论著·临床医学

基于系统评价和Meta分析的糖尿病足溃疡患者截肢风险预测模型的开发和验证

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[摘要] **目的** 基于系统评价和Meta分析开发并验证一种预测糖尿病足溃疡(diabetic foot ulcers,DFU)患者截肢风险的模型。**方法** 采用主题词+自由词的检索方式,检索关于研究DFU患者截肢风险因素的文献。经筛选最终纳入37项队列研究,采用纽卡斯尔-渥太华量表(Newcastle-Ottawa Scale,NOS)进行质量评价。对DFU的截肢风险因素进行Meta分析。DFU截肢风险预测模型纳入Meta分析中具有统计学意义的风险因素,根据各风险因素合并的比值比(odds ratio,OR)计算其相应β系数并进行评分赋值,建立评分制模型。收集2021年至2023年于陆军军医大学第一附属医院内分泌科住院的453例DFU患者的临床数据作为验证队列,对模型进行验证。模型性能评估基于受试者工作特征曲线下面积(area under the curve of receiver operating characteristic,AUC),通过灵敏度和特异性计算最大约登指数来确定最佳界值分数。**结果** Meta分析显示在11 779例DFU患者中,累积截肢率约34.65%。最终的风险预测模型纳入5个风险因素,包括坏疽[*OR*=11.92(5.86~24.24)]、溃疡深度[*OR*=4.93(2.52~9.64)]、骨髓炎[*OR*=3.19(2.36~4.29)]、既往截肢史[*OR*=3.19(2.00~5.09)]和下肢动脉疾病[*OR*=3.10(2.31~4.17)]。根据各风险因素的权重,模型总分为76分,最佳界值分数为36.5分。预测模型性能良好,*AUC*=0.864(0.824~0.903),灵敏度为0.743,特异性为0.859,准确率为83.00%。**结论** 本研究开发了一种基于风险因素评分的DFU截肢风险预测模型,模型具有良好的区分度和校准度,为DFU截肢相关的临床研究和临床决策提供有效的科学依据。

[关键词] 糖尿病足溃疡;截肢;Meta分析;预测模型

[中图法分类号] R181.23;R587.2;R687.31 [文献标志码] A

Development and validation of a prediction model for amputation risk in patients with diabetic foot ulcers based on systematic review and meta-analysis

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[**Abstract**] Objective To develop and validate a prediction model for risk of amputation in patients with diabetic foot ulcers (DFU) based on systematic review and meta-analysis. Methods The studies on the risk factors of amputation in DFU patients was retrieved by using subject words+free words. After screening, 37 cohort studies were finally included, and the Newcastle-Ottawa scale (NOS) was used for quality evaluation. Meta-analysis was performed on the risk factors of amputation in DFU. Then a prediction model for DFU amputation risk were constructed based on the statistically significant risk factors in the meta-analysis. The corresponding β value was calculated based on the combined odds ratio (OR) value of each risk

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factor, and each risk factor was scored to establish a scoring system model. The clinical data of 453 DFU patients hospitalized in our department from 2021 to 2023 were collected as a validation cohort. Receiver operating characteristic (ROC) curve analysis was used to evaluate the model performance. The area under the curve (AUC) was calculated, and the optimal cutoff score was determined by calculation of the maximum Youden index through sensitivity and specificity. **Results** Our meta-analysis showed a cumulative amputation rate of approximately 34.65% in 11 779 DFU patients. The final risk prediction models include gangrene [*OR*=11.92 (5.86~24.24)], ulcer depth [*OR*=4.93 (2.52~9.64)], osteomyelitis [*OR*=3.19 (2.36~4.29)], previous amputation history [*OR*=3.19 (2.00~5.09)] and lower extremity arterial disease [*OR*=3.10 (2.31~4.17)]. According to the weights of each risk factor, the total score of the model is 76, and the optimal cut-off score is 36.5. The prediction model performed well, with an AUC value of 0.864 (0.824, 0.903), a sensitivity of 0.743, a specificity of 0.859, and an accuracy rate of 83.00%. **Conclusion** A prediction model for DFU amputation risk is developed based on risk factor scoring, and has good discrimination and calibration, providing effective scientific basis for clinical research and clinical decision-making related to DFU amputation.

[**Key words**] diabetic foot ulcer; amputation; meta-analysis; prediction model

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糖尿病足溃疡(diabetic foot ulcer,DFU)是糖尿病患者常见且严重的并发症之一,其不仅影响患者的生活质量,还可能导致截肢等严重后果[1]。由于周围神经病变、周围血管病变、高血糖环境、炎症紊乱等因素,DFU的愈合受损或延迟,导致糖尿病慢性难治性溃疡的形成[2]。全球40%~60%的非创伤性下肢截肢与糖尿病并发症相关,而DFU是这些截肢中最常见的诱因(80%)[3]。糖尿病足截肢伴随高致残率与高死亡率。一项前瞻性队列研究发现,糖尿病引起的截肢(包括大截肢和小截肢),5年生存率为41%~48%,而仅小截肢患者5年生存率也只有59%[4]。因此,准确识别截肢风险因素对DFU患者大有裨益。

既往已有部分研究对DFU截肢的相关风险因素进行探讨,但结果并不一致,研究质量参差不齐,各风险因素的重要性及量效关系也仍未可知。现阶段针对DFU截肢开发的预测模型较少,常用模型构建方法主要包括两大类:一是传统算法,如Logistic回归等;二是机器学习算法,如决策树、随机森林等。在实际研究中,风险因素分析常以单中心研究为主,数据来源和维度存在一定程度的局限性。上述模型在训练过程可能会学习到训练数据中的噪声和异常值,导致过拟合。此外,样本较少的数据往往无法提供足够的信息来有效估计模型参数,导致模型的稳定性和可靠性下降。因此本研究旨在利用Meta分析融合多中心数据,基于高质量证据开发和验证DFU截肢的风险预测模型,并确定这些特征在评估DFU截肢风险方面的预测价值,以期为医护人员提供必要的预测信息,早期识别高风险患者,从而制定个性化的干预策略,为个人和医疗保健系统节省大量成本。

1 对象与方法

1.1 Meta分析

1.1.1 文献检索 在Pubmed、Embase、Web of Science和Cochrane Library数据库中检索关于研究DFU患者截肢风险因素的原始研究文献。采用主题词+自由词的检索方式,并结合布尔逻辑运算符(AND、OR)进行组合,以提高文献检索的全面性。

1.1.2 文献纳排标准 纳入标准:①研究类型为已发表的队列研究,包括前瞻性和回顾性;②研究对象为确诊为DFU的患者;③结局指标为下肢截肢,包括大截肢和/或小截肢;④截肢风险相关的影响因素,如年龄、性别、溃疡深度等;⑤时间限制为2000年以后发表的研究。排除标准:①综述、意见稿、会议摘要、动物实验及重复文献;②非英文文献;③排除样本量<50的病例报告等小样本研究。

1.1.3 文献筛选 两位研究人员分别独立对检索到的研究进行筛选,如存在意见分歧,通过协商或与第三位研究者评议解决。根据既定检索策略共检索得到相关文献4 839篇,剔除重复文献1 768篇后剩余3 071篇;通过阅读题目和摘要,剔除无关文献、非原始研究文献和动物实验文献2 931篇;全文阅读后剔除不符合纳排标准文献103篇,最终纳入37篇文献(图1)。

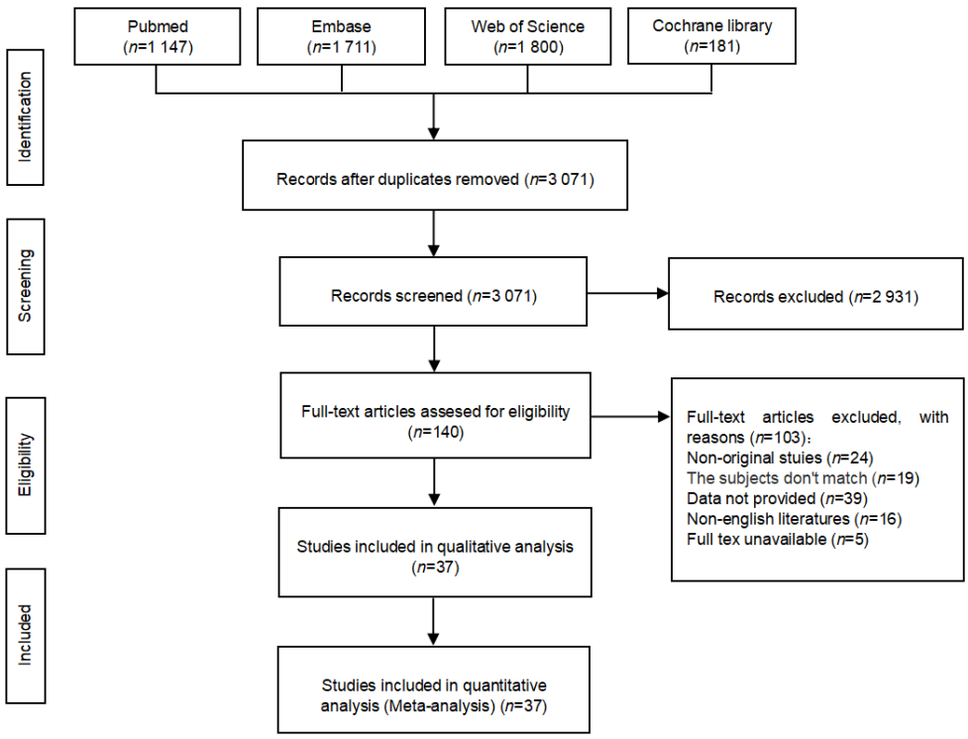


图1 文献筛选流程图

Figure 1 Flowchart of study selection

1.1.4 *数据提取与文献质量评估* 数据提取:①文献基本信息,包括作者、发表年份、研究地域、研究类型、随访时间;②受试者信息,包括样本量、截肢率、各风险因素的比值比(odds ratio, OR)或相对危险度(relative risk, RR)及其95%*CI*。质量评估:本研究采用纽卡斯尔-渥太华量表(Newcastle-Ottawa Scale, NOS)对文献质量进行评价。NOS量表详细评估观察性研究中的选择偏倚、比较的相似性和结果的准确性,是评价研究质量的系统化工具。该量表共8个评价指标,满分为9分,7~9分为高质量研究,4~6分为中等质量研究,<4分为低质量研究。数据提取与文献质量评估均由两位研究者同时独立进行,如存在意见分歧,通过协商或与第三位研究者评议解决。

1.2 *模型开发和验证*

1.2.1 *临床定义* DFU被定义2型糖尿病并发足部溃疡,且溃疡处于Wagner 1级或以上。下肢动脉疾病根据临床体征和症状,包括间歇性疼痛、跛行和无动脉搏动,并辅以下肢动脉超声进行明确评估。骨髓炎的诊断通过临床体征、骨探针测试、影像学检查[包括足部X片和磁共振成像(magnetic resonance imaging, MRI)检查]和骨活检结果进行综合评估。截肢事件包括大截肢(踝关节水平以上)和/或小截肢(踝关节水平以下)。

1.2.2 *风险预测模型的开发* 基于系统评价和Meta分析结果,纳入具有统计学意义的风险因素进入模型。通过各风险因素的*OR*值和95%*CI*,计算相应的β系数:β=ln(*OR*)。β系数是一种风险指标,它表明随着风险因素的增加,疾病风险增加的倍数。基于β系数的这一特性,将β系数乘以10并四舍五入到最接近的整数来计算各风险因素的评分。对风险预测模型中的所有风险因素进行评分,将每个风险因素的分数相加计算总评分。DFU患者的总评分越高,发生截肢的风险就越大。

1.2.3 *风险预测模型的验证* 验证队列来自于2021年1月至2023年12月在陆军军医大学第一附属医院内分泌科住院的DFU患者的临床资料。纳入标准:①明确诊断为DFU的住院患者;②年龄≥18岁;③根据Wagner分级系统为Wagner 1~5级。排除标准:①患有严重肝脏疾病、凝血功能障碍、恶性肿瘤并发症的患者;②临床资料严重缺损。本研究经陆军军医大学第一附属医院伦理委员会批准[(B)KY2024237]。根据已建立的风险评分系统计算验证队列基线变量的总评分,基于总评分通过受试者工作特征曲线(receiver operating characteristic curve, ROC)计算模

型的灵敏度、特异性、最佳界值分数和受试者工作特征曲线下面积(area under the receiver operating characteristic curve,AUC)。

1.3 统计学分析

采用Stata 17.0和Revman 5.4进行Meta分析,通过*OR*或*RR*及其95%*CI*来评估各风险因素。*OR*与*RR*的转换公式为:$OR=[RR*(1-P_0)]/[1-(RR*P_0)]$,$P_0$为非暴露组中截肢事件的发生率,当截肢率<10%时,*RR*值近似于*OR*值。通过Q检验和I^2检验分析研究之间的异质性,若$I^2\leqslant 50\%$,则认为研究间异质性尚可;若$I^2>50\%$,则认为研究间具有较大的异质性。统计模型均选用随机效应模型,亚组分析根据研究类型分为前瞻性研究和回顾性研究。$P<0.05$被认为具有统计学意义。采用通过漏斗图和Egger检验对发表偏倚进行分析,$P<0.05$提示存在发表偏移。剪补法用于对存在发表偏移的指标进行效应值的调整。采用SPSS 26.0软件进行数据分析。根据ROC曲线评价DFU截肢风险预测模型的预测价值,并计算AUC值。最大约登指数被用于确定模型的最佳界值分数。Hosmer-Lemeshow检验用于判断模型校准度,$P>0.05$表示模型拟合效果良好。

2 结果

2.1 文献筛选和质量评价

如表1所示,最终纳入37篇文献,包括9项前瞻性研究和28项回顾性研究。纳入研究共涉及11 779例患者,累积截肢率约34.65%,随访时间为0.25~22.00年。根据NOS量表评分标准,本研究纳入的37篇研究中,72.97%为高质量研究,27.03%为中等质量研究,无低质量研究。

表1 文献基线特征

Table 1 Baseline characteristics of the literatures

Author	Year of Publication	Country/ Region	Follow-up Time / years	Sample Size	Amputation Rate	Outcomes	NOS Score/ Point
XU[5]	2024	Spain	5.00	650	0.44	major/minor amputation	8
JEYARAMAN[6]	2019	Australia	12.40	513	0.51	major/minor amputation	7
AYDIN[7]	2010	Turkey	6.00	74	0.22	major/minor amputation	6
JEON[8]	2017	South Korea	5.00	137	0.49	major/minor amputation	7
JEONG[9]	2018	South Korea	3.70	192	0.59	major/minor amputation	7
PENG[10]	2021	China	5.00	125	0.46	major/minor amputation	8
LEUNG[11]	2001	China	5.00	340	0.30	major amputation	7
BLUMBERG[12]	2014	America	1.00	234	0.42	major/minor amputation	7
MUSA[13]	2018	Saudi Arabia	2.00	82	0.40	major/minor amputation	7
GUO[14]	2019	China	3.75	475	0.12	major/minor amputation	7
LI[15]	2011	China	9.70	450	0.22	major/minor amputation	6
ZUBAIR[16]	2012	India	2.25	162	0.28	major/minor amputation	6
YESIL[17]	2009	Turkey	9.40	574	0.37	major/minor amputation	8
UGWU[18]	2019	Nigeria	1.00	336	0.35	major/minor amputation	7
SALEEM[19]	2017	Saudi Arabia	1.50	112	0.28	major/minor amputation	6
FERREIRA[20]	2018	Portugal	1.00	479	0.10	major/minor amputation	7
WANG[21]	2022	China	8.00	856	0.57	major/minor amputation	7
PERNG[22]	2021	China	5.25	646	0.25	major/minor amputation	8
SAYINER[23]	2019	Turkey	5.00	400	0.36	major/minor amputation	7
KURNIAWATI[24]	2019	Indonesia	1.00	73	0.19	major amputation	6
LEE[25]	2020	South Korea	9.00	351	0.48	major/minor amputation	7
BEKELE[26]	2020	Ethiopia	0.25	115	0.30	major/minor amputation	6
MOON[27]	2021	South Korea	16.30	169	0.09	major amputation	5
ZHANG[28]	2024	China	4.00	200	0.34	major/minor amputation	6
AKINCI[29]	2011	Turkey	5.00	165	0.42	major/minor amputation	6

续表1 文献基线特征

Table 1(continued) Baseline characteristics of the literatures

Author	Year of Publication	Country/ Region	Follow-up Time / years	Sample Size	Amputation Rate	Outcomes	NOS Score/ Point
ZENGIN[30]	2023	Turkey	15.00	507	0.21	major amputation	7
YUZUGULDU[31]	2023	Turkey	15.00	518	0.64	major/minor amputation	8
CHEN[32]	2024	China	6.00	634	0.11	major amputation	8
BEANEY[33]	2016	America	2.25	165	0.20	major/minor amputation	7
SOLIMAN[34]	2020	Egypt	2.00	112	0.52	major/minor amputation	8
ABBAS[35]	2022	Tanzania	22.00	103	0.21	major/minor amputation	7
LEE[36]	2022	South Korea	5.00	131	0.50	major/minor amputation	8
CHE[37]	2024	China	3.50	526	0.50	major/minor amputation	8
PICKWELL[38]	2015	Europe	1.00	575	0.28	major/minor amputation	7
UYSAL[39]	2017	Turkey	2.00	379	0.33	major/minor amputation	6
PEMAYUN[40]	2015	Indonesia	3.00	94	0.15	major/minor amputation	7
KANG[41]	2024	India	5.00	125	0.18	major amputation	7

表2 DFU截肢潜在风险因素的亚组分析结果

Table 2 Subgroup analysis of potential risk factors for DFU amputation

Risk Factors	Prospective Study			Retrospective Study		
	Number of Literatures	*RR*(95%*CI*)	*P*	Number of Literatures	*OR*(95%*CI*)	*P*
Age/years	6	1.39(0.92~2.10)	0.11	16	1.02(1.00~1.03)	0.06
Gender	6	1.21(0.72~2.02)	0.48	15	1.35(1.05~1.63)	0.02
Smoking	3	1.09(0.63~1.91)	0.75	10	1.31(1.10~1.55)	<0.01
BMI/(kg/m^2)	2	0.97(0.88~1.06)	0.02	5	0.98(0.96~1.00)	0.07
Hypertension	4	1.26(0.60~2.68)	0.54	12	1.38(1.03~1.85)	0.03
LEAD	4	3.95(2.57~6.07)	<0.01	16	2.96(2.13~4.12)	<0.01
DPN	5	1.56(0.81~2.99)	0.18	9	1.62(1.16~2.25)	<0.01
Osteomyelitis	4	4.26(3.03~6.00)	<0.01	10	2.78(1.85~4.18)	<0.01
PHA	2	4.13(1.58~10.78)	<0.01	8	3.12(1.84~5.29)	<0.01
Ulcer depth	1	3.49(1.84~6.61)	<0.01	5	5.38(2.37~12.23)	<0.01
Ulcer infection	2	5.40(0.57~50.70)	0.14	3	4.67(2.16~10.11)	<0.01
Gangrene	1	14.92(6.06~36.78)	<0.01	4	11.49(4.77~27.65)	<0.01
Ulcer area/cm^2	3	1.66(0.89~3.08)	0.11	4	1.66(0.96~2.86)	0.07
WBC/(×10^9/L)	3	2.88(1.97~4.21)	<0.01	13	1.46(1.13~1.88)	<0.01
Hemoglobin/(g/L)	1	1.54(0.87~3.07)	0.22	8	0.92(0.81~1.04)	0.18
Albumin/(mmol/L)	1	1.92(0.84~4.43)	0.12	9	0.99(0.65~1.50)	0.97
HbA1c/%	4	0.70(0.35~1.40)	0.31	15	1.12(1.03~1.23)	0.01

BMI: Body mass index; LEAD: Lower extremity arterial disease; DPN: Diabetic peripheral neuropathy; PHA: Previous history of amputation; WBC: White blood cell count; HbA1c: Hemoglobin A1c

2.2 DFU截肢的风险因素

本研究对17个潜在风险因素分别进行定量分析。亚组分析分为前瞻性研究和回顾性研究2组,坏疽、溃疡深度、骨髓炎、既往截肢史、下肢动脉疾病和白细胞计数在2组间均为DFU截肢的影响因素,差异具有统计学意义(表2)。通过Meta分析合并效应量,各风险因素相应的*OR*及95%*CI*结果显示,白细胞计数的研究报道存在明显发表偏移,经剪补法调整后*OR*=1.15(0.83~1.61),提示无统计学意义(表3)。因此,预测模型最终纳入5个具有统计学意义的风险因素:坏疽、溃疡深度、骨髓炎、既往截肢史和下肢动脉疾病。

2.3 风险预测模型的开发

DFU截肢风险预测模型纳入的风险因素、风险分层、*OR*(95%*CI*)、β和各风险因素评分如表4所示。本研究建立了一个简单的临床评分模型用于预测DFU截肢事件,该模型纳入5个风险因素,总分范围为0~76分,总分越高截肢风险越大。

表3 DFU截肢潜在风险因素的Meta分析结果

Table 3 Meta-analysis results of potential risk factors for DFU amputation

Risk factors	Number of Literatures	Heterogeneity Test		*OR*(95%*CI*)	*P*	Egger Test/*P*	*OR*(Trim and Fill Method)
		I^2/%	*P*				
Age/years	5~9,11~13,16~18,19,22,27,29~32,35,36,40,41	73.46	<0.01	1.02(1.00~1.04)	0.021	0.018	1.02(1.00~1.04)
Gender	5~9,12,13,16~19,21~23,26,30~32,35,36,41	60.07	<0.01	1.32(1.06~1.63)	0.013	0.933	–
Smoking	5,7,9,12,13,17,22,23,26,29,30,32,41	0.00	0.96	1.29(1.09~1.52)	0.002	0.343	–
BMI/(kg/m^2)	5,22,26,35~37,41	16.59	0.30	0.98(0.96~1.00)	0.052	0.203	–
Hypertension	5,7~9,12,13,16,17,19,22,23,26,30,31,36,41	49.99	0.02	1.38(1.05~1.79)	0.019	0.774	–
LEAD	5~10,12,16,18,20~23,26,30~33,35,40	70.76	<0.01	3.10(2.31~4.17)	<0.001	0.875	–
DPN	6,8,16,18,19,23,24,26,30,32,35,36,40,41	33.35	0.08	1.59(1.20~2.11)	0.001	0.278	–
Osteomyelitis	5,6,7,12,16,17,18,21,22,25,29,39,40,41	72.16	<0.01	3.19(2.36~4.29)	<0.001	0.056	–
PHA	5,6,9,12,20,23,25,34,35,41	62.08	<0.01	3.19(2.00~5.09)	<0.001	0.711	–
Ulcer depth	9,11,17,27,38,40	79.54	<0.01	4.93(2.52~9.64)	<0.001	0.550	–
Ulcer infection	9,18,20,34,40	78.07	<0.01	4.83(1.99~11.77)	<0.001	0.280	–
Gangrene	12,17,29,30,40	81.25	<0.01	11.92(5.86~24.24)	<0.001	0.269	–
Ulcer area/cm^2	12,16,17,21,26,29	56.70	<0.01	1.62(1.12~2.35)	0.010	0.459	–
WBC/($\times10^9$/L)	5,8,9,10,12,15~18,24,28~31,36,41	98.14	<0.01	1.64(1.27~2.11)	<0.001	0.001	1.15(0.83~1.61)
Hemoglobin/(g/L)	8,16,17,28,32,36,37,40,41	98.63	<0.01	0.93(0.82~1.07)	0.317	0.123	–
Albumin/(mmol/L)	5,10,11,17,29,31,32,37,40,41	99.48	<0.01	1.04(0.70~1.55)	0.829	0.837	–
HbA1c/%	5,8,10,12~14,16~19,22,24,30~32,36,37,40,41	69.78	<0.01	1.11(1.02~1.21)	0.015	0.055	–

BMI: Body mass index; LEAD: Lower extremity arterial disease; DPN: Diabetic peripheral neuropathy; PHA: Previous history of amputation; WBC: White blood cell count; HbA1c: Hemoglobin A1c

表4 糖尿病足溃疡截肢风险预测模型各风险因素评分

Table 4 Scores of risk factors in DFU amputation risk prediction model

Risk Factors	Risk Stratification	*OR*(95%*CI*)	β	Scores	
				No	Yes
Gangrene	Yes/No	11.92(5.86~24.24)	2.48	0	25
Ulcer depth	Yes/No	4.93(2.52~9.64)	1.59	0	16
Osteomyelitis	Yes/No	3.19(2.36~4.29)	1.16	0	12
PHA	Yes/No	3.19(2.00~5.09)	1.16	0	12
LEAD	Yes/No	3.10(2.31~4.17)	1.13	0	11

Ulcer depth only indicated whether bone level was involved. PHA: Previous history of amputation; LEAD: ; Lower extremity arterial disease

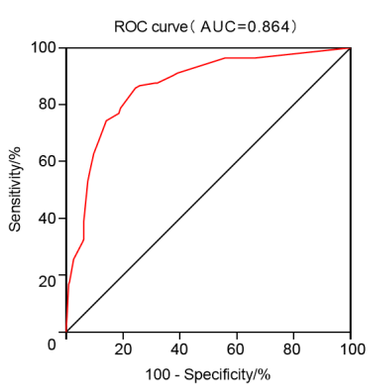


图2 风险预测模型的受试者工作特征曲线

Figure 2 Receiver operating characteristic (ROC) curve of the risk prediction model

2.4 风险预测模型的验证

验证队列共纳入DFU患者453人,其中男性321人(70.86%),截肢113人(24.94%)。患者基线显示,146人出现坏疽,123人溃疡深度至骨,209人伴骨髓炎,157人伴下肢动脉疾病,52人有既往截肢史。在验证队列中,风险预测模型的曲线下面积*AUC*=0.864(0.824~0.903)(图2)。根据最大约登指数确定最佳界值分数为36.5分,灵敏度为0.743,特异性为0.859,准确率为83.00%。Hosmer-Lemeshow检验结果显示*P*=0.301,提示模型拟合效果良好。为更好地应用于临床实践,本研究建立列线图使模型图示化,将5个变量标度对应的分数相加,就可预测DFU患者的截肢风险(图3)。本研究将453名DFU患者分为低风险组(*n*=321)和高风险组(*n*=132),截肢率分别为9.03%和63.64%,其对应的风险总评分分别为0~36分和37~76分。高风险组发生截肢事件的风险是低风险组的7.05倍,*RR*=7.05(5.64~8.26),差异具有统计学意义(*P*<0.001)。

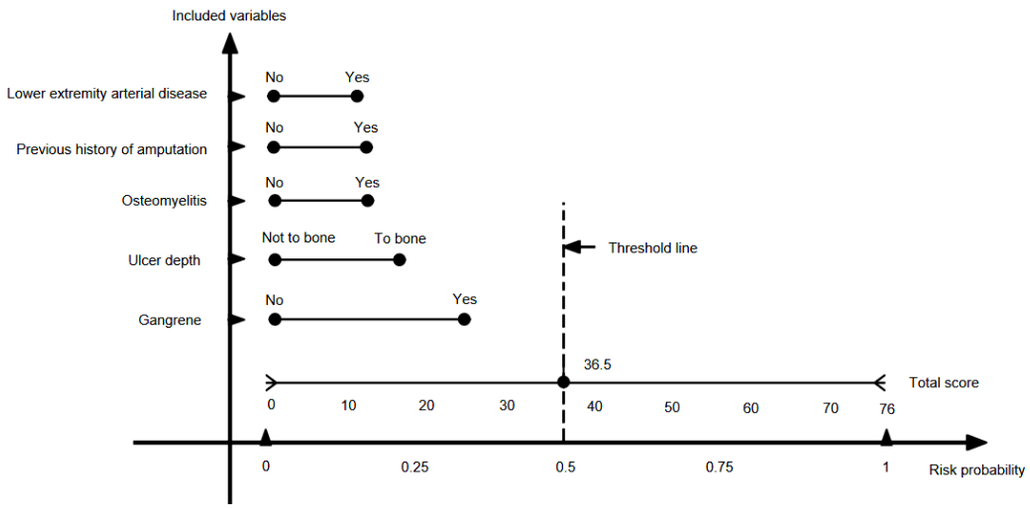


图3 糖尿病足溃疡截肢风险预测模型列线图

Figure 3 Nomogram of the prediction model for diabetic foot ulcers amputation risk

3 讨论

3.1 模型性能

本模型是基于系统评价和Meta分析建立的DFU截肢风险预测模型,可根据每个风险因素的评分评估DFU患者发生截肢的风险。该模型ROC的*AUC*>0.85,表现出良好的区分度,能够以83.00%的准确率预测截肢事件。Hosmer-Lemeshow检验*P*>0.05,表明模型具有良好的拟合效果。最佳界值分数为36.5分,意味着评分为37分或更高的患者有极大风险发生截肢事件。目前SÁNCHEZ等[42-44]也已经开发DFU患者截肢的预测模型,AUC值为0.76~0.84。相比之下,本研究的模型性能表现更为优异。SÁNCHEZ等[42-44]的预测模型均是采用机器学习的方法通过对观察性研究的事后分析建立起来的,有其固有的局限性。机器学习模型在使用单一数据库进行训练时可能会出现过拟合的问题。机器学习的另一个固有限制是大数据悖论,这使得研究者对数据的准确性和有用性的信心可能会错误增加。Meta分析是循证医学领域评价医疗干预措施的金标准,能通过整合不同研究的结果,精准计算出各影响因素的权值大小,提高样本容量和统计效能,提供更为可靠的结论[45-47]。因此,本研究基于Meta分析结果建立的DFU截肢风险预测模型,整合多中心数据,避免了单一数据库带来的过拟合现象,在一定程度上提高了模型的检验效能。此外,本模型相较机器学习建立的模型具有更强的解释性和更佳的可视化效果。

3.2 模型解释

本研究发现,坏疽、溃疡深度、骨髓炎、既往截肢史和下肢动脉疾病为DFU下肢截肢的有效预测变量,其中前三者均为DFU的伤口特征。CHO等[48]的研究表明伤口特征是预测慢性伤口愈合的重要指标。模型中坏疽的影响权重最大,2019年关于DFU患者下肢截肢风险因素的一篇系统综述也将坏疽(*OR*=6.487)视为DFU截肢最重要的风险因素[49]。坏疽是组织缺血、感染、坏死三者的恶性循环,如不及时处理,可能增加全身感染的风险,甚至引发中毒性休克等严重并发症[50]。JEONG等[9]的研究发现伤口深度是住院DFU患者下肢截肢的重要预测因素,本研究结论也支持此观点。骨髓炎的出现常常提示着伤口组织破坏严重、感染难以控制,美国糖尿病足工作组建议对于伴发骨髓炎的DFU患者进行感染骨骼手术切除并结合抗生素治疗[51]。据文献报道,发生下肢截肢的患者中超过50%在未来3~5年内需要再次截肢[52-53],这表明既往截肢史的存在可能显著增加DFU患者的截肢风险。UGWU等[18]的多中心观察研究提示外周动脉疾病与DFU患者下肢截肢高度相关。外周动脉疾病常导致血管狭窄甚至闭塞,阻碍血液流动,导致下肢组织缺血缺氧,增加截肢风险。本模型中纳入的风险因素也被其他临床研究强调为DFU截肢的重要危险因素,这表明模型输出与临床解释之间的一致性。另一方面,本研究未纳入一些存在争议的重要因素,如糖化血红蛋白和白细胞计数等。LI等[54]人的研究显示DFU重度溃疡组的HbA1c水平明显高于轻度溃疡组,提示血糖控制不佳与DFU病情进展密切相关。本

研究中Meta分析显示,糖化血红蛋白虽然在回顾性研究中存在统计学意义,但在前瞻性研究中结论相反。回顾性研究常仅以患者第一次入院或就诊时的糖化血红蛋白值作为基准,忽视了血糖管理的动态变化过程,这降低了结论的可信性。白细胞计数作为临床常用的炎症指标,对DFU重度感染具有提示作用[51]。但本研究显示白细胞计数的研究报道存在明显发表偏移,经剪补法调整后*OR*=1.15(0.83~1.61),提示无统计学意义。这些重要因素虽未被本模型纳入,但在未来仍具有研究价值。

本研究也存在一些局限性。纳入Meta分析的文献在研究设计和数据收集上不可避免地存在异质性,虽然进行了发表偏移分析并利用剪补法降低由此带来的影响,但仍然无法完全避免这一问题。本模型预测的结局事件包括大截肢和/或小截肢,没有进一步分别区分大截肢和小截肢做独立预测。本研究的临床队列数据均来自住院的DFU患者,基线特征与Meta分析纳入的研究存在一定差异,可能导致模型验证结果的偏移。但Meta分析纳入的研究数量较多,基线信息均波动在一定范围(如截肢率波动在9.0%~63.9%),这使得合并的效应量具有较好的稳定性,因此上述偏移对模型泛化性的影响有限。未来的研究可在多中心和多个时间点收集更多数据,以追踪截肢风险的轨迹。另外,可考虑将模型集成到电子病历系统或构建简易的评分模型APP作为截肢风险的预测工具,可以进一步验证模型的有效性和稳健度。

综上所述,本研究通过系统综述和Meta分析整合37项高质量的队列研究,确定了5个有效预测变量,并开发了一个预测性能良好的DFU截肢风险预测模型。该模型采用评分体系,无需复杂的数学计算,指标获取方便,可解释性强,是一种直观易懂且操作简单的临床工具,有助于临床医生的医疗决策。

利益冲突 本文所有作者声明不存在利益冲突

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