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ORIGINAL ARTICLE

Negative Lymph Node Count is an Independent Impact Factor for Predicting the Specific Survival of Primary Duodenal Neoplasms under Surgical Procedures

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SUMMARY

Background: **The work aimed to assess the influence of negative lymph node numbers on specific survival of primary duodenal neoplasms under surgical procedures.**
Methods: **This study focused on the primary duodenal neoplasm patients that have been registered in the "surveillance, epidemiology, and end results" (SEER). First, the important factors were screened by the Kaplan-Meier (Log-rank) in R and the Cox's proportional hazards regression model. Subsequently, a nomogram was established based on key proportional hazards including the negative lymph node count. Finally, the analysis of the specific survival by Kaplan-Meier (Log-rank) and X-Tile was performed to identify the cutoff values of negative lymph node numbers.**
Results: **There were 463 selected patients. Five impact factors were screened including the negative lymph node count (between 10 and 32), age (< 73), differentiation of cancers (well or moderate), primary tumors' invasion to tissues' superficial parts, no distant metastasis. The C-index of the nomogram in this paper was 0.74.**
Conclusions: **The negative lymph node count and the other four factors were used for predicting the specific survival of primary duodenal neoplasms under surgical treatment, and the highest 2-year cancer's specific survival occurred when the negative lymph node numbers were 10 - 32. Besides, the nomogram in this paper proved to be more useful in predicting the survival effects than the traditional American Joint Committee on Cancer classification methods.**
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KEY WORDS

duodenal neoplasms, negative lymph node, nomogram, SEER

LIST OF ABBREVIATIONS

PDN - primary duodenal neoplasms
SIC - small intestine cancer
AJCC - American Joint Committee on Cancer
NLNC - negative lymph node count
IPF - independent prognosis factor
DG - differentiation grade
HC - histopathological classification
SEER - surveillance, epidemiology, and end results
CSS - cancer's special survival
Stage_T - the primary tumor's condition

Stage_N Stage - the regional lymph node involvement
Stage_M - the distant metastasis
Stage - the cancer staging
IQR - interquartile range
Nom Model - the nomogram constructed with the screened 5 IPFs in this paper
Nom AJCC - the nomogram constructed with the 4 IPFs in the 7-edition AJCC
COX - Cox's proportional hazards regression model
K-M - Kaplan-Meier (Log-rank)
C-index - concordance index

INTRODUCTION

Primary duodenal neoplasms (PDN) account for 50% of small intestine cancer (SIC). The disease presents a low incidence rate and a high degree of malignancy [1]. Surgical treatment is a common therapy and its prognosis effect is not satisfying enough.

Prognosis factors for PDN have long been confusing. Currently, the American Joint Committee on Cancer (AJCC) staging system is widely employed for cancer staging and as a prognosis indicator including conditions of primary tumor (Stage_T), regional lymph node metastasis (Stage_N), distant metastasis (Stage_M), and cancer staging (Stage), etc. However, the selected indexes were incapable of accurate prognostic judgment. The lymph node count was selected as another prognosis factor for cancer, specifically gastric cancer [2,3], non-small cell lung cancer [4], and oral cancer [5]. The lymph node number includes positive lymph nodes and negative lymph nodes.

Recently, the negative lymph node count (NLNC) has raised concerns as a prognosis indicator for cancers. It can be applied as a prognosis indicator in cancers of different classification, such as breast cancer [6,7] and esophageal cancer [8], rectum cancer [9,10], and oral cancer [5]. Besides, the ratio of positive lymph nodes and negative lymph nodes can also be used for cancer prognosis [11]. However, there is little research regarding the relationship between NLNC and PDN's prognosis.

In this paper, a hypothesis that NLNC is an independent prognosis factor (IPF) in PDN is established. The research objective was the "surveillance, epidemiology, and end results" (SEER) data base to screen out PDN, and data analysis was conducted by the packages in R. To begin with, the Cox multivariate regression analysis was adopted to confirm whether the NLNC is an IPF. Then the nomogram was built based on the IPFs and was compared with the existing American Joint Committee on Cancer (AJCC) staging system. Finally, the relative packages in R were introduced for further analysis of the relationship between the sub-group NLNC and the positive lymph nodes count. The result proved that the NLNC was one of the key prognosis factors whose best examination scope is 10 - 32; it also demonstrated some other factors including age, differentiation grade (DG) of the tumor, and the primary tumor's condition (Stage_T) and the distant metastasis (Stage_M). The result showed no relationship between the NLNC and the positive ones. The established nomogram proved to be more useful than the traditional AJCC in prediction. Particularly, the research first proposed that the NLNC served as the IPF of the PDN.

MATERIALS AND METHODS

Materials

The sample data was obtained from the SEER (1973 - 2013 Research Data in ASCII Text Format April 15, 2016) (https://seer.cancer.gov). The data was downloaded following the approvals of our application and then they were screened for negative lymph nodes whose number was calculated. The selection process was conducted under the following 9 criteria including (1) small intestine cancers (cs0204schema, code: 141); (2) primary site is duodenum (ICD-O-3, Primary Site, code: 170) [12]; (3) have specific races (RAC_RECA), (4) conduct TNM staging and stage classification according to AJCC (code: DAJCC7T, DAJCC7N, DAJCC7M, DAJCC7STG); (5) have specific tissue-type (HIST REC); (6) have cancer grade code (GRADE); (7) at least one lymph node was detected (at least one lymph node (must include positive ones) in total was detected); (8) under surgical treatment (NO_SURG, code: 0).

Methods

In the beginning, the impact factors were analyzed. The gender, race, age, DG, histopathological classification (HC), tumor's size, Stage_T, Stage_M, the regional lymph node involvement (Stage_N), Stage, NLNC, and cancer's special survival (CSS) were obtained from the SEER. The NLNC was calculated according to the total lymph node number and positive lymph node number (the negative ones = the total number - the positive ones). The CSS was calculated based on specific dates of diagnosis and death. The Stage_T, Stage_N, Stage_M, and the Stage were considered as the categorical variables. The X-tile [13] software can be adapted to divide the NLNC into different groups based on the 2-year CSS. By the same method, the continuous variables of cancer's age and size can also be grouped. At last, the quantile function in R (https://www.rproject.org) was performed to observe NLNC in each group, and the data was present in the form of the median and interquartile range (IQR). The statistical analysis was conducted through R. When the p-values on both sides were smaller than 0.05, the statistical results can be deemed as significant. The Kaplan-Meier survival analysis (log-rank inspection) in the R can be introduced to study the differences of 2-year CSS in different groups. The first screen factors can be targeted as the analyzing elements in the following part. Finally, the cox multivariate regression analysis in the R was used to search the IPFs for the PDN.

Subsequently, the nomogram was established [14]. The patients were numbered in sequence as 1, 2, and 3. The information numbered as 1 and 2 were grouped as the 1st group for development_model establishment and the information numbered as 3 was grouped as the 2nd group for validation_model. A nomogram was constructed with the selected IPFs by the previous approaches in the development_model. The values of the concordance index (C-index) of development_model and each IPF was calculated by rcorr.cens function in the Hmisc package in R. The validation_model was for a external examination of the nomogram. In the end, the nomogram was compared with the one constructed by the IPFs in the traditional AJCC.

Next, selecting the cutoff values of NLNC. The NLNC was divided into two groups by X-Tile. The demarcation point was the one cutoff point, the result was exhibited by Kaplan-Meier (log-rank) in R. The other cutoff point was determined by the changes of survival rates with different groupings.

Finally, we explored the significant differences among NLNC and other IPF subgroups. We analyzed whether the positive lymph node was the negative lymph nodes' confounding factor by the cortex function (Pearson's correlation coefficient) in R.

RESULTS

Features of the patients from the SEER

The patients' general conditions were summarized in Table 1. The NLNC were divided into 2 groups according to the 2-year CSS: the less-than-9 group and the no-less-than-10 group ($p = 0.03$, $\chi^2 = 10.68$). The age was also divided into 2 groups according to the 2-year CSS: the younger-than-73 group and the older-than-74 group ($p = 0.00$, $\chi^2 = 35.37$). The tumor's sizes were divided into 2 groups based on 2-year CSS: the larger-than-28 mm group and the no-more-than-28 mm group ($p = 0.70$, $\chi^2 = 2.85$).

Screening the IPFs for PDN

The median of the NLNC was 9 (IQR 5, 13). The 2-year CSS was 58.5% (IQR 53.3%, 64.2%). The survival rates of the two groups of NLNC were shown in Figure 1. The result showed that 7 factors were the PDN's prognosis impact factors by Kaplan-Meier survival analysis (log-rank inspection), as shown in Table 2. Additionally, the number of the IPFs changed into 5 by Cox's proportional hazards regression model, as shown in Table 2.

The building of the nomogram

At first, the data was divided into two groups, one of which was used for development_model containing 309 patients and the other for validation_model containing 154 patients. Then, two nomograms were built, one was the nomogram constructed with the screened 5 IPFs in this paper (Nom Model), the other was the nomogram constructed with the 4 IPFs in the 7-edition AJCC (Nom AJCC). There were 5 impact factors for further analyses of the Nom Model by the same method in 3.2, the result was shown in Figure 2. The C-index of the development_model (0.74) was greater than 0.7, showing a good discrimination. The correction curves of 2_year_CSS of the development_model and the validation_model were shown in Figure 3. According to the values of C-index, the order of the IPFs is 1st: Stage_T; 2nd: Differentiation Grade; 3rd: Stage_M; 4th: Age; 5th: NLNC.

The Nom AJCC was established including Stage_T, Stage_N, Stage_M, and Stage, the result was shown in Figure 2. The C-index of development_model (0.65) was lower than the one in the first nomogram. The calibrations of 2_year_CSS of the development_model and the validation_model were shown in Figure 3. The gap between the predicted and actual values was smaller in the Nom Model compared with Nom AJCC.

The cutoff values of the NLNC

Nine was chosen as the lower cutoff point, the specific survival rate was shown in Figure 1. When the number was larger than nine, the survival rate increased significantly. Thirty-two was chosen as the upper cutoff point, the specific survival rate was shown in Figure 4. The nodes in the range of 10 - 63 were analyzed showing that when the lymph node number exceeded 32, the 2-year CSS dropped from 63.4% to 61.9%, rather than growing. Thirty-two was selected as the higher cutoff node.

The Kruskal.test (more than 3 groups) or the Wilcox.test (2 groups) functions in R were introduced to analyze the changes of sub-grouped NLNC in age, DG, HC, Stage_T, and Stage_M. The results showed that the p-values of all subgroups were all larger than 0.05 and presented no statistical difference (age $p = 0.17$; DG $p = 0.89$; Stage_T $p = 0.45$; Stage_M $p = 0.39$). Therefore, the cutoff values of the NLNC in the sub-groups were not calculated.

The relation between the negative lymph nodes and the positive ones

The cor.test function (Pearson's examination) in R was used in the analysis. The correlation coefficient proved to be -0.07, and the p-value < 0.12.

DISCUSSION

The NLNC, together with the other four factors including the age, DG, Stage_T, and Stage_M are the key IPFs of PDNs, with the confounding factor of positive lymph node count being excluded. When the NLNC lies between 10 to 32, the 2-year CSS is rather high and the nomogram in this paper presents better prognosis results.

The nomogram including NLNC established in this study has a better prognosis result. Although, some re-

Table 1. The selected 463 patients' characteristics.

	NLNC (0 - 9), n (%)	NLNC (10 - 64), n (%)	Totally, n (%)	p-value by K-M	p-value by COX
	Median (IQR)	Median (IQR)			HR (95% Cl)
Gender				p = 0.49	
Female	79 (35.75%) 4.50 (2.25, 6.75)	142 (64.25%) 37.00 (23.5, 50.5)	221 (47.73%)		
Male	85 (35.12%) 5.00 (3.00, 7.00)	157 (23.75%) 36.00 (23.00, 49.00)	242 (52.26%)		
Age				p = 0.00 **	p = 0.00 ** HR = 1.04
-73	129 (38.74%) 4.50 (2.25, 6.75)	204 (61.26%) 37.00 (23.50, 50.50)	333 (71.92%)		
74-	62 (46.97%) 4.50 (2.25, 6.75)	68 (51.52%) 33.50 (21.75, 45.25)	130 (28.08%)		
Differentiation Grade				p = 0.00 **	p = 0.00 ** HR = 1.63
Grade1, Grade 2	118 (41.40%) 5.00 (3.00, 7.00)	167 (58.60%) 34.0 (22.50, 45.50)	285 (61.56%)		
Grade3, Grade 4	73 (40.12%) 4.50 (2.25, 6.75)	105 (59.88%) 15.50 (12.75, 18.25)	178 (38.44%)		
Stage				p = 0.00 **	p = 0.65 HR = 1.20
Stage 0, Stage I	26 (42.62%) 5.00 (3.00, 7.00)	35 (57.38%) 26.00 (18.00, 34.00)	61 (13.17%)		
Stage II, Stage III	152 (40.97%) 5.00 (3.00, 7.00)	219 (59.03%) 22.50 (16.25, 28.75)	371 (80.13%)		
Stage IV	13 (41.94%) 4.50 (2.25, 6.75)	18 (58.06%) 18.00 (14.00, 22.00)	31 (6.7%)		
Stage_T				p = 0.00 **	p = 0.00 ** HR = 1.58
Tis	1 (33.33%) 1.00 (1.00, 1.00)	2 (66.67%) 18.00 (16.00, 20.00)	3 (0.65%)		
T1, T2	36 (40.45%) 5.00 (3.00, 7.00)	43 (48.31%) 19.50 (14.75, 24.25)	79 (17.06%)		
T3, T4	154 (40.42%) 4.50 (2.25, 6.75)	227 (59.58%) 37.00 (23.50, 50.50)	381 (82.29%)		
Histopathological Classification				p = 0.04 *	p = 0.05 HR = 2.55
ADE and CYS	188 (44.34%) 4.50 (2.25, 6.75)	263 (55.66%) 20.50 (15.25, 25.75)	451 (97.4%)		
Others	3 (25%) 7.50 (6.75, 8.25)	9 (75%) 16.00 (13.00, 19.00)	12 (2.59%)		
Stage_N				p = 0.00 **	p = 0.45 HR = 1.16
N0, N1	140 (39.55%) 5.00 (3.00, 7.00)	214 (60.45%) 33.50 (21.75, 45.25)	354 (76.46%)		
N2	51 (46.79%) 4.50 (2.25, 6.75)	58 (53.21%) 22.50 (16.25, 28.75)	109 (23.54%)		
Stage_M				p = 0.00 **	p = 0.04 * HR = 2.61
M0	78 (41.20%) 4.50 (2.25, 6.75)	254 (58.80%) 37.0 (23.50, 50.50)	432 (93.30%)		
M1	13 (43.75%) 4.50 (2.25, 6.75)	18 (56.25%) 18.00 (14.00, 22.00)	31 (6.70%)		

Table 1. The selected 463 patients' characteristics (continued).

	NLNC (0 - 9), n (%)	NLNC (10 - 64), n (%)	Totally, n (%)	p-value by K-M	p-value by COX
	Median (IQR)	Median (IQR)			HR (95% Cl)
Cancer Size				p = 0.05	
2 - 28 mm	44 (41.90%) 4.50 (2.25, 6.75)	61 (58.10%) 37.00 (23.50, 50.50)	105 (22.68%)		
29- mm	147 (41.06%) 4.50 (2.25, 6.75)	211 (58.94%) 36.00 (23.00, 49.00)	358 (77.32%)		
Race				p = 0.16	
White	140 (40.46%) 4.50 (2.25, 6.75)	206 (59.54%) 36.00 (23.00, 49.00)	346 (74.73%)		
Black	39 (49.37%) 4.50 (2.25, 6.75)	40 (50.63%) 20.00 (15.00, 25.00)	79 (17.02%)		
Other	12 (31.58%) 5.00 (3.00, 7.00)	26 (68.42%) 37.00 (23.50, 50.50)	38 (8.21%)		
NLNC				p = 0.00 **	p = 0.00 ** HR = 0.97
0 - 9	191 (41.25%) 4.50 (2.25, 6.75)		191 (41.25%)		
10-		272 (58.75%) 37.00 (23.50, 50.50)	272 (58.75%)		

* - p < 0.05, ** - p < 0.01. N0 - no regional lymph node metastasis, N1 - 1 - 3 regional lymph node metastases, N2 - 4- regional lymph node metastasis. Tis - carcinoma-in-situ, T1 - tumors invade tunicae propria and submucosa, T2 - tumors invade muscularis propria, T3 - tumors penetrate the muscularis propria and reach the subserosa, or invade parts of the pancreas without peritoneum, the range less than 2 cm, T4 - tumors penetrate peritoneum visceral and directly invade bile duct or pancreas structures. Grade 1 - well differentiated, Grade 2 - moderately differentiated, Grade 3 - poorly differentiated, Grade 4 - undifferentiated. M0 - without distant metastasis, M1 - with distant metastasis. NLNC - negative lymph node count. IQR - interquartile range. ADE and CYS - adenoma and adenocarcinoma, cystic, mucinous, and serous neoplasm. Others - Complex mixed and stromal neoplasm, Ductal and lobular neoplasm, Epithelial neoplasms. Other - American Indian, AK Native, Asian/Pacific Islander. K-M - Kaplan-Meier (log-rank). COX - Cox's proportional hazards regression model.

Table 2. The results of the Cox analysis and the validation for the NOM model.

Analysis method	COX for the NOM model, p; HR	C-index for the NOM model p; C-index (95% Cl)
Stage	p = 0.39; HR = 0.50	
Stage_M	p = 0.03 *; HR = 6.85	p = 0.00 *; C-index = 0.81 (0.68 - 0.93)
Stage_N	p = 0.28; HR = 1.26	
Stage_T	p = 0.03 *; HR = 4.56	p = 0.00 **; C-index = 0.84 (0.79 - 0.89)
Age	p = 0.00 **; HR = 1.05	p = 0.00 **; C-index = 0.71 (0.68 - 0.74)
DG	p = 0.00 **; HR = 1.93	p = 0.00 **; C-index = 0.81 (0.76 - 0.86)
Cancer Size	p = 0.08; HR = 1.00	
NLNC	p = 0.00 **; HR = 0.96	p = 0.00 **; C-index = 0.63 (0.59 - 0.66)

* - p < 0.05, ** - p < 0.01. COX - Cox's proportional hazards regression model. Nom Model - the nomogram constructed with the screened five IPFs. Nom AJCC - the nomogram constructed in the 7-edition AJCC. DG - differentiation grade. HC - histopathological classification. NLNC - negative lymph node count.

searchers claimed that the number of lymph nodes and the ratio of the ones played important roles in PDN, the exact number of negative lymph nodes was not mentioned [15,16]. Furthermore, the data which the nomogram was based on was updated or different from the one before [15-17]. Last, more diagnostical information

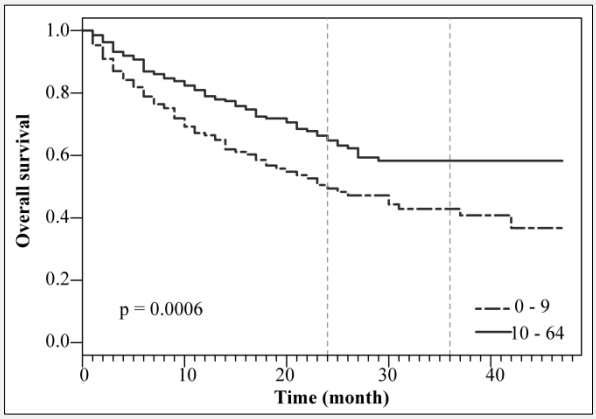

Figure 1. The lower limit of the NLNC's cut-off values.

The vertical ordinate represents the cancer's special survival rate, the horizontal coordinate represents the time in months. Linear representation of the less-than-9 group, dotted representation no-less-than-10 group. The two cross points of four lines (the time's lines and the survival curves) represent the specific survival rates of different groups of 2 and 3 years, respectively. NLNC - negative lymph node count. Nine is the lower limit of the NLNC's cutoff values.

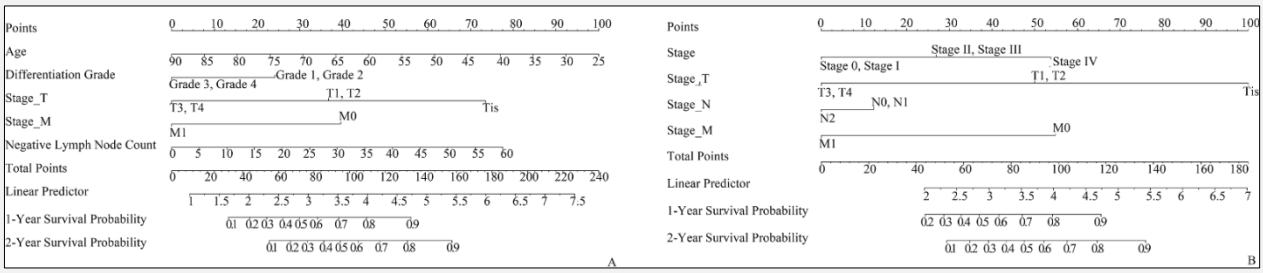

Figure 2. The comparison of the two nomograms.

A: The nomogram based on the 5 screened impact factors in this paper. B: The nomogram based on the 4 impact factors in the AJCC.

was provided by many of the IPFs.

NLNC served as a risk factor of the PDN. Researchers like Young JI et al. [18] also held that advanced cancer's low differentiation degree was an important factor for the SIC's prognosis. The PDN mentioned here is one type of SIC. The fact that the survival period was chosen as 2 years instead of 3 years or 5 years can be explained by the high death rate of PDN [1]. There is no relevance between the NLNC and the positive ones and the confounding factors in the PLNC can be ruled out. Researchers like Chen K et al. also thought that the PLNC was almost irrelevant to the prognosis and was relevant to some features of advanced cancer [19]. In actuality, the NLNC was not always effective in predicting prognoses and should be integrated with certain diseases for specific analyses. For example, NLNC was IPF of the breast cancer patients and disease-free survival, while it was useless in the prognosis of breast cancers within different sub-groups [20].

Some studies found that black people were prognosis factors of SIC [18], while in this paper we did not find it so. Some other researches declared there was no statistical difference between the white people and the black people in the prognosis of intestinal surgery possibly attributed to the small sampling size. For the same reason, there are still scholars holding that cancer staging [18]

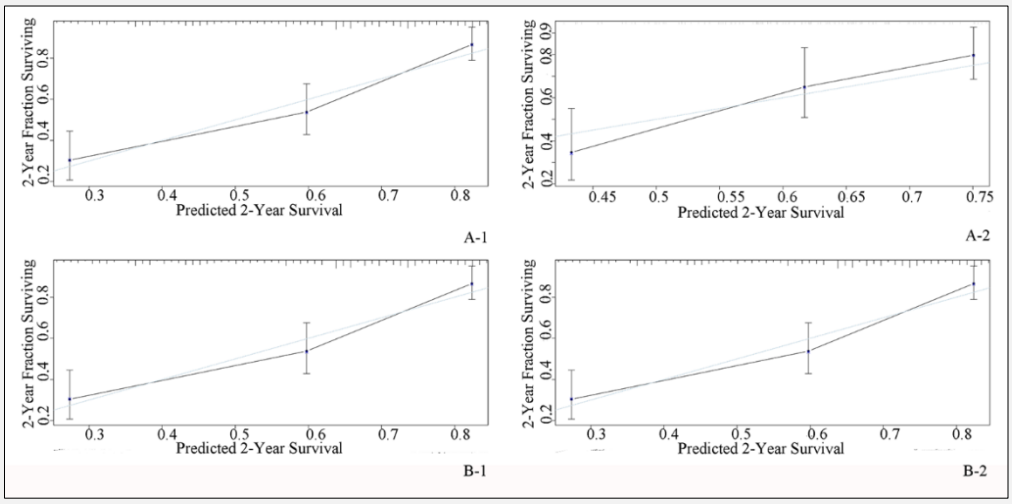

Figure 3. The correction curves of the nomograms.

A-1: Two-year CSS's correction curve of the "model group" in the Nom Model. A-2: Two-year CSS's correction curve of the "validation group" in the Nom Model. B-1: Two-year CSS's correction curve of the "model group" in the Nom AJCC. B-2: Two-year CSS's correction curve of the "validation group" in the Nom AJCC. The consistency verification was conducted with the node being 2 years. Light color lines represent the model's fitting data, dark color lines represent the model's real data. The closer the space between the dark and light color lines, the better. CSS - cancer's special survival. Nom Model - the nomogram constructed with the screened five IPFs. Nom AJCC - the nomogram constructed in the 7-edition AJCC.

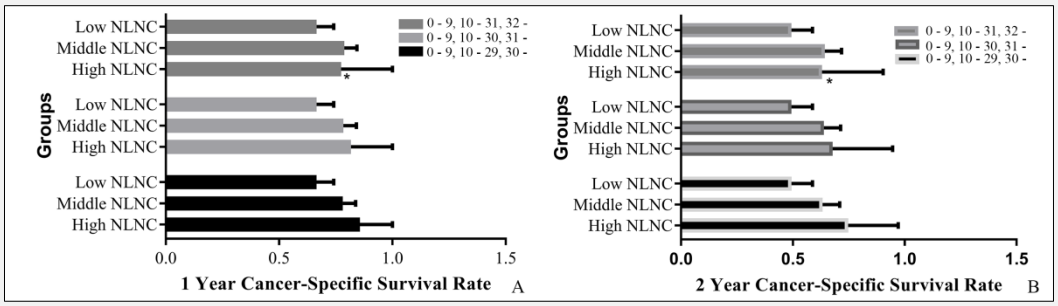

Figure 4. The upper limit of the NLNC's cutoff values.

A: The upper limit of the NLNC's cutoff values based on 1-Year Specific Survival. B: The upper limit of the NLNC's cutoff values based on 2-Year Specific Survival. A: the horizontal ordinate represents the cancer's special survival rate, the vertical coordinate represents the different groups of NLNC. B: the same with a. The High NLNC (32-) group with the declined specific survival rates compared with High NLNC (31-) and High NLNC (30-) groups were marked with * in the upper right corner. NLNC - negative lymph node count. Thirty-two is the upper limit of the NLNC's cutoff values.

and histopathological classification [21] may influence the prognosis, which demands more samples to verify. Besides an increase of sample size is required for confounding factors such as special molecular markers, radiotherapy, and chemotherapy, and more detailed lymph node groupings can also contribute to the result differences.

Compared with the nomogram constructed in the 7-edition AJCC, the nomogram constructed with the screened 5 IPFs (Nom Model) had better anastomosis between

real and hypothetical predictions, especially in external validation. Researchers like Zhang Z et al. also took that the Nom Model built with NLNC was more useful in survival prediction [20] than the models established with traditional classifications.

CONCLUSION

This paper found that the growth of PDN 2-year CSS could be caused by the increase of NLNC, patients aged under 73, the well or moderate differentiation of cancers, primary tumors' invasion to tissues' superficial parts, and no distant metastasis. Besides, the nomogram established in this paper proved to be convenient and could calculate the total score according to the patients' features and predict the PDN's 2-year CSS. The nomogram is useful for the doctors to conduct personalized survival predictions in clinical practices and can also serve as a layer tool to help clinical practitioners with more precise clinical decisions.

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Declaration of Interest:
None.

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