·论著·

高级别宫颈鳞状上皮内病变冷刀锥切术后复发的危险因素分析及其风险模型建立

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摘要 目的 探讨高级别宫颈鳞状上皮内病变(HSIL)患者冷刀锥切术(CKC)后复发的危险因素并构建风险预测模型。**方法** 回顾性分析2018年1月至2023年9月辽宁省人民医院妇科采用CKC治疗的270例HSIL患者临床资料。采用χ^2检验比较复发组(n = 28)与未复发组(n = 242)患者临床指标的差异;采用Cox单因素和多因素回归分析术后复发的危险因素,并构建复发风险预测模型;采用受试者操作特征(ROC)曲线评估各危险因素及模型的预测效能。**结果** 与未复发组比较,复发组在初次性生活年龄<18岁、CINⅢ级、切缘阳性、术后高危型HPV持续感染、多象限病变、腺体受累及ENO1和TOP2A强阳性表达占比均显著增加(均$P < 0.05$)。单因素Cox回归分析结果显示,上述危险因素均显著增加复发风险(均$P < 0.05$)。多因素Cox回归分析结果显示,术后高危型HPV持续感染、切缘阳性、腺体受累及TOP2A强阳性表达为复发的独立危险因素(均$P < 0.05$)。成功构建了复发风险预测模型。列线图模型Bootstrap校正后一致性指数(C-index)为0. 844。ROC曲线分析表明,基于高危型HPV持续感染、切缘阳性、腺体受累及TOP2A强阳性表达4项指标的联合预测模型(AUC=0.851)较单一指标具有更高的预测准确性(DeLong检验,均$P < 0.05$)。**结论** 术后高危型HPV持续感染、切缘阳性、腺体受累及TOP2A强阳性表达是HSIL患者CKC术后复发的独立危险因素。因此,术前充分评估手术切除范围和深度,术后加强高风险人群的随访和管理可能降低复发风险。

关键词 高级别宫颈鳞状上皮内病变; 冷刀锥切术; 复发; 危险因素
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Risk factor analysis and risk model establishment for recurrence following cold knife conization in patients with high-grade cervical squamous intraepithelial lesion

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Abstract Objective To determine the risk factors and develop a risk prediction model for recurrence after cold knife conization (CKC) in patients with high-grade cervical squamous intraepithelial lesion (HSIL). **Methods** A retrospective analysis was conducted on the clinical data of 270 patients with HSIL treated with CKC at the Liaoning Provincial People's Hospital from January 2018 to September 2023. A chi-square test was used to compare the differences in clinical indicators between the recurrence group (n = 28) and the non-recurrence group (n = 242). Cox univariate and multivariate regression analyses were performed to identify the risk factors for postoperative recurrence, and a recurrence risk prediction model was constructed. The predictive efficacy of each risk factor and the overall model was evaluated using receiver operating characteristic (ROC) curves. **Results** Compared with the non-recurrence group, the recurrence group showed a significantly higher proportion of patients with initial sexual intercourse at age < 18 years, CINⅢ grade, positive surgical margins, persistent high-risk human papilloma virus (HPV) infection postoperatively, multi-quadrant lesions, glandular involvement, and strong positive expression of ENO1 and TOP2A (all $P < 0.05$). The results of univariate Cox regression indicated that these risk factors were all significantly associated with an increased risk of recurrence (all $P < 0.05$). Multivariate Cox regression analysis revealed that persistent high-risk HPV infection, positive surgical margins, glandular involvement, and strong positive expression of TOP2A were independent risk factors for recurrence (all $P < 0.05$). A recurrence risk prediction model was successfully constructed. The concordan-

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ce index (after bootstrap correction) of the nomogram model was 0.844. ROC curve analysis showed that the predictive model based on the four indicators of persistent HPV infection, positive surgical margins, glandular involvement, and strong positive expression of TOP2A had a higher predictive accuracy (area under the curve = 0.851) than that of any single indicator (DeLong test, all $P < 0.05$). **Conclusion** Persistent HPV infection, positive surgical margins, glandular involvement, and strong positive expression of TOP2A were independent risk factors for recurrence after CKC in patients with HSIL. Therefore, a thorough preoperative assessment of the surgical resection range and depth, along with enhanced follow-up and management of high-risk populations postoperatively, may help reduce the risk of recurrence.

Keywords　high-grade cervical squamous intraepithelial lesion; cold knife conization; recurrence; risk factor

宫颈癌是全球女性群体中高发的恶性肿瘤，其致死率处于较高水平，已成为全球癌症相关死亡的主要原因之一[1-4]。高级别宫颈鳞状上皮内病变（high-grade cervical squamous intraepithelial lesion，HSIL）是宫颈癌前病变，若未进行规范化治疗或治疗不彻底，则可能进一步发展为浸润性宫颈癌。目前，冷刀锥切术（cold knife conization，CKC）是HSIL治疗的主要术式之一。CKC通过局部切除宫颈病变区域，有效地阻止了病变进展为宫颈癌，具有良好的治疗效果，临床上已获得广泛认可[5-8]。然而，已有研究[9]显示，术后仍有5.3%~12.0%患者复发。因此，明确HSIL患者CKC术后复发的影响因素具有重要意义。

近年来研究[6,10-14]表明，HSIL患者CKC术后复发不仅受手术操作的影响，患者的临床病理特征，尤其是术后高危型人乳头瘤病毒（human papilloma virus，HPV）感染情况、宫颈病变累及范围及病变的深度也可能影响术后复发。同时，随着肿瘤分子病理学的发展，越来越多证据[15-20]提示代谢相关蛋白以及增殖标志物在宫颈癌前病变的发生发展中发挥作用。其中，α–烯醇化酶（α-enolase，ENO1）和拓扑异构酶Ⅱα（topoisomerase Ⅱα，TOP2A）因与细胞能量代谢重编程、DNA拓扑调控和异常增殖密切相关而备受关注。本研究采用回顾性分析方法，将患者ENO1、TOP2A指标纳入，探讨影响HSIL患者CKC术后复发的危险因素，并进一步构建复发风险预测模型，旨在为临床提供更精准的预后评估手段，为高风险患者制定个性化的随访与治疗方案提供依据。

1　材料与方法

1.1　临床资料及分组

收集2018年1月至2023年9月间于辽宁省人民医院妇科诊断为HSIL且实施CKC的270例患者的临床资料。纳入标准：（1）经病理学诊断为HSIL；（2）术后6个月完成复查，复查包括HPV检测、液基薄层细胞学检查（thinprep cytologic test，TCT）和（或）阴道镜检查及活检，且临床、实验室、影像学及随访资料完整；（3）无自身免疫性疾病、代谢性疾病史或未接受类固醇药物治疗；（4）既往未患有其他恶性肿瘤；（5）随访时间＞24个月。本研究获得辽宁省人民医院伦理委员会批准（2025K091），已获得免除知情同意。术后随访6个月，宫颈活检病理确诊为HSIL或宫颈鳞状细胞癌时为复发；进而将患者分为复发组（n = 28）和未复发组（n = 242）。

1.2　研究指标

收集并记录患者的相关指标，包括首诊年龄、初次性生活年龄、孕次、产次、性伴侣数量、CIN分级、病变累及范围、腺体受累、切缘状态、术后高危型HPV持续感染（术前及术后6个月随访，HPV检测结果显示存在同一型别高危型HPV感染为HPV持续感染）、ENO1及TOP2A表达。

1.3　免疫组织化学检测

将患者的组织样本切片经过常规脱蜡、重水化处理后，采用抗ENO1抗体（11204-1-AP，武汉三鹰生物技术有限公司）和抗TOP2A抗体（24641-1-AP，武汉三鹰生物技术有限公司）进行一抗反应，PBS清洗后滴加二抗孵育。DAB显色系统染色后显微镜下观察。采用H-score评分评估ENO1与TOP2A的表达水平。

H-score评分标准：（1）阳性细胞百分比评分，无阳性细胞为0分；<10%为1分；10%~<50%为2分，50%~<80%为3分，≥80%为4分。（2）染色强度评分，无染色为0分；弱染色为1分；中等染色为2分；强染色为3分。阳性细胞染色评分和百分比评分乘积为H-score评分，0~3分为阴性（–），1~4分为弱阳性（+），2~8分为中等阳性（++），9~12分为强阳性（+++）。

H-score评分由2位经验丰富的病理学专家独立完成，平均值计入结果。

1.4　统计学分析

采用R语言（4.3.1）及 SPSS 23.0 软件进行数据统计分析。计量资料采用$\bar{x} \pm s$表示，计数资料采用率（%）表示。采用Cox单因素回归分析筛选HSIL患者术后复发的危险因素。将单因素分析中具有统计学意义（$P < 0.05$）变量纳入Cox多因素回归模型，确定HSIL患者术后复发的独立危险因素。在多因素Cox回归模型的基础上，采用R语言rms包构建列线图来预测HSIL患者术后复发风险。采用一致性指数（concordance index，C-index）评估列线图模型的区分度。首先计算模型的表观C-index，随后通过Bootstrap 重抽样方法（重复抽样1 000 次）对模型进行内部验证，并计算校正后的C-index，以减少模型过拟合带来的偏倚。

以是否发生术后复发作为结局变量，构建各单一指标及联合预测模型的受试者操作特征（receiver operating characteristic，ROC）曲线，计算曲线下面积（area under the curve，AUC）来评价单一指标及联合预测模型对复发风险的预测效能。采用DeLong检验对不同ROC曲线的AUC进行比较。$P < 0.05$为差异有统计学意义。

2　结果

本研究纳入270例患者，平均年龄（46.6 ± 7.5）岁；术后复发28例，复发率为10.37%。

2.1　复发组与未复发组患者各项临床指标比较

结果显示，复发组患者初次性生活年龄<18岁、CINⅢ级、CKC切缘阳性、术后高危型HPV持续感染、腺体受累、多象限病变、ENO1和TOP2A强阳性表达患者比例显著高于未复发组（均$P < 0.05$）。见表1、图1。

2.2　单因素Cox回归分析

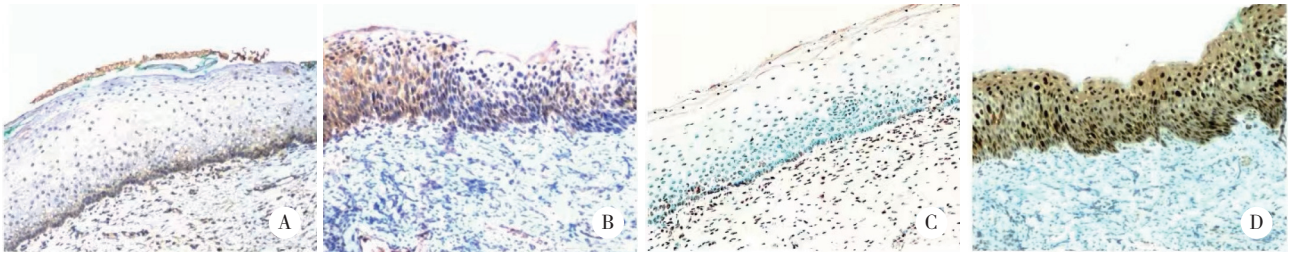
表1　2组患者临床指标比较[n (%)]

Tab.1　Comparison of general clinical data between recurrence and non-recurrence groups [n (%)]

Item	Recurrence group (n = 28)	Non-recurrence group (n = 242)	χ^2	P
Age at first diagnosis			1.80	0.180
<45 years	15 (54)	165 (68)		
≥45 years	13 (46)	77 (32)		
Marriage			0.00	1.000
No	4 (14)	36 (15)		
Yes	24 (86)	206 (85)		
Age of first sexual intercourse			5.43	0.020
<18 years	5 (18)	12 (5)		
≥18 years	23 (82)	230 (95)		
CIN grade			4.70	0.030
CIN Ⅰ/Ⅱ	12 (43)	159 (66)		
CINⅢ	16 (57)	83 (34)		
Number of pregnancies			0.00	1.000
≤3	19 (68)	165 (68)		
>3	9 (32)	77 (32)		
Parity			0.34	0.562
<2	5 (18)	60 (25)		
≥2	23 (82)	182 (75)		
Number of sexual partners			0.02	0.886
≤2	12 (43)	112 (46)		
>2	16 (57)	130 (54)		
CKC margin status			15.62	<0.001
Positive	16 (57)	51 (21)		
Negative	12 (43)	191 (79)		

（续表）

Item	Recurrence group (n = 28)	Non-recurrence group (n = 242)	χ^2	P
Postoperative high-risk HPV status			20.54	<0.001
Positive	16 (57)	43 (18)		
Negative	12 (43)	199 (82)		
Gland involvement			9.07	0.003
No	8 (29)	146 (60)		
Yes	20 (71)	96 (40)		
Multi-quadrant lesions			5.52	0.019
No	7 (25)	122 (51)		
Yes	21 (75)	120 (49)		
ENO1 expression			8.03	0.045
–	3 (11)	50 (21)		
+	2 (7)	54 (22)		
++	9 (32)	70 (29)		
+++	14 (50)	68 (28)		
TOP2A expression			8.09	0.044
–	2 (7)	48 (20)		
+	3 (11)	58 (24)		
++	10 (36)	73 (30)		
+++	13 (46)	63 (26)		



A, negative expression of ENO1 protein in the non-recurrence group; B, strong positive expression of ENO1 protein in the recurrence group; C, negative expression of TOP2A protein in the non-recurrence group; D, strong positive expression of TOP2A protein in the recurrence group.

图1　免疫组织化学检测各组HSIL组织中ENO1与TOP2A的表达　×200

Fig.1　Expression of ENO1 and TOP2A in HSIL tissues by Immunohistochemistry　×200

单因素Cox回归分析结果显示，初次性生活年龄<18岁（HR = 3.516，P = 0.012）、CINⅢ级（HR =3.086，P = 0.005）、切缘阳性（HR = 6.475，P < 0.001）、术后高危型HPV持续感染（HR = 4.126，P < 0.001）、多象限病变（HR = 5.218，P < 0.001）、腺体受累（HR = 4.297，P = 0.003）、ENO1强阳性（HR = 7.214，P = 0.001）以及TOP2A强阳性（HR = 10.919，P < 0.001）均显著增加复发风险。见表2。

2.3　多因素Cox回归分析

结果显示，术后高危型HPV持续感染（HR = 3.121，P = 0.004）、切缘阳性（HR = 3.368，P = 0.023）、腺体受累（HR = 4.127，P = 0.021）和TOP2A强阳性表达（HR = 3.970，P = 0.036）为HSIL患者CKC术后复发的独立危险因素。其余变量（初次性生活年龄、CIN分级和多象限受累）在多因素调整后均失去统计学意义（P > 0.05），其中ENO1强阳性表达的P值为0.050，提示其可能是潜在的风险因素，见表3。

2.4　HSIL患者CKC术后复发风险的列线图构建

根据多因素回归分析结果构建列线图模型。各因素得分：首次性生活年龄<18岁5分，腺体受累87分，多象限受累20分，CINⅢ级20分，切缘阳性86分，术后高危型HPV持续感染68分，ENO1强阳性表

达76分，TOP2A强阳性表达100分，总分462分，风险率0.10~0.90，总评分越高术后复发风险越高。Bootstrap校正后C-index为0.844。见图2。

2.5　基于 ROC 曲线的单一指标及联合模型的复发预测能力评估

ROC曲线分析结果显示，术后高危型HPV持续感染（AUC=0.697）、切缘阳性（AUC=0.680）、腺体受累（AUC=0.659）及TOP2A强阳性表达（AUC=0.719）均对HSIL患者术后复发具有一定预测价值。由上述4项指标构建的联合预测模型的AUC值最高，为0.851，显著优于各单一指标（DeLong检验，均 $P<0.05$），提示联合模型具有更好的预测准确性。见图3。

表2　HSIL患者CKC后复发的单因素Cox回归分析

Tab.2　Univariate Cox regression analysis of recurrence after CKC in HSIL patients

Variable	Assignment	β	*SE*	Wald χ^2	*P*	*HR*	95%*CI*	
							Lower	Upper
Age of first sexual intercourse	≥18 = 0, <18 = 1	1.257	0.498	2.525	0.012	3.516	1.325	9.328
CIN grade	CIN Ⅰ/Ⅱ = 0, CIN Ⅲ = 1	1.127	0.404	2.792	0.005	3.086	1.399	6.808
CKC margin status	Negative = 0, Positive = 1	1.868	0.405	4.614	<0.001	6.475	2.929	14.318
Postoperative high-risk HPV status	Negative = 0, Positive = 1	1.417	0.390	3.638	<0.001	4.126	1.923	8.855
Multi-quadrant lesions	No = 0, Yes = 1	1.652	0.466	3.545	<0.001	5.218	2.093	13.006
Gland involvement	No = 0, Yes = 1	1.458	0.498	2.928	0.003	4.297	1.619	11.402
ENO1 expression	−/+ = 0, ++/+++ = 1	1.976	0.614	3.218	0.001	7.214	2.165	24.037
TOP2A expression	−/+ = 0, ++/+++ = 1	2.391	0.615	3.889	<0.001	10.919	3.274	36.420

表3　HSIL患者CKC术后复发的多因素Cox回归分析

Tab.3　Multivariate Cox regression analysis of recurrence after CKC in HSIL patients

Variable	Assignment	β	*SE*	Wald χ^2	*P*	*HR*	95%*CI*	
							Lower	Upper
Age of first sexual intercourse	≥18 = 0, <18 = 1	0.325	0.524	0.619	0.536	1.384	0.495	3.867
CIN grade	CIN I/II = 0, CIN III = 1	0.226	0.545	0.415	0.678	1.254	0.431	3.647
CKC margin status	Negative = 0, Positive = 1	1.214	0.536	2.266	0.023	3.368	1.178	9.626
Postoperative high-risk HPV status	Negative = 0, Positive = 1	1.138	0.400	2.848	0.004	3.121	1.426	6.830
Gland involvement	No = 0, Yes = 1	1.418	0.613	2.312	0.021	4.127	1.241	13.724
Multi-quadrant lesions	No = 0, Yes = 1	0.429	0.596	0.720	0.472	1.536	0.477	4.938
ENO1 expression	−/+ = 0, ++/+++ = 1	1.287	0.657	1.960	0.050	3.622	1.000	13.116
TOP2A expression	−/+ = 0, ++/+++ = 1	1.379	0.658	2.097	0.036	3.970	1.094	14.404

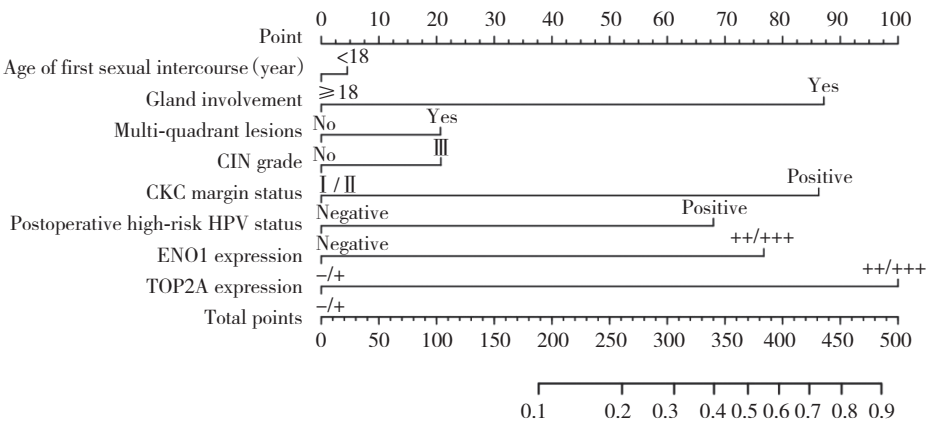


图2　HSIL患者CKC术后复发风险的列线图模型

Fig.2　Nomogram model for recurrence risk in patients with HSIL undergoing CKC

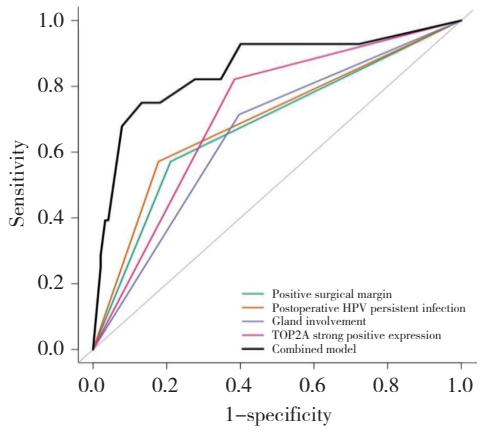


图3　各指标及联合模型对复发预测的ROC曲线

Fig.3　ROC curves of the individual parameters and the combined model for recurrence prediction

3　讨论

本研究结果显示，术后高危型HPV持续感染、CKC切缘阳性、腺体受累及TOP2A强阳性是HSIL患者CKC术后复发的独立危险因素，基于上述危险因素构建联合预测模型显著优于各单一指标（DeLong检验，均 $P<0.05$），说明联合模型具有更好的预测准确性。因此，可以使用联合模型加强高风险人群的管理和随访，从而改善患者预后。

术后高危型HPV持续感染可显著增加复发风险，与既往研究[6,21]结果一致。高危型HPV感染为宫颈癌主要病因[22]，术后高危型HPV持续感染可导致病变区域上皮细胞持续受损与异常增殖，进而诱导复发。因此，对此类患者需加强随访，定期进行HPV检测和TCT，必要时行阴道镜检查及活检，以尽早发现复发[23-24]；同时建议适龄人群积极接种HPV疫苗，降低复发风险。

CKC切缘阳性为术后复发的危险因素[6,13]，与本研究结果一致。提示尽管CKC可切除大部分宫颈病变组织，但病变范围广或深度大的患者仍可能存在切缘阳性风险。因此，术前阴道镜评估可用来指导锥切范围与深度，减少病变残留风险。

腺体受累已被证实为CKC术后复发的独立危险因素[25]，与本研究结果一致。提示宫颈腺体内可能存在未彻底切除的异常细胞，此类细胞术后可进展并导致复发。既往研究[26]显示，腺体受累患者复发率显著高于非腺体受累者，分析其原因可能与手术切除深度不足或宫颈管病灶残留有关。因此，针对腺体受累患者手术中应根据病变深度与范围适当调整。

TOP2A强阳性表达是术后复发的独立危险因素。TOP2A是一种DNA拓扑异构酶，集中作用于细胞核与线粒体内，是调控染色体浓缩与分离、细胞周期推进及细胞增殖等多个重要生物过程的核心调节因子。研究已证实TOP2A在多种恶性肿瘤组织中显著高表达，其表达水平与肿瘤的病理分级及侵袭性行为密切相关。在宫颈癌中，TOP2A促进了肿瘤细胞的迁移、侵袭能力，并推动上皮–间质转化过程[27]。TOP2A的表达随宫颈病变的严重程度而增加[28]。因此，检测TOP2A表达情况有助于HSIL患者预后评估和个体化治疗。

综上所述，术后高危型HPV持续感染、切缘阳性、腺体受累及TOP2A强阳性表达是HSIL患者CKC术后复发的独立危险因素；根据以上危险因素构建的联合模型具有较好的术后复发预测效能。然而，本研究仍存在一定局限性，样本量有限且为单中心回顾性研究，可能存在选择性偏倚，后续需开展多中心、大样本研究来进一步论证。

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