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· 论 著 ·

侵袭性毛霉病并发血栓性疾病的临床特征、诊治及预后因素分析

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[摘要] **目的** 探讨侵袭性毛霉病并发血栓性疾病的主要临床特征、诊治过程及预后影响因素。**方法** 回顾性分析 2021 年 1 月—2025 年 1 月某院收治的 5 例侵袭性毛霉病并发血栓性疾病病例, 并对国内外报道的该类病例进行总结。**结果** 共纳入 33 例病例, 男性 14 例, 女性 19 例, 其中死亡 21 例, 存活 12 例, 病死率达 63.64%。31 例存在 1 种及以上基础疾病, 仅 2 例无基础疾病史。所有患者临床表现均有不同程度的感染中毒症状(如发热、咳嗽、气促、病灶肿痛出血、休克等)或血栓性疾病引发的包括意识障碍、感觉及运动障碍、脏器功能损伤等。病原学结果显示: 直接涂片镜检阳性 7 例, 真菌培养阳性 11 例, 分子生物学检测阳性 9 例, 病理活检阳性 20 例, 此外还有尸检阳性 4 例; 仅有 17 例明确毛霉的具体菌属。血栓均通过影像学检查(包括超声、动脉血管成像、血管造影等)诊断, 常规血液检查中, 该院 5 例病例中血栓指标 D-二聚体、纤维蛋白降解产物(FDP)、凝血酶-抗凝血酶复合物测定(TAT)、纤溶酶- α_2 抗纤溶酶复合物(PIC)均存在异常。33 例病例中, 29 例(87.88%)采取了含两性霉素 B 的治疗方案, 14 例(42.42%)进行病灶切除或清创治疗。不同治疗方式患者的生存率比较, 差异有统计学意义($P < 0.05$); 生存的 12 例患者中, 83.33% 使用两性霉素 B 联合其他真菌药物治疗。**结论** 合并血栓性疾病的毛霉病疗效差, 病死率高, 常发生于合并基础疾病的免疫力低下患者, 检查手段包括镜检、真菌培养、病理学诊断及分子生物学等检查, 影像学诊断在血栓性疾病临床诊断中至关重要, 抗真菌治疗方案显著影响患者预后。

[关键词] 毛霉病; 血栓性疾病; 临床特征; 诊断; 治疗

[中图分类号] R519

Clinical characteristics, diagnosis and treatment, and prognostic factors of invasive mucormycosis complicated with thrombotic diseases

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[Abstract] **Objective** To explore the main clinical characteristics, diagnosis and treatment process, as well as prognostic factors of invasive mucormycosis complicated with thrombotic diseases. **Methods** Five cases of invasive mucormycosis complicated with thrombotic diseases and admitted to a hospital from January 2021 to January 2025 were analyzed retrospectively. Furthermore, such cases reported both domestically and internationally were summarized. **Results** A total of 33 patients were included in the analysis (14 males and 19 females), with 21 deaths and 12 survivors, yielding a mortality of 63.64%. 31 patients had one or more underlying diseases, while only 2 had no history of underlying diseases. The clinical manifestations of all patients showed varying degrees of infection and poisoning symptoms (such as fever, cough, shortness of breath, swelling, pain and bleeding of lesions, and shock, etc.) or thrombotic diseases-induced manifestations, such as disturbance of consciousness, sensory and motor

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disorders, organ function damage, *etc.* Pathogenicity results showed that 7 cases were positive for direct smearing in microscopic examination, 11 cases were positive for fungal culture, 9 cases were positive for molecular biology detection, 20 cases were positive for pathological biopsy, and 4 cases were positive for autopsy, only 17 cases were identified with specific genera of *Mucor*. Thrombosis was diagnosed through imaging examination (including ultrasound, arterial vascular imaging, angiography, *etc.*). In routine blood tests, thrombus indicators like D-dimer, fibrin degradation products (FDP), thrombin-antithrombin complex (TAT), and plasmin- α 2-plasmin inhibitor complex (PIC) presented abnormality in all 5 patients in this hospital. Among the 33 cases, 29 cases (87.88%) were treated with a regimen containing amphotericin B, and 14 cases (42.42%) underwent lesion resection or debridement treatment. The survival rates of patients treated with different methods were statistically different ($P < 0.05$). Among the 12 patients survived, 83.33% received amphotericin B combined with other antifungal treatment.

Conclusion Mucormycosis combined with thrombotic diseases has poor therapeutic efficacy, high mortality, and often occurs in immunocompromised patients complicated with underlying diseases. Examination methods include microscopy, fungal culture, pathological diagnosis, and molecular biology detection. Imaging diagnosis is crucial in the clinical diagnosis of thrombotic diseases, and antifungal treatment scheme significantly affects the prognosis of patients.

[**Key words**] mucormycosis; thrombotic disease; clinical characteristics; diagnosis; treatment

毛霉病(mucormycosis)是由毛霉引起的侵袭性真菌病,既往曾称接合菌病。其中,根霉属最常见,其次为横梗霉属、毛霉属、根毛霉属和小克银汉霉属^[1-2]。毛霉对血管有特殊亲和力,可侵犯小动脉,破坏血管内皮完整性,促进血小板黏附、聚集,引起血栓和致命性大出血^[3]。血栓栓塞性疾病已成为全球人口死亡的首要原因,其涉及范围包括静脉血栓栓塞性疾病和动脉血栓栓塞性疾病^[4]。毛霉感染病死率极高,若合并血栓性疾病显著加重病情进展。为提高毛霉病的诊治水平,我国发布了《中国毛霉病临床诊疗专家共识(2022)》^[5],但目前对毛霉病并发血栓性疾病的系统总结尚欠缺。

本研究收集湖南省人民医院(湖南师范大学附属第一医院)2021年1月—2025年1月5例毛霉病并发血栓性疾病病例资料,同时结合中国知网、PubMed数据库2000—2025年相关报道,回顾性分析其临床特点及诊治过程,以期提高医务人员对该病的认识,实现早期诊断及治疗,改善患者生存率。

1 对象与方法

1.1 研究对象 2021年1月—2025年1月湖南省人民医院收治的5例毛霉病并发血栓性疾病患者,根据诊断及排除标准在PubMed、中国知网数据库中检索2000—2025年确诊的毛霉病并发血栓性疾病的病例28例^[6-31],共收集33例病例。本研究经该院伦理委员会批准(伦理审批号[2025]-192)。

1.2 诊断标准 毛霉病诊断根据《中国毛霉病临床诊疗专家共识(2022)》,均通过组织或体液等标本包

括微生物学、组织病理学或分子生物学[如宏基因组测序(mNGS)]等方法进行确诊。血栓性疾病诊断标准根据《中国血栓性疾病防治指南(2018)》,并均完善血管造影、磁共振、计算机体层血管成像(CTA)、超声等影像学检查,明确合并血栓性疾病(包括深静脉血栓、肺栓塞、脑梗死、脏器梗死等)。

1.3 排除标准 (1)重复报道病例;(2)临床资料不详细的病例,包括既往病史、临床表现、诊断方法、影像学资料、具体治疗情况及预后等内容;(3)报道部位既往存在血栓,非新发血栓的病例。

1.4 研究方法 在PubMed数据库中以All Fields(mucormycosis) AND (thrombosis)为检索式,中国知网中以“毛霉菌”“血栓”为主题词进行检索,检索时间为2000—2025年发表的所有文献,并逐个查阅文献内容,筛选符合诊断的病例报道。筛选过程由双人独立筛选,若存在分歧,咨询第3人协助解决。回顾性收集患者的一般资料、临床表现、实验室资料、影像学检查与诊断方法、治疗用药及转归等情况。

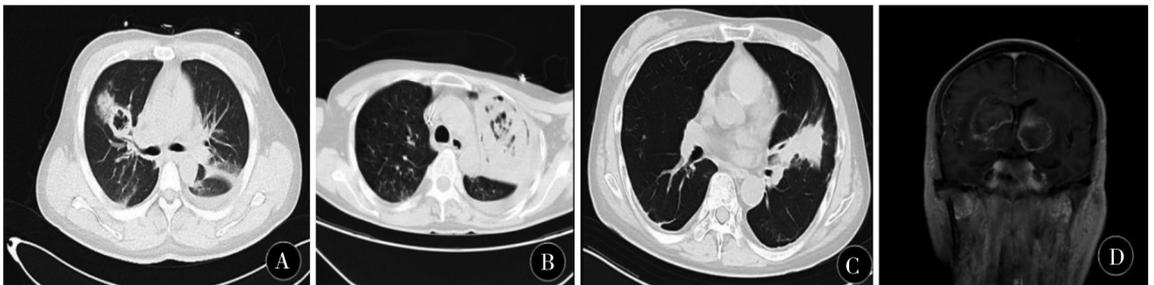
1.5 统计学分析 应用Microsoft Excel软件逐项录入上述病例信息,对资料进行描述性分析。应用SPSS 26.0软件进行统计分析,正态分布的计量资料以 $\bar{x} \pm s$ 表示,采用独立样本 t 检验进行比较;计数资料以例数(%)表示,采用卡方或Fisher确切概率检验进行比较。 $P \leq 0.05$ 为差异具有统计学意义。

2 结果

2.1 一般资料与临床特征 共收集33例毛霉病并

发血栓性疾病病例,其中 5 例为本院收治,28 例为数据库检索。男性 14 例(42.42%),女性 19 例(57.58%),年龄 7~76 岁,平均(48.70±19.49)岁。31 例(93.94%)患者合并至少 1 种基础疾病。本院收治的 5 例患者中 2 例合并糖尿病,且血糖控制欠佳;1 例确诊慢性阻塞性肺疾病(COPD)10 余年,反复住院及使用糖皮质激素;2 例合并血液系统疾病,包括再生障碍性贫血和弥漫大 B 细胞淋巴瘤各 1 例;其他合并的基础疾病包括 3 例高血压,1 例冠心病。数据库检索的 28 例患者中,18 例合并糖尿病,6 例合并血液系统疾病,3 例近期有外科手术史(包括腹腔镜手术、腹主动脉瘤修复手术及鼻内镜手术各 1 例),另有 COPD、哮喘及系统性红斑狼疮各 1 例,5 例存在其他基础疾病[包括 2 例肾衰竭,人类免疫缺陷病毒(HIV)感染、冠心病及结节病各 1 例],此外上述患者中有 3 例近期有新型冠状病毒感染史。仅有 2 例患者无基础疾病史。33 例患者临床表现均有不同程度的感染中毒症状(包括发热、咳嗽、气促、病灶肿痛出血、休克等)或血栓性疾病引发的包括意识障碍、感觉及运动障碍、脏器功能损伤等。

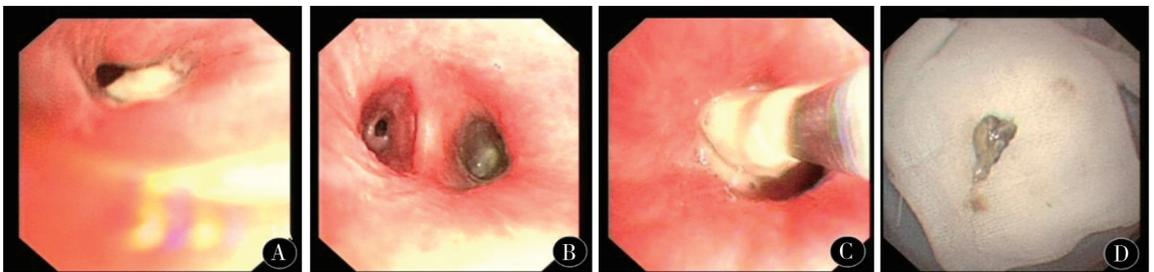
2.2 检查与诊断 33 例病例均通过影像学及病原学检查确诊为毛霉菌(其中鼻眶脑型 20 例,肺型 4 例,胃肠型 4 例,播散型毛霉菌 2 例,其他包括肾型、扁桃体周围型及单纯脑型各 1 例)。33 例病例中有 15 例确诊根霉感染,2 例为小克银汉霉感染。本院收治的 5 例病例部分 CT/MRI 检查结果见图 1,其中有 3 例完善了支气管镜检查并行支气管肺泡灌洗液 mNGS 检查,提示毛霉,且有 2 例同时进行支气管肺泡灌洗液病理和组织病理学检查,发现大量真菌孢子及菌丝,见图 2、3。其余 2 例因病情未行支气管镜而经血 mNGS 检查发现毛霉。此外有 1 例支气管肺泡灌洗液、血及脑脊液 mNGS 检查均提示毛霉,最终确诊播散型毛霉菌。本院收治的 5 例患者确诊根霉 3 例,小克银汉属 2 例,均通过 mNGS 确定。检索的 28 例中,直接涂片镜检 7 例阳性,11 例真菌培养阳性,4 例分子生物学[包括聚合酶链式反应(PCR)、基因测序]检测阳性,18 例病理活检阳性,4 例尸检阳性。但仅 12 例明确具体毛霉菌属,且均为根霉(确诊方式多为培养及分子生物学方法)。



注:A、B、C 为内壁不规则的空洞影、实变以及结节等影像,D 为播散型病例头部 MRI 提示双侧基底节区混杂密度灶。

图 1 本院收治的毛霉菌病合并血栓性疾病患者 CT 检查结果

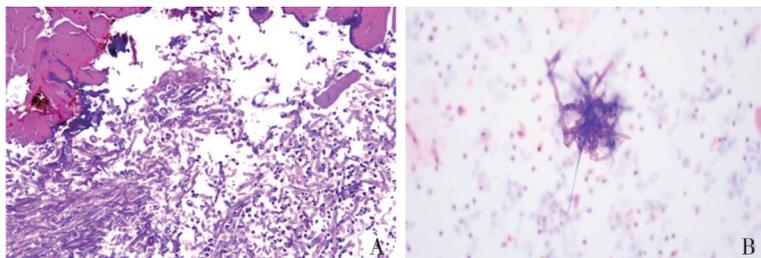
Figure 1 CT examination results of patients with mucormycosis combined with thrombotic diseases admitted to this hospital



注:A 为右上叶前段大量黄色脓性分泌物,B 为左下肺可见基底段坏死物堵塞,C 为支气管镜下冷冻治疗,D 为套扎的部分坏死物。

图 2 本院收治的毛霉菌病合并血栓性疾病患者支气管镜下表现

Figure 2 Bronchoscopic manifestations of patients with mucormycosis combined with thrombotic diseases admitted to this hospital



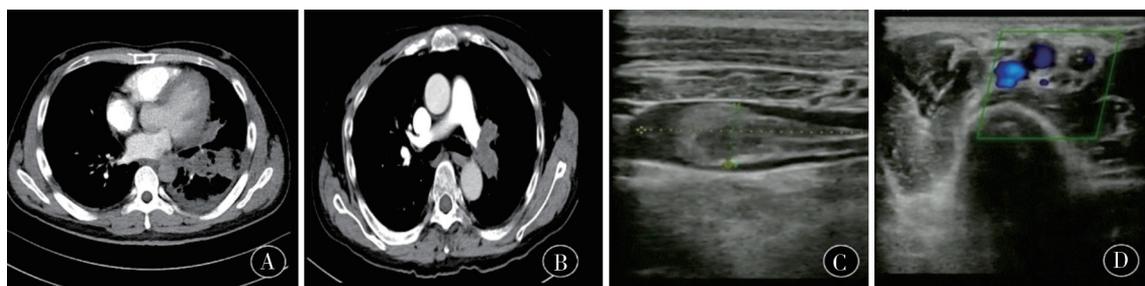
注:A 坏死物圈套组织镜下见坏死组织中大量孢子及菌丝(HE 染色 400×),B 支气管肺泡灌洗液可见局部直角分支菌丝(瑞氏染色 400×)。

图 3 本院收治的毛霉菌合并血栓性疾病患者病理学检查结果

Figure 3 Pathological examination results of patients with mucormycosis combined with thrombotic diseases admitted to this hospital

血栓诊断多依赖于影像学检查,33 例中有 28 例(84.85%)CT/MRI 提示血栓性疾病,4 例超声提示异常,肺显像和腹部探查各发现异常 1 例,并有 2 例患者同时尸解诊断血栓。本院收治 5 例患者中有 2 例通过完善肺动脉 CTA 确诊合并肺栓塞,有 1 例床旁心脏彩超亦可见左肺动脉血栓回声团,有 4 例患者均存在四肢深静脉血栓,见图 4。33 例患者血栓部位分别为颅内血栓(部分为多处血栓,包

括海绵窦血栓 16 例,颈内动脉 10 例,大脑中动脉 2 例,基底动脉 1 例),其他器官血管血栓(四肢深静脉 4 例,肾动脉及肺动脉各 3 例,脾动脉及眼动脉各 2 例,上颌内动脉及肠系膜静脉各 1 例)。15 例根霉感染病例中,颅内血栓 10 例,其他器官血栓 5 例(包括四肢深静脉 2 例,肺动脉 2 例,下颌上动脉 1 例)。2 例小克银汉霉感染病例中肺动脉及四肢深静脉血栓各 1 例。



注:A 左下肺基底段充盈缺损,B 左肺主干栓塞,C、D 血管内实性低回声团。

图 4 本院收治的毛霉菌合并血栓性疾病患者血栓影像学检查结果

Figure 4 Thrombosis imaging results of patients with mucormycosis and thrombotic diseases admitted to this hospital

2.3 其他实验室检查结果 本院收治的 5 例患者白细胞计数(1.85~18.89)×10⁹/L,降钙素原(PCT)0.52~96.58 ng/mL、C 反应蛋白(CRP)38.56~370 mg/L,均有不同程度升高。凝血系统指标异常,其中 D-二聚体 1.92~13.75 mg/L,纤维蛋白降解产物(FDP)6.5~22.4 μg/mL,凝血酶-抗凝血酶复合物(TAT)3.3~15.4 ng/mL,纤溶酶-α2 纤溶酶抑制物(PIC)0.76~2.48 μg/mL。数据库检索的 28 例病例中上述实验室检查指标不完整。

2.4 治疗及预后 33 例病例中 29 例(87.88%)采

取了含两性霉素 B 的治疗方案,14 例(42.42%)实行了病灶切除或清创,最终 21 例(63.64%)治疗后死亡,存活 12 例。其中 16 例使用两性霉素 B 为主的 2 种以上抗真菌药物。不同治疗方式患者的生存率比较,差异有统计学意义(P<0.05),生存的 12 例患者中,83.33%使用两性霉素 B 联合其他抗真菌药物治疗。不同年龄、基础疾病或近期手术史、是否为颅内血栓、病灶清创或切除、毛霉菌类型、病原体属患者的生存情况比较,差异均无统计学意义(均 P>0.05)。见表 1。

表 1 不同分组毛霉病合并血栓性疾病患者预后情况比较

Table 1 Comparison of prognosis of patients with different groups of mucormycosis combined with thrombotic diseases

项目	全部病例(n = 33)	存活组(n = 12)	死亡组(n = 21)	t/χ ²	P
年龄($\bar{x} \pm s$, 岁)	48.70 ± 19.49	44.42 ± 25.61	51.14 ± 15.16	- 0.83	0.419
性别[例(%)]				-	0.716
男	14(42.42)	6(50.00)	8(38.10)		
女	19(57.58)	6(50.00)	13(61.90)		
基础疾病或近期手术史[例(%)]				-	0.523
是	31(93.94)	12(100)	19(90.48)		
否	2(6.06)	0(0)	2(9.52)		
颅内血栓[例(%)]				-	0.471
是	22(66.67)	7(58.33)	15(71.43)		
否	11(33.33)	5(41.67)	6(28.57)		
治疗方式[例(%)]				8.71	0.009
两性霉素 B	13(39.39)	2(16.67)	11(52.38)		
两性霉素 B 联合其他抗真菌药物	16(48.49)	10(83.33)	6(28.57)		
未使用两性霉素 B	4(12.12)	0(0)	4(19.05)		
病灶清创或切除[例(%)]				-	0.273
是	14(42.42)	7(58.33)	7(33.33)		
否	19(57.58)	5(41.67)	14(66.67)		
病原体属[例(%)]				4.37	0.089
根霉	15(45.45)	8(66.67)	7(33.33)		
未分型	16(48.49)	3(25.00)	13(61.90)		
小克银汉霉	2(6.06)	1(8.33)	1(4.76)		
毛霉病类型[例(%)]				4.78	0.317
鼻眶脑型	20(60.61)	8(66.67)	12(57.14)		
播散型	2(6.06)	0(0)	2(9.52)		
肺型	4(12.12)	3(25.00)	1(4.76)		
胃肠型	4(12.12)	1(8.33)	3(14.29)		
其他	3(9.09)	0(0)	3(14.29)		

注：- 表示采用 Fisher 确切概率法检验。

3 讨论

国外多中心研究发现,毛霉病一年内的病死率为 14.7%^[32]。本研究共收集 33 例毛霉病合并血栓性疾病病例,其中死亡 21 例,存活 12 例,病死率达 63.64%,病死率较高。毛霉病通常发生于患有严重基础疾病的患者,且患者多存在免疫缺陷等情况。研究^[33]发现,糖尿病会放大葡萄糖调节蛋白 78 (GRP78)基因的表达,从而增加真菌侵袭和生长的风险。此外,自 2019 年底以来,国际上陆续报道了新型冠状病毒感染后发生毛霉感染的病例^[34]。本

研究中大多数患者亦存在基础疾病。

根据毛霉侵袭性的特点,医务人员在毛霉病治疗中应警惕血栓形成。血栓性疾病根据血栓部位不同,可能出现一系列的症状,包括疼痛、肿胀、神经系统症状及器官功能障碍等。早期的预防与治疗是降低致死率和致残率的重要措施^[35-36]。在本院收集的 5 例患者中,有 2 例患者因肺栓塞出现胸痛,其余 3 例因血栓发现较早,经及时处理未进一步发展为肺栓塞。提示对于侵袭性毛霉病应保持警惕并及时干预,当患者出现胸痛、神经系统异常及腹痛等情况时,也需要警惕是否合并血栓的可能。

随着分子生物学技术的进展,毛霉感染的临床

诊断率有望提高^[37-38],近年来兴起的病原体 mNGS 检查是一种快速且高效的方法,该技术推动了对毛霉基因组结构、耐药机制、诊断方法的研究进展,为毛霉的基础研究和临床应用带来机遇,有助于应对其高致死率和有限治疗选择等临床挑战^[39]。血栓的诊断方式包括多种实验室和影像学检查方法。传统实验室检查包括 D-二聚体、FDP,二者是体内血栓形成和纤溶系统激活的重要标志物。D-二聚体检测被广泛用于静脉血栓栓塞(VTE)、肺栓塞等疾病的辅助诊断和风险评估,具有较高敏感性^[40]; FDP 还有助于评估深静脉血栓形成患者的血栓演变^[41]。TAT 和 PIC 是反映体内凝血和纤溶系统活性的敏感分子标志物,在血栓形成的早期诊断和风险评估中具有重要价值。研究^[42-43]表明,TAT 和 PIC 与 VTE 或深静脉血栓(DVT)的发生密切相关,在术后早期或急性事件发生时,能有效评估临床血栓风险并指导早期干预。本院的 5 个病例中 D-二聚体、FDP、TAT、PIC 有一定程度改变,但在数据库检索的 28 例病例中,相关检查结果尚缺乏,故实验室检查对于侵袭性毛霉并发血栓性疾病的早期诊断价值仍有待进一步研究。影像学诊断在血栓性疾病临床诊断中至关重要,能够帮助早期发现和精准定位血栓,从而指导治疗。常用的影像学方法包括静脉超声(尤其适用于下肢深静脉血栓)、CT 肺动脉造影(诊断肺栓塞的首选)、MRI、正电子发射断层扫描(PET)、单光子发射计算机断层扫描(SPECT)等^[44-45]。近年来,分子影像学快速发展,靶向造影剂和高分辨率成像技术进一步实现了对血栓及易破裂动脉粥样斑块的直接可视,有望实现更早期和个体化的诊断^[46-48]。

对于原发毛霉病及血栓的治疗,抗真菌药物首选两性霉素 B,但单药疗效有限。研究^[17, 49]表明,联合其他抗真菌药物(如泊沙康唑、棘白菌素类)可能产生协同效应,部分患者常联合手术清创。本研究中,不同抗真菌治疗方案对患者的生存率有影响。在血栓治疗方面,由于毛霉感染也易出现出血等并发症,抗凝等治疗目前未作为临床常规推荐,使用需谨慎。目前部分报道病例中,血管内血栓可通过手术或介入手段(如支架植入)恢复血流^[19],但总体疗效欠佳。近年来,针对毛霉血管侵袭机制的免疫治疗(如抗 CotH 抗体)显示出阻断血管侵袭、增强宿主免疫清除能力的潜力^[50],为今后侵袭性毛霉病并发血栓性疾病提供了新的治疗方向。本研究亦存在局限性,包括样本量偏少,研究为回顾性病例收集,

所检索的文献可能存在异质等情况,这些因素可能导致结果偏倚,且部分数据(如 D-二聚体、FDP、TAT 等)不完整,仍有待多中心研究进一步验证。

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