

ORIGINAL ARTICLE



A novel nomogram based on a retrospective study of 346 patients to predict the recurrence risk of condyloma acuminatum after 5-aminolevulinic acid photodynamic therapy

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Funding information

This work was financially supported by grants from the China National Natural Science Foundation (NO.81903246 and 82073472), the Science Foundation of Nantong (No. JC2019024), the Priority Academic Program Development (PAPD) of Jiangsu Higher Education Institutions, and Outstanding Young and Middle-aged Talents Support Program of the First Affiliated Hospital of Nanjing Medical University (Jiangsu Province Hospital).

Abstract

Condyloma acuminatum (CA) is a sexually transmitted disease caused by human papillomavirus (HPV) often with high recurrence rate after treatment. This study aimed to construct and evaluate a nomogram model containing three clinical parameters to predict the recurrence risk of CA after 5-aminolevulinic acid photodynamic therapy (ALA-PDT). A predictive model was established based on a training cohort of 346 CA patients treated with ALA-PDT between January 2013 and July 2018. A validation cohort of 123 CA patients was recruited from August 2018 to December 2019. The least absolute shrinkage and selection operator (LASSO) regression model was used to optimize the clinical feature selection. A nomogram predicting the recurrence of CA after ALA-PDT was constructed based on the predictors identified by LASSO regression. C-index and area under the curve (AUC) values were used to evaluate the discrimination. Calibration was evaluated with a calibration curve. The net benefit was performed via decision curve analysis (DCA).

In the training cohort, 55 (15.89%) patients experienced recurrences after ALA-PDT. Predictors selected by LASSO regression were concomitant human immunodeficiency virus (HIV) infection [Hazard ratio (HR) = 4.4; 95% confidence interval (CI), 2.5–7.9; $p < 0.001$], skin and mucosa as affected area (HR = 1.7; 95% CI, 0.9–3.1; $p = 0.109$), and more than one time of CO₂ laser therapy (HR = 6.3; 95% CI, 2.8–13.9; $p < 0.001$). The nomogram showed a good performance in predicting recurrence as the C-indexes were 0.843 (95% CI, 0.799–0.887) in the training cohort, and 0.831 (95% CI, 0.727–0.934) in the validation cohort. The AUCs of the nomogram were 0.85 in training and 0.8 in validation. DCA confirmed the nomogram was clinically useful when the intervention was determined at the non-adherence possibility threshold of 5%. This nomogram can provide individualized prediction for the recurrence risk of CA in patients treated by ALA-PDT.

KEYWORDS

condyloma acuminatum, nomogram, photodynamic therapy, recurrence, retrospective study

1 | INTRODUCTION

Condyloma acuminatum (CA) or anogenital warts, a benign epithelial neoplasm caused by human papillomavirus (HPV) infection,

is a most frequent sexually transmitted disease (STI).^{1,2} The World Health Organization reports that 101 million people are infected with CA each year globally, and the incidence rate reaches 0.5–1% with an increasing trend year by year.^{3,4} CA is also listed as one of the

national priorities for prevention because it is closely related to cervical cancer and penile cancer.⁵ Partial CA, especially which has not been cured for a long time and recurred often, may be transformed into vaginal intraepithelial neoplasia or squamous cell carcinoma.⁴

Traditional treatments for CA, including topical medicine and physiotherapies (such as CO₂ laser therapy, liquid nitrogen cryotherapy and surgery), aim to remove the visible wart lesions.^{6,7} However, after such treatments, the recurrence rate of CA still ranges from 30% to 65%, which partly results from the fact that HPV usually locates as far as 1 cm from the clinically visible border of the warts.^{2,8} The 5-aminolevulinic acid photodynamic therapy (ALA-PDT), which produces reactive oxygen species in the HPV-infected cells to induce apoptosis and cytotoxic effect under irradiation of 635 nm red light,⁹ can effectively remove the sub-clinical or latent HPV-infected lesions.¹⁰ A meta-analysis showed that ALA-PDT could decrease the recurrence of CA within 24 weeks after treatment (vs. CO₂ laser) [risk ratio (RR), 0.24, 95% confidence interval (CI), 0.17–0.35].¹¹

In recent years, ALA-PDT treatment for CA has been widely conducted in clinical practice with a recurrence rate of 2.9%–25.8%,^{8,10} but the related clinical factors for recurrence have not been fully understood. Multiple-type HPV infection, abnormal T cell subsets, multiple lesions, and staying up late have been reported as risk factors for CA recurrence after physiotherapies.¹² Yet, to our knowledge, there have been no reports on the clinical factors related to CA recurrence after photodynamic therapy. Therefore, there is still an unmet need for accurate CA recurrence risk prediction and optimized management of ALA-PDT. For CA patients who have a low recurrence risk, the excessive treatment may not be cost-effective.

Nomogram, an intuitive graphical prediction model providing individualized risk predictions for each patient,^{13,14} can predict and quantify risks for prognosis by incorporating some relevant factors.¹⁵ In clinical practice, the nomogram serves as a practical tool of preventive interventions and a guide of clinical treatment.¹⁶ Here, we conducted a retrospective study of 346 CA patients treated with ALA-PDT to investigate the predictors affecting the CA recurrence, then established and evaluated a nomogram for individualized recurrence risk prediction in CA patients.

2 | METHODS

2.1 | Study design and patient population

This retrospective study was conducted in accordance with the declaration of Helsinki and approved by the Institutional Review Board of Nantong Third People's Hospital Affiliated to Nantong University (No: EL2020003). Eligible patients with integrated baseline data recruited in the Department of Dermatology from January 1, 2013, through July 31, 2018 were included in the training cohort for nomogram development, and those recruited from August 1, 2018, through December 31, 2019, were included in the validation cohort.

Inclusion criteria were as follows: (a) diagnosis of CA by two clinical dermatologists according to clinical manifestations, history

of sexual behavior, combined with acetowhite test or pathological examination of hollow cells;⁹ (b) consecutive ALA-PDT for at least three sessions. Exclusion criteria were: (a) previous surgical or any other treatments on lesions, including ALA-PDT, laser, cryotherapy or imiquimod within 6 months; (b) the lack of complete follow-up records.

Before the study, two dermatologists with more than 5 years' experience were trained in data collection protocols to guarantee the quality of data collection. The data were double checked to ensure the accuracy.

2.2 | ALA-PDT treatment protocol

After routine sterilization and local anesthesia, the lesions and their adjacent normal skin (area within 5 mm from the visible lesion border) were vaporized with CO₂ laser (Jilin Keying Laser Technology Co. Ltd., Shanghai, China) one by one until all the visible lesions were completely removed. A 20% (w/v) 5-ALA (Fudan Zhangjiang Bio-Pharm Co. Ltd., Shanghai, China) solution or gel was prepared (ALA powder dissolved into sterile 0.9% NaCl or moisturizing gel) immediately prior to application. Cotton pieces soaked with 20% ALA solution or gel were placed on the area within 1 cm beyond the lesion edge, and then covered by a layer of opaque film and surgical gauze to avoid solution loss and facilitate absorption. For lesions in the vagina, cervix, or anal canal, the cuff embolus evenly smeared with 20% ALA gel and attached with multiple thin cotton pieces soaked with 20% ALA gel were applied. One vial ALA solution (containing 118mg 5-ALA) was applied in an area of 3.14 cm². After 3–5 h incubation, irradiation with red light (LED PDT instrument, Wuhan Yage Optic and Electronic Technique Co. Ltd., Wuhan, China; 635 nm, 80 mW/cm²) was applied for 20 min to the treatment field. There was a 7- to 10-day interval between each treatment. If the warts were not completely removed (confirmed by acetowhite test), a repeated CO₂ laser + ALA-PDT treatment session was given. In patients with complete lesion removal, only PDT was performed. About 7–10 days after three consecutive sessions of ALA-PDT treatment, the acetowhite test was conducted to re-examine the lesions. For patients with negative test results, the treatment ended. But for those with positive results, the treatment was repeated until negative results were achieved. All patients were followed up for 6 months, twice in the first month after treatment and then once a month afterward. Recurrence was defined as the presence of new warts in or around the original lesion site and positive result of acetic acid test during the follow-up period.

2.3 | Data collection

We extracted prognostic factors in the "Guideline for the Clinical Management of Anogenital Warts in China (2021)" from each patient's electronic medical record¹⁷ into our univariable analysis anonymously, including age, sex, marital status, HIV infection, HPV

type (low-risk HPV: HPV 6, 11, 40, 42, 43, 44, 55, 61, 81, 83; high-risk HPV: HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 82; low and high-risk HPV: coinfection with low-risk and high-risk genotypes), warts distribution (perianal, genitals, perianal and genitals, inguinal), affected area (skin, mucosa, skin and mucosa), underlying diseases (hypertension, diabetes, hepatitis, nephropathy, autoimmune diseases), concomitant medication (topical wart removal lotion: a traditional Chinese medicine lotion containing 30 g of isatis root, mountain bean root, Equisetum and Cyperus, 20 g of raw coix seed, purslane and white fresh skin, 10 g of hive, asarum, safflower and *Angelica dahurica*, and 6 g of alum), topical antivirals (recombinant human interferon 2b gel), oral resistance-enhancing agents (thymosin enteric-coated tablets), incubation time of photosensitizer (h), times of CO₂ laser treatment, number of PDT sessions, number of ALA vials for each treatment session.

2.4 | Statistical calculation and nomogram construction

Categorical data were summarized using frequencies and proportions. Non-normally distributed continuous variables were expressed by the median (min-max). Categorical variables were compared using chi-square analysis, while continuous variables using the Mann-Whitney test.

The least absolute shrinkage and selection operator (LASSO)¹⁴ was used to select the best predictive factors for CA recurrence. Candidates with non-zero coefficients were selected to establish the LASSO model. Then, the selected factors were used to establish the prediction model by the multivariate Cox regression analysis. The nomogram was based on proportionally converting each regression coefficient in multivariate Cox regression to a scale of 0–100 points. The effect of the variable with the highest β coefficient (absolute value) was assigned 100 points. These points were added across predictors to derive the “Total Points”, which was converted to a linear predictor and then to predicted probabilities.¹⁴ Internal validation was then performed using the validation datasets.

The receiver operating characteristic (ROC) curve was analyzed to determine the as-constructed nomogram performance. The accuracy of nomogram was analyzed by Harrell C-index, together with the area under the time-dependent ROC curve (AUC). A greater C-index value indicated a better performance of the nomogram in predicting the prognosis. A calibration curve of the nomogram was drawn to evaluate the consistency between the observed and estimated recurrence. Decision curve analysis (DCA) was performed to assess the clinical net benefit. Net benefit was defined as the proportion of true positive minus the proportion of false positive as weighted by the relative risk of false positive and false negative results.

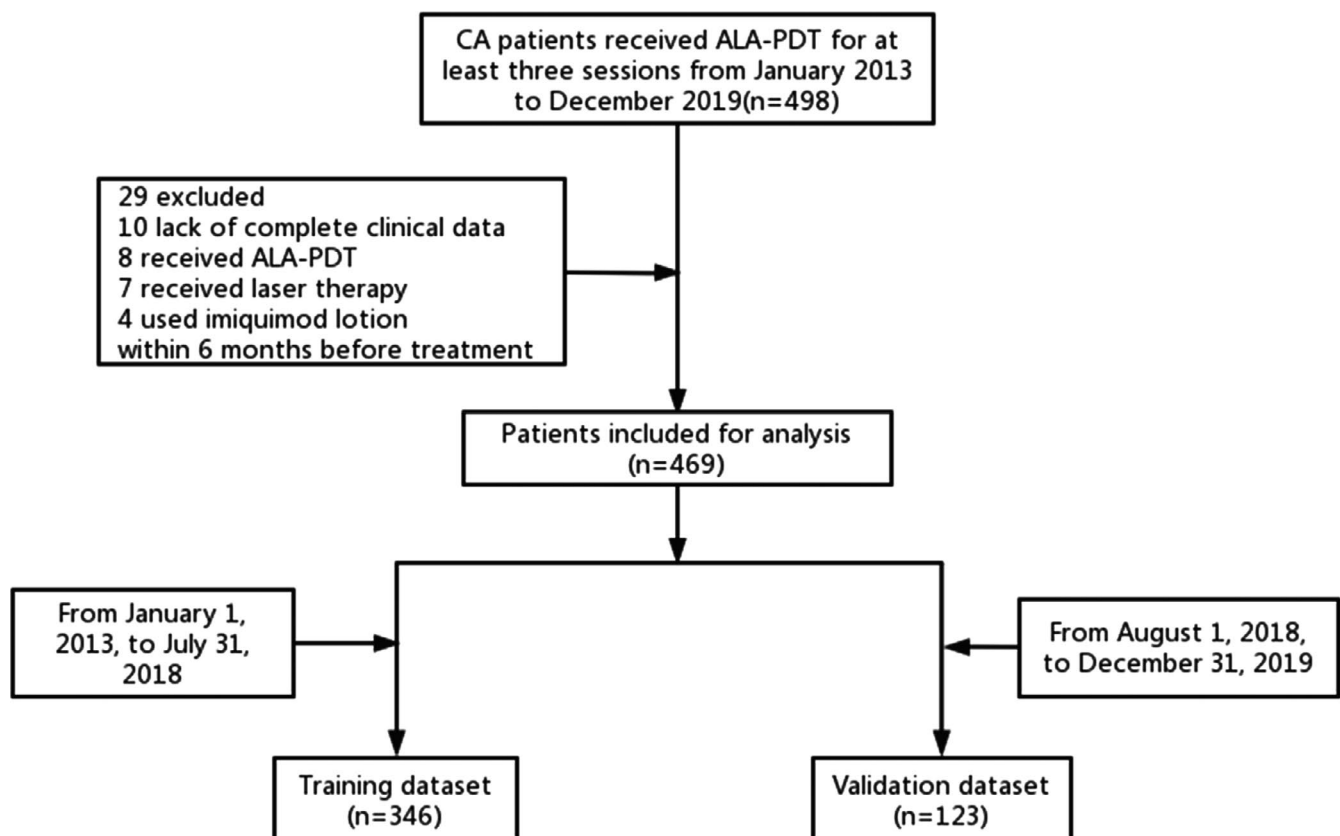


FIGURE 1 The flowchart of applying the inclusion and exclusion criteria and constructing the training and validation datasets. CA, Condyloma acuminatum; ALA-PDT, 5-aminolevulinic acid photodynamic therapy

TABLE 1 Basic characteristics of the patients

Variable	Training dataset (n = 346)		p-Value	Validation dataset (n = 123)		p-Value
	Non-recurrent (n = 291)	Recurrent (n = 55)		Non-recurrent (n = 103)	Recurrent (n = 20)	
Age (years) [median (range)]	31.0 (17.0–83.0)	34.0 (17.0–80.0)	0.098	32.0 (19.0–84.0)	32.5 (18.0–63.0)	0.231
Sex, n (%)			0.353			0.444
Female	98 (33.68)	15 (27.27)		30 (29.13)	6 (30.00)	
Male	193 (66.32)	40 (72.72)		73 (70.87)	14 (70.00)	
Marital status, n (%)			0.97			0.621
Unmarried	96 (32.99)	18 (32.73)		31 (30.09)	4 (20.00)	
Married	195 (67.01)	37 (67.27)		72 (69.90)	16 (80.00)	
Concomitant HIV, n (%)			<0.001			<0.001
None	282 (96.91)	33 (60.00)		100 (97.09)	16 (80.00)	
Yes	9 (3.09)	22 (40.00)		3 (2.91)	4 (20.00)	
HPV types, n (%)			0.027			<0.001
Low-risk	76 (26.11)	6 (10.91)		30 (29.13)	0 (0.00)	
High-risk	7 (2.41)	0 (0.00)		3 (2.91)	0 (0.00)	
Low and high risk	21 (7.22)	9 (16.36)		2 (1.94)	5 (25.00)	
Not detected	175 (60.14)	38 (69.09)		64 (62.14)	14 (70.00)	
Negative	12 (4.12)	2 (3.64)		4 (3.88)	1 (5.00)	
Wart distribution, n (%)			<0.001			<0.001
Perianal	40 (13.75)	20 (36.36)		15 (14.56)	5 (25.00)	
Genitals	227 (78.01)	22 (40.00)		81 (78.64)	10 (50.00)	
Perianal and genitals	21 (7.22)	13 (23.64)		6 (5.83)	5 (25.00)	
Inguinal	3 (1.03)	0 (0.00)		1 (0.97)	0 (0.00)	
Affected area, n (%)			<0.001			<0.001
Skin	160 (54.98)	17 (30.91)		55 (53.40)	2 (10.00)	
Mucosa	63 (21.65)	3 (5.45)		21 (20.39)	4 (20.00)	
Skin and mucosa	68 (23.37)	35 (63.64)		27 (26.21)	14 (70.00)	
Underlying diseases, n (%)			0.054			0.003
Yes	13 (4.47)	6 (10.91)		5 (4.85)	4 (20.00)	
No	278 (95.53)	49 (89.09)		98 (95.15)	16 (80.00)	
Concomitant medication, n (%)			0.029			0.011
Topical wart removal lotion	25 (8.6)	12 (21.8)		3 (2.9)	4 (20.0)	
Topical antivirals	47 (16.2)	7 (12.7)		20 (19.4)	2 (10.0)	
Oral resistance-enhancing agents	112 (38.5)	16 (29.1)		38 (36.9)	4 (20.0)	
None	107 (36.8)	20 (36.4)		42 (40.8)	10 (50.0)	
Incubation time of photosensitizer (h), n (%)			0.918			0.489
<4	92 (31.62)	17 (30.91)		33 (32.00)	8 (40.00)	
≥4	199 (68.38)	38 (69.09)		70 (68.00)	12 (60.00)	
CO ₂ laser times, n (%)			<0.001			<0.001
1	204 (70.10)	8 (14.55)		80 (77.67)	5 (25.00)	
2	30 (10.31)	14 (25.45)		7 (6.80)	5 (25.00)	
3	39 (13.40)	22 (40.00)		12 (11.65)	6 (30.00)	
4	16 (5.509)	3 (5.45)		2 (1.94)	1 (5.00)	
5	2 (0.69)	6 (10.91)		2 (1.94)	2 (10.00)	
6	0 (0.00)	2 (3.64)		0 (0.00)	1 (5.00)	

TABLE 1 (Continued)

Variable	Training dataset (n = 346)		p-Value	Validation dataset (n = 123)		p-Value
	Non-recurrent (n = 291)	Recurrent (n = 55)		Non-recurrent (n = 103)	Recurrent (n = 20)	
Times of PDT, n (%)			0.145			0.274
3	218 (74.91)	36 (65.45)		74 (71.84)	15 (75.00)	
>3	73 (25.09)	19 (34.55)		29 (28.16)	5 (25.00)	
Number of ALA vials for each treatment session, n (%)			<0.001			<0.001
1	49 (16.84)	1 (1.82)		14 (13.59)	1 (5.00)	
2	80 (27.49)	12 (21.82)		22 (21.36)	5 (25.00)	
3	85 (29.21)	12 (21.82)		36 (34.95)	6 (30.00)	
4	50 (17.18)	12 (21.82)		20 (19.42)	2 (10.00)	
5	19 (6.53)	9 (16.36)		6 (5.83)	4 (20.00)	
6	4 (1.37)	6 (10.91)		1 (0.97)	1 (5.00)	
7	4 (1.37)	2 (3.64)		2 (1.94)	1 (5.00)	
8	0 (0.00)	1 (1.82)		2 (1.94)	0 (0.00)	

Abbreviations: ALA, 5-Aminolevulinic acid; HIV, human immunodeficiency virus; HPV, human papillomavirus; PDT, photodynamic therapy.

The statistical package R (<http://www.r-project.org>), together with EmpowerStats software (www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA) was employed for statistical analysis. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Characteristics of patients

Among the 498 CA patients initially registered in our study, 29 were excluded, including 10 with incomplete follow-up clinical data, 8 with pre-treatment of ALA-PDT sessions, 7 with pre-treatment of laser therapy, and 4 with pre-treatment of imiquimod lotion within 6 months before treatment. We finally enrolled 469 CA patients, of whom, 346 patients from January 1, 2013, through July 31, 2018 were included in the training cohort, and 123 patients from August 1, 2018, through December 31, 2019 in the validation cohort. The study flowchart is shown in Figure 1.

The characteristics of the two cohorts are listed in Table 1. In the training cohort, 55 patients showed recurrence (15.89%). There were significant differences in concomitant HIV infection, HPV type, wart distribution, affected area, concomitant medication, CO₂ laser times, number of ALA vials for each treatment session between the recurrence and non-recurrence patients ($p < 0.05$). In the validation cohort, 20 patients showed relapse (16.26%). The result of comparison between recurrent and non-recurrent groups in the validation cohort was basically consistent with that in the training cohort (Table 1).

3.2 | Construction and validation of the nomogram model

Three potential predictors based on the training cohort with non-zero coefficients were selected by the LASSO regression model, including HIV infection, affected area, CO₂ laser times (Figure 2). Table 2 shows the risk predictors for recurrence in the univariate and multivariate Cox regression analysis. The multivariate Cox regression showed that using non-HIV patients as the reference, concomitant HIV patients were associated with a higher risk of recurrence [hazard ratio (HR) = 4.4, 95% CI, (2.5, 7.9), $p < 0.001$]. Compared with patients with only one time of CO₂ laser, patients receiving more than one time of CO₂ laser had a higher risk of recurrence [HR = 6.3, 95% CI, (2.8, 13.9), $p < 0.001$]. Patients with warts in the skin and mucosa had a higher risk of recurrence than those with lesions only in the skin area (HR = 1.7; 95% CI, 0.9–3.1; $p = 0.109$).

The risk of recurrence could be estimated by the proposed nomogram (Figure 3). To use the nomogram: mark on the variable axis based on an individual patient's condition, and draw a vertical line from the mark upward to the "Points" axis to determine the value for each variable. The formula for calculating the total score is: $-1.40174 \cdot A^1 + 0.11909 \cdot A^2 - 0.84447 \cdot A^3$. A refers to the value for each variable (A^1 , HIV infection; A^2 , affected area; A^3 , CO₂ laser times). According to the total score, a vertical line is drawn downward from the "Total Points" axis. Thus, the recurrence probability of the patient is obtained. Based on this model, an HIV-infected patient ($A^1 = 82$) who has received more than one time of CO₂ laser therapy ($A^2 = 100$) with warts on the skin ($A^3 = 50$) has a total score of 232. Therefore, this patient's predicted risk of recurrence is 50%.

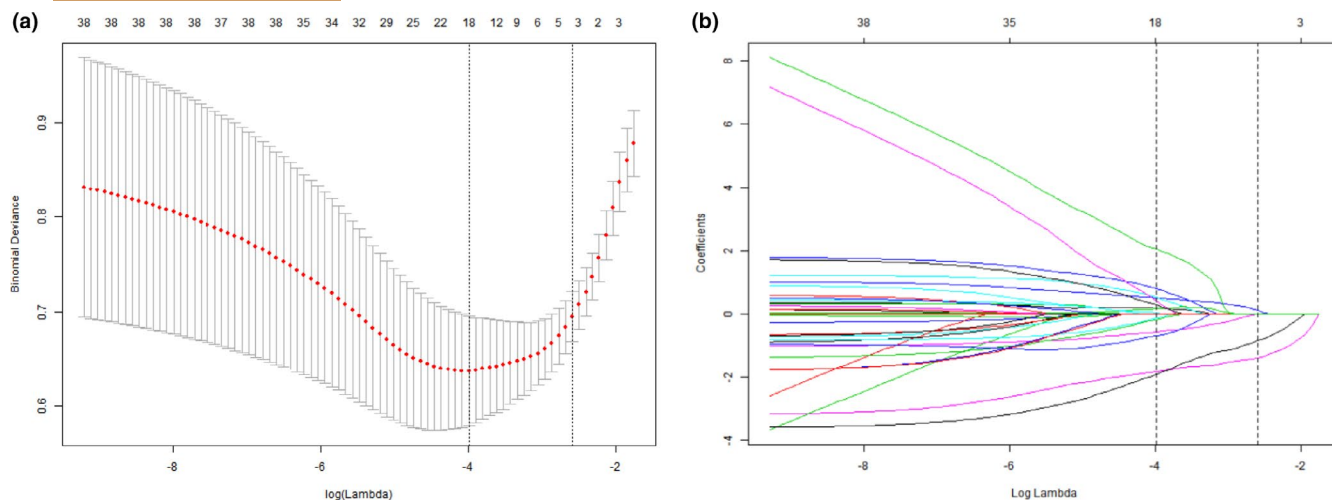


FIGURE 2 Risk predictors selection using the LASSO logistic regression model. (a) Optimal parameter (lambda) selection by LASSO used fivefold cross-validation via minimum criteria. The minimum criteria and the one SE of the minimum criteria (the 1-SE criteria) were used to draw the dotted vertical line at the optimum value; (b) LASSO coefficient profiles of the 39 predictors. A coefficient profile plot was developed against the log (lambda) sequence. Vertical line was drawn at the value selected with fivefold cross-validation, where optimal lambda resulted in three predictors with non-zero coefficients. LASSO, the least absolute shrinkage and selection operator

Characteristics	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	p-Value	Hazard ratio (95% CI)	p-Value
Concomitant HIV				
None	1		1	
Yes	9.5 (5.5, 16.4)	<0.001	4.4 (2.5, 7.9)	<0.001
Affected area				
Skin	1		1	
Mucosa	0.5 (0.1, 1.6)	0.213	0.4 (0.1, 1.4)	0.158
Skin and mucosa	4.1 (2.3, 7.3)	<0.001	1.7 (0.9, 3.1)	0.109
Times of CO ₂ laser				
Once	1		1	
More than once	11.0 (5.2, 23.4)	<0.001	6.3 (2.8, 13.9)	<0.001

Note: Mucosa area: urethra, vagina, cervix, and anal canal. CI, confidence interval. LASSO, least absolute shrinkage and selection operator.

TABLE 2 Univariate and multivariate Cox regression analysis for predictive factors associated with recurrence after 5-aminolevulinic acid photodynamic therapy (ALA-PDT) selected from LASSO regression in the training dataset

The C-indexes for the training set and the validation set were 0.843 (95% CI, 0.799–0.887) and 0.831 (95%CI, 0.727–0.934) respectively, indicating a promising predictive ability of the nomogram. The ROC prediction performance of nomogram was shown in Figure 4. The AUC values for the training cohort and validation cohort were 0.85 (95% CI, 0.873 to 0.910) and 0.8 (95% CI, 0.834 to 0.918) respectively, indicating good discrimination capabilities of the model. The calibration curve showed a good agreement between the predictive risk and the actual probability (Figure 5).

The DCA curve (Figure 6) showed that the net benefit of the nomogram was higher than both extreme curves when the threshold probability set between 5% and 75% in the training dataset and 3% and 60% in the validation dataset, suggesting its potential clinical benefits. By weighing the net benefit of differentiating threshold

probability, the nomogram can make personalized pre-treatment clinical decisions for different risk group easily and timely.

4 | DISCUSSION

In this single-center retrospective study of Chinese CA patients, we constructed a nomogram to predict the recurrence risk of CA after ALA-PDT. HIV infection, affected area, CO₂ laser times were the clinical factors included in our prediction model. These easily-available clinical variables may offer insights into the probability of recurrence in CA patients and help doctors determine appropriate treatment plan.

HIV infection is a common risk factor for recurrence of CA. Our study suggested that HIV infection in CA patients was associated with

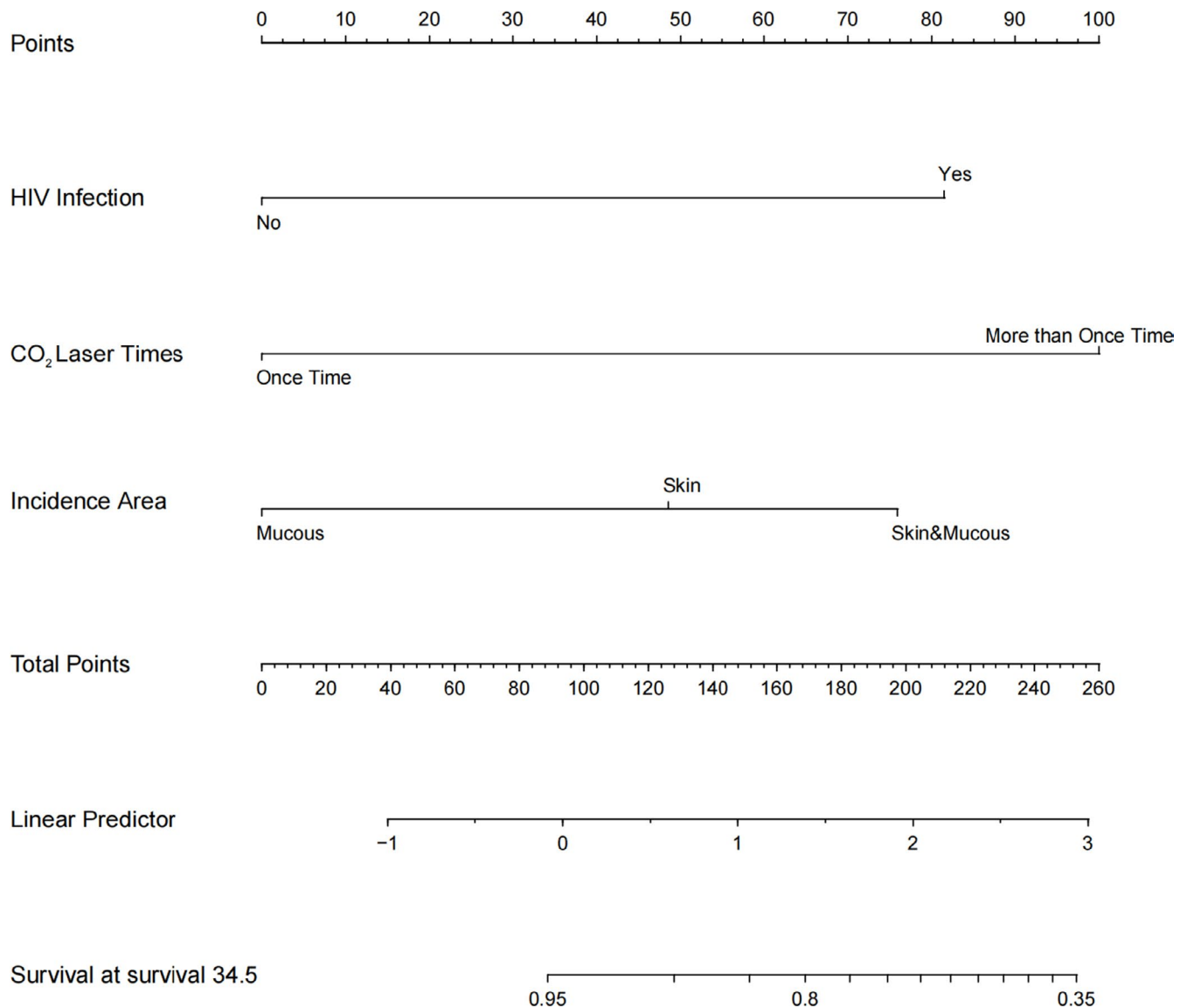


FIGURE 3 Nomogram predicting the risk of recurrence after 5-aminolevulinic acid photodynamic therapy (ALA-PDT) in training cohort

about a four times higher risk of recurrence compared with non-HIV patients. Previous studies have also reported a higher prevalence of HPV infection in HIV-infected individuals globally.^{18,19} In addition, an observational study showed that HIV-infected individuals had a reduced rate of HPV clearance compared to non-HIV ones.¹⁸ This may be attributable to the common transmission mode of HPV and HIV, HPV persistence as a result of the inability to clear HPV infections, as well as reactivation of latent HPV infections.²⁰ Furthermore, from the cytological perspective, the numbers of Langerhans cells, CD4⁺ T lymphocytes, macrophages, neutrophils and natural killer cells are reduced in HIV-infected patients, leading to the changes in local immunity and thus modulating HPV infection at the tissue level.^{21,22} Therefore, repeated or prolonged treatments, such as more times of PDT sessions, may be necessary for HIV-infected CA patients.

Our study indicated that lesions on skin and mucosa area were 1.7 times (compared with lesions on skin only) more likely to recur locally. This result is in accordance with that in the study by Zhang

et al.²³ A study including 138 patients for evaluating the efficacy of ALA-PDT indicated that HPV infection status was not correlated with site distribution (multisite infection or not, $p = 0.116$) or lesion location (internal lesion or not, $p = 0.183$). The multivariate analysis also indicated that patients with multisite HPV infection might require more PDT sessions compared with single-site infected patients ($p = 0.003$).¹ However, another study argued that the extensive CA lesions on both skin and mucosa might be a clinical manifestation of multiple types of HPV infection.²⁴ In our opinion, the effect of PDT is limited by irregular skin folds, which hinders the uniform distribution of photosensitizers and also may lead to insufficient therapeutic doses under red light irradiation.²⁵ The treatment field for some internal anatomical sites, such as the vagina, cervix, and anal canal, is commonly folded and therefore hard to expose sufficiently. Also, access of CA in the urethra is difficult, which may result in insufficient treatment and increase the total number of PDT sessions.²⁶ In summary, we speculate that multisite infections are associated

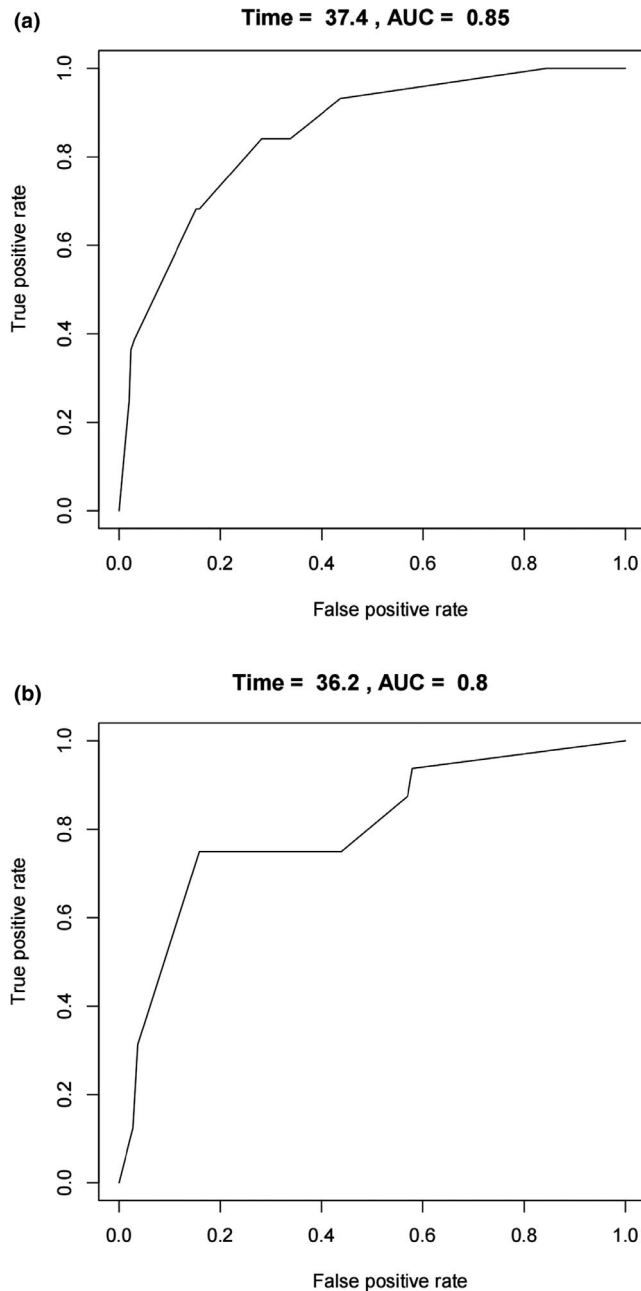


FIGURE 4 The ROC curves represent the discrimination ability of the model. The AUC of the nomogram was 0.85 in training (a), while was 0.8 in validation (b), demonstrating very good prediction performance. ROC, receiver operating characteristic curve; AUC, area under receiver operating characteristic curve

with recurrence, but more evidence is needed regarding whether multisite infection is related to multi-type HPV infection. For lesions located in the anatomical sites involving both skin and mucosa, apart from increasing ALA amount and PDT sessions, podophyllotoxin, imiquimod or topical wart removal lotion are acceptable combined modality treatments.^{7,17}

A randomized study comparing ALA-PDT with CO₂ laser in 65 CA patients showed a 95% complete removal rate for PDT and 100% for laser, but with fewer recurrences following PDT (6.3% versus 19.1%).²⁷ Similarly, a larger study with 90 patients also demonstrated

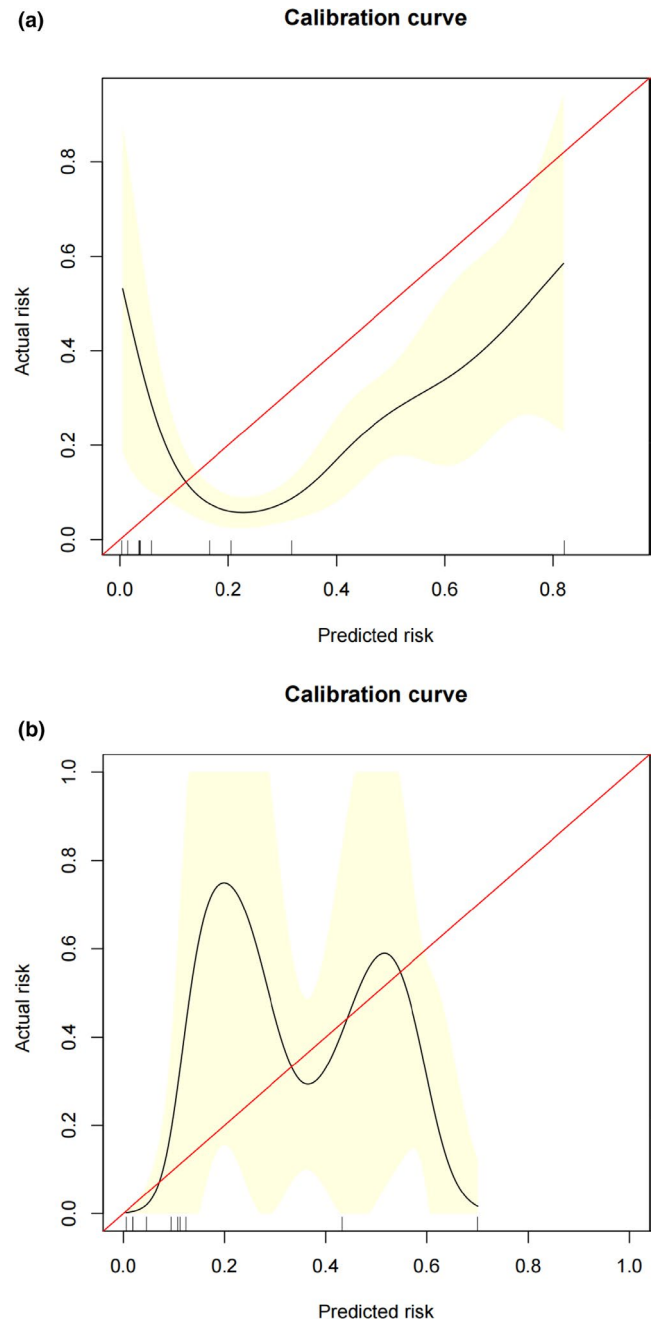


FIGURE 5 Calibration curves were used to compare the relationship of the predicted probabilities based on the nomogram and actual values of the training dataset (a) and validation dataset (b). The predicted recurrence risk is shown on the X-axis. The actual risk is shown on the Y-axis. Diagonal red line, the perfect prediction of an ideal model; Solid line, the performance of the line diagram. The closer the scatter points are to the diagonal line, the better the prediction efficiency of the nomogram is

a lower recurrence rate for PDT than for CO₂ laser (9% versus 17%).²⁸ The results indicated that despite the high skin lesion clearance rate by laser therapy, the potential HPV infection still exists.²⁹ The high frequency of CO₂ laser therapies reflects a high viral load, which seems to be indicative of viral persistence and disease progression, whereas a low viral load is more often associated with viral

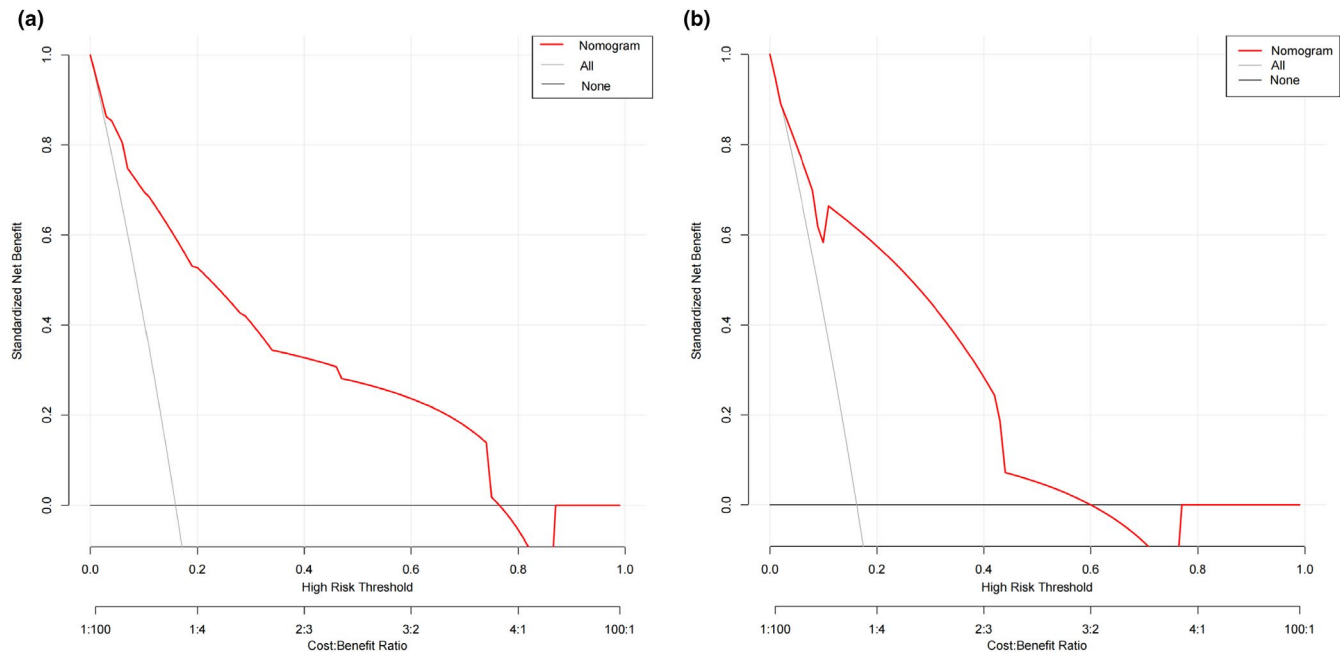


FIGURE 6 Decision curve analysis (DCA) for the recurrence risk nomogram (a, training dataset; b, validation dataset). The red line represents the recurrence risk nomogram. The thin solid line represents the hypothesis that all patients have recurrence. The thick solid line represents the hypothesis that no patients have recurrence. The DCA in the training cohort demonstrates that if the threshold probability is between 0.05 and 0.75, while in the validation dataset between 0.03 and 0.6, using the nomogram to predict recurrence is more beneficial than treating all or no patients

clearance.³⁰ A higher viral load indicates a larger number of infected cells and a higher chance of virus latent in an unusual cell type,³¹ which heralds the increased difficulty in complete elimination of the latent HPV infection and a high risk of recurrence.

To the best of our knowledge, this retrospective study has the largest sample size by far in investigating the CA recurrence after ALA-PDT, and is also the first to construct a predictive nomogram. There are some limitations in this study. First, this is a single-center study, meaning that all CA patients were from a tertiary hospital specializing in infectious disease. The conditions of the patients included were relatively serious and complex, so they might have a higher chance of recurrence. Second, in this study, the acetowhite test, which was used to determine the endpoint of treatment, could only identify foci of sub-clinical infection, thus having a limited accuracy in HPV diagnosis. The latent HPV infection around the lesions might be ignored.³² A recent study showed that negative results of HPV DNA tests as the endpoint of treatment would lead to a lower clinical recurrence rate (2.9%) than the actual rate.¹ If the endpoint can be determined more accurately, and even if the frequency of treatment will be increased, the recurrence rate will be further reduced, which is worthy. Third, the primary clinical records failed to provide other recurrence risk factors, such as staying up late or smoking. Fourth, external validations are needed to verify our findings. However, our nomogram has excellent prediction performance in internal validation based on the accessible clinical risk factors. In future research, we plan to include multiple medical centers, expand the sample size of CA patients, further optimize the selection of valuable predictors based on the current

research results, and improve the performance of the present nomogram.

In conclusion, we developed and validated a nomogram model to predict the recurrence risk of CA after ALA-PDT. This nomogram incorporates clinical parameters, namely HIV infection, incidence area, and CO₂ laser times, and may help doctors determine the appropriate treatment plan. External validation studies, and further prospective clinical studies with larger sample sizes are warranted to refine the predictors and further verify our findings.

ACKNOWLEDGMENT

This work was financially supported by grants from the China National Natural Science Foundation (NO.81903246 and 82073472), the Science Foundation of Nantong (No. JC2019024), the Priority Academic Program Development (PAPD) of Jiangsu Higher Education Institutions, and Outstanding Young and Middle-aged Talents Support Program of the First Affiliated Hospital of Nanjing Medical University (Jiangsu Province Hospital).

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Conception and design: S Zhou, H Hua, B Zhou; Administrative support: H Hua, B Zhou; Provision of study materials or patients: S Zhou, H Hua, B Zhou; Data Collection and assembly: S Zhou, H Hua, L Gu; Data analysis and interpretation: L Gu, Z Shi, Q Gu; Manuscript writing: S Zhou, H Hua, B Zhou; Final approval of manuscript: All authors.

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How to cite this article: Zhou S, Gu L, Shi Z, Gu L, Zhou B, Hua H. A novel nomogram based on a retrospective study of 346 patients to predict the recurrence risk of condyloma acuminatum after 5-aminolevulinic acid photodynamic therapy. *J Dermatol*. 2021;00:1–10. <https://doi.org/10.1111/1346-8138.16218>