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ORIGINAL RESEARCH

Development of a Nomogram for Predicting 6-Month HPV Persistence After Cold Knife Conization in Chinese Women with High-Grade Squamous Intraepithelial Lesions

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Purpose: This study aimed to develop and validate a nomogram to predict the risk of persistent human papillomavirus (HPV) infection after cold knife conization (CKC) in Chinese women with high-grade squamous intraepithelial lesions (HSIL).

Methods: A single-center retrospective study included 476 HPV-positive patients with HSIL who underwent CKC between January 1 2020 and December 31 2023. Patients were randomly divided into a training cohort (n=333) and a validation cohort (n=143) in a 7:3 ratio. Univariate and multivariate logistic regression analyses were used to identify predictors of HPV persistence after CKC, which was defined as the presence of the same HPV genotype both before and 6 months after surgical intervention. A nomogram was constructed using the independent risk factors. The validation of the prognostic model was evaluated by concordance index (C-index), calibration curves, and decision curve analyses (DCAs).

Results: HPV persistence was detected in 120 patients (25.21%) at 6 months post-CKC. Multivariate analysis revealed that the factors associated with HPV persistence after CKC were age, menopausal status, and number of types of HPV infections. The nomogram was constructed based on the above 3 factors. The nomogram demonstrated moderate and acceptable discrimination (AUC=0.700; 95% CI: 0.606–0.794, Youden index = 0.30, sensitivity = 0.636, specificity = 0.664), good calibration, and positive net benefit in the validation cohort.

Conclusion: We successfully developed the first nomogram to predict the risk of HPV persistence at 6 months after CKC in Chinese women with HSIL using risk factors of age, menopausal status, and number of types of HPV infections, with HPV multiplicity being a novel and key predictor.

Keywords: HPV persistence, nomogram, cold knife conization, risk, high-grade squamous intraepithelial lesions

Introduction

Cervical cancer remains a global health burden, with persistent infection by high-risk human papillomavirus (HR-HPV) as its principal etiological agent.[1] Fortunately, the well-characterized precancerous stages, collectively termed high-grade squamous intraepithelial lesions (HSIL) or cervical intraepithelial neoplasia grade 2/3 (CIN2/3), offer a critical window for intervention to prevent progression to invasive carcinoma. Among the established treatment modalities for HSIL/CIN2+, cold knife conization (CKC), which can effectively remove precancerous tissue, stands as a cornerstone surgical procedure.[2]

However, persistent HPV infection after CKC has been identified as a major risk factor of treatment failure and lesion recurrence. A 10-year retrospective cohort study found that the risk of residual or recurrent HSIL+ was higher in patients with HPV persistence after CKC.[3] A cohort study by Byun et al[4] similarly identified persistent HPV infection following CKC as a predictor of high-grade CIN recurrence. Understanding the factors influencing post-treatment HPV clearance is therefore paramount for optimizing patient management, risk stratification, and long-term outcomes.

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Previously, Baser et al[5] investigated risk factors for high-risk HPV persistence in women undergoing CKC for high-grade CIN, identifying patient age and cone depth as significant independent predictors. Zhang et al[6] demonstrated that vaginal microecological imbalance (flora density, flora diversity, and dominant bacteria) was an independent risk factor for persistent HPV infection after CKC treatment in patients with HSIL. Gao et al[7] conducted a retrospective study enrolled 334 patients with CIN2/3 and found that age was an important risk factor for the recovery of HPV infection after CKC surgery. Similarly, Zhang et al[8] identified that age above 55 years was a prognostic factor for post-operative high-risk HPV infection clearance.

A prediction model which can predict the risk of HPV persistence after CKC could help women receive appropriate post-operative surveillance strategies. Failure to identify women at high risk for HPV persistence may lead to delayed intervention and an increased risk of lesion recurrence and progression to cervical cancer. To the best of our knowledge, no straightforward prediction model of HPV persistence after CKC has been constructed using the data from Chinese women. The nomogram is a simple-to-implement visualization tool for implementation of individual predictions. This study aims to develop a nomogram to predict HPV persistence after CKC, thereby improving risk assessment and ultimately enhancing long-term preventive management for women treated for cervical precancer.

Methods

Patients

This single-center retrospective study was approved by the ethics committee of our hospital in accordance with Declaration of Helsinki. Written informed consent was obtained from all patients.

In this retrospective study, we collected data from patients who underwent CKC at our hospital from January 1 2020 to December 31 2023 due to pathological results of colposcopy biopsy CIN2-CIN3. Inclusion criteria were as followed: (1) patients aged 18 years or older; (2) patients with pathological confirmation of HSIL (CIN2/3) under colposcopy; (3) preoperative HPV positive and clear typing results. (4) the patient underwent CKC; (5) informed consent of the patient. Exclusion criteria included: prior hysterectomy for any reason, concomitant malignancy, pregnancy, or incomplete follow-up data.

The enrolled patients were randomly separated into the training and validation sets in a 7:3 ratio. The training set was applied to construct the nomogram and the validation set was used to validate the nomogram.

Data Collection

HPV test results from all patients who met the standards at 6 months after surgery were collected. Persistent HPV infection was defined as the presence of the same HPV genotype both before and after surgical intervention.[4] Patients with persistent HPV infection were included in the experimental group, while women without persistent HPV infection were included in the control group.

HPV testing was performed as follows: Cervical scrape specimens were collected from the squamocolumnar junction using a sampling brush. HPV genotyping was conducted using the 23-HPV Genotyping Real-time PCR Kit (Hybribio, China) according to the manufacturer's instructions.

The selected factors for analysis, which were the potential confounders of HPV persistence after CKC, were identified in previous studies.[5–8] The selected factors for analysis included age, gravidity, parity, preoperative HPV results, ThinPrep cytologic test (TCT) results, diameter and cone height of the cervical resection section and pathological status of surgical specimen edge. The data of above factors were obtained from the medical records in our hospital.

Statistical Analysis

Statistical analyses were performed using R software (version 3.6.2) and SPSS (version 23.0). The training set was used to develop a nomogram based on logistic regression analysis. Univariate analysis identified potential predictors of HPV persistence after CKC ($p < 0.10$). These selected factors were subsequently analyzed in a multivariable logistic regression model. The nomogram was constructed using the independent predictors identified in the final multivariable model. The validation set was then employed to assess the nomogram's performance. Predictive accuracy was evaluated using

calibration curves, while discrimination was assessed using receiver operating characteristic (ROC) curves. Decision curve analysis (DCA) evaluated the nomogram's clinical utility. Results are presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Statistical significance was defined as $p < 0.05$. For nomogram development studies, sample size depends critically on the number of outcome events; at least 10 events per variable (EPV) are required.[9]

For greater transparency and replicability, the following specifics are noted: The continuous variable "age" was categorized into three groups (<35, 35–45, >45 years) based on both clinical relevance (reflecting reproductive stages and menopausal transition) and the distribution of our patient data to ensure sufficient sample size in each category for stable statistical estimation. The nomogram was constructed using the rms package in R software. The points assigned to each variable in the nomogram were derived directly from the scaled coefficients (beta values) of the final multivariable logistic regression model.

Results

During the study period, a total of 476 patients with HSIL who underwent CKC in our hospital were included in this study. Of these patients, 312 (65.55%) had CIN 2 and 164 (34.45%) had CIN 3. Mean patient age was 39.32 ± 9.46 years (range 22–70 years). 394 (82.77%) women were premenopausal and 82 (17.23%) were postmenopausal. Median gravidity and parity were 2 (range 0–8) and 1 (range 0–4), respectively. 72 (15.13%) patients were nulliparous and 404 (84.87%) had at least 1 prior delivery. In 73 (15.34%) patients, surgical margins were positive after the CKC procedure. HPV persistence after CKC was detected in 120 (25.21%) patients at 6 months after surgery. The enrolled patients were randomly divided into a training cohort (n = 333) and a validation cohort (n = 143) at a ratio of 7:3. The baseline characteristics of the two cohorts are shown in Table 1. The chi-square test results showed that the baseline characteristics in the training and validation cohorts were balanced (all $p > 0.05$). The proportion of patients with HPV persistence in the training and validation datasets was 26.13% and 23.08%, respectively.

Table 1 The Demographic Data for the Enrolled Patients, n (%)

Characteristics	Training Set (n=333)	Validation Set (n=143)	*p* value
Age (years)			0.548
< 35	129 (38.74)	49 (34.27)	
35–45	123 (36.94)	60 (41.96)	
> 45	81 (24.32)	34 (23.78)	
Menopausal status			0.531
Premenopausal	278 (83.48)	116 (81.12)	
Postmenopausal	55 (16.52)	27 (18.88)	
Gravidity			0.918
0	27 (8.11)	12 (8.39)	
≥ 1	306 (91.89)	131 (91.61)	
Parity			0.702
0	49 (14.71)	23 (16.08)	
≥ 1	284 (85.29)	120 (83.92)	
Lesion type			0.228
CIN 2	224 (67.27)	88 (61.54)	
CIN 3	109 (32.73)	55 (38.46)	
Preoperative HPV-16 infection	148 (44.44)	70 (48.95)	0.336
Preoperative HPV-18 infection	17 (5.11)	7 (4.9)	0.924
Number of types of HPV infections			0.412
1	218 (65.47)	88 (61.54)	
≥ 2	115 (34.53)	55 (38.46)	

(*Continued*)

Table 1 (Continued).

Characteristics	Training Set (n=333)	Validation Set (n=143)	*p* value
Preoperative TCT results			0.254
Normal or Inflammatory	123 (36.94)	39 (27.27)	
AUS-CS	77 (23.12)	41 (28.67)	
AUS-H	26 (7.81)	13 (9.09)	
LSIL	68 (20.42)	31 (21.68)	
HSIL	38 (11.41)	17 (11.89)	
AGC	1 (0.3)	2 (1.4)	
Cone height, mm			0.403
< 15	118 (35.44)	45 (31.47)	
≥ 15	215 (64.56)	98 (68.53)	
Cone diameter, mm			0.784
< 20	76 (22.82)	31 (21.68)	
≥ 20	257 (77.18)	112 (78.32)	
Pathological status of surgical margins			0.259
Positive	47 (14.11)	26 (18.18)	
Negative	286 (85.89)	117 (81.82)	
HPV persistence after CKC			0.482
No	246 (73.87)	110 (76.92)	
Yes	87 (26.13)	33 (23.08)	

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; TCT, ThinPrep cytologic test; AUS-CS, Atypical squamous cells of undetermined significance; AUS-H, Atypical Squamous Cells, HSIL cannot be excluded; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; AGC, atypical glandular cells; CKC, cold knife conization.

We used univariate logistic regression to determine the risk factors associated with HPV persistence after CKC using the training set. The results showed that age (35–45 years vs < 35 years, $p = 0.003$; > 35 years vs.< 35 years, $p < 0.001$), menopausal status (postmenopausal status vs premenopausal status, $p < 0.001$) and number of types of HPV infections (≥ 2 vs 1, $p = 0.007$) were potential risk factors. Then, the selected factors obtained from the univariate analysis were analyzed in the multivariate logistic regression model. At the multivariate level, the factors associated with HPV persistence after CKC were age (35–45 years vs < 35 years, OR = 2.843, 95% CI = 1.398–5.781, $p = 0.004$; > 35 years vs.< 35 years, OR = 4.469, 95% CI = 1.644–12.146, $p = 0.003$), menopausal status (postmenopausal status vs premenopausal status, OR = 3.149, 95% CI = 1.175–8.440, $p = 0.023$) and number of types of HPV infections (≥ 2 vs 1, OR = 1.868, 95% CI = 1.076–3.243, $p = 0.026$). The results of the univariate and multivariate analyses are shown in Table 2.

Table 2 Univariate and Multivariate Logistic Regression Analysis of Study Variables

Characteristics	Univariate Analysis		Multivariate Analysis	
	OR [95% CI]	*p* value	OR [95% CI]	*p* value
Age (years)				
< 35	Reference		Reference	–
35–45	2.878 [1.421, 5.829]	0.003	2.843 [1.398, 5.781]	0.004
> 45	10.097 [4.913, 20.753]	< 0.001	4.469 [1.644, 12.146]	0.003
Menopausal status				
Premenopausal	Reference		Reference	
Postmenopausal	7.037 [3.778, 13.106]	< 0.001	3.149 [1.175, 8.440]	0.023

(*Continued*)

Table 2 (Continued).

Characteristics	Univariate Analysis		Multivariate Analysis	
	OR [95% CI]	*p* value	OR [95% CI]	*p* value
Gravidity				
0	Reference		–	
≥ 1	1.653 [0.766, 3.567]	0.200	–	
Parity				
0	Reference		–	
≥ 1	2.105 [0.707, 6.270]	0.181	–	
Lesion type				
CIN 2	Reference		–	
CIN 3	0.989 [0.586, 1.670]	0.968	–	
Preoperative HPV-16 infection				
No	Reference		–	
Yes	1.270 [0.776, 2.077]	0.342	–	
Preoperative HPV-18 infection				
No	Reference		–	
Yes	2.100 [0.773, 5.702]	0.145	–	
Number of types of HPV infections				
1	Reference		Reference	
≥ 2	1.994 [1.206, 3.298]	0.007	1.868 [1.076, 3.243]	0.026
Preoperative TCT results				
Normal or Inflammatory	Reference		–	
AUS-CS	0.998 [0.521, 1.910]	0.995	–	
AUS-H	0.517 [0.166, 1.615]	0.256	–	
LSIL	1.024 [0.522, 2.006]	0.945	–	
HSIL	1.313 [0.593, 2.903]	0.502	–	
AGC	0 [0, Inf]	0.988	–	
Cone height, mm				
< 15	Reference		–	
≥ 15	0.843 [0.507, 1.400]	0.509	–	
Cone diameter, mm				
< 20	Reference		–	
≥ 20	1.107 [0.615, 1.991]	0.735	–	
Pathological status of surgical margins				
Positive	Reference		–	
Negative	0.547 [0.245, 1.222]	0.141	–	

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; TCT, ThinPrep cytologic test; AUS-CS, Atypical squamous cells of undetermined significance; AUS-H, Atypical Squamous Cells, HSIL cannot be excluded; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; AGC, atypical glandular cells; CKC, cold knife conization; OR, odds ratio; CI, confidence interval.

After variable selection, 3 risk factors were identified in the final multivariable model, including age, menopausal status and number of types of HPV infections. A nomogram for predicting risk of HPV persistence after CKC that integrated the above 3 independent prognostic factors is shown in Figure 1.

The nomogram's performance was evaluated using the validation cohort. The area under the ROC curve (AUC) was 0.700 (95% CI: 0.606–0.794, $p < 0.001$), indicating good discriminative ability (Figure 2). The Youden index of the model was 0.30, with a sensitivity of 0.636 and a specificity of 0.664. Calibration plots demonstrated good agreement between the nomogram's predicted risk of HPV persistence after CKC and actual observations (Figure 3). Decision curve analysis (DCA) further indicated that the nomogram provided substantial positive net clinical benefit for predicting HPV persistence risk (Figure 4).

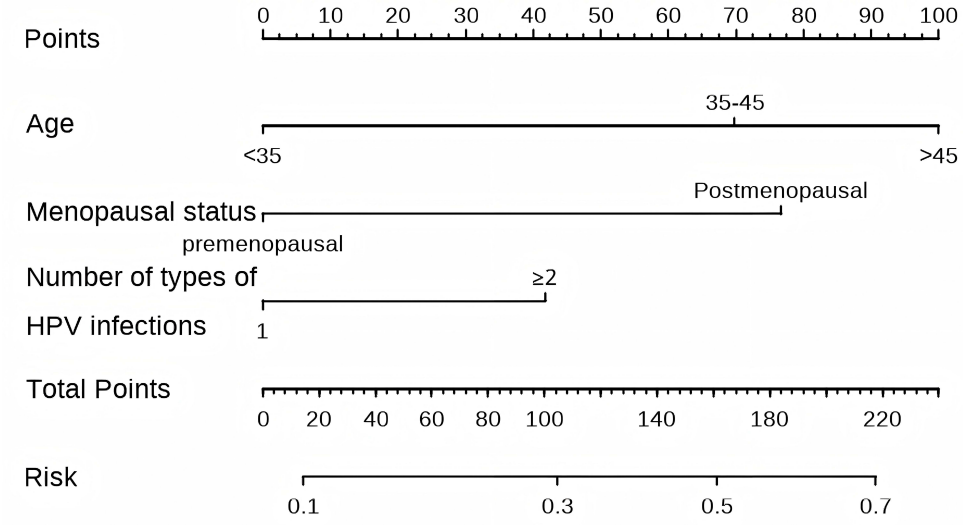

Figure 1 The nomogram for predicting HPV persistence after cold knife conization (CKC) in Chinese women with high-grade squamous intraepithelial lesions (HSIL).

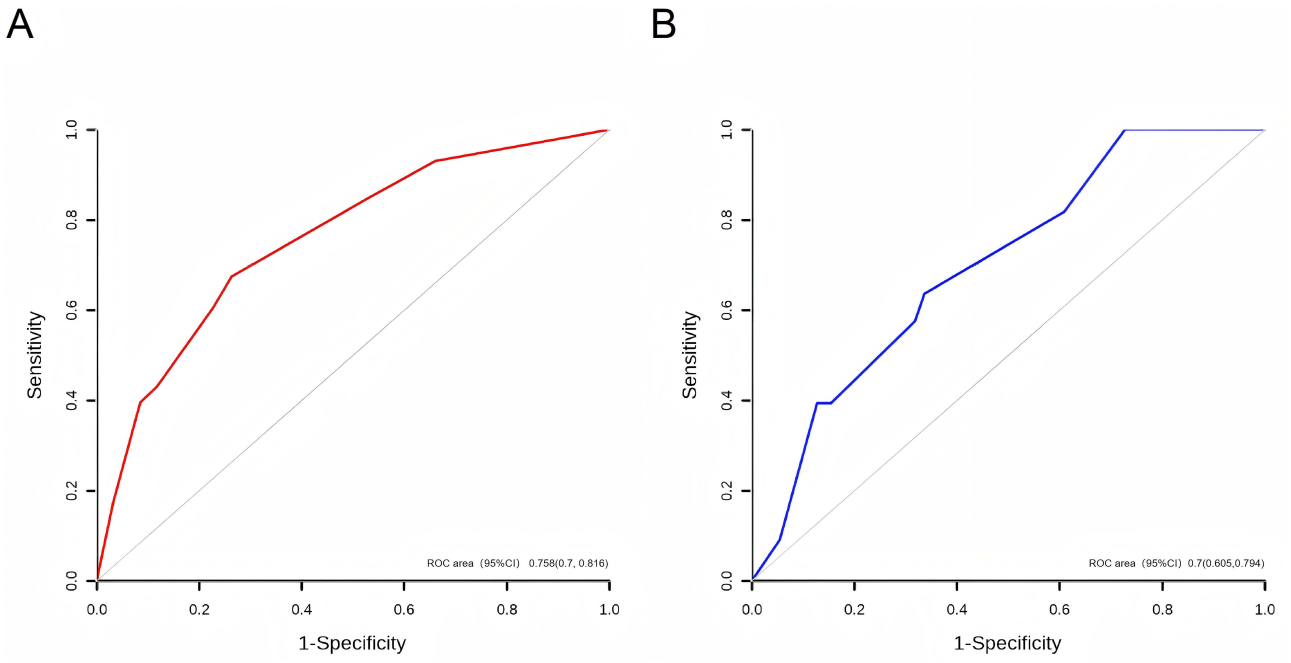

Figure 2 ROC curves of the established model for predicting risk of HPV persistence after cold knife conization. (**A**) training cohort, (**B**) validation cohort. Red curve (**A**): Represents the model's performance in the training cohort (n=333), used to develop the nomogram. Blue curve (**B**): Represents the model's performance in the validation cohort (n=143), used to independently test the nomogram's predictive accuracy.
Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve.

Discussion

This study developed and validated a clinical prediction tool for a well-defined clinical scenario. While the identified predictors (age, menopausal status, HPV multiplicity) are not novel in themselves, the primary contribution of this work lies in their integration into the first nomogram for predicting HPV persistence after CKC specifically in Chinese women with HSIL. This addresses a gap in tailored risk assessment for this population.

Persistent infection with high-risk HPV genotypes has been described as the most common non-systemic biological risk factor for the development of cervical cancer.[10,11] To better understand the factors influencing post-treatment HPV clearance, we conducted this study. The identified predictors in our final model align with the established literature on

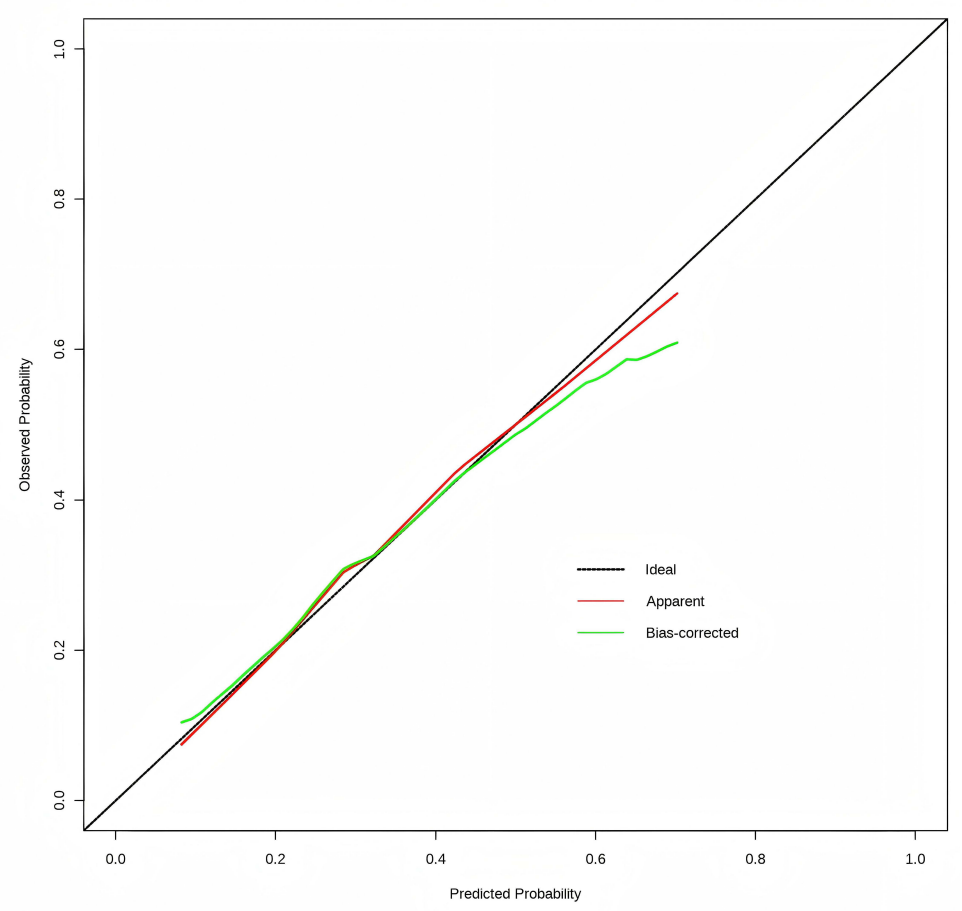

Figure 3 Calibration curve of the model in the validation set.

factors influencing HPV clearance post-treatment. The significant association of increasing age with higher risk of HPV persistence strongly corroborates previous studies. For instance, Baser et al[5] identified age as a significant independent predictor of HPV persistence following CKC for high-grade CIN. Similarly, Gao et al[7] in their retrospective study of CIN2/3 patients, found age to be an important risk factor for delayed HPV clearance post-CKC. Furthermore, Zhang et al[8] specifically highlighted age ≥ 55 years as a poor prognostic factor for HPV clearance after CKC in CIN3 patients. Our study found a stepwise increase in risk of post-CKC HPV persistence across age groups (< 35, 35–45, > 45 years), particularly among women > 45 years, confirming that older age impairs post-treatment viral clearance. Studies indicate that immunosuppressive responses may facilitate HPV immune evasion, leading to persistent infection.[10] In advanced age, immune changes due to "immune-senescence" could affect the acquisition and reactivation of HPV infections.[12,13] Consequently, older patients exhibit increased risk of HPV persistence following CKC.

Our finding indicated that postmenopausal status was an independent predictor of HPV persistence after CKC, further supporting the role of age and hormonal milieu in HPV persistence. While not all prior studies explicitly separated menopausal status from chronological age, the hormonal changes associated with menopause, including alterations in local immunity and cervical epithelial characteristics, are biologically plausible contributors to reduced viral clearance efficiency.[5] This aligns with the broader understanding that older age groups, predominantly including postmenopausal women, face higher HPV persistence risks.

A previous study enrolled 7372 Chinese women aged 18–45 years revealed that multiple HPV infections were observed in 25.2% of HPV-positive women, which increased the risk of cervical disease.[14] In the present study, we found that multiple HPV type infections was another risk factor for HPV persistence after CKC. The inclusion of multiple HPV type infections (≥ 2 types) as a significant predictor of HPV persistence adds another dimension consistent with

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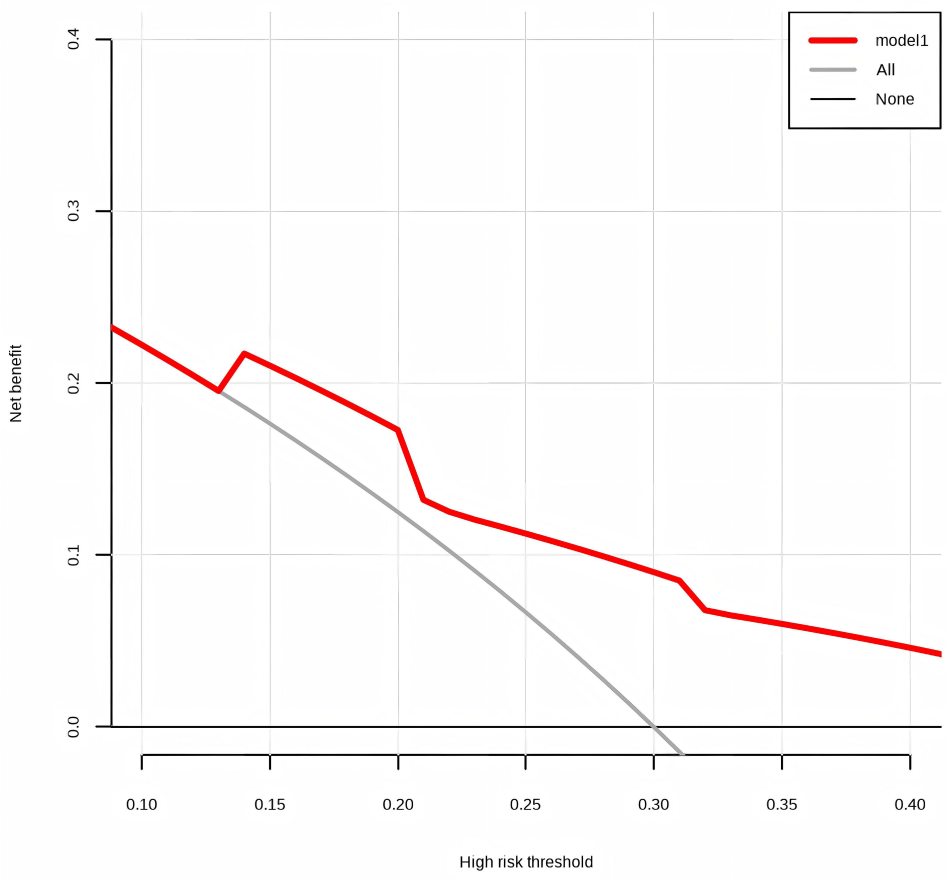

Figure 4 Decision curve analysis of the nomogram for predicting risk of HPV persistence after cold knife conization.

immunological principles. Co-infection with multiple HPV types implies either higher viral loads or inadequate immune control, resulting the impaired HPV clearance.[15–17] While not directly replicated in every previous model, the association between HPV multiplicity and persistence risk is mechanistically sound. To our knowledge, this study presents the first nomogram developed specifically for predicting HPV persistence after CKC in Chinese women with HSIL. Its modest novelty and primary contribution lie in the incorporation of HPV multiplicity as a key, readily available predictor, alongside age and menopausal status, thereby offering a practical tool for initial individualized risk stratification in clinical practice.

Based on the risk factors of age, menopausal status, and the number of HPV types infected, we successfully developed a nomogram to predicate the risk of post-CKC HPV persistence in Chinese women. Our model has 3 predictor variables, so the number of positive events should be a minimum of 30.[9,18] The actual number of positive events in the training cohort in the present study was 87, which was within the acceptable range. The discriminative performance of our nomogram (C-index = 0.700) is comparable to some existing models predicting related outcomes in cervical precancer management.[19,20] While models incorporating more complex biomarkers might achieve higher AUCs. The calibration curve showing good agreement between predicted and observed risks, along with the positive net benefit demonstrated by DCA, further supports the model's potential clinical applicability in risk stratification.

The present study has several limitations. Firstly, the single-center, retrospective design is a primary limitation of our study. The patient population from a single institution may not be fully representative of the broader Chinese population with HSIL, introducing potential selection bias. This limits the immediate generalizability of our findings and the nomogram's applicability to other clinical settings. Secondly, the follow-up period was restricted to 6 months post-CKC. While this timeframe is clinically relevant for identifying early persistence and guiding initial post-operative management, it is insufficient to establish a definitive link between the predicted HPV persistence and the long-term risk of

histologically confirmed lesion recurrence. Future studies with extended follow-up are needed to validate the nomogram's prognostic value for predicting clinically significant endpoints like disease recurrence. Thirdly, the retrospective nature of our study limited the breadth of variables available for analysis. Several factors with known biological plausibility for influencing HPV persistence, such as vaginal microbiota composition, HPV viral load, and specific cellular immune responses, were not routinely tested or documented in the medical records and thus could not be included in our univariate analysis. This omission may mean our model does not capture the full spectrum of predictors. Additionally, key surgical variables such as the precise volume of the cone specimen, which is a function of both height and base dimensions, could not be accurately calculated or analyzed due to inconsistencies in retrospective documentation. The inclusion of cone volume might have improved the predictive accuracy of the model. Most importantly, our nomogram has only undergone internal validation. External validation using prospective, multi-center datasets is essential to confirm the model's stability, calibrate its performance across different populations and clinical practices, and ultimately confirm its clinical utility before widespread adoption can be recommended.

Collectively, these limitations define clear pathways for future research and highlight that our model should be viewed as a foundational step. Its real-world applicability and potential to improve patient outcomes will be determined by successfully addressing these gaps, particularly through rigorous external validation and long-term outcome assessment.

The potential clinical utility of this nomogram lies in stratifying post-CKC surveillance intensity. For instance, based on the Youden index-derived probability threshold in our cohort, patients identified as "high-risk" (eg, with a predicted probability exceeding a certain value) could be considered for more frequent follow-up, such as co-testing (HPV and cytology) at shorter intervals (eg, 6–12 months) as per clinician judgment, or more intensive counseling regarding adherence to follow-up. Conversely, "low-risk" patients might adhere to standard follow-up protocols. However, the determination of an optimal, universally applicable risk threshold requires further prospective validation and cost-effectiveness analysis. This model provides a quantitative starting point for such personalized management discussions.

Conclusion

In conclusion, we have developed and internally validated a nomogram incorporating age, menopausal status, and HPV multiplicity to predict the risk of 6-month HPV persistence after CKC in Chinese women with HSIL. The model demonstrated moderate discriminative ability (AUC=0.700) and good calibration. While this tool represents a practical first step towards individualized risk assessment, its current utility is preliminary. The model's performance warrants confirmation through external validation in independent, multi-center cohorts. Its generalizability is unproven and must be established through external validation in diverse settings before broader clinical implementation can be recommended. Future research should focus on this validation and on linking the predicted short-term persistence to long-term recurrence risks. Furthermore, future studies with longer follow-up are essential to establish the critical link between the predicted HPV persistence and the long-term risk of disease recurrence, which is the ultimate clinical endpoint.

Artificial Intelligence (AI)

The authors did not use generative AI or AI-assisted technologies in the development of this manuscript.

Data Sharing Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Maternal and Child Health Hospital of Tongzhou. Written informed consent was obtained from all participants.

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Disclosure

All of the authors had no any personal, financial, commercial, or academic conflicts of interest separately.

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