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糖尿病足患者溃疡创面感染病原菌及其预测模型构建

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摘　要

目的：分析糖尿病足患者并发溃疡创面感染病原菌分布特征及其感染的危险因素，并构建预测模型。方法：回顾性收集2021年1月~2022年12月安徽医科大学第二附属医院整形与创面修复外科收治的56例糖尿病足发生溃疡感染患者(感染组)及10例未发生溃疡感染患者(未感染组)的临床资料。分析糖尿病足并发溃疡感染病原菌分布，多因素Logistic回归分析糖尿病足并发溃疡感染的危险因素，并构建预测模型，其预测价值采用受试者工作特征(receiver operating characteristic, ROC)曲线分析。结果：66例糖尿病足患者中有56例发生创面感染，56例糖尿病足并发溃疡感染患者共检出92株病原菌，主要感染病原菌为大肠埃希菌、铜绿假单胞菌、金黄色葡萄球菌、无乳链球菌、阿萨希丝孢酵母菌。多因素Logistic分析结果显示，合并糖尿病肾病、合并骨髓炎均为糖尿病足并发溃疡感染的危险因素(P < 0.05)。据此构建的模型预测糖尿病足并发溃疡感染的曲线下面积(area under curve, AUC)为0.740，敏感度为69.87%，特异度为90.20%。结论：糖尿病足患者并发溃疡感染主要感染病原菌种类包括大肠埃希菌、铜绿假单胞菌、金黄色葡萄球菌、无乳链球菌、阿萨希丝孢酵母菌，主要危险因素包括合并糖尿病肾病、合并骨髓炎。且据此建立危险因素模型对糖尿病足患者发生创面感染具有中等预测价值，临床可据此给予伴有以上情况的患者针对性干预措施，从而降低糖尿病足患者创面感染的发生风险。

关键词

糖尿病足，溃疡感染，病原菌，分布特征，危险因素，预测模型

Pathogens of Ulcer Wound Infection in Patients with Diabetic Foot and Construction of Its Prediction Model

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Abstract

Objective: Analyze the distribution characteristics of pathogenic bacteria in ulcerative wound infections among diabetic foot patients and their risk factors for infection, and construct a predictive model. Methods: A retrospective collection of clinical data from January 2021 to December 2022 on 56 patients with diabetic foot ulcers and infections (the infected group) and 10 patients without ulcer infections (the non-infected group) treated by the Department of Plastic Surgery and Wound Repair Department at the Second Affiliated Hospital of Anhui Medical University. Analyzing the distribution of pathogenic bacteria in diabetic foot ulcer complications, a multifactorial Logistic regression analysis identifies the risk factors for infections associated with diabetic foot ulcers, and constructs a predictive model. The predictive value of this model is assessed using the receiver operating characteristic (ROC) curve analysis. Result: Among 66 patients with diabetic foot ulcers, 56 developed wound infections. From these 56 infected wounds, a total of 92 pathogenic strains were isolated. The predominant pathogens were *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus agalactiae*, and *Trichosporon asahii*. Multivariate logistic regression analysis revealed that concomitant diabetic nephropathy and osteomyelitis were independent risk factors for ulcer infection in diabetic foot ($P < 0.05$). A predictive model incorporating these factors demonstrated an area under curve (AUC) of 0.740, with a sensitivity of 69.87 % and a specificity of 90.20 %. Conclusion: The main pathogens responsible for ulcer infection in diabetic foot patients are *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus agalactiae*, and *Trichosporon asahii*. Diabetic nephropathy and osteomyelitis are key risk factors. The constructed risk-factor model offers moderate predictive value for wound infection in this population. Clinicians can use this model to deliver targeted interventions for high-risk patients, thereby reducing the incidence of diabetic foot ulcer infections.

Keywords

Diabetic Foot, Ulcer Infection, Pathogen, Distribution Characteristics, Risk Factor, Prediction Model

1. 引言

1.1. 糖尿病足流行病学

糖尿病足是个缓慢发展的过程，多数患者早期会有下肢皮肤干燥，变黑，弹性差，皮温低等症状，下肢远端神经异常和不同程度的血管病变导致的足部感染，溃疡或深层组织破坏[1]。约 20%糖尿病足溃疡患者因中至重度感染导致下肢截肢，溃疡患者的死亡率为每 1000 人年 231 例死亡[2]，而无足溃疡的糖尿病患者为每 1000 人年 182 例死亡[3]。周围神经病变引起的感觉减退[4]，对足部损伤的易感性增加并延迟了患者的感觉。糖尿病足溃疡和软组织感染的病理生理学由多种复杂因素叠加，包括糖尿病性神经病变与外周微血管功能障碍，感染等。

1.2. 糖尿病足神经病变与感染

神经病变本身不会导致足部溃疡[5]：它是感觉丧失和其他因素的结合，例如外部创伤或高足部压力，最终导致足部破裂[6] [7]。在大型英国一项针对 2 型糖尿病诊断患者的前瞻性研究[8]发现，13%的患者在

诊断糖尿病时，已经患有使他们面临足部溃疡风险的神经病变。在没有溃疡病史的严重神经病变患者中，发生溃疡的年风险则是无神经病变患者的 5 至 7 倍[9]-[13]。几乎所有终末期肾病患者都具有足部溃疡的神经性危险因素[14]，透析本身是足部病变发展的独立危险因素。存在糖尿病周围神经病变的足部叠加其他因素导致发生溃疡与足部感染的风险大大提高[15] [16]。

1.3. 糖尿病足微循环与感染

健康个体的皮肤微循环是由微动脉、后微动脉、毛细血管前括约肌、真毛细血管、通血毛细血管、动－静脉吻合支和微静脉等七个部分组成。皮肤血流的控制依赖于一个复杂的调节系统，该系统既包括全身皮肤的循环，也包括局部反射[17]。机体体温调节是通过大量动静脉吻合在手和脚上实现的，小动脉和静脉丛之间的直接交流，将大量血液分流到皮肤表面以散热[18]。血流的局部调节主要由局部血管反应和神经源性 c 纤维通过神经轴突反射介导，神经轴突反射受到包括机械、化学和热损伤在内的一系列有害刺激的刺激。直接损伤如将皮肤加热至 42℃以上，通过降低毛细血管前括约肌张力，增加损伤部位的血流量，是一种直接的血管机制。周围皮肤的血流量也会增加，这是神经介导的，血管活性物质(包括 P 物质、组胺和降钙素基因相关肽)释放到损伤部位的皮肤周围引起血管舒张[19]-[21]。糖尿病患者微循环中最显著的解剖结构变化是毛细血管基底膜增厚，毛细血管管腔大小减小，包裹全身毛细血管和小静脉内皮细胞的收缩细胞即周细胞变性。内皮功能障碍导致体内的免疫细胞如白细胞等无法及时迅速反应并运输到炎症部位[22]-[27]，细菌在局部繁殖并产生各种炎性因子对正常组织产生破坏作用。

1.4. 糖尿病患者外周动脉病变与感染

大约一半的糖尿病足溃疡患者存在外周动脉疾病。外周动脉缺血灌注不足是糖尿病足局部感染的基础。糖尿病伴有下肢硬化性闭塞病导致缺血后，会使原有的局限性感染病灶迅速扩散为骨髓炎，甚至引起全身感染。内膜钙化导致进行性动脉狭窄和终末器官灌注减少[28]，缺血会限制免疫细胞到达感染部位，加速感染灶的进展。另外氧分压低、高血糖、营养不良等均可引发足部酸积聚，高渗，低效无氧代谢，此环境更加有利于病原菌的生长与繁殖。同时限制了抗生素的运输，降低对病原菌的杀伤效率，引起足部软组织感染的加剧。而内侧钙化导致弹性蛋白和平滑肌功能障碍。导致血管顺应性降低、血管硬度增加和对血管收缩或血管舒张刺激的反应迟钝[29]。

1.5. 糖尿病患者足部骨髓炎与感染

糖尿病足骨髓炎长期以来一直是一种复杂的感染，既难以诊断和治疗，又与高复发率和肢体丧失有关。葡萄球菌是骨髓炎感染最常见也是感染率最高的病原体，葡萄球菌增加破骨细胞分化和骨吸收，减少成骨细胞介导的骨基质产生和矿化，从而推动骨骼破坏[30]-[36]。电子显微镜已经证明，注射金黄色葡萄球菌后，胚胎雏鸡的成骨细胞和骨细胞中存在细菌，表明骨细胞的内化也发生在体内[37] [38]。同时葡萄球菌自发产生的突变形式，并表现出增强的抗菌素耐药性[39]。关注并阐明这些侵袭性骨骼感染中宿主和病原体之间的复杂相互作用，以便于临床制定更有效的治疗方案[40]-[42]。糖尿病足合并溃疡感染是糖尿病患者常见并发症，也是导致糖尿病患者截肢的主要易感因素之一[43] [44]，影响糖尿病足患者合并溃疡感染严重程度和治疗效果的主要因素为感染病原菌种类及其对抗菌药物的敏感性[45]，因此明确糖尿病足患者溃疡感染的病原菌种类对于临床抗菌药物的选择具有重要意义[46] [47]。此外，对于改善患者预后具有重要意义[48] [49]，而目前临床关于糖尿病足患者并发溃疡感染的相关易感因素尚未完全明确，为了解糖尿病足溃疡发生的易感因素，及主要易感因素对患者预后的影响，基于此，本研究通过调查糖尿病足并发溃疡感染病原体分布特征及其易感因素，并构建预测模型，利用 Logistic 回归方程，为糖尿病足患者并发溃疡感染的预防提供参考和依据。

2. 一般资料与方法

2.1. 对象

回顾性收集2021年1月~2022年12月安徽医科大学第二附属医院整形与创面修复外科收治的66例糖尿病足患者的临床资料。患者在院期间统一每日由护士监测血糖水平，予以口服药物或胰岛素注射治疗，血糖基本控制在合理范围内。足部创面均视患者实际情况于术前术后予以适当合理的消毒换药频率。本研究已经获得病人的知情同意，文中不涉及病人姓名等隐私数据。纳入标准：(1) 糖尿病足诊断符合《中国2型糖尿病防治指南(2017年版)》；(2) 糖尿病足感染诊断符合《医院感染防控指南》；(3) 无免疫及血液系统疾病。排除标准：(1) 肿瘤患者，合并严重感染，肝肾功能衰竭，合并中枢神经系统疾病、免疫性疾病；(2) 凝血功能障碍；(3) 妊娠，哺乳期妇女等。脱落及剔除标准：临床资料不完整者。

2.2. 方法

糖尿病足患者溃疡创面用无菌生理盐水将表面的坏死组织、脓液、及黑痂清洗露出新鲜肉芽后用无菌棉拭子插入新鲜溃疡创面深部并适度挤压将溃疡创面内部的分泌物挤出后旋转棉拭子数秒确保采样准确。将棉拭子样本置于无菌采样瓶中送检，对采样的分泌物进行药敏实验并记录菌种检出率(注意采样瓶上需粘贴含有患者一般信息的条码)。病原菌培养参照《全国临床检验操作规程》。病原菌的分离鉴定采用微生物鉴定仪。

2.3. 资料收集

通过医院电子病历系统收集患者性别、年龄、体质指数、是否合并糖尿病大血管病变、是否合并糖尿病肾病、是否合并高血压、是否合并冠心病、是否合并骨髓炎、糖尿病病程、糖尿病足病程、溃疡病程、溃疡数目、空腹血糖、抗菌药物使用疗程、抗菌药物联合使用种类等一般资料。其中空腹血糖采用血糖全自动生化分析仪进行检测，血液指标检测方法为：患者禁食12小时或以上，住院第二天清晨予以抽取肘静脉血液5 mL离心(3500/min, 10 min)收集血清，用酶联免疫吸附法检测。所有病历及患者资料均由双人收集整理，交换核对无误后予以录入本次数据系统。

2.4. 统计分析

本研究所用分析软件为SPSS 26.0。计数资料的比较采用卡方或Fisher检验，用[n (%)]进行表示。单因素分析有统计学差异的结果纳入多因素分析，多因素Logistic回归分析法，对糖尿病足患者创面感染的危险因素进行分析，Hosmer Lemeshow检验模型拟合度。采用MedCalc 11.4绘制受试者工作特征(Receiver operating characteristic, ROC)曲线分析预测模型对糖尿病足患者创面感染的预测价值，获取曲线下面积(area under curve, AUC)、敏感度及特异度。$P < 0.05$认为差异具有统计学意义。

3. 结果

3.1. 糖尿病足并发溃疡感染病原菌分布

56例糖尿病足并发溃疡感染患者共检出92株病原菌，其中革兰阴性菌52株，占比56.5%；革兰阳性菌38株，占比41.3%；真菌2株，占比2.17%，见表1。

3.2. 糖尿病足并发溃疡感染的单因素分析

单因素分析结果显示，溃疡数目、合并糖尿病肾病、合并骨髓炎是糖尿病足并发溃疡感染的危险因素($P < 0.05$)，见表2。

3.3. 糖尿病足并发溃疡感染的多因素 Logistic 回归分析

将单因素分析有统计学意义的因素作为自变量，将糖尿病足并发溃疡感染发生情况作为因变量，多因素 Logistic 回归分析结果显示，合并糖尿病肾病、合并骨髓炎均为糖尿病足并发溃疡感染的危险因素($P < 0.05$)，见表 3。

3.4. 糖尿病足并发溃疡感染预测模型的构建及评价

根据多因素 Logistic 回归分析，筛选出的独立危险因素构建回归方程：Logit(P) = 20.744 + 合并糖尿病肾病 × 2.819 + 合并骨髓炎 × (−1.999)。

3.5. 糖尿病足并发溃疡感染模型的预测价值

采用 Logistic 回归模型分析数据(如表 1~3 所示)，得到糖尿病足并发溃疡感染的预测概率 Logit(P)。按照诊断概率 Logit(P)绘制预测糖尿病足并发溃疡感染发生的 ROC 曲线，当 Logit(P) > 12.83 时，AUC 为 0.740，95% CI 为 0.628~0.864，敏感度为 69.87%，特异度为 90.20%，见图 1。

Table 1. Distribution of the pathogens isolated from the diabetic foot patients complicated with ulcer infection
表 1. 糖尿病足并发溃疡感染病原菌分布

病原菌	株数(n = 92)	构成比(%)
革兰阴性菌	52	56.5%
大肠埃希菌	14	15.20%
铜绿假单胞菌	12	13.04%
普通变形杆菌	6	6.52%
阴沟肠杆菌	4	4.35%
摩根摩根菌	4	4.35%
肺炎克雷伯菌	2	2.17%
鲍曼不动杆菌	2	2.17%
弗劳地氏枸橼酸杆菌	2	2.17%
木糖氧化无色杆菌	2	2.17%
变栖克雷伯菌	2	2.17%
其他	2	2.17%
革兰阳性菌	38	41.30%
金黄葡萄球菌	18	19.57%
无乳链球菌	8	8.70%
松鼠葡萄球菌	4	4.35%
粪肠球菌	2	2.17%
停乳链球菌	2	2.17%
模仿葡萄球菌	2	2.17%
其他	2	2.17%
真菌	2	2.17%
阿萨希丝孢酵母菌	2	2.17%

Table 2. Univariate analysis of the ulcer infection in the diabetic foot patients [n (%)]
表 2. 糖尿病足并发溃疡感染的单因素分析[n (%)]

	因素	感染组 (n = 56)	未感染组 (n = 10)	χ^2 值	P 值
性别	男	36	5	0.736	0.391
	女	20	5		
高血压	否	16	1	1.53	0.216
	是	40	9		
冠心病	否	49	9	0.05	0.823
	是	7	1		
合并大血管病变	否	7	2	0.405	0.524
	是	49	8		
合并糖尿病肾病	否	44	3	9.764	0.002
	是	12	7		
合并骨髓炎	否	6	5	9.429	0.002
	是	50	5		
糖尿病病程(年)	<10	19	3	0.059	0.808
	≥10	37	7		
糖尿病足病程(d)	<30	22	2	1.364	0.243
	≥30	34	8		
溃疡病程(d)	≤30	24	2	1.857	0.173
	>30	32	8		
空腹血糖(mmol/L)	≤10	42	9	0.779	0.378
	>10	14	1		
溃疡数目	<3	39	9	4.089	0.043
	≥3	17	1		
抗菌药物使用疗程(d)	≤14	26	7	2.04	0.153
	>14	30	3		
抗菌药物联合使用种类(种)	1	45	9	2.407	0.121
	≥2	11	1		

Table 3. Multivariate Logistic regression analysis of the ulcer infection in the diabetic foot patients
表 3. 糖尿病足并发溃疡感染的多因素 Logistic 回归分析

因素	β	SE	Wald	P 值	OR	95%CI
合并糖尿病肾病	2.819	0.932	9.149	0.002	16.758	2.697~9.112
溃疡数目	−20.530	8544.609	7.541	0.198	2.879	1.287~6.543
合并骨髓炎	−1.999	0.990	4.077	0.043	0.135	1.019~3.943
常量	20.744	8544.609	6.010	0.998	10.20562334	...

注：“…”该项无数据。

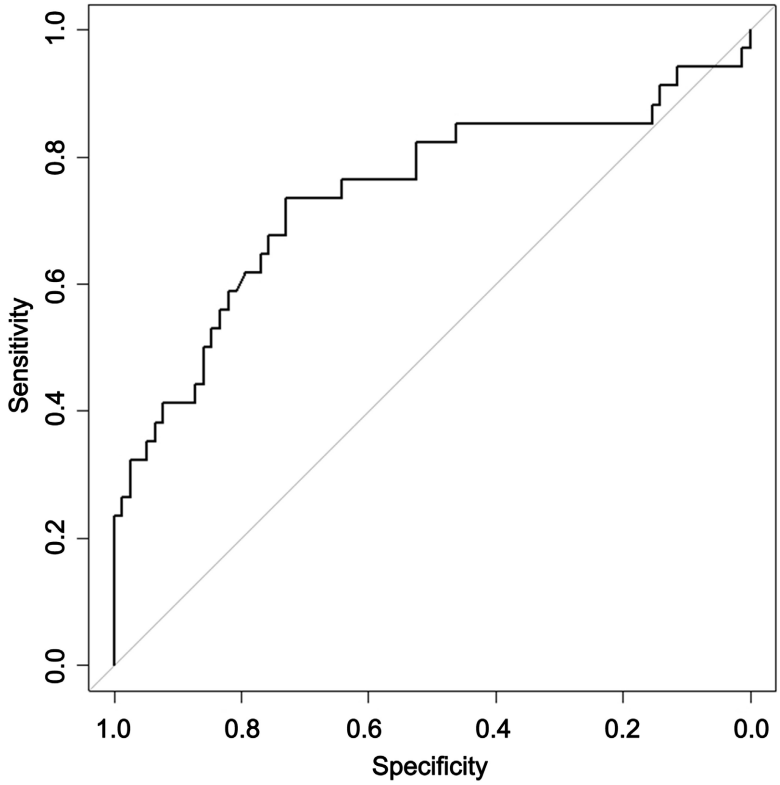

Figure 1. ROC curves of the model in prediction of ulcer infection in the diabetic foot patients
图 1. 模型预测糖尿病足并发溃疡感染发生的 ROC 曲线

4. 讨论

4.1. 糖尿病足微循环血流动力学改变加重感染

糖尿病患者长期高血糖状态，相关的微血管糖化。Parving 等人提出了“血流动力学理论”来解释糖尿病患者中的微血管病[50] [51]。该理论提出，增加的微血管血流量会引发血管内皮损伤反应，随后是微血管硬化。这些变化可能导致微循环和内皮的一些功能异常，如微循环最大充血反应受损、组织对损伤的反应减少、血流的自动调节和血管张力的变化。对于健康人来说，微循环对炎症反应存在高度反应，并在其中起着关键作用，如微动脉、毛细血管和微静脉，都会对炎症做出反应，并努力将炎症细胞输送到受伤或感染的组织部位[52]。糖尿病患者的微血管病使其微循环炎症应对反应受损，糖尿病患者微循环的炎症反应减退，包括血管舒缩功能受损、毛细血管灌注减少、白细胞和血小板粘附、凝血级联反应激活、血栓形成增强、血管通透性增加以及血液和淋巴管增殖率增加[53] [54]。毛细血管基底膜增厚是糖尿病患者毛细血管和小动脉的另一发现，血管内皮对非特异性慢性损伤[54]的增殖性反应[55] [56]。肾脏毛细血管通透性增加，毛细血管基底膜增厚，肾脏损伤的标志物较常见的指标是尿蛋白肌酐比值，尿蛋白肌酐比值的升高通常意味着存在血管内皮功能障碍，肾脏代谢异常的患者，体内血液多处于高凝状态，容易发生血栓，导致微血管管腔变窄，器官组织缺血。另一方面肾脏是人体的重要代谢器官，因为肾脏受损导致人体的代谢产物难以排出体外，无法完成血液的过滤净化，导致机体继发性的组织缺血缺氧，机体正常状态下产生的炎症因子无法被肾脏及时代谢清除，未被清除的炎症因子随着血液的循环扩散运送到机体不同的地方，引起新的炎症的反应，加重机体的感染。糖尿病肾病患者因为肾脏受损，血液高凝，易形成血栓，同时伴随机体的炎症因子清除障碍，持续存在于体内，产生不必要的炎性级联反应，

缺血缺氧导致机体的感染加重。

4.2. 糖尿病足骨髓炎加重感染

骨髓炎导致感染加重：糖尿病骨髓炎是糖尿病一种较严重的并发症，可以累及骨膜，骨小梁或骨皮质，骨髓，糖尿病患者骨髓炎的发病机理较复杂，大部分由邻近的软组织感染病灶的局部传播引起，同时糖尿病患者存在继发性血管功能不全，血运障碍，促使骨髓炎的发生发展，主要的组织病理学是死骨片，包括坏死骨的形成，位于感染组织的中间，死骨源于炎症因子对骨组织和骨基质的破坏，包括增加破骨细胞活性的细胞和细胞因子，化脓性骨髓炎本身相对急性骨髓炎更难治疗，不容易治愈且容易复发，原因可能与病原菌生物膜的形成有关，该生物膜表面覆盖着细菌自身产生的聚合物基质，形成了由病原菌形成的细菌细胞结构簇，且伴有骨髓炎的溃疡感染，因为病变处于骨髓腔内位置较深，容易出现引流不畅，缺乏血管化，免疫细胞无法到达，局部抗生素难以达到有效灭菌浓度，病原体在局部形成病灶，后期继发其他病原体的感染，加上糖尿病患者的血糖较高，有利于细菌的滋生，也为细菌在骨髓腔内部提供了良好是生长环境。相比糖尿病软组织感染更难清除且具有更强的持久性，死骨片包裹的感染性病灶，病原体嵌于骨片中，本身血管存在硬化，血运比单纯的糖尿病软组织感染更差，以上皆导致并发骨髓炎的糖尿病患者的感染，截肢率更高，抗菌药物用量与种类也比单纯的软组织感染大很多。越来越多的实验支持表明，葡萄球菌对成骨细胞的侵袭，最有可能通过金黄色葡萄球菌的纤连蛋白－整合素桥接机制，可能在骨感染的发病机制中发挥作用。细胞内位置可以为细菌提供受保护的环境，通过逃避抗菌剂和宿主免疫机制来帮助延长细菌生存的持久性，并可能通过诱导感染细胞凋亡来促进骨损伤[57]-[60]。X 线摄影和 MR 成像是疑似足部感染的糖尿病患者的首选方式[61]-[67]。

4.3. 糖尿病患者外周血管闭塞加重感染

血管自身变化均会连锁性影响血流动力学，影响内皮细胞分泌炎性因子及细胞因子，促使局部处于高炎性反应状态。足部溃疡患者的外周动脉疾病与愈合失败、截肢、心血管事件和过早死亡风险增加有关，需要早期诊断和专家评估外周动脉疾病，并采取针对性的措施可降低截肢和心血管事件的风险，同时确定是否需要血运重建以促进溃疡愈合。严重灌注不足的患者可能会影响溃疡愈合。诊断为外周动脉疾病时，应明确灌注不足的程度。需要进一步影像学检查以确定足部血管结构，以此作为是否血运重建手术的指标。脉搏减弱或消失、抬高时苍白、下降时足部发红、脚趾毛细血管再充盈缓慢、指甲增厚或脚趾毛缺失等发现与足部动脉灌注受损一致。

5. 结论

综上所述，糖尿病足患者并发溃疡感染主要感染病原菌种类包括大肠埃希菌、铜绿假单胞菌、金黄色葡萄球菌、无乳链球菌、阿萨希丝孢酵母菌，主要危险因素包括合并糖尿病肾病、合并骨髓炎。据此构建的模型具备中等预测价值，临床可据此给予伴有以上情况的患者针对性干预措施，为临床防治及干预糖尿病足患者溃疡创面感染提供依据。但本研究结果可能因研究样本量少、仅为单中心研究，实验中未将患者年龄纳入统计范畴等不足之处而存在一定偏倚，因此，为提高临床研究结果的准确度及可靠性，有待临床进一步扩大样本量进行多中心研究。

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