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## 早期乳腺癌腋窝淋巴结转移风险因素及风险预测模型的建立\*

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**摘要 目的:**探究早期乳腺癌腋窝淋巴结转移的独立危险因素,并建立有效的风险预测模型。**方法:**回顾性分析辽宁省肿瘤医院2016年6月至2017年12月收治的404例早期乳腺癌患者的临床资料,采用 $\chi^2$ 检验或Fisher确切概率法对临床病理特征与腋窝淋巴结转移情况进行单因素分析,采用多元逐步 Logistic 回归分析探索腋窝淋巴结转移的独立危险因素,根据各危险因素的回归系数进行赋值,建立风险预测模型,采用 ROC 曲线验证其检验效能并绘制校准曲线评估其与真实情况的一致性。**结果:**早期乳腺癌发生腋窝淋巴结转移与肿瘤大小、病理分级、脉管侵袭、ER 表达、KI67 大小、分子亚型和淋巴结总数 $\geq 14$ 枚(14枚为淋巴结平均数)之间存在统计学差异( $P < 0.05$ ),而与年龄、绝经与否、肿瘤位置、病理类型、PR 等因素无关( $P > 0.05$ )。单因素及多因素分析结果显示肿瘤 $> 2$  cm、病理分级 III 级、存在脉管侵袭及 ER 表达 $\geq 50\%$ 是早期乳腺癌发生腋窝淋巴结转移的独立危险因素( $P < 0.05$ )。风险预测模型 ROC 曲线下面积为 0.852(95%CI 为(0.812,0.892), $P < 0.01$ )。校准曲线  $R^2=0.9086$ ( $P < 0.05$ )。**结论:**肿瘤 $> 2$  cm、病理分级 III 级、存在脉管侵袭、ER 表达 $\geq 50\%$ 早期乳腺癌患者发生腋窝淋巴结转移风险较高。

**关键词:**早期乳腺癌;腋窝淋巴结转移;风险因素;模型

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## Risk Factors and Establishing Predictive Risk-scoring Model for Axillary Lymph Node Metastasis in Early Breast Cancer\*

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**ABSTRACT Objective:** To explore the independent risk factors of axillary lymph node metastasis in early breast cancer and establishing an effective risk prediction model. **Methods:** The clinical data of 404 early breast cancer patients from June 2016 to December 2017 in Liaoning Cancer Hospital were enrolled in this study. The chi-square test or Fisher's exact test were used to analyze the clinical pathological characteristics and axillary lymph node metastasis. Multivariate stepwise logistic regression analysis was used to explore the independent risk factors of axillary lymph node metastasis. Risk prediction model was established according to the regression coefficients of each risk factor. ROC curve was used to verify the effectiveness of the test and calibration curve was drawn to evaluate its consistency with the real situation. **Results:** Axillary lymph node metastasis in early breast cancer was significantly different( $P < 0.05$ ) between tumor size, pathological grade, vascular invasion, ER expression, size of KI67, molecular subtype and total number of lymph nodes $\geq 14$  (14 were the average number of lymph nodes), but not related to age, menopause, tumor location, pathological type, PR and other factors ( $P > 0.05$ ). Univariate and multivariate analysis showed that tumor $> 2$  cm, pathological grade III, vascular invasion and ER expression $\geq 50\%$  were independent risk factors for axillary lymph node metastasis in early breast cancer( $P < 0.05$ ). The area under the ROC curve was 0.852 (95% CI was (0.812, 0.892),  $P < 0.01$ ). The calibration curve  $R^2=0.9086$  ( $P < 0.05$ ). **Conclusion:** Tumor $> 2$  cm, pathological grade III, vascular invasion, and ER $\geq 50\%$  are independent risk factors for axillary lymph node metastasis in early breast cancer.

**Key words:** Early breast cancer; Axillary lymph node metastasis; Risk factors; Models

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### 前言

乳腺癌目前已成为全世界女性发病率最高的恶性肿瘤<sup>[1]</sup>,其病死率位居女性恶性肿瘤的第6位<sup>[2,3]</sup>。自19世纪末Halsted报道乳腺癌根治术以来,腋窝手术已成为乳腺癌局部治疗中不

可或缺的疗法,准确的腋窝状态评估是乳腺癌患者预后评价和辅助治疗决策的重要依据。腋窝淋巴结清扫术(Axillary lymph node dissection, ALND)是乳腺癌腋窝分期的标准手术方式,然而70%的早期乳腺癌患者未发生腋窝淋巴结转移<sup>[4,5]</sup>,对于这些患者,ALND是一种过度的治疗方式。20世纪90年代前哨淋

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巴结活检术(Sentinel lymph node biopsy, SLNB)成为早期乳腺癌腋窝分期的主要手段<sup>[6]</sup>。随着对乳腺癌腋窝淋巴结转移方式的深入研究,腋窝淋巴结跳跃式转移已越来越受到人们重视,有研究发现腋窝淋巴结跳跃式转移的发生率为5.5%-19.2%<sup>[7,8]</sup>。一旦发生淋巴结跳跃式转移将会导致患者错误分期,不仅会指导错误的后续辅助治疗,而且会影响患者的预后生存<sup>[9,10]</sup>。本研究通过分析早期乳腺癌(T<sub>1-2</sub>N<sub>0-1</sub>M<sub>0</sub>)患者的临床基本数据,分析腋窝淋巴结转移与临床病理特征之间的关系,并根据相关的独立危险因素建立风险预测模型,为外科医生制定合理的治疗方案提供可靠依据。

## 1 资料与方法

### 1.1 一般资料

选取2016年6月至2017年12月期间辽宁省肿瘤医院收治的404例早期乳腺癌患者作为研究对象。纳入标准:(1)均为原发性早期乳腺癌(T<sub>1-2</sub>N<sub>0-1</sub>M<sub>0</sub>);(2)术后病理均证实为浸润性乳腺癌;(3)由2名主任医师完成腋窝触诊,乳腺X线,彩超及MRI均证实腋窝淋巴结为cN<sub>0-1</sub>乳腺癌;(4)术前辅助检查排除严重心脑血管疾病,肝肾功能障碍及其他恶性肿瘤者。排除既往接受内分泌治疗,化疗,放疗及腋窝手术者。所有患者均行乳腺癌保乳手术或者乳房切除术,腋窝行前哨淋巴结活检术或腋窝淋巴结清扫术。本研究符合医院伦理委员会审查标准,所有患者均签署知情同意书。

### 1.2 观察指标

本研究结合常见的临床病理特征及最新版美国综合肿瘤网络中心(National Comprehensive Cancer Network, NCCN)指南<sup>[11]</sup>,对以下指标进行分析:(1)年龄;(2)绝经状态;(3)肿瘤大小:术后病理中的最大径,分为≤2 cm和>2 cm;(4)肿瘤位置:

外上,外下,内上,内下,中央区;(5)病理分级:I级、II级、III级;(6)脉管侵袭:根据病理报告有无淋巴结转移进行分组,其中淋巴结无转移235例,淋巴结转移169例;(7)病理类型:分为浸润性导管癌,浸润性小叶癌,髓样癌,粘液腺癌,其他;(8)雌激素受体ER:根据表达情况的不同分为三组<30%,30%-49%,≥50%;(9)孕激素受体PR:根据表达情况不同分为<20%和≥20%;(10)人表皮生长因子受体-2(Her-2)分为阳性和阴性;(11)KI-67表达水平:分为<14%,14%-19%,20%-25%,≥25%;(12)依据2011年St.Gallen专家共识分子亚型:分为Luminal A型,Luminal B型,HER-2型,Triple negative型;(13)术后病理淋巴结总数≥14枚的人数情况。

### 1.3 统计学方法

采用SPSS 25.0统计软件进行统计及分析,定量资料采用t检验或秩和检验,定性资料采用频数及百分比(%)进行统计描述,组间比较采用 $\chi^2$ 检验或Fisher确切概率法。筛选单因素分析P<0.05的指标作为自变量,进行多元逐步Logistic回归分析探索腋窝淋巴结转移的独立危险因素。根据独立危险因素回归系数对其赋分,建立风险评分系统,并采用ROC曲线分析评估其准确性。以P<0.05差异具有统计学意义。

## 2 结果

### 2.1 两组间各临床病理特征的单因素分析结果

两组间各临床病理特征的单因素分析结果显示,早期乳腺癌发生腋窝淋巴结转移与肿瘤大小、病理分级、脉管侵袭、ER表达、KI67大小、分子亚型和淋巴结总数≥14枚(14枚为淋巴结平均数)之间存在统计学差异(P<0.05),而与年龄、绝经与否、肿瘤位置、病理类型、PR等因素无关(P>0.05),见表1。

表1 两组间各临床病理特征的单因素分析结果

Table 1 Single factor analysis of clinicopathological features between the two groups

| Clinicopathological features | n   | No lymph node metastasis group(n=235) | Lymph node metastasis group(n=169) | $\chi^2$ | P      |
|------------------------------|-----|---------------------------------------|------------------------------------|----------|--------|
| Age(year)                    |     |                                       |                                    | 2.692    | 0.446# |
| <35                          | 2   | 2(100.00)                             | 0(0.00)                            |          |        |
| 35-39                        | 6   | 2(33.33)                              | 4(66.67)                           |          |        |
| 40-49                        | 140 | 80(57.14)                             | 60(42.86)                          |          |        |
| 50                           | 256 | 151(58.98)                            | 105(41.02)                         |          |        |
| Menopause or not             |     |                                       |                                    | 0.388    | 0.533  |
| No menopause                 | 153 | 86(56.21)                             | 67(43.79)                          |          |        |
| Menopause                    | 251 | 149(59.36)                            | 102(40.64)                         |          |        |
| Tumor size(cm)               |     |                                       |                                    | 93.549   | 0.000  |
| 2 cm                         | 235 | 184(78.30)                            | 51(21.70)                          |          |        |
| >2 cm                        | 169 | 51(30.18)                             | 118(69.82)                         |          |        |
| Tumor location               |     |                                       |                                    | 4.136    | 0.388  |
| On the outside               | 175 | 93(53.14)                             | 83(47.43)                          |          |        |
| Out and down                 | 70  | 43(61.43)                             | 27(38.57)                          |          |        |
| Inside                       | 99  | 63(63.64)                             | 36(36.36)                          |          |        |
| Inside and below             | 26  | 17(65.38)                             | 9(34.62)                           |          |        |

|                                |     |            |            |        |       |
|--------------------------------|-----|------------|------------|--------|-------|
| Central area                   | 33  | 19(57.58)  | 14(42.42)  |        |       |
| Pathological grading           |     |            |            | 70.689 | 0.000 |
| I grade                        | 22  | 20(90.91)  | 2(9.09)    |        |       |
| II grade                       | 313 | 205(65.50) | 108(34.50) |        |       |
| III grade                      | 69  | 10(14.49)  | 59(85.51)  |        |       |
| Vessel invasion                |     |            |            | 26.580 | 0.000 |
| No                             | 364 | 227(62.36) | 137(37.64) |        |       |
| Yes                            | 40  | 8(20.00)   | 32(80.00)  |        |       |
| Pathological type              |     |            |            | 5.706  | 0.148 |
| Invasive ductal carcinoma      | 383 | 219(57.18) | 164(42.82) |        |       |
| Infiltrating lobular carcinoma | 10  | 7(70.00)   | 3(30.00)   |        |       |
| Medullary carcinoma            | 1   | 0(0.00)    | 1(100.00)  |        |       |
| Mucous adenocarcinoma          | 8   | 7(87.50)   | 1(12.50)   |        |       |
| Others                         | 2   | 2(100.00)  | 0(0.00)    |        |       |
| ER                             |     |            |            | 12.437 | 0.002 |
| <30%                           | 131 | 92(70.23)  | 39(29.77)  |        |       |
| 30%-49%                        | 21  | 13(61.90)  | 8(38.10)   |        |       |
| 50%                            | 252 | 130(51.59) | 122(48.41) |        |       |
| PR                             |     |            |            | 2.546  | 0.111 |
| <20%                           | 191 | 119(62.30) | 72(37.70)  |        |       |
| 20%                            | 213 | 116(54.46) | 97(45.54)  |        |       |
| HER2                           |     |            |            | 1.264  | 0.261 |
| Negative                       | 287 | 172(59.93) | 115(40.07) |        |       |
| Positive                       | 117 | 63(53.85)  | 54(46.15)  |        |       |
| KI67                           |     |            |            | 9.114  | 0.028 |
| <14%                           | 81  | 59(72.84)  | 22(27.16)  |        |       |
| 14%-19%                        | 35  | 18(51.43)  | 17(48.57)  |        |       |
| 20%-25%                        | 64  | 35(54.69)  | 29(45.31)  |        |       |
| >=26%                          | 224 | 123(54.91) | 101(45.09) |        |       |
| Molecular subtype              |     |            |            | 16.177 | 0.001 |
| Luminal A                      | 69  | 51(73.91)  | 18(26.09)  |        |       |
| Luminal B                      | 227 | 113(49.78) | 114(50.22) |        |       |
| Her-2                          | 54  | 35(64.81)  | 19(35.19)  |        |       |
| Triple negative                | 54  | 36(66.67)  | 18(33.33)  |        |       |
| Total number of lymph nodes    |     |            |            | 4.997  | 0.025 |
| nodes ≥ 14                     |     |            |            |        |       |
| No                             | 201 | 128(63.68) | 73(36.32)  |        |       |
| Yes                            | 203 | 107(52.71) | 96(47.29)  |        |       |

Note: #The Fisher exact probability method was adopted.

## 2.2 淋巴结转移危险因素的多元逐步 Logistic 回归分析

进一步筛选单因素分析  $P < 0.05$  的 7 个因素 (肿瘤大小、病理分级、脉管侵袭、ER、KI67、分子亚型和淋巴结总数  $\geq 14$  枚) 作为自变量, 以淋巴结转移情况 (无转移赋值为 0, 转移赋值为 1) 为因变量, 进行多元 Logistic 回归分析, 结果显示肿瘤大小  $> 2$  cm、病理分级为 III 级、有脉管侵袭和  $ER \geq 50\%$  是早期乳腺癌发生腋窝淋巴结转移的独立危险因素 ( $P < 0.05$ ), 见表 2。

## 2.3 建立早期乳腺癌腋窝淋巴结转移风险预测模型

根据多因素分析的结果, 将  $P < 0.05$  的独立危险因素纳入评分系统 (先计算各因素回归系数 / 最小回归系数, 本研究最小回归系数为“脉管侵袭”的回归系数 1.757, 然后通过四舍五入法得到各个危险因素评分)。进一步利用 ROC 曲线检验风险预测模型的检验效能, 其 AUC 为 0.852 (95% CI 为 (0.812, 0.892),  $P < 0.01$ ), 可见该风险预测模型对早期乳腺癌腋窝淋巴结转移的预测具有中等准确度 (0.5-0.7 为低, 0.7-0.9 为中等, 0.9-1 为高准确度), 见图 1。

表 2 淋巴结转移危险因素的多元逐步 Logistic 回归分析

Table 2 Multivariate Logistic regression analysis of risk factors for lymph node metastasis

| Indexes                              | Regression coefficient | Standard error | Wald   | P     | OR(95%CI)                 | Score assignment |
|--------------------------------------|------------------------|----------------|--------|-------|---------------------------|------------------|
| Tumor size>2 cm                      | 2.238                  | 0.290          | 59.434 | 0.000 | 9.379<br>(5.309-16.570)   | 1                |
| The pathological grade was grade III | 3.511                  | 0.940          | 13.939 | 0.000 | 33.466<br>(5.300-211.337) | 2                |
| Vascular invasion                    | 1.757                  | 0.499          | 12.392 | 0.000 | 5.796<br>(2.179-15.418)   | 1                |
| ER $\geq$ 50%                        | 1.901                  | 0.739          | 6.612  | 0.010 | 6.696<br>(1.572-28.523)   | 1                |

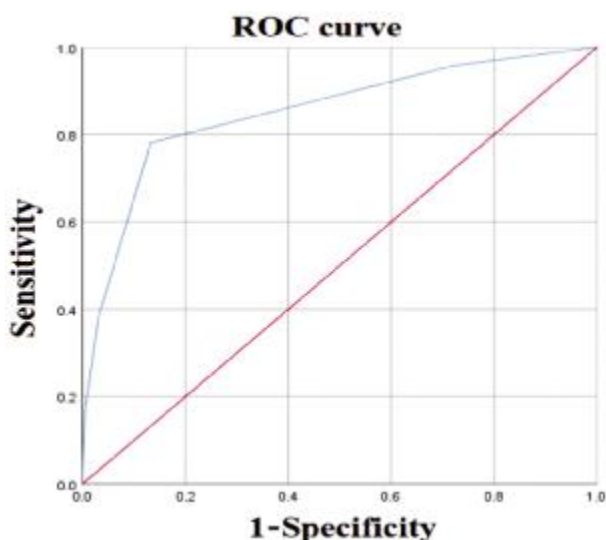


图 1 风险预测模型的受试者工作特征曲线

Fig.1 Receiver operating characteristic curve of risk prediction model

## 2.4 各评分及不同评分分组的淋巴结转移情况分析

随着评分的增加,淋巴结转移率呈上升趋势。将评分进一步分组行差异性检验分析显示低评分组(0-1分)、中等评分组(2-3分)、高分组(4-5分)三组间淋巴结转移率差异具有统计学意义( $P<0.05$ )。进一步两两比较结果显示,4-5分组的转移率显著高于0-1分组( $\chi^2=93.371$ 、 $P=0.000$ )和2-3分组( $\chi^2=5.553$ 、 $P=0.018$ ),2-3分组的转移率显著高于0-1分组( $\chi^2=142.274$ 、 $P=0.000$ ),见表3和表4。

## 2.5 风险预测模型的校准曲线

为评估该风险预测模型预测值与真实情况的一致性,绘制校准曲线。该模型校准曲线的回归方程为  $y=1.0026x+0.0009$  ( $R^2=0.9086$ ),很接近参考线的回归方程( $y=x$ ),故可认为该风险预测模型的一致性很好,即该风险预测模型预测的结果与真实情况具有很好的一致性,见图2。

表 3 各评分下淋巴结转移率分析

Table 3 Analysis of lymph node metastasis rate under each score

| Score | Sample size (n=404) | Transfer number (n=169) | Transfer rate(%) |
|-------|---------------------|-------------------------|------------------|
| 0     | 72                  | 7                       | 9.72             |
| 1     | 169                 | 30                      | 17.75            |
| 2     | 92                  | 68                      | 73.91            |
| 3     | 42                  | 36                      | 85.71            |
| 4     | 25                  | 24                      | 96.00            |
| 5     | 4                   | 4                       | 100.00           |

表 4 各评分分组淋巴结转移率的比较分析

Table 4 Comparison of lymph node metastasis rates in each scoring group

| Groups    | Sample size (n=404) | Transfer number (n=169) | Transfer rate(%) | $\chi^2(P)^*$     | $\chi^2(P)^{\#}$   |
|-----------|---------------------|-------------------------|------------------|-------------------|--------------------|
| 0-1 score | 241                 | 37                      | 15.35            | 75.631<br>(0.000) | 163.962<br>(0.000) |
| 2-3 score | 134                 | 104                     | 77.61            |                   |                    |
| 4-5 score | 29                  | 28                      | 96.55            |                   |                    |

Note: \*was the results of the difference test, # was the trend chi square test results.

## 3 讨论

如今乳腺癌被诊断时的分期越来越早,如何准确的无创评

估早期乳腺癌患者腋窝淋巴结状态非常具有挑战,但这对于患者的后续治疗非常重要<sup>[12-14]</sup>。目前已有许多无创评估腋窝淋巴结状态的工具,包括彩超、X线、磁共振、腋窝增强CT及

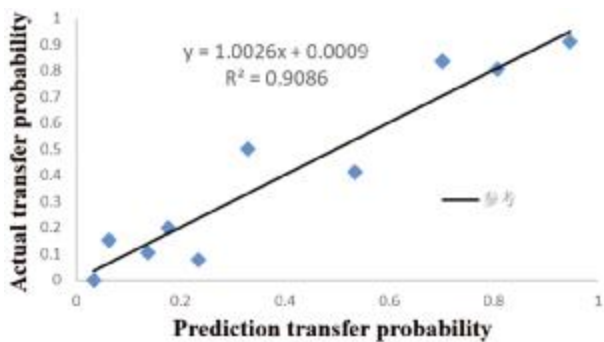


图2 风险预测模型的校准曲线

Fig.2 Calibration curve of risk prediction model

PET-CT 等<sup>[15-17]</sup>,国内有研究证实彩超评估腋窝 I、II、III 组淋巴结状态的假阴性率各为 2.2%、22.2%及 33.3%<sup>[18]</sup>,而磁共振及 PET-CT 由于价格昂贵,无法在每个患者中实施。前哨淋巴结活检作为早期乳腺癌腋窝淋巴结状态有创评估的主流工具,据国外研究报道 SLNB 仍具有一定的假阴性率 6.6%<sup>[19]</sup>,并且腋窝淋巴结转移方式存在一定跳跃式转移可能,导致早期乳腺癌前哨淋巴结活检的准确性及安全性存在着一些争议。开发一种无创、实用、准确的腋窝淋巴结转移风险临床决策工具,对于腋窝淋巴结手术方式的选择具有重要指导意义,也给乳腺癌患者的后续治疗带来更多指导。

在本研究中,我们建立了一个准确的早期乳腺癌腋窝淋巴结转移风险预测模型,该模型具有很好的检验效能,其 AUC 为 0.852。该模型预测的结果与真实情况具有很好的一致性,校准曲线  $R^2=0.9086$ 。多因素分析中发现原始肿瘤 >2 cm、病理分级 III 级、存在脉管侵袭及 ER 的表达  $\geq 50\%$  是早期乳腺癌发生腋窝淋巴结转移的独立危险因素,这与多数研究也相符<sup>[20-22]</sup>。年轻乳腺癌患者比老年患者有更高的局部复发率及远处转移率<sup>[23]</sup>,年轻也是乳腺癌患者预后不良的危险因素之一,但本研究发现年龄与腋窝淋巴结转移无关,这与国内一些研究相符<sup>[24]</sup>。Her-2 状态在本研究与腋窝淋巴结转移的发生无相关性,可能与部分患者 FISH 检测处于临界值有关<sup>[25-26]</sup>。在本研究中,我们发现 ER 表达 ( $\geq 50\%$ ) 与腋窝淋巴结转移具有较高的相关性,类似于国外研究发现<sup>[27]</sup>,这种现象的原因可能是 ER 弱表达更倾向于发生血行转移而不是淋巴结转移。进一步对全部患者总评分分析发现,随着评分的增加淋巴结的转移率呈上升趋势,并且低、中、高分组具有显著差异,线性趋势也很显著。目前乳腺癌的治疗越来越精准,已进入分子时代,而在早期乳腺癌中腋窝淋巴结的状态直接关系到患者的后续治疗及预后<sup>[28,29]</sup>。早期乳腺癌腋窝手术方式的选择取决于术前腋窝状态的精准评估,目前循证医学 I 级证据证实 SLNB 的安全性及准确性,前哨淋巴结阴性的患者 SLNB 可以替代传统的 ALND,染色法及和核素法联合使用可以提高前哨淋巴结活检的检出率<sup>[30]</sup>。但目前临床上普遍使用冰冻快速病理判断前哨淋巴结的状态,相比免疫组化就存在一定的假阴性率,且腋窝淋巴结转移存在跳跃转移的可能。确定腋窝淋巴结转移的危险因素及建立可靠的风险预测模型,在术前评估患者腋窝淋巴结转移的概率,明确 SLNB 的适应症,这对于临床工作具有一定的指导意义。

综上所述,早期乳腺癌患者肿瘤大于 2 cm、病理分级 III

级、存在脉管侵袭、ER 表达  $\geq 50\%$  都是发生腋窝淋巴结转移的高危因素,本研究建立的模型可进一步提高术前腋窝淋巴结评估的准确性,为早期乳腺癌患者提高更加精准个体化治疗提高依据。尽管本研究中的风险预测模型提供了很有前景的预测价值,但其也有一定的限制。首先该模型未能够在外部大型实验组中得到验证,其次肿瘤大小、病理分级、脉管侵袭及 ER 表达的大小都受到观察者差异的影响。所以该模型并不能成为 SLNB 的替代品,需要不断的临床实践及更多的前瞻性研究来验证其准确性及特异性。

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