后,加入化学发光底物进行显色,最后利用ChemiDoc MP凝胶成像系统捕获特异性条带信号。判读时,在膜条对应SSA或SSB抗原位置出现清晰条带判定为阳性,表明样本中存在相应抗体;若条带不明显或未出现,则判定为阴性。

采用散射速率比色法测定补体3(complement 3, C3)、补体4(complement 4, C4)、免疫球蛋白、C反应蛋白(C-reactive protein, CRP)水平。采用魏氏法测定红细胞沉降率(erythrocyte sedimentation rate, ESR)水平。采用免疫比浊法测定类风湿因子(rheumatoid factor, RF)水平。采用电化学发光免疫分析法检测降钙素原(procalcitonin, PCT)水平。

1.4 资料收集 收集患者的性别、年龄、体重指数、pSS病程、接受糖皮质激素及免疫抑制剂治疗情况。所有患者均行疾病活动度评分(EULAR Sjögren's syndrome disease activity index,

ESSDAI),其中ESSDAI ≤ 4 分为低疾病活动度,5~13分为中疾病活动度,>14分为高疾病活动度^[12]。记录患者临床症状。

1.5 统计学方法 应用SPSS 22.0统计软件分析数据。符合正态分布的计量资料以($\bar{x} \pm s$)表示,比较采用 t 检验;计数资料以例数(%)表示,比较采用 χ^2 检验或Fisher精确概率法;pSS发生ILD的影响因素确定采用Logistic回归分析;采用受试者工作特征(receiver operating characteristic, ROC)曲线分析预测价值。 $P < 0.05$ 为差异有统计学意义。

2 结 果

2.1 观察组和对照组临床一般资料比较 观察组年龄和病程明显高于对照组($P < 0.05$);观察组ESSDAI评分 ≥ 5 分、咳嗽咳痰、活动后喘憋比例明显高于对照组($P < 0.05$)。见表1。

表1 观察组和对照组临床一般资料比较

Table 1 Comparison of clinical general data between the observation group and the control group

组别	例数	性别(例数,%)		年龄 ($\bar{x} \pm s$,岁)	体重指数 ($\bar{x} \pm s$)	pSS病程 ($\bar{x} \pm s$,年)	ESSDAI评分 ≥ 5 分 (例数,%)	吸烟 (例数,%)
		男性	女性					
观察组	50	4(8.00)	46(92.00)	58.26 $\pm$ 11.06	22.10 $\pm$ 1.91	7.22 $\pm$ 1.54	41(82.00)	6(12.00)
对照组	80	1(1.25)	79(98.75)	49.40 $\pm$ 12.25	22.05 $\pm$ 1.43	6.03 $\pm$ 1.60	36(45.00)	9(11.25)
χ^2/t 值		—		4.162	0.170	4.185	17.444	0.017
P 值		0.072		<0.001	0.865	<0.001	<0.001	0.896
组别	例数	临床症状(例数,%)						
		发热	咳嗽咳痰	活动后喘憋	雷诺现象	口眼干	晨僵	皮疹
观察组	50	9(18.00)	38(76.00)	29(58.00)	5(10.00)	46(92.00)	7(14.00)	7(14.00)
对照组	80	12(15.00)	10(12.50)	10(12.50)	6(7.50)	65(81.25)	7(8.75)	9(11.25)
χ^2/t 值		0.205	53.272	30.333	—	2.849	0.883	0.216
P 值		0.651	<0.001	<0.001	0.748	0.091	0.348	0.624

—表示使用Fisher精确概率法

2.2 观察组和对照组实验室指标比较 观察组抗SSA抗体阳性和IgG >16 g/L比例、CRP和ESR明显高于对照组($P < 0.05$);观察组和对照组ANA阳性、抗SSB抗体阳性、RF >20 U/L、

IgA >4.0 g/L、IgM >2.3 g/L、C3 <0.79 g/L和C4 <0.1 g/L比例比较差异无统计学意义($P > 0.05$)。见表2。

2.3 观察组HRCT特征情况 观察组50例中,

表2 观察组和对照组实验室指标比较

Table 2 Comparison of laboratory indicators between the observation group and the control group

组别	例数	ANA 阳性 (例数, %)	抗 SSA 抗体阳性 (例数, %)	抗 SSB 抗体阳性 (例数, %)	RF > 20 U/L (例数, %)	IgA > 4.0 g/L (例数, %)	IgG > 16 g/L (例数, %)
观察组	50	50(100.00)	43(86.00)	34(68.00)	21(42.00)	20(40.00)	29(58.00)
对照组	80	79(98.75)	49(61.25)	53(66.25)	37(46.25)	31(38.75)	22(27.50)
χ^2/t 值		0.000	9.111	0.043	0.225	0.020	12.006
P值		1.000	0.003	0.837	0.635	0.887	0.001
组别	例数	IgM > 2.3 g/L (例数, %)	C3 < 0.79 g/L (例数, %)	C4 < 0.1 g/L (例数, %)	CRP ($\bar{x} \pm s$, mg/L)	ESR ($\bar{x} \pm s$, mm/1 h)	PCT ($\bar{x} \pm s$, mg/L)
观察组	50	21(42.00)	14(28.00)	13(26.00)	22.20 ± 9.29	55.54 ± 20.10	0.10 ± 0.03
对照组	80	31(38.75)	25(31.25)	22(27.50)	13.34 ± 4.45	43.36 ± 15.56	0.09 ± 0.03
χ^2/t 值		0.135	0.155	0.035	7.305	3.874	1.849
P值		0.713	0.694	0.851	< 0.001	< 0.001	0.067

HRCT 影像特征主要以肺外带网格影、磨玻璃影、小叶间隔增厚为主, 见表3。用力肺活量占预计值: 74.40%~94.54%, 平均(84.50 ± 6.65)%; 第一秒用力呼气容积值占预计值: 67.60%~88.04%, 平均(77.30 ± 5.51)%; 氧分压: 57~82 mmHg (1 mmHg = 0.133 kPa), 平均(68.29 ± 9.29) mmHg; 二氧化碳分压: 36~54 mmHg, 平均(41.10 ± 5.56) mmHg。

表3 观察组 HRCT 特征分布

Table 3 Distribution of HRCT characteristics in the observation group

影像特征	例数	比例(%)
肺外带网格影	23	46.00
磨玻璃影	20	40.00
小叶间隔增厚	16	32.00
胸膜下线影	14	28.00
囊性病变	9	18.00
实变影	7	14.00
牵拉性支气管扩张	5	10.00
蜂窝影	4	8.00

2.4 pSS 发生ILD 影响因素的多因素分析 将年龄、ESSDAI 评分、咳嗽咳痰、活动后喘憋、抗 SSA 抗体和 IgG 作为自变量, 是否合并ILD 作为因变量进行 Logistic 回归分析, 赋值见表4, 结果显示: 年龄、ESSDAI 评分、咳嗽咳痰、活动后喘憋、抗 SSA 抗体是 pSS 发生ILD 的影响因素 ($P < 0.05$), 见表5。

表4 pSS 合并ILD 影响因素的多因素分析

Table 4 Multivariate analysis of influencing factors of pSS-ILD

因素	符号	赋值
ILD	Y	无=0, 有=1
年龄	X1	< 60岁=0, ≥60岁=1
ESSDAI 评分	X2	< 5分=0, ≥5分=1
咳嗽咳痰	X3	无=0, 有=1
活动后喘憋	X4	无=0, 有=1
抗 SSA 抗体	X5	阴性=0, 阳性=1
IgG	X6	≤16g/L=0, >16g/L=1
CRP	X7	连续变量
ESR	X8	连续变量

表5 pSS 合并ILD 影响因素的 Logistic 回归分析

Table 5 Logistic regression analysis of influencing factors of pSS-ILD

因素	回归系数	标准误	Wald χ^2 值	P值	OR 值	95% CI
年龄	0.678	0.178	14.508	< 0.001	1.970	1.390~2.792
ESSDAI 评分	1.102	0.299	13.584	< 0.001	3.010	1.675~5.409
咳嗽咳痰	0.665	0.166	16.048	< 0.001	1.944	1.404~2.692
活动后喘憋	0.901	0.203	19.700	< 0.001	2.462	1.654~3.665
抗 SSA 抗体	1.044	0.301	12.030	< 0.001	2.841	1.575~5.124
IgG	0.456	0.665	0.470	0.601	1.578	0.429~5.809
CRP	0.334	0.565	0.349	0.687	1.397	0.461~4.227
ESR	0.293	0.334	0.770	0.556	1.340	0.697~2.580
常数项	-2.454	0.872	7.920	0.321	—	—

2.5 预测ILD 的价值分析 将 Logistic 回归方程: $\text{Logit}(P) = 0.678 \times \text{年龄} + 1.102 \times \text{ESSDAI 评分}$

$+ 0.665 \times \text{咳嗽咳痰} + 0.901 \times \text{活动后喘憋} + 1.044 \times \text{抗 SSA 抗体}$ 进行 ROC 曲线分析, 其预

测ILD的ROC曲线下面积为0.942(95%CI: 0.901~0.983),敏感度和特异度分别为91.70%和86.80%,见图2。

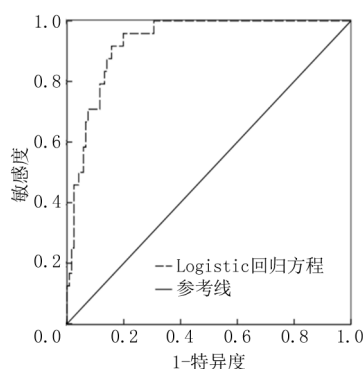


图2 预测ILD的ROC曲线图

Figure 2 ROC curve for predicting interstitial lung disease

3 讨 论

pSS是一种以侵犯外分泌腺为主的自身免疫性疾病,患者典型表现为口干、眼干,并可伴皮肤干燥等腺外表现,严重时可累及血管、肺及其他器官系统^[13-14]。ILD是pSS的常见并发症,也是导致患者死亡的重要因素。本研究探究合并症患者临床特征、HRCT特征。

分析临床资料显示,观察组年龄明显高于对照组;观察组ESSDAI评分 ≥ 5 分、咳嗽咳痰、活动后喘憋比例显著高于对照组。随着年龄增大,机体接触肺间质纤维化物质就越多,机体免疫调节因子出现紊乱,诱发导致ILD的发生^[15-16]。此外,衰老可使得肺泡大小和表面积改变,导致胶原蛋白沉积及弹性纤维破坏,上述情况可诱导肺组织重塑,促进ILD的发生发展^[17]。因此,对于年龄较大者,需要更加关注pSS患者合并ILD的可能性^[18-19]。观察组患者ESSDAI评分更高,疾病活动度更高,病情较复杂,提示pSS疾病活动与ILD的发生有关,这与以往文献^[20-21]报道相符。观察组咳嗽咳痰症状显著与患者气道内腺体分泌减少导致气道明显干燥有关。当患者进行活动时,身体对氧气的需求增加,而由于肺部病变,氧气交换受到限制,无法满足身体的需求。这就导致了活动后喘憋的发生率增高^[22]。也有研究认为pSS患者并发ILD时会出现阻塞性通气功能障碍,导致肺泡通气分布不均,这也会影响呼吸功能^[23-24]。尽管对照组为pSS患者未合并ILD,但仍有部分患者出现咳嗽咳痰(12.96%)及活动后喘憋(9.26%)症状,分析是pSS对呼吸系统产生

了直接影响,其能造成气道环境的干燥化、黏膜组织的损伤,甚至诱发气道高反应性或轻度的气道炎症等肺部并发症,进而诱发咳嗽、咳痰以及活动后的憋喘等临床表现。

观察组抗SSA抗体阳性和IgG > 16 g/L比例明显高于对照组。本研究结果显示,抗SSA抗体阳性与原发干燥综合征患者发生ILD风险增加相关。这与部分研究^[25]存在差异,可能源于研究视角的不同。一方面,抗SSA抗体所针对的抗原Ro-52在固有免疫应答和细胞凋亡调控中扮演重要角色,其自身抗体的产生可能参与了肺组织的免疫损伤过程,从而增加ILD的易感性^[26-27]。另一方面,有研究在已确诊ILD的患者群体中发现,抗SSA抗体阳性可能与更差的预后相关,这提示在ILD发生后的病程演进中,抗体状态可能具有不同的意义^[28]。抗SSA抗体阳性的ILD患者或许存在其他更强烈的促纤维化或炎症驱动因素,导致其疾病进展更快、死亡风险更高。因此,抗SSA抗体阳性可能更主要地关联于ILD的发生风险,而其在疾病进展与预后中的作用则可能更为复杂,需要结合其他临床与生物学指标综合判断。自身免疫性疾病多伴随球蛋白水平及免疫球蛋白异常^[29-30]。本研究中观察组IgG > 16 g/L比例更高,可能与观察组肺血管炎较为严重相关。高免疫球蛋白会促进免疫复合物激活,促进中性粒细胞释放氧自由基及胶原酶这一过程,造成对肺实质的破坏,诱发ILD^[31]。由此,在pSS合并ILD的诊断及病情监测中应重点关注抗SSA抗体阳性比例及免疫球蛋白等免疫学指标变化。CRP和ESR作为常用的炎症标志物,其升高通常反映体内存在急性或慢性炎症反应^[32]。笔者研究结果显示观察组CRP、ESR水平明显高于对照组,观察组患者CRP和ESR水平的增高可能归因于ILD引起的肺部炎症和组织损伤,这些病理变化进一步激发了机体的免疫反应,导致炎症标志物的释放增加。

pSS合并ILD变多出现于中下肺,逐渐向上进展。在观察组中,HRCT影像特征主要以肺外带网格影、磨玻璃影、小叶间隔增厚为主。研究^[33]发现,pSS合并ILD的病理类型主要有非特异性间质性肺炎和寻常型肺间质病变,前者被认为是淋巴细胞浸润性间质病变,影像学上常见磨玻璃影。后者病灶纤维化程度多变,病变呈现复杂分布,在影像学上的表现也具有多样化,主要表现为网格影^[34]。在疾病进展过程中,肺泡腔内会出现纤维蛋白的沉积,形成Masson小体,在HRCT上呈

现为多灶性结节实变影,并出现小叶间隔增厚。观察组患者主要呈现淋巴浆细胞、单核细胞和成纤维细胞等的肺间质弥漫性损伤。上述情况会造成肺泡上皮细胞基膜发生改变,导致肺泡壁、肺泡腔内出现大量纤维素渗出物及炎性渗出物,因此形成前述影像学征象。

本研究通过 Logistic 回归分析证实年龄增长、ESSDAI 评分升高、咳嗽咳痰、活动后喘憋及抗 SSA 抗体是 pSS 患者并发 ILD 的独立影响因素。基于这些因素所构建的预测模型在本研究队列内展现出良好的判别效能,ROC 曲线下面积达 0.942,且具有较高的敏感度与特异度。这表明该模型在本研究人群中对于识别 ILD 高风险患者具有较好的应用潜力。虽然部分因素如高龄或特定抗体状态的关联性在既往文献中有所提及,但本研究整合了多维度临床与实验室指标构建预测模型,有助于深化对疾病发生机制的理解。临床可参考此模型对 pSS 患者进行风险评估。

然而,本研究亦存在一定的局限性。首先,研究为单中心回顾性设计,且观察组与对照组的样本量相对有限,研究结论的外推性可能受到影响。未来需要更大样本、多中心的前瞻性研究加以验证。其次,本研究构建的预测模型尚未进行独立的外部验证,其广泛的适用性及稳定性有待进一步评估。

综上所述,pSS 合并 ILD 患者具有以下临床特征:患者年龄偏大,临床症状以咳嗽、咳痰及活动后气促(喘憋)为主,实验室检查显示抗 SSA 抗体阳性率显著升高;HRCT 影像学特征主要表现为双肺外带网格状影、磨玻璃样密度影及小叶间隔增厚;且患者年龄、ESSDAI 评分等因素与 pSS 患者并发 ILD 的发生风险密切相关。

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