



系统性红斑狼疮继发真菌感染影响因素分析*

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【摘要】目的 探讨系统性红斑狼疮(systemic lupus erythematosus, SLE)患者继发真菌感染的影响因素。**方法** 回顾性选取2021年6月—2025年1月我院收治的310例SLE患者作为研究对象,根据有无继发真菌感染分为未感染组和感染组,经倾向性评分法(propensity score matching, PSM)进行5:1匹配后,未感染组和感染组分别纳入患者230例、46例。分析SLE患者继发真菌感染现状,通过Logistic回归分析SLE患者继发真菌感染的影响因素,并采用受试者工作特征(receiver operating characteristic, ROC)曲线评估模型预测效能,构建预测SLE患者继发真菌感染的列线图模型。**结果** 在纳入的310例SLE患者中真菌感染46例(14.84%),以肺部感染(50.0%)和胃肠道感染(23.9%)为主。匹配分组后,二元Logistic回归分析结果显示,狼疮活动度(OR=10.734, 95%CI=2.015~57.184)、抗菌药物应用时间(OR=13.826, 95%CI=2.995~63.822)、CRP(OR=9.927, 95%CI=1.024~96.188)、白细胞计数(OR=11.784, 95%CI=1.568~88.553)、补体C4(OR=16.392, 95%CI=3.899~68.909)、24 h Pro(OR=9.391, 95%CI=1.195~73.813)均为SLE患者继发真菌感染的独立危险因素($P<0.05$)。ROC曲线评估显示,狼疮活动度、抗菌药物应用时间、C反应蛋白、白细胞计数、补体C4、24 h尿蛋白对SLE患者继发真菌感染均有一定的预测能力,六者联合预测的曲线下面积(area under the curve, AUC)为0.821, 95%CI为0.720~0.922,优于单一指标(AUC 0.593~0.672)。此六者联合纳入构建列线图模型。**结论** 狼疮活动度、抗菌药物应用时间、CRP、WBC、补体C4、24 h Pro是SLE患者继发真菌感染的影响因素。

【关键词】 系统性红斑狼疮 真菌感染 影响因素 倾向性评分法

Influencing Factors for Secondary Fungal Infections in Systemic Lupus Erythematosus

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[Abstract] Objective To investigate the influencing factors for secondary fungal infections in patients with systemic lupus erythematosus (SLE). **Methods** A total of 310 SLE patients admitted to our hospital between June 2021 and January 2025 were retrospectively enrolled. They were divided into an infection group and a non-infection group based on the presence or absence of secondary fungal infections. After 5:1 matching using propensity score matching (PSM), 230 patients in the non-infection group and 46 patients in the infection group were included in the final analysis. The characteristics of secondary fungal infections in patients with SLE were analyzed. Logistic regression analysis was performed to identify factors associated with secondary fungal infections, and receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive performance of the model. A nomogram model for predicting secondary fungal infections in SLE patients was subsequently established. **Results** Among the 310 SLE patients enrolled, fungal infection occurred in 46 cases (14.84%), predominantly involving the lung (50.0%) and the gastrointestinal tract (23.9%). After PSM, binary logistic regression analysis revealed that lupus disease activity (odds ratio [OR] = 10.734, 95% CI: 2.015-57.184), duration of antibiotic use (OR = 13.826, 95% CI: 2.995-63.822), C-reactive protein (CRP) (OR = 9.927, 95% CI: 1.024-96.188), white blood cell (WBC) count (OR = 11.784, 95% CI: 1.568-88.553), complement C4 (OR = 16.392, 95% CI: 3.899-68.909), and 24-hour urine protein (24 h Pro) (OR = 9.391, 95% CI: 1.195-73.813) were independent risk factors for secondary fungal infections in SLE patients (all $P < 0.05$). ROC curve analysis demonstrated that lupus disease activity, duration of antibiotic use, CRP, WBC count, complement C4, and 24 h Pro all demonstrated predictive value for secondary fungal infections. The combined model incorporating all 6 indicators achieved an area under the ROC curve (AUC) of 0.821 (95% CI: 0.720-0.922), outperforming any individual indicator (AUC range: 0.593-0.672). A nomogram

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prediction model was subsequently established based on these 6 indicators. **Conclusion** Lupus activity, duration of antibiotic use, CRP, WBC, complement C4, and 24 h Pro are the influencing factors of secondary fungal infection in SLE patients.

[Key words] Systemic lupus erythematosus Fungal infection Influencing factors Propensity score matching

系统性红斑狼疮(systemic lupus erythematosus, SLE)属于累及全身多脏器的慢性自身免疫病,最新流行病学调查报告显示^[1],SLE的全球患病率约为30/10万~150/10万,年发病率约2.2/10万~23.1/10万,我国发病率为30.13/10万~70.41/10万左右,且高发于育龄期女性群体。

在SLE的临床管理实践中,伴随着疾病治疗手段的不断发展与广泛应用,一系列新的临床问题也逐渐显现出来。具体而言,由于糖皮质激素在临床中长期应用、广谱抗菌药物广泛使用以及免疫抑制剂对机体免疫功能的损害,复杂感染已成为影响SLE预后的关键因素;其中真菌感染因其起病隐匿、诊断困难、治疗棘手等特点,更是当前危重症患者死亡的主要诱因之一^[2]。真菌感染不仅可诱发并加剧SLE,更贯穿疾病全程^[3];相关研究表明^[4],近5年真菌感染发生率已达20世纪90年代的2倍,且发病率持续攀升,显著增加了临床诊疗难度和患者死亡风险,应引起临床的高度重视。鉴于上述严峻形势,预防SLE患者继发真菌感染已成为临床防控重点,而要实现有效的预防,早期识别相关危险因素是制定精准防治策略的关键前提。

倾向性评分法(propensity score matching, PSM)是对观察研究中偏差问题进行处理的一种统计学方法,目的是对随机分配效果进行模拟,减少非随机分配所引起的选择偏差,提高因果推断的准确性^[5]。本研究即根据PSM采用单因素和多因素Logistic回归模型探究SLE患者继发真菌感染的影响因素,并建立风险预测模型,为临床早期防治提供科学参考。

1 资料与方法

1.1 样本量和分组

本研究为回顾性研究,经武汉市中西医结合医院伦理委员会批准,伦理批号:科伦预审[2024]54号,严格遵循《赫尔辛基宣言》伦理准则。

参考文献^[6]计算样本量,采用统计学标准公式: $N=Z^2\times[P(1-P)]/E^2$,其中各参数定义为: N 代表所需最小样本量, Z 对应标准正态分布临界值, P 表示预期总体率, E 为允许的最大抽样误差范围,该公式通过控制 I 类错误概率和估计精度,确保研究具有足够的统计检验效能,当置信度为95%时, $Z=1.96$, $P=0.2$, $E=5\%$,向上取整 N 为246例,即最低需纳入246例患者,考虑到10%~20%样本脱落率,最低需纳入296例患者。

本研究选取2021年6月—2025年1月我院收治的310例SLE患者作为研究对象,根据有无继发真菌感染,将研究对象分为未感染组264例和感染组46例。采用PSM对两组患者进行5:1匹配,卡钳值为0.02。协变量包括性别、年龄、身体质量指数(body mass index, BMI)、吸烟、饮酒。匹配完成后,通过统计学方法验证协变量的均衡性, $P>0.05$ 即为分布均衡。最终未感染组和感染组分别纳入患者230例、46例。匹配前,未感染组与感染组在性别、年龄方面差异有统计学意义($P<0.05$)。匹配后,两组基线资料均衡($P>0.05$),见表1。

1.2 资料收集

本研究采用双人背对背质控流程收集电子病历数

表 1 PSM匹配前后基线资料对比
Table 1 Comparison of baseline data before and after PSM

Baseline data		Before matching				After matching			
		Non-infection group (n = 264)	Infection group (n = 46)	χ^2/t	P	Non-infection group (n = 230)	Infection group (n = 46)	χ^2/t	P
Sex/case (%)	Male	110 (41.7)	12 (26.1)	3.984	0.046	86 (37.4)	12 (26.1)	2.139	0.144
	Female	154 (58.3)	34 (73.9)			144 (62.6)	34 (73.9)		
Age/yr., $\bar{x} \pm s$		45.26 $\pm$ 9.74	37.08 $\pm$ 10.32	5.210	< 0.001	39.51 $\pm$ 10.25	37.08 $\pm$ 10.32	1.466	0.144
BMI/(kg/m ²), $\bar{x} \pm s$		24.58 $\pm$ 2.42	24.65 $\pm$ 3.64	0.166	0.868	23.82 $\pm$ 3.77	24.65 $\pm$ 3.64	1.371	0.172
Smoking/case (%)	Yes	81 (30.7)	15 (32.6)	0.068	0.794	73 (31.7)	15 (32.6)	0.013	0.908
	No	183 (69.3)	31 (67.4)			157 (68.3)	31 (67.4)		
Drinking/case (%)	Yes	103 (39.0)	19 (41.3)	0.086	0.769	97 (42.2)	19 (41.3)	0.012	0.913
	No	161 (61.0)	27 (58.7)			133 (57.8)	27 (58.7)		

PSM: propensity score matching; BMI: body mass index.

据。收集一般资料:病程、住院时间(根据住院时间28 d为感染风险评估的核心分界值分为 ≤ 4 周、 >4 周)、日均体温、狼疮活动度、泼尼松等效剂量、免疫抑制剂应用种类、抗菌药物应用时间、器官受损累及数目。

在患者入院第2天早晨抽取空腹肘静脉血5 mL,采用ELISA测定血清C反应蛋白(C-reactive protein, CRP)水平,采用全血细胞分析仪(深圳迈瑞生物医疗电子股份有限公司,型号:BC-5 140)测定白细胞(white blood cell, WBC)、外周血CD4⁺T淋巴细胞计数,采用全自动生化分析仪(美国贝克曼库尔特有限公司,型号:AU5800)检测补体C3、补体C4、白蛋白(albumin, ALB)。在患者入院第2天开始留取患者24 h尿量,采用比色法测定24 h尿蛋白定量(24 hour urinary protein quantitative, 24 h Pro)。

1.3 标准和定义

诊断标准: SLE诊断标准参考文献^[7]进行判断。(2)真菌感染标准参考文献^[8]进行判断。

纳入标准: ①符合SLE诊断标准; ②年龄 >18 岁; ③临床资料完整; ④患者或家属知情且签订知情同意书。

排除标准: ①合并严重心脑血管疾病且预计生存时间不足3个月; ②临床依从性差, 不配合试验; ③合并血管炎、类风湿关节炎等其他结缔组织病, 或病毒性肝炎、活动性结核等急慢性感染; ④合并人类免疫缺陷病毒(human immunodeficiency virus, HIV)感染、恶性肿瘤等原发性免疫缺陷疾病。

采用系统性红斑狼疮疾病活动性指数(systemic lupus erythematosus disease activity index, SLEDAI)^[9]评估狼疮活动度, 0~4分为疾病基本无活动, 无需强化治疗; 5~9分为轻度活动, 需密切监测并调整维持治疗方案; 10~14分为中度活动, 应加强免疫抑制治疗; ≥ 15 分为重度活动, 需紧急干预。SLEDAI评分分为轻度(0~9分)和中重度(≥ 10 分)。

泼尼松等效剂量: ≤ 15 mg/d泼尼松等效剂量为维持治疗剂量, 用于病情稳定期, 对免疫功能抑制较轻; >15 mg/d为诱导治疗剂量, 用于活动期, 需较强免疫抑制作用, 易导致免疫功能低下。

免疫抑制剂应用种类: 单药或2种免疫抑制剂联用为标准方案, 适用于多数稳定期或轻度活动期患者; >2 种联用仅用于难治性或重度活动期患者, 免疫抑制强度更高。

抗菌药物应用时间: 推荐的抗菌药物标准疗程为7~14 d。

器官受损累及数目: 累及 ≤ 3 个器官为轻度器官受累, >3 个器官为多器官受累, 提示病情更严重, 免疫功能更紊乱。

CRP正常参考值为0~10 mg/L, >10 mg/L提示存在急性炎症反应。成人WBC正常参考值为 $4 \times 10^9 \sim 10 \times 10^9 \text{ L}^{-1}$, $3 \times 10^9 \text{ L}^{-1}$ 低于正常下限, 提示WBC减少。外周血CD4⁺T淋巴细胞计数 ≤ 200 细胞/ μL 提示细胞免疫功能严重低下。成人补体C3正常参考值为0.9~1.8 g/L, ≤ 0.8 g/L提示补体系统激活消耗。成人补体C4正常参考值为0.1~0.4 g/L, >0.4 g/L提示补体系统代偿性升高。ALB ≤ 30 g/L为中度低蛋白血症。24 h Pro >3.5 g提示肾病综合征型狼疮肾炎。

1.4 结局指标

1.4.1 主要结局指标

SLE患者继发真菌感染的发生情况。根据真菌感染诊断标准^[8], 判断患者是否发生真菌感染, 并记录感染部位(如肺部、胃肠道、泌尿生殖道、血液及中枢神经系统等)。

1.4.2 次要结局指标

CRP、WBC、CD4⁺、补体C3、补体C4、ALB、24 h Pro。

1.5 统计学方法

本研究采用SPSS 27.0和R软件(4.3.1)进行统计分析。计量资料以 $\bar{x} \pm s$ 表示, 组间比较采用 t 检验; 计数资料以例数(%)表示, 组间比较采用 χ^2 检验; 通过单因素及多因素Logistic回归分析SLE患者继发真菌感染的影响因素, 采用受试者工作特征(receiver operating characteristic, ROC)曲线评估指标的预测效能, 构建预测SLE患者继发真菌感染的列线图模型, $\alpha=0.05$ 。

2 结果

2.1 SLE患者继发真菌感染现状

在纳入的310例SLE患者中真菌感染46例, 感染率为14.84%。其中肺部23例(50.0%)、胃肠道11例(23.9%)、泌尿生殖道4例(8.7%)、血液及中枢神经系统3例(6.5%)、腹腔1例(2.2%)、骨髓1例(2.2%)、混合3例(6.5%), SLE患者继发真菌感染以肺部感染和胃肠道感染为主。见表2。

表2 SLE患者继发真菌感染部位分析

Table 2 Analysis of secondary fungal infection sites in SLE patients

Infection site	Case	Proportion/%
Lung	23	50.0
Gastrointestinal tract	11	23.9
Urogenital tract	4	8.7
Blood and central nervous system	3	6.5
Abdominal cavity	1	2.2
Bone marrow	1	2.2
Mixed	3	6.5
Total	46	100.0

2.2 SLE患者继发真菌感染单因素分析

感染组患者在住院时间>4周、狼疮活动度中重度、泼尼松等效剂量>15 mg/d、抗菌药物应用时间>2周、器官受损累及数目>3、CRP>10 mg/L、WBC>3×10⁹ L⁻¹、

CD4⁺≤200细胞/μL、补体C3≤0.8 g/L、补体C4>0.4 g/L、24 h Pro>3.5 g的比例均显著高于未感染组,差异具有统计学意义($P<0.05$),两组病程、日均体温、免疫抑制剂应用种类、ALB比较差异无统计学意义($P>0.05$),见表3。

表 3 SLE患者继发真菌感染与未继发真菌感染者的临床指标比较

Table 3 Comparison of clinical characteristics between SLE patients with secondary fungal infections and those without secondary fungal infections				
Factors		Non-infection group (n = 230)	Infection group (n = 46)	χ^2/t P
Course of disease/year, $\bar{x} \pm s$		43.92 ± 11.76	44.60 ± 12.18	0.356 0.722
Length-of-stay/case (%)	≤ 4 weeks	130 (56.5)	14 (30.4)	10.455 0.001
	> 4 weeks	100 (43.5)	32 (69.6)	
Average daily body temperature/℃, $\bar{x} \pm s$		37.90 ± 8.47	38.62 ± 9.09	0.520 0.604
Lupus activity/case (%)	Mild	96 (41.7)	10 (21.7)	6.482 0.011
	Moderate to severe	134 (58.3)	36 (78.3)	
Equivalent dose of prednisone/case (%)	≤ 15 mg/d	176 (76.5)	26 (56.5)	7.814 0.005
	> 15 mg/d	54 (23.5)	20 (43.5)	
The number of immunosuppressants applied/case (%)	≤ 2 kinds	148 (64.3)	29 (63.0)	0.028 0.866
	> 2 kinds	82 (35.7)	17 (37.0)	
Duration of antibacterial drug administration/case (%)	≤ 2 weeks	136 (59.1)	18 (39.1)	6.217 0.013
	> 2 weeks	94 (40.9)	28 (60.9)	
The number of organs involved in damage/case (%)	≤ 3	142 (61.7)	19 (41.3)	6.586 0.010
	> 3	88 (38.3)	27 (58.7)	
CRP/case (%)	≤ 10 mg/L	154 (67.0)	15 (32.6)	19.051 0.000
	> 10 mg/L	76 (33.0)	31 (67.4)	
WBC/case (%)	≤ 3 × 10 ⁹ L ⁻¹	122 (53.0)	15 (32.6)	6.403 0.011
	> 3 × 10 ⁹ L ⁻¹	108 (47.0)	31 (67.4)	
CD4 ⁺ /case (%)	≤ 200 cells/μL	81 (35.2)	25 (54.3)	5.931 0.015
	> 200 cells/μL	149 (64.8)	21 (45.7)	
Complement C3/case (%)	≤ 0.8 g/L	108 (47.0)	31 (67.4)	6.403 0.011
	> 0.8 g/L	122 (53.0)	15 (32.6)	
Complement C4/case (%)	≤ 0.4 g/L	139 (60.4)	17 (37.0)	8.599 0.003
	> 0.4 g/L	91 (39.6)	29 (63.0)	
ALB/case (%)	≤ 30 g/L	104 (45.2)	25 (54.3)	1.284 0.257
	> 30 g/L	126 (54.8)	21 (45.7)	
24 h Pro/case (%)	≤ 3.5 g	93 (40.4)	10 (21.7)	5.728 0.017
	> 3.5 g	137 (59.6)	36 (78.3)	

CRP: C-reactive protein; WBC: white blood cell; ALB: albumin; 24 h Pro: 24 hour urinary protein quantitative.

2.3 SLE患者继发真菌感染多因素Logistic回归分析

以SLE患者有无继发真菌感染为因变量,将表3中差

异具有统计学意义的因素(住院时间、狼疮活动度、泼尼松等效剂量、抗菌药物应用时间、器官受损累及数目、

CRP、WBC、CD4⁺、补体C3、补体C4、24 h Pro)作为自变量纳入二元Logistic回归分析中,赋值见表4。二元Logistic回归分析结果显示,狼疮活动度(OR= 10.734, 95%CI= 2.015 ~ 57.184)、抗菌药物应用时间(OR= 13.826, 95%CI= 2.995 ~ 63.822)、CRP(OR= 9.927,

95%CI= 1.024 ~ 96.188)、WBC(OR= 11.784, 95%CI= 1.568 ~ 88.553)、补体C4(OR= 16.392, 95%CI= 3.899 ~ 68.909)、24 h Pro(OR= 9.391, 95%CI= 1.195 ~ 73.813)均为SLE患者继发真菌感染的独立危险因素($P < 0.05$),见表5。

表 4 赋值方法

Table 4 Value assignment method

Factors	Assignment methods
Are there any secondary fungal infections in SLE patients	0 = Non-infection, 1 = Infection
Length-of-stay	0 = ≤ 4 weeks, 1 = > 4 weeks
Lupus activity	0 = Mild, 1 = Moderate to severe
Equivalent dose of prednisone	0 = ≤ 15 mg/d, 1 = > 15 mg/d
Duration of antibacterial drug administration	0 = ≤ 2 weeks, 1 = > 2 weeks
The number of organs involved in damage	0 = ≤ 3 , 1 = > 3
CRP	0 = ≤ 10 mg/L, 1 = > 10 mg/L
WBC	0 = $\leq 3 \times 10^9 \text{ L}^{-1}$, 1 = $> 3 \times 10^9 \text{ L}^{-1}$
CD4 ⁺	0 = > 200 cells/ μL , 1 = ≤ 200 cells/ μL
Complement C3	0 = > 0.8 g/L, 1 = ≤ 0.8 g/L
Complement C4	0 = ≤ 0.4 g/L, 1 = > 0.4 g/L
24 h Pro	0 = ≤ 3.5 g, 1 = > 3.5 g

All abbreviations are given in the footnote to Table 3.

表 5 SLE患者继发真菌感染多因素Logistic回归分析

Table 5 Multivariate logistic regression analysis of secondary fungal infection in SLE patients

Factors	<i>B</i>	SE	Wald χ^2	<i>P</i>	OR	95% CI	
						Lower limit	Upper limit
Length-of-stay	-1.759	1.283	1.880	0.170	0.172	0.014	2.129
Lupus activity	2.373	0.854	7.732	0.005	10.734	2.015	57.184
Equivalent dose of prednisone	0.131	0.703	0.034	0.853	1.139	0.287	4.521
Duration of antibacterial drug administration	2.627	0.780	11.327	< 0.001	13.826	2.995	63.822
The number of organs involved in damage	-1.199	1.010	1.410	0.235	0.302	0.042	2.181
CRP	2.295	1.159	3.924	0.048	9.927	1.024	96.188
WBC	2.467	1.029	5.746	0.017	11.784	1.568	88.553
CD4 ⁺	0.639	0.609	1.099	0.295	1.894	0.574	6.252
Complement C3	-1.237	1.113	1.237	0.266	0.290	0.033	2.568
Complement C4	2.797	0.733	14.572	< 0.001	16.392	3.899	68.909
24 h Pro	2.240	1.052	4.534	0.033	9.391	1.195	73.813
Constant	-7.802	1.077	52.503	< 0.001	0.000	—	—

B: partial regression coefficient; SE: standard error; OR: odds ratio; CI: confidence interval. The other abbreviations are explained in the note to Table 3.

2.4 SLE患者继发真菌感染的预测价值分析

分别以狼疮活动度、抗菌药物应用时间、CRP、白细胞计数、补体C4、24 h Pro这6个指标预测SLE患者继发真

菌感染,CRP的曲线下面积(area under the curve, AUC)为0.672,高于其他5个指标。6个指标联合的AUC为0.821,预测价值优于单一指标。见表6、图1。

表 6 ROC曲线评估各指标对SLE患者继发真菌感染的预测价值
Table 6 Analysis of the predictive value of various measures for secondary fungal infections in SLE patients

Factors	AUC	P	95% CI	
			Lower limit	Upper limit
Lupus activity	0.600	0.032	0.515	0.685
Duration of antibacterial drug administration	0.600	0.032	0.511	0.689
CRP	0.672	0.000	0.586	0.758
WBC	0.602	0.029	0.514	0.690
Complement C4	0.617	0.012	0.529	0.706
24 h Pro	0.593	0.045	0.508	0.679
Joint prediction	0.821	0.000	0.720	0.922

All abbreviations are explained in the note to Table 3.

2.5 SLE患者继发真菌感染的列线图模型构建

将多因素Logistic回归分析中筛选出的6项独立危险因素(狼疮活动度、抗菌药物应用时间、CRP、WBC、补体C4、24 h Pro)纳入列线图模型的构建,预测SLE患者继发真菌感染的风险,如图2所示。例如,某SLE患者为中重度狼疮活动(得分为55分)、抗菌药物

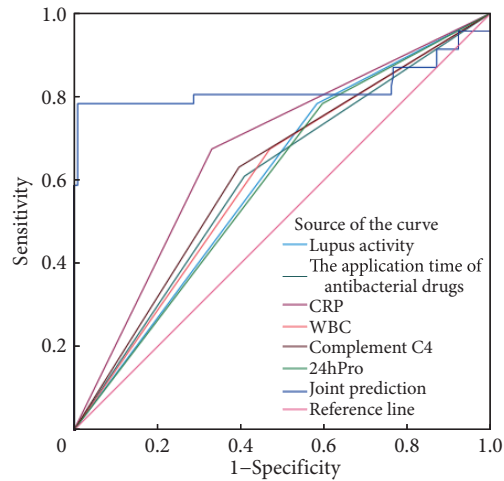


图 1 SLE患者继发真菌感染的ROC曲线
Fig 1 The ROC curve of secondary fungal infection in patients with SLE
All abbreviations are explained in the note to Table 3.

应用时间>2周(得分为60分)、CRP>10 mg/L(得分为50分)、WBC>3×10⁹ L⁻¹(得分为55分)、补体C4>0.4 g/L(得分为65分)、24 h Pro>3.5 g(得分为50分),则总分为335分,对应预测风险约为75%,提示该患者为继发真菌感染的高危人群,应加强监测并考虑预防性抗真菌治疗。

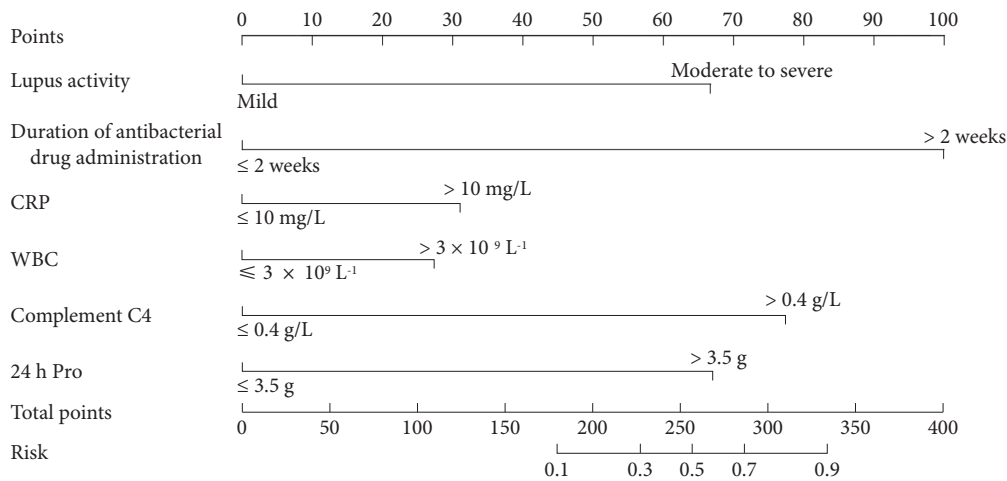


图 2 SLE患者继发真菌感染的列线图模型
Fig 2 Nomogram model for predicting secondary fungal infection in patients with SLE
All abbreviations are explained in the note to Table 3.

3 讨论

目前已知近500种真菌可对人类构成潜在威胁,在合并真菌感染的基础疾病中,风湿性疾病位居第2位^[10]。SLE因其自身遗传缺陷与免疫系统紊乱,需长期接受免疫抑制剂及糖皮质激素治疗,显著削弱了机体抗感染防御能

力,致使此类患者感染风险显著升高,在风湿性疾病合并真菌感染的病例中,近半数源自SLE^[11]。本研究调查结果显示,SLE患者继发真菌感染的发生率为14.84%,Roberts等^[12]调查发现,2009-2021年美国儿童及青少年SLE患者的感染发生率为13%,与本研究结果相近;且该人群感染风险呈时间依赖性增长趋势,因此挖掘SLE患者继发真菌感染

的影响因素及风险在临床中有着重大的意义。

本研究结果发现,狼疮活动度、抗菌药物应用时间、CRP、WBC、补体C4、24 h Pro均为SLE患者继发真菌感染的独立危险因素。分析原因,中重度狼疮活动度通过多通路协同作用显著增加了真菌感染风险:首先,中重度疾病活动度直接破坏了免疫防御体系,表现为补体C3消耗性降低、中性粒细胞数量减少及功能障碍、T淋巴细胞深度耗竭,三者协同削弱抗真菌能力;其次,失控的细胞因子在破坏皮肤黏膜屏障及血管内皮完整性的同时,抑制了特异性抗真菌免疫应答;最后,活动性器官损伤形成级联效应,肾脏病变致大量蛋白尿引发免疫球蛋白丢失,肺部含铁渗出液为曲霉菌提供增殖基质,皮肤溃疡形成真菌定植入口,共筑侵袭性微环境^[13,14]。钟会英等^[6]研究显示,SLEDAI评分 ≥ 10 分是SLE患者继发深部真菌感染的影响因素,与本研究结果完全一致。广谱抗菌药物无差别杀菌,破坏细菌对真菌的竞争性抑制,使念珠菌、曲霉菌等条件致病菌获得生长优势。同时,黏膜的细菌生物膜受损,增强了真菌的黏附与侵袭能力,易引发深部感染。此外,长期联用抗菌药物与激素或环磷酰胺,可协同抑制巨噬细胞吞噬及中性粒细胞趋化功能,削弱机体清除真菌的能力^[15]。CRP升高反映了系统性炎症失控,提示补体过度激活及中性粒细胞功能障碍,直接削弱了念珠菌/曲霉菌清除能力;其次,CRP升高掩盖感染征象,因SLE本身可致CRP上升,易误判真菌感染早期表现为疾病复发,延误治疗并促进播散;最终,为控制CRP对应的疾病活动而强化免疫抑制治疗,进一步加剧了T细胞耗竭及黏膜损伤,长期广谱抗生素破坏了微生态,促使真菌在肺/肠定植^[16]。Carvalho等^[17]表明,CRP预测SLE患者发生感染的灵敏度和特异度均为67%,本研究中CRP对SLE继发真菌感染的预测效能与之相近(敏感度67.40%,特异度67.00%),进一步验证了该生物标志物的临床价值。SLE活动期过量炎症因子刺激骨髓过度生成白细胞,但多为未成熟/功能缺陷细胞,吞噬杀菌功能低下;此外,WBC升高常合并CD4⁺细胞减少,致使抗真菌细胞因子分泌不足,提升感染风险^[18]。补体C4水平升高本质是补体系统功能紊乱的病理代偿表现:活动期SLE患者因经典补体途径持续激活,促进肝细胞代偿性合成C4,但该过程伴随自身免疫介导的C4功能破坏,抗C1q抗体等攻击使C4分子构象异常,丧失了形成C3转化酶的能力;这种“数量升高而功能瘫痪”的矛盾状态又导致了三大病理后果,即升高的非功能性C4竞争性占据补体受体,阻碍正常调理作用;曲霉、念珠菌等真菌分泌的蛋白酶裂解了异常地C4,产生促炎片段C4a,加剧组织损伤;补体终末膜攻击

复合物形成障碍,使病原体溶解失效^[19]。对于24 h Pro,首先,大量蛋白尿导致免疫球蛋白和补体经肾脏持续丢失,显著削弱了抗体介导的病原清除及补体调理吞噬功能;同时,继发低蛋白血症引发了全身机能紊乱,蛋白质营养不良抑制淋巴细胞增殖与巨噬细胞吞噬活性,组织水肿阻碍免疫细胞向感染部位迁移,并降低了抗真菌药物游离浓度;最终,肾功能不全致尿毒症毒素蓄积,直接抑制了中性粒细胞趋化与氧化爆发能力,促进了念珠菌在泌尿道的黏附定植,高渗肾小管液更成为真菌增殖的理化温床^[20-21]。

本研究整合狼疮活动度、抗菌药物应用时间、CRP、WBC、补体C4及24 h Pro六项危险因素,构建风险预测模型,其预测效能优于任一单一指标,有助于临床早期识别高危患者。为进一步便于应用,基于上述变量构建列线图预测模型,将Logistic回归结果转化为可视化个体风险评分工具,临床医师根据各指标取值对应赋分求和,即可快速获取个体化真菌感染预测概率。该模型操作便捷,适用于门诊筛查与住院动态评估。未来可嵌入电子病历或移动终端,实现自动化风险预警。临床可实施“筛查-阻断-预防”三级防治策略,动态风险分层:ROC模型识别高危患者纳入强化监控,密切追踪SLEDAI评分、抗菌药物应用时间、CRP、WBC、补体C4、24 h Pro。病理机制靶向干预:甲强龙冲击后续4周内泼尼松减量至 ≤ 10 mg/d,CD4⁺ ≤ 100 个/ μ L时换用贝利尤单抗;抗菌药物疗程严控两周内,广谱药物联用 ≤ 1 周;CRP/降钙素原分离时立即行(1,3)- β -D葡聚糖和曲霉菌半乳甘露聚糖试验,不明原因发热超过72 h立刻启动经验性抗真菌治疗;动态追踪白介素-6、CD4⁺等免疫指标,WBC $> 3 \times 10^9$ L⁻¹合并免疫缺陷时立即启动抗真菌预防;C4升高伴CH50下降者使用依库珠单抗;24 h Pro > 3.5 g者在羟氯喹+血管紧张素转换酶抑制剂/血管紧张素受体拮抗剂基础上加用他克莫司。精准预防:曲霉高危用泊沙康唑200 mg/d,念珠菌高危用氟康唑400 mg/周,持续至SLEDAI < 6 分且补体C4正常化。

综上所述,狼疮活动度、CRP、补体C4、24 h Pro是SLE患者继发真菌感染的独立危险因素,其联合构建的风险预测模型在预测真菌感染中有着较高的价值,这对临床防治有着重要的参考价值。本研究尚存在一定不足,例如样本量较小、数据来源较为单一,故后续还需扩大样本开展多中心研究,以为临床提供更科学、可靠、普适性的参考依据。

* * *

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