Prediction of Lymph Node Metastasis in Penile Cancer: Evaluation of Clinicopathological Factors, Validation of an Existing Model, and Development of Novel Nomogram

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Primary research

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Abstract

Objective

To investigate the predictive factors of lymph node metastasis (LNM) and evaluate the usefulness of prediction nomograms.

Methods

This study analyzed data of 300 patients diagnosed with penile squamous cell carcinoma at West China Hospital (WCH) of Sichuan University (Chengdu, China) and 412 cases acquired from the Surveillance, Epidemiology, and End Results (SEER) program. Logistic regression analysis was performed on these cohorts to investigate the predictive factors of LNM. We evaluated a recently developed prediction nomogram for LNM, which was established based on the National Cancer Database (NCDB). Moreover, we developed a novel nomogram using cases from the WCH for the prediction of lymphatic metastasis.

Results

Logistic analysis identified that younger age at diagnosis, invasion of the penis body, poorer pT stage, cN stage, nuclear grade and the presence of lymph vascular invasion (LVI) were significantly correlated with LNM in WCH cases; however, only race, poorer T stage and cN stage were significantly associated with LNM among the cases from the SEER. Multivariate analysis demonstrated that younger age, poorer T stage, cN stage and nuclear grade were independent predictors of LNM. Receiver operating characteristic curve analysis of WCH cases showed that the tumor T stage 8th edition has better area under the curve than 7th stage (0.672 vs 0.636, respectively). Moreover, well AUC were seen in external validation of NCDB nomogram in WCH cohorts and SEER series (0.833 vs 0.795). The new nomogram included the aforementioned independent predictors and the bootstrap-corrected concordance was 0.876.

Conclusion

Younger diagnose age, poorer pT stage, cN stage, nuclear grade and LVI were the most important predictors of LNM in patients with penile cancer. 8th T stage performed better than 7th version in predicting LNM. NCDB nomogram have some application value in both WCH and SEER cases, and our novel model further improved the predictive accuracy.

Introduction

Penile squamous cell carcinoma (PSCC) is a relative rare genitourinary tumor, with an overall incidence of < 1 in 100,000 males in the USA and Europe (1, 2). However, this number is markedly higher and increasing in developing countries (3). Metastasis of penile cancer to the inguinal lymph nodes, the most

common metastatic site for this type of malignancy, is always associated with a poor prognosis (3, 4). While inguinal lymph node dissection (ILND) can assist in tumor grading and reduce the risk of mortality, this technique is also associated with a high incidence of complications, with an incidence of complications (70%) (5, 6). Hence, it is important to identify patients who will benefit from ILND and to avoid unnecessary surgery.

Previous studies demonstrated that the development of lymph node metastasis (LNM) depends on several clinicopathological factors, such as tumor T stage, nuclear grade, lymph vascular invasion (LVI), etc (7, 8). Models combine these factors could help on the accurate prediction of lymphatic metastasis (9–11). Taylor et al, established a LNM prediction nomogram based on clinicopathological features (nuclear grade, cN stage and LVI) of patients recorded in National Cancer Database (NCDB), this prediction nomogram exhibited high discrimination in its internal validation (11). In the present study, we analyzed the predictive value of several clinicopathological factors in patient cohorts from West China Hospital (WCH) of Sichuan University (Chengdu, China) and the Surveillance, Epidemiology, and End Results Program (SEER) database, evaluated the clinical usefulness of the NCDB nomogram, and subsequently developed a novel nomogram using data of PSCC cohort of our institute.

Materials And Methods

Patient selection

This study included patients who were diagnosed with PSCC and underwent complete excision of the lesion through partial or radical penectomy in the Department of Urology at WCH of Sichuan University between September 2008 and October 2020. The exclusion criteria were: 1) presence of unresectable disease or cN3 disease; 2) Eastern Cooperative Oncology Group score > 1; and 3) unwillingness of patients to provide information regarding their disease. Patients provided informed written consent prior to the collection of data. Finally, 300 patients with PSCC included in this study.

Clinical and pathological features

Patient clinical data (e.g., age at diagnosis, smoking history, duration of disease, tumor growth velocity, clinical lymph node stage) were retrieved from the medical records of our hospital. All pathological reports were provided by the Pathology Department of our institute, including histopathological type, pathological T stage, tumor size, nuclear grade and LVI. Pathological T stage was adjusted according to the Union for International Cancer Control (UICC) TNM classification system 7th and 8th editions, and the largest diameter of the tumor was recorded to determine its size. Clinical N stage was recorded at the first outpatient visit, which is 1 month after primary resection.

Follow-up

ILND was recommended for patients with pT1G2 or higher stage diseases, and those with palpable inguinal lymph node at the first postoperative outpatient visit. Patients were followed-up through clinical

examination once every 3 months during the first year and every 6 months thereafter. Ultrasonography of the groin was performed every 6 months for the first 2 years after surgery. Metastatic inguinal lymph nodes were confirmed by surgical resection or biopsy during follow-up.

SEER data resource and cohort selection

All cases of patients with PSCC for whom data were available in the SEER database were examined (SEER Research Data, 18 registries, Nov 2019 Sub; n=5222). We included those who had complete records in terms of cN stage, tumor nuclear grade, LVI, regional lymph node examined status, survival length and status, and those with cN3 disease were excluded. Except for the above-mentioned factors, clinicopathological data (e.g., age, race, tumor location, T stage, tumor size and ILND history) were also collected. There were finally 412 SEER cases included in our study.

Statistical methods

Univariate and multivariate logistic regression analyses were performed to determine the clinicopathological parameters associated with LNM. In univariate analysis, factors with statistical significance were included in the multivariate analysis, and independent predictors of LNM were selected to generate a novel nomogram. Bootstrapping was used to calculate the corrected c-index, and a calibration curve was created. Moreover, patients (WCH and SEER cohorts) were scored using the NCDB nomogram. Receiver operating characteristic curve analysis was used to evaluate predicted value of different clinicopathological factors, the NCDB nomogram and new-established WCH nomogram. Statistical analyses were performed using the SPSS Statistics 25 (IBM Corporation, Armonk, NY, USA) and The R Programming Language 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). A $P< 0.05$ denoted statistically significant differences.

Results

Table 1 presents the clinicopathological data of 300 patients with PSCC. The mean age was 54.2 years (standard deviation: 13.9 years), and the median follow-up time was 35.1 months (interquartile range: 15.0–86.6 months). ILN metastasis occurred in 93 of patients during follow-up. The 2 years cancer-specific-survival rate for lymph node positive or negative series were 53.8% and 98.9% respectively. The clinicopathological data of 412 SEER cases were also shown in Table 1. The median follow-up time was 8.5 months (interquartile range: 4.0–15.0 months). In this cohort, LNM occurred in 6 patients during the follow-up. The 2 years cancer-specific-survival rate for lymph node positive and negative groups was 37.5% and 83.7% separately.

Table 1
Clinicopathological features for PSCC patients in WCH and SEER database

Variants	WCH (300 patients)	SEER (412 patients)
Age of diagnosis (years)		
< 50	127	36
50–69	128	170
≥ 70	45	206
Smoking history		
No	141	NA
Yes	159	NA
Race		
White	0	341
Black	0	44
Asian and Pacific islander	300	15
American Indians and Alaska native	0	5
Unknown	0	7
Tumor growth velocity in recent 3 months		
< 1cm/month	214	NA
≥ 1cm/month	86	NA
Tumor location		
Prepuse	15	45
Glans penis	166	151
Body of penis	7	24
Overlapping lesion of penis	112	15
unknown	0	177
Tumor size		
< 1cm	6	39
1-4cm	212	199

WCH: West China Hospital; SEER: Surveillance, Epidemiology, and End Results Program; LVI: lymph vascular invasion; ILND: inguinal lymph node dissection.

Variants	WCH (300 patients)	SEER (412 patients)
≥ 4cm	82	109
unknown	0	65
T stage (7th edition)		
T_1	110	224
T_2	171	95
T_3	19	6
T_4	0	64
unknown	0	23
T stage (8th edition)		
T_1	110	NA
T_2	100	NA
T_3	90	NA
T_4	0	NA
Nuclear grade		
Well differentiated	98	123
Moderately differentiated	146	188
Poorly/ undifferentiated	56	101
Lymph vascular invasion		
Negative or unknown	278	351
Positive	22	61
Clinical N stage		
N_0	202	383
N_1	37	9
N_2	61	20
ILND operation		

WCH: West China Hospital; SEER: Surveillance, Epidemiology, and End Results Program; LVI: lymph vascular invasion; ILND: inguinal lymph node dissection.

Variants	WCH (300 patients)	SEER (412 patients)
No surgery or unknown	164	397
Operation performed	136	15
Positive inguinal lymph node		
No	207	406
Yes	93	6

WCH: West China Hospital; SEER: Surveillance, Epidemiology, and End Results Program; LVI: lymph vascular invasion; ILND: inguinal lymph node dissection.

For the 300 WCH cases, the univariate analysis revealed that younger age at diagnosis, invasion of the penis body, poorer T stage, cN stage, nuclear grade and presence of LVI were significantly correlated with ILN metastasis. However, for the 412 SEER cases, only American Indian/ Alaska native race, poorer T stage and cN stage were significantly associated with LNM ($P < 0.05$, Table 2). The multivariate analysis for the WCH cohort demonstrated that all aforementioned factors, except the location of the lesion, were independent predictors of LNM ($P < 0.05$, Table 3).

Table 2
Univariate analysis of PSCC patients in WCH and SEER database.

Clinical pathological data	WCH (300 patients)			SEER (412 patients)		
	P value	Risk ratio	95% CI	P value	Risk ratio	95% CI
Smoking[a]	0.872	1.041	0.639–1.695	NA	NA	NA
50 ≤ Diagnosis age < 70 years[b]	0.058	0.603	0.357–1.018	0.998	NA	NA
Diagnosis age > 70 years[b]	0.021	0.385	0.171–0.868	0.998	NA	NA
Black[c]	NA	NA	NA	0.552	1.959	0.214–17.935
Asian or Pacific Islander[c]	NA	NA	NA	0.999	NA	NA
American Indian/ Alaska Native[c]	NA	NA	NA	0.013	21.063	1.905-232.833
Glans penis[d]	0.892	1.086	0.329–3.581	1.000	NA	NA
Body of penis[d]	0.022	16.500	1.487–183.070	0.998	NA	NA
Overlapping lesion of penis[d]	0.576	1.412	0.421–4.733	0.998	NA	NA
1cm ≤ Tumor size < 4cm[e]	0.414	2.465	0.283–21.502	0.998	NA	NA
Tumor size ≥ 4cm[e]	0.517	2.069	0.229–18.656	0.998	NA	NA
Tumor growth ≥ 1cm/month[f]	0.540	0.843	0.488–1.456	NA	NA	NA
T_2 (7th edition)[g]	0.001	4.376	2.377–8.059	0.388	2.387	0.331–17.200
T_3 (7th edition)[g]	0.076	2.712	0.900-8.171	0.018	22.200	1.718-286.849
T_4 (7th edition)[g]	NA	NA	NA	0.997	NA	NA

[a]: reference group is no-smoker; [b]: reference group is diagnosis age < 50; [c]: reference group is White patients; [d]: reference group is those tumor in prepuse; [e]: reference group is tumor size < 1cm; [f]: reference group is Tumor growth < 1cm/month; [g]: reference group is $T_{1;}$ [h]: reference group is nuclear well differentiated group; [i]: LVI negative; [j]: reference group is cN_0. WCH: West China Hospital; SEER: Surveillance, Epidemiology, and End Results Program; LVI: lymph vascular invasion.

Clinical pathological data	WCH (300 patients)			SEER (412 patients)		
T_2 (8th edition)[g]	0.001	3.305	1.693–6.452	NA	NA	NA
T_3 (8th edition)[g]	0.001	5.375	2.744–10.529	NA	NA	NA
T_4 (8th edition)[g]	NA	NA	NA	NA	NA	NA
Moderately differentiated[h]	0.001	5.470	2.546–11.752	0.557	1.978	0.203–19.239
Poorly/ undifferentiated[h]	0.001	15.283	6.400-36.493	0.464	2.465	0.220–27.580
LVI present/ identified[i]	0.001	6.717	2.537-17-787	0.997	NA	NA
cN_1[j]	0.005	3.008	1.407–6.430	0.001	54.429	6.681-443.449
cN_2[j]	0.001	16.588	8.226–33.452	0.003	21.167	2.819-158.952

[a]: reference group is no-smoker; [b]: reference group is diagnosis age < 50; [c]: reference group is White patients; [d]: reference group is those tumor in prepuse; [e]: reference group is tumor size < 1cm; [f]: reference group is Tumor growth < 1cm/month; [g]: reference group is $T_{1;}$ [h]: reference group is nuclear well differentiated group; [i]: LVI negative; [j]: reference group is cN_0. WCH: West China Hospital; SEER: Surveillance, Epidemiology, and End Results Program; LVI: lymph vascular invasion.

Table 3
Multivariate analysis of PSCC patients in WCH cases.

Clinical pathological data	WCH 300 patients		
	P value	Risk ratio	95% CI
50 ≤ Diagnosis age < 70 years[a]	0.063	0.512	0.252–1.038
Diagnosis age > 70 years[a]	0.004	0.199	0.066–0.602
Glans penis[b]	0.218	0.397	0.091–1.725
Body of penis[b]	0.467	3.105	0.147–65.743
Overlapping lesion of penis[b]	0.103	0.275	0.058-1.300
T_2 (8th edition)[c]	0.052	2.531	0.991–6.469
T_3 (8th edition)[c]	0.005	3.975	1.527–10.350
Moderately differentiated[d]	0.005	3.954	1.526–10.248
Poorly/ undifferentiated[d]	0.001	14.861	4.930-44.795
LVI present/ identified[e]	0.054	3.463	0.978–12.259
cN_1[f]	0.028	2.679	1.114–6.442
cN_2[f]	0.001	14.642	6.303–34.013

[a]: reference group is diagnosis age < 50; [b]: reference group is those tumor in prepuse; [c]: reference group is T_1; [d]: reference group is nuclear well differentiated group; [e]: LVI negative; [f]: reference group is cN_0. WCH: West China Hospital; LVI: lymph vascular invasion.

Prediction effects of above independent predictors for LNM were evaluated (Fig. 1A, B). In the WCH cases, higher AUC were seen in cN stage and nuclear grade, which were 0.754 and 0.722 respectively; AUC for all other factors were lower than 0.70, and 8th T stage showed better predictive effect than 7th (AUC: 0.672 vs 0.636). In the SEER cases, factors with completed records (grade, LVI and cN stage) were evaluated, and only cN stage had AUC higher than 0.70. Besides, external validations of the NCDB nomogram (11) were performed using both the SEER and WCH cohorts: for these two patient cohorts, the area under the curve (AUC) was 0.833 and 0.795, respectively (Fig. 1C, D).

For better prediction of LNM, a new nomogram was established using clinicopathological data of WCH cases (Fig. 2). All the factors included in the model were previously proven independent predictors of LNM. The bootstrap corrected c-index of model was 0.876, which was similar to the AUC (Fig. 1E). Figure 3 illustrates consistency between the predicted risk and observed incidence.

Discussion

The occurrence of PSCC metastasis of the inguinal lymph node is linked to poor prognosis (12). Lymph node dissection is the most important approach for the prevention and treatment of LNM. However, surgeons must consider the balance between survival benefit and the high rate of complications (3). The use of dynamic sentinel node biopsy has been advocated to avoid unnecessary ILND, though the risk of false-negative results remains inevitable (13). Therefore, it is necessary to make an accurate prediction of LNM. This study demonstrated that age at diagnosis, cN stage and pathological data (T stage, nuclear grade and LVI) were independent predictors for LNM. The new nomogram established based on the above factors showed good discrimination. Thus, we think that it will be helpful in the decision-making regarding ILND.

Previous studies identified several factors associated with LNM of PSCC, such as tumor size, nuclear grade, and LVI, as well as invasion of the corpus, corpus spongiosum, urethra, nerves, etc (7, 8, 14). The UICC pathological T stage combined those factors which describe the growth and invasion of primary tumors, and was shown to be significantly correlated with LNM (9, 10, 12). The 8th edition of the UICC TNM classification includes the following changes in the definitions of T1, T2 and T3: T1 was stratified into two different groups depending on LVI; T2 denoted invasion of the corpus spongiosum; and T3 indicated invasion of the corpus cavernosum (15). In the present study, cN stage got the highest AUC both in WCH and SEER cohorts, which indicates that postoperative examination of groin area should not be ignored. Moreover, the 8th T stage showed better AUC than 7th version, which supports the application of the 8th T stage when predicting LNM.

This study also demonstrated that younger patients are at a higher risk of developing LNM. This relationship has rarely been reported in the past. Geise et al., retrospectively reviewed 378 patients with PSCC and found that younger patients had a higher frequency of morphological features(16). In their study, the frequency of LNM was 49% 34% and 21% for patients aged < 40 years, 40–60 years and > 60 years, separately. However, Zhu et al., and Peak et al., did not report age-related differences with regard to LNM (10, 11). In fact, onset age is a factor that has been neglected for a long time: its predictive value for the development of LNM and prognosis should be further validated. Additionally, further investigations on the clinicopathological characteristics of younger patients with PSCC are warranted.

Nomogram based on the aforementioned prediction factors have been established to accurately predict the occurrence of LNM. In 2006, Ficarra et al., reported a nomogram which predicted LNM in patients with PSCC (8). A total of 175 patients were included in their study, and the nomogram was produced using the following factors: tumor thickness, growth pattern, grade, embolization, invasion of the corpus cavernosa, corpus spongiosum and urethra, and cN stage. In their internal validation, the AUC of the nomogram was 0.876. In 2010, Zhu et al, developed a nomogram which included 110 patients and combined T stage, grade, LVI and p53 expression (10). The internal validation showed a c-index of 0.79. An external validation, performed by Maciel et al., 65 patients yield a c-imdex of 0.783 (17). In recent years, a more simplified nomogram was established based on 1,636 patients from the NCDB (11). This model included

grade, cN stage and LVI, its internal validation was produced an AUC of 0.880. Our present study showed relatively high accuracy of external verification both in WCH and SEER cases, which reflected the role of grade, cN and LVI in the prediction of LNM. After combined these factors with latest T stage and diagnostic age, we got high c-index of 0.876. It is anticipated that this novel model may have greater application value for Asian population which our patient series belongs to.

There were some limitations in this study. Firstly, the population included in our nomogram derived from a single source. Although some systematic errors (such as religion, race and medical-care conditions) could be reduced, the usefulness of this model in other geographic regions and populations of other racial backgrounds could not be evaluated. Furthermore, we did not analyze molecular targets that may be associated with LNM. The present model just incorporated the most important and routine clinicopathological factors; thus, we hope that this approach may facilitate to clinical practice and its further evaluation.

Conclusions

For patients with PSCC, age at diagnosis, pathological T stage, nuclear grade, LVI, and cN stage were independent predictors of LNM. The UICC 8th T stage has better predictive value for LNM than 7th edition. The NCDB nomogram has acceptable predictive value in WCH and SEER series. In this study, a novel LNM prediction nomogram for LNM was generated based on WCH cases. This model incorporates the aforementioned independent-prediction factors and show good predictive power.

Declarations

Ethics approval and consent to participate

This retrospective study was approved Ethics Committee of West China Hospital, Sichuan University, with the whole process supervised. Patients and their authorized family members had been fully informed before follow-up work was performed, with informed consent signed.

Consent for publication

Consent for publication was obtained from all participants.

Availability of data and materials

The dataset supporting the conclusions of this article is included within the supplementary materials.

Competing interests

None declared.

Fundings

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authors contribution

X.L. designed the study, guided experiments, carried out analysis and reviewed the manuscript. Y.S., K.W. and T.L contributed to the study design, collected the data, performed analysis, and wrote the manuscript. X.H., S.R., Z.Y. and Y.L. contributed to the data collection and analysis and reviewed the manuscript. S.X., W.D., S.F. and Y.W., helped with data collation and statistical analysis and reviewed the manuscript.

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Figures

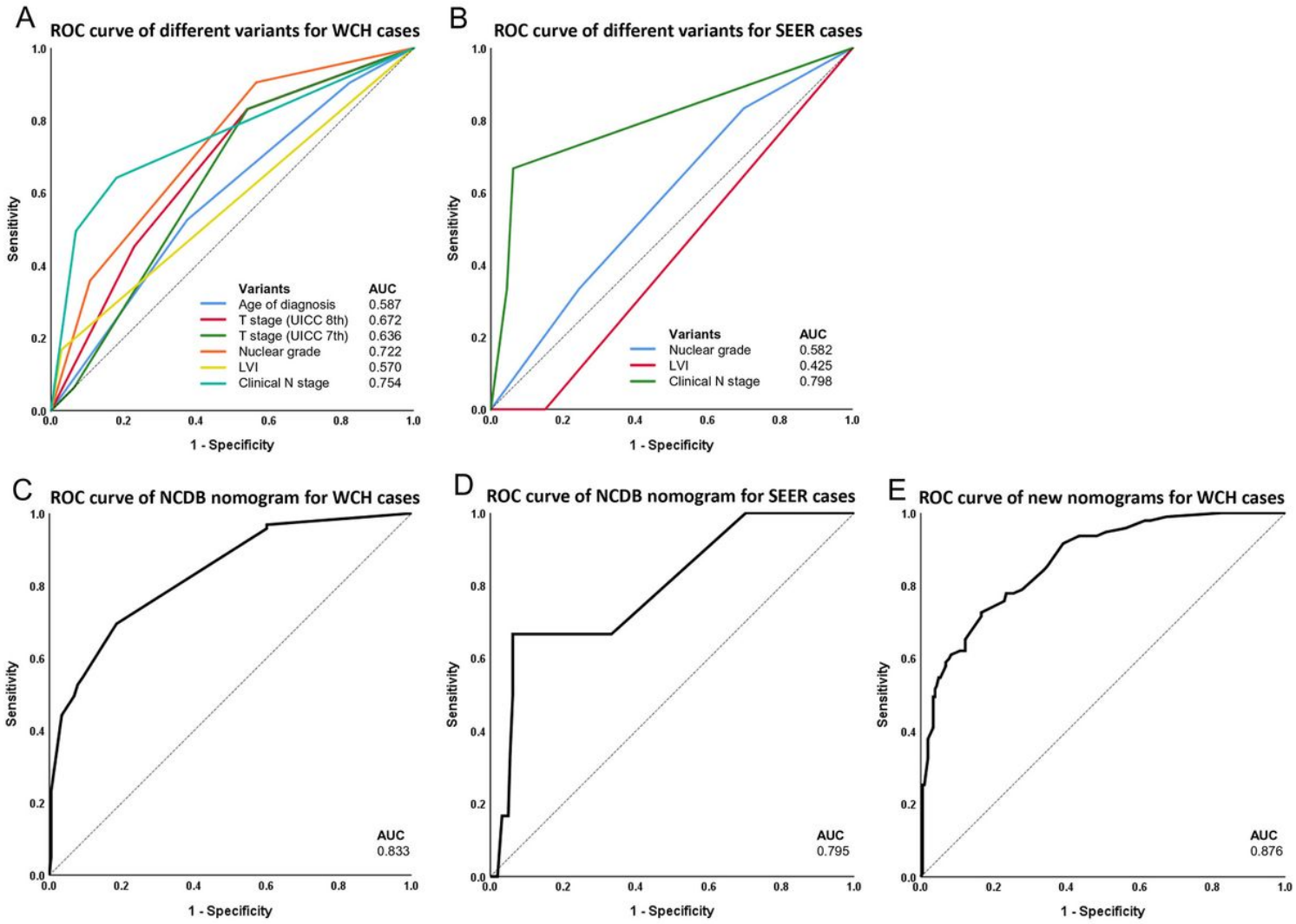

Figure 1

ROC curve of different variants and nomograms. (A) ROC curve of different variants for WCH cases. (B) ROC curve of different variants for SEER cases. (C) ROC curve of NCDB nomogram for WCH cases. (D) ROC curve of NCDB nomogram for SEER cases; (E) ROC curve of new nomograms for WCH cases. ROC: Receiver Operating Characteristic Curve; AUC: Area Under the Curve; WCH: West China Hospital; SEER: Surveillance, Epidemiology, and End Results Program; UICC: Union for International Cancer Control; LVI: lymph vascular invasion.

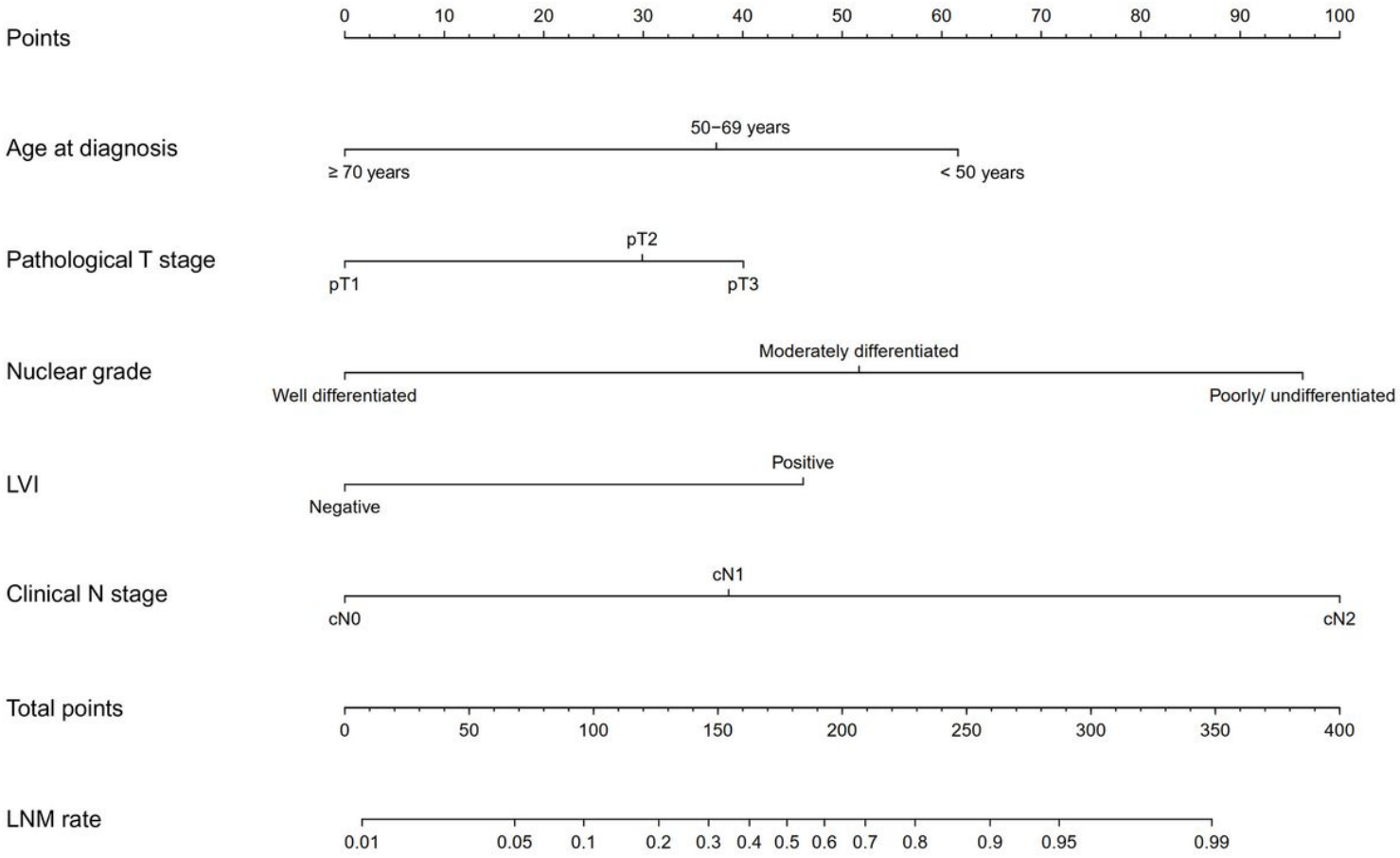

Figure 2

Novel nomogram predicting LNM in patients with cN0-2 PSCC. PSCC: penile squamous cell carcinoma; LVI: lymph vascular invasion; LNM: lymph node metastasis.

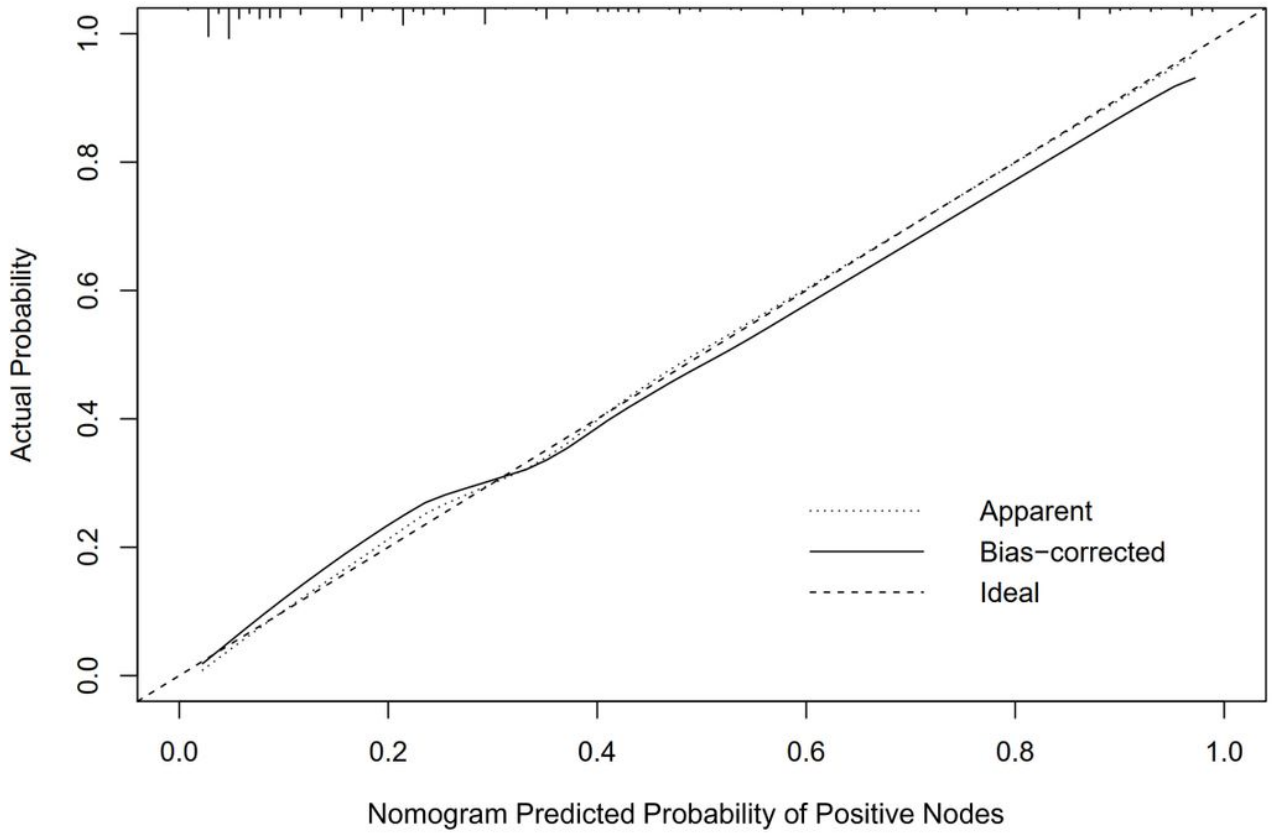

Figure 3

Calibration plot for WCH novel nomogram predicting LNM.