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Predictive value of number of metastatic lymph nodes and lymph node ratio for prognosis of patients with FIGO 2018 stage IIICp cervical cancer: a multi-center retrospective study

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Abstract

Background To identify the cut-off values for the number of metastatic lymph nodes (nMLN) and lymph node ratio (LNR) that can predict outcomes in patients with FIGO 2018 IIICp cervical cancer (CC).

Methods Patients with CC who underwent radical hysterectomy with pelvic lymphadenectomy were identified for a propensity score-matched (PSM) cohort study. A receiver operating characteristic (ROC) curve analysis was performed to determine the critical nMLN and LNR values. Five-year overall survival (OS) and disease-free survival (DFS) rates were compared using Kaplan–Meier and Cox proportional hazard regression analyses.

Results This study included 3,135 CC patients with stage FIGO 2018 IIICp from 47 Chinese hospitals between 2004 and 2018. Based on ROC curve analysis, the cut-off values for nMLN and LNR were 3.5 and 0.11, respectively. The final cohort consisted of nMLN ≤ 3 ($n = 2,378$) and nMLN > 3 ($n = 757$) groups and LNR ≤ 0.11 ($n = 1,748$) and LNR > 0.11 ($n = 1,387$) groups. Significant differences were found in survival between the nMLN ≤ 3 vs the nMLN > 3 (post-PSM, OS: 76.8% vs 67.9%, $P = 0.003$; hazard ratio [HR]: 1.411, 95% confidence interval [CI]: 1.108–1.798, $P = 0.005$; DFS: 65.5% vs 55.3%, $P < 0.001$; HR: 1.428, 95% CI: 1.175–1.735, $P < 0.001$), and the LNR ≤ 0.11 and LNR > 0.11 (post-PSM, OS: 82.5% vs 76.9%, $P = 0.010$; HR: 1.407, 95% CI: 1.103–1.794, $P = 0.006$; DFS: 72.8% vs 65.1%, $P = 0.002$; HR: 1.347, 95% CI: 1.110–1.633, $P = 0.002$) groups.

Conclusions This study found that nMLN > 3 and LNR > 0.11 were associated with poor prognosis in CC patients.

Keywords Cervical cancer, FIGO 2018 IIIC, Number of metastatic lymph nodes, Lymph node ratio, Oncological outcome

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Background

Cervical cancer (CC) is a significant global health concern. In 2020, there were 604,000 new patients with CC globally, and 342,000 patients died from CC. CC has become the most lethal cancer in 36 countries [1]. Tumor staging indicates the extent of disease, guiding treatment options, as well as in prognostication. Several studies have demonstrated lymph node metastasis to be a poor prognostic factor [2–5]; therefore, FIGO 2018 staging includes metastasis to pelvic lymph nodes as IIC1 and to para-aortic lymph nodes as IIC2, whereby, the annotation "r" or "p" indicates radiological or pathological involvement [6].

Metastatic lymph node is closely related to the prognosis of stage IIC, and researchers have attempted to use various parameters related to lymph node (LN), including the number of metastatic lymph nodes (nMLN), number of examined lymph nodes, size of metastatic lymph node, lymph node ratio (LNR), and log odds of metastatic lymph nodes, as prognostic factors in CC. Log odds of metastatic lymph nodes is defined as logarithm of the probability of being a metastatic lymph node versus the probability of being a negative LN (the log of [metastatic lymph node \pm 0.5/the number of removed LNs – metastatic lymph node + 0.5]). While nMLN is one of the most commonly used features to predict prognosis [7–15]; recently, the LNR which is defined as the number of metastatic lymph nodes divided by the total number of removed lymph nodes (nMLN/the number of removed LNs) has also gained attention as a prognostic factor [11, 15–26]. Nevertheless, the specific values of nMLN and LNR are still being explored for stage IIC CC, with cut-off values of nMLN ranging from ≥ 2 to > 5 [10, 12–15] and those of LNR ranging from 0.05 to 0.2 [11, 15, 18–20, 23–26]. However, the predictive outcomes based on nMLN and LNR in patients with stage IIC CC remain controversial and warrant further exploration, especially regarding cut-off values [7]. Therefore, this study aims to explore the specific cut-off values of nMLN and LNR that can accurately predict survival outcomes in patients with FIGO 2018 stage IICp CC. The findings will contribute to survival risk stratification and the development of individualized treatment strategies for these patients, providing real-world evidence for clinical decision-making.

Methods

Study design

This retrospective study aimed to explore the specific cut-off values of nMLN and LNR that can accurately predict survival outcomes in patients with FIGO 2018 stage IICp CC. We used data obtained from the Chinese Cervical Cancer Clinical Research Database developed through a clinical trial (Project 1538; Ethics Clearance

NFEC-2017–135; Clinical Trial Registration Number: CHICTR1800017778, <http://apps.who.int/trialsearch/>). The database includes 63,926 cases of CC from 47 hospitals in China and contains patients' clinical information, pretreatment biopsy findings, laboratory and imaging information, treatment-related information, treatment complications, and postoperative pathology. Data were collected by two gynecologists who received specific training for the clinical trial using EpiData 3.1 (EpiData Association, Odense, Denmark) for dual data entry and standard interviews for follow-up data by telephone or outpatient visits. Details of the data collection and follow-up methods have been previously described [26–28].

Inclusion and exclusion criteria

The inclusion criteria for eligible cases were: age ≥ 18 years; CC detected through biopsy of the uterine cervix; histological confirmation; adenocarcinoma, adenosquamous cell carcinoma, or squamous cell carcinoma type CC; FIGO 2018 stage IICp; underwent Q-M type-B or type-C radical hysterectomy with pelvic \pm para-aortic lymphadenectomy; had complete information on LN dissection and postoperative pathology; underwent standardized adjuvant therapy; and had complete follow-up history.

The exclusion criteria include violation of selection criteria, missed visits, cancer of the uterine cervix stump, and CC combined with other malignancies or pregnancy.

Diagnostic criteria for metastatic lymph nodes

The diagnosis of metastatic LNs was determined by two pathologists with 15 years of practice. The pathologist tests all surgically resected LNs and diagnoses metastatic LNs when a tumor lesion is found.

Outcomes

The outcomes for this study were 5-year disease-free survival (DFS) and overall survival (OS) after treatment. DFS is the terminal time point from diagnosis to follow-up, relapse, or death. OS was defined as the terminal time point from diagnosis to a valid follow-up or death for any reason.

Statistical analysis

LNR (%) is the ratio of the nMLN to the total number of removed LNs (values are totals for both left and right sides). Receiver operating characteristic (ROC) curve analysis was used to determine the optimal nMLN and LNR values. If in normal distribution, sequential variables were characterized by mean \pm standard deviation, and an independent sample t-test was employed for comparison between groups. If in non-normal distribution, the continuous measurement data were expressed

as median and interquartile range and tested with the Mann–Whitney U test. Categorical data was presented as frequency and percentage values, and comparison was done using Chi square or Fischer’s exact test as appropriate. Survival analysis was performed using the Kaplan–Meier method. Independent risk factors were identified through Cox proportional hazards models, and hazard ratios (HRs) and 95% confidence intervals (95% CI) were calculated. Propensity score matching (PSM) was applied to decrease the effect of baseline discrepancies within groups. The analyses were all conducted using SPSS (version 29; IBM Corp., Armonk, N.Y., USA), with significance defined at a *P*-value < 0.05.

Results

Case screening results and cut-off value determination

From the database, 3,135 CC cases with FIGO 2018 stage IIICp (FIGO 2009 stages I-IIB with metastatic lymph node) met our inclusion and exclusion criteria, with no missing values. The selection process for these cases is illustrated in Fig. 1. The sequential variables were in normal distribution. The median number of removed LNs was 20 (range, 7–116). The ROC curve analysis showed that the optimal cut-off values of nMLN and LNR to predict 5-year OS and DFS were 3.5 and 0.11, respectively. Therefore, patients were divided into nMLN ≤ 3 (*n* = 2,378) and nMLN > 3 (*n* = 757) groups, and

LNR ≤ 0.11 (*n* = 1,748) and LNR > 0.11 (*n* = 1,387) groups. Baseline comparisons of patients in the nMLN ≤ 3 vs nMLN > 3 groups and LNR ≤ 0.11 vs LNR > 0.11 groups (pre-PSM and post-PSM) are shown in Tables 1 and 2.

Survival analysis of all patients (pre-PSM)

Before PSM, the HRs for lower survival in the nMLN > 3 groups were as follows: OS: 1.437, 95% CI: 1.155–1.789, *P* = 0.001, and DFS: 1.468, 95% CI: 1.228–1.754, *P* < 0.001, while those in the LNR > 0.11 group were as follows: OS: 1.454, 95% CI: 1.181–1.790, *P* < 0.001; DFS: 1.392, 95% CI: 1.177–1.646, *P* < 0.001. Adenocarcinoma correlated with worse 5-year OS and DFS than squamous cell carcinoma (*P* < 0.001), while adenosquamous cell carcinoma correlated with worse 5-year OS (*P* = 0.006) but not with DFS (*P* = 0.069). Tumor diameter > 4 cm and unknown tumor diameter correlated with worse 5-year OS and DFS (*P* < 0.05) compared to tumor diameter ≤ 4 cm. Compared to negative lymphovascular space invasion, positive lymphovascular space invasion correlated with a worse 5-year OS (*P* = 0.005) but not with DFS (*P* = 0.471). Compared to cervical stromal invasion ≤ 1/2, cervical stromal invasion > 1/2 correlated with a worse 5-year OS and DFS (*P* < 0.001), while unknown cervical stromal invasion correlated with a worse 5-year OS (*P* = 0.041) but not with DFS (*P* = 0.065). Compared to

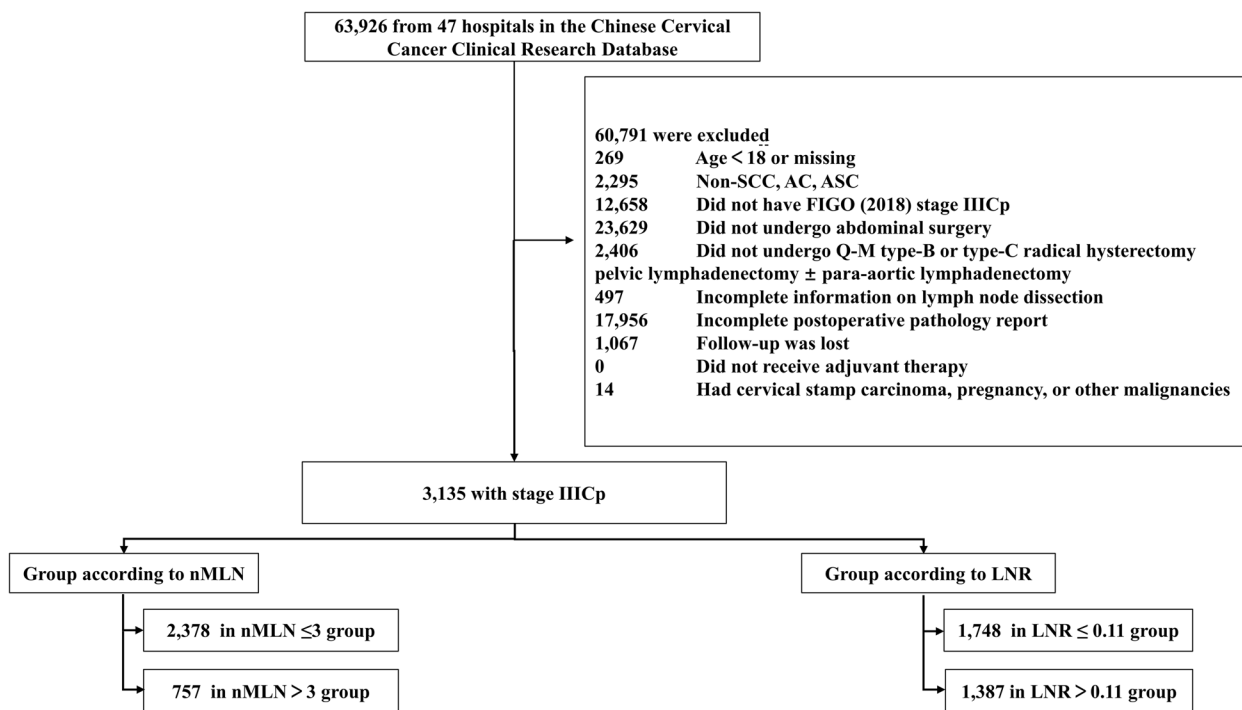


Fig. 1 Patient selection flow diagram

Table 1 Clinicopathological characteristics of patients in the nMLN ≤ 3 and nMLN > 3 groups

Variables	pre-PSM		P	post-PSM		P
	nMLN ≤ 3 group (n = 2378)	nMLN > 3 group (n = 757)		nMLN ≤ 3 group (n = 703)	nMLN > 3 group (n = 532)	
Age (years)	48.24 \pm 9.357	48.02 \pm 9.854	0.773	47.39 \pm 9.145	47.53 \pm 9.166	0.971
Histological type			0.353			0.991
Squamous cell carcinoma	2101(88.4%)	654(86.4%)		621 (88.3%)	470 (88.3%)	
Adenocarcinoma	206(8.6%)	76(10.0%)		60(8.6%)	46 (8.7%)	
Adenosquamous cell carcinoma	71(3.0%)	27(3.6%)		22 (3.1%)	16(3.0%)	
Hysterectomy type			0.674			0.881
Type QM-B	1690(71.1%)	491(64.9%)		466 (66.3%)	343(64.5%)	
Type QM-C1	10 (0.4%)	1 (0.1%)		3 (0.4%)	2 (0.4%)	
Type QM-C2	668(28.1%)	264(34.9%)		206 (29.3%)	162 (30.4%)	
Unknown	10 (0.4%)	1 (0.1%)		28(4.0%)	25(4.7%)	
Tumor diameter(cm)			0.545			0.866
≤ 4	1369(57.5%)	431(56.9%)		404 (57.4%)	308 (57.9%)	
> 4	865(36.4%)	287(37.9%)		250 (35.6%)	191 (35.9%)	
Unknown	144(6.1%)	39(5.2%)		49(7.0%)	33 (6.2%)	
Lymphovascular space invasion			$<$ 0.001			0.121
negative	1572(66.1%)	412(54.4%)		448 (63.7%)	316 (59.4%)	
positive	806(33.9%)	345(45.6%)		255 (36.3%)	216 (40.6%)	
Cervical stromal invasion			0.010			0.689
$\leq 1/2$	421(17.7%)	99(13.1%)		123(17.5%)	84 (15.8%)	
$> 1/2$	1822(76.6%)	617(81.5%)		534(76.0%)	415 (78.0%)	
Unknown	135(5.7%)	41(5.4%)		46(6.5%)	33 (6.2%)	
Parametrial involvement			$<$ 0.001			0.222
Negative	2270(95.5%)	689(91.0%)		667 (94.9%)	496 (93.2%)	
Positive	108(4.5%)	68(9.0%)		36 (5.1%)	36(6.8%)	
Vaginal margin			0.025			0.381
Negative	2298(96.6%)	718(94.8%)		684 (97.3%)	513 (96.4%)	
Positive	80(3.4%)	39(5.2%)		19 (2.7%)	19 (3.6%)	
Para-aortic lymph node			$<$ 0.001			0.705
Negative	413(17.4%)	153(20.2%)		99 (14.1%)	84 (15.8%)	
Positive	13(0.5%)	63(8.3%)		8 (1.1%)	6 (1.1%)	
Unremoved	1952(82.1%)	541(71.5%)		596 (84.8%)	442(83.1%)	
LNR			$<$ 0.001			0.054
≤ 0.11	1716(72.2%)	30(4.0%)		63(9.0%)	32(6.0%)	
> 0.11	662(27.8%)	727(96.0%)		640(91.0%)	500(94.0%)	

LNR Lymph node ratio, nMLN Number of metastatic lymph nodes, PSM Propensity score matching, QM Querleu-Morrow

negative parametrial involvement, positive parametrial involvement correlated with worse 5-year DFS ($P < 0.001$) but not with OS ($P = 0.149$). Additionally, there were no effects of age, hysterectomy type, vaginal margin, or para-aortic lymph node metastasis on either 5-year OS or DFS ($P > 0.05$) (Table 3).

Comparison of oncological outcomes in nMLN ≤ 3 and nMLN > 3 groups

The Kaplan–Meier analysis revealed significant differences in survival between the nMLN ≤ 3 and nMLN > 3 groups with OS: 81.0% vs 66.0%, $P < 0.001$, and DFS: 70.3% vs 51.5%, $P < 0.001$ (pre-PSM); OS: 76.8% vs 67.9%,

Table 2 Clinicopathological characteristics of patients in the LNR ≤ 0.11 and LNR > 0.11 groups

Variables	pre-PSM		P	post-PSM		P
	LNR ≤ 0.11 group (n = 1748)	LNR > 0.11 group (n = 1387)		LNR ≤ 0.11 group (n = 1058)	LNR > 0.11 group (n = 629)	
Age (years)	48.22 ± 9.347	47.36 ± 9.310	0.719	47.94 ± 8.616	48.07 ± 8.672	0.735
Histological type			0.810			0.883
Squamous cell carcinoma	1542(88.2%)	1213(87.5%)		939(88.8%)	562 (89.4%)	
Adenocarcinoma	153(8.8%)	129(9.3%)		88(8.3%)	51(8.1%)	
Adenosquamous cell carcinoma	53(3.0%)	45(3.2%)		31(2.9%)	16(2.5%)	
Hysterectomy type			0.387			0.758
Type QM-B	1102(63.1%)	903(65.1%)		705(66.6%)	428(68.0%)	
Type QM-C1	9(0.5%)	8 (0.6%)		6(0.6%)	3 (0.5%)	
Type QM-C2	549(31.4%)	422(30.4%)		315(29.8%)	175(27.8%)	
Unknown	88(5.0%)	54 (3.9%)		32(3.0%)	23(3.7%)	
Tumor diameter(cm)			0.537			0.308
≤ 4	1012(57.9%)	788(56.8%)		612(57.8%)	357(56.8%)	
> 4	643(36.8%)	509(36.7%)		397(37.5%)	232(36.9%)	
Unknown	93(5.3%)	90(6.5%)		49(4.6%)	40(6.3%)	
Lymphovascular space invasion			< 0.001			0.821
negative	1168(66.8%)	816(58.8%)		694(65.6%)	416(66.1%)	
positive	580(33.2%)	571(41.2%)		364(34.4%)	213(33.9%)	
Cervical stromal invasion			0.180			0.849
≤ 1/2	308(17.6%)	212(15.3%)		173(16.3%)	109(17.3%)	
> 1/2	1347(77.1%)	1092(78.7%)		825(78.0%)	483(76.8%)	
Unknown	93(5.3%)	83(6.0%)		60(5.7%)	37(5.9%)	
Parametrial involvement			0.007			0.962
Negative	1667(95.4%)	1292(93.2%)		1007(95.2%)	599(95.2%)	
Positive	81(4.6%)	95(6.8%)		51(4.8%)	30(4.8%)	
Vaginal margin			0.947			0.786
Negative	1682(96.2%)	1334(96.2%)		1027(97.1%)	612(97.3%)	
Positive	66(3.8%)	53(3.8%)		31(2.9%)	17(2.7%)	
Para-aortic lymph node			< 0.001			0.416
Negative	343(19.6%)	223(16.1%)		136(12.9%)	89(14.1%)	
Positive	11(0.6%)	65(4.7%)		8(0.8%)	8(1.3%)	
Unremoved	1394(79.8%)	1099(79.2%)		914(86.3%)	532(84.6%)	
nMLN			< 0.001			0.052
≤ 3	1716(98.2%)	662(47.7%)		1029(97.3%)	600(95.4%)	
> 3	32(1.8%)	725(52.3%)		29(2.7%)	29(4.6%)	

LNR Lymph node ratio, nMLN Number of metastatic lymph nodes, PSM Propensity score matching, QM Querleu-Morrow

$P=0.003$ and DFS: 65.5% vs 55.3%, $P<0.001$ (post-PSM) (Fig. 2).

After PSM, the HRs for lower survival for the nMLN > 3 group were as follows, OS: 1.411, 95% CI: 1.108–1.798, $P=0.005$, and DFS: 1.428, 95% CI: 1.175–1.735, $P<0.001$. LNR > 0.11 was associated with a worse 5-year OS ($P=0.026$) but not DFS ($P=0.114$), compared to LNR ≤ 0.11. While adenocarcinoma correlated with worse 5-year DFS than squamous cell carcinoma ($P=0.047$) but not with OS ($P=0.129$), adenosquamous

cell carcinoma did not affect either 5-year OS or DFS ($P>0.05$). Compared to Type QM-B, Type QM-C2 was associated with poorer 5-year OS and DFS ($P<0.05$). However, Type QM-C1 and unknown hysterectomy types were not associated with worse 5-year OS or DFS ($P>0.05$). Compared to tumor diameter ≤ 4 cm, tumor diameter > 4 cm correlated with a worse 5-year OS ($P=0.035$) but not with DFS ($P=0.050$); unknown tumor diameter were not associated with worse 5-year OS or DFS ($P>0.05$). Cervical stromal invasion > 1/2

Table 3 Cox multivariate survival analysis of all patients (pre-PSM)

Variables	5-year OS			5-year DFS		
	HR	95%CI	P	HR	95%CI	P
Age(years)	1.006	0.997–1.015	0.197	1.001	0.994–1.008	0.729
nMLN						
≤ 3	1(Ref)	-	-	1(Ref)	-	-
> 3	1.437	1.155–1.789	0.001	1.468	1.228–1.754	<0.001
LNR						
≤ 0.11	1(Ref)	-	-	1(Ref)	-	-
> 0.11	1.454	1.181–1.790	<0.001	1.392	1.177–1.646	<0.001
Histological type			<0.001			<0.001
Squamous cell carcinoma	1(Ref)	-	-	1(Ref)	-	-
Adenocarcinoma	1.590	1.226–2.063	<0.001	1.498	1.217–1.845	<0.001
Adenosquamous cell carcinoma	1.779	1.177–2.690	0.006	1.398	0.974–2.007	0.069
Hysterectomy type			0.490			0.886
Type QM-B	1(Ref)	-	-	1(Ref)	-	-
Type QM-C1	0.636	0.158–2.564	0.524	1.035	0.892–1.201	0.648
Type QM-C2	1.102	0.917–1.325	0.300	1.045	0.431–2.531	0.923
Unknown	0.813	0.488–1.354	0.427	0.898	0.624–1.294	0.565
Tumor diameter(cm)			<0.001			<0.001
≤ 4	1(Ref)	-	-	1(Ref)	-	-
> 4	1.408	1.183–1.675	<0.001	1.365	1.187–1.569	<0.001
Unknown	1.424	1.023–1.981	0.036	1.474	1.137–1.913	0.003
Lymphovascular space invasion						
Negative	1(Ref)	-	-	1(Ref)	-	-
Positive	1.283	1.080–1.524	0.005	1.053	0.916–1.211	0.471
Cervical stromal invasion			0.001			<0.001
≤ 1/2	1(Ref)	-	-	1(Ref)	-	-
> 1/2	1.738	1.313–2.301	<0.001	1.581	1.278–1.957	<0.001
Unknown	1.593	1.019–2.491	0.041	1.391	0.980–1.975	0.065
Parametrial involvement						
Negative	1(Ref)	-	-	1(Ref)	-	-
Positive	1.275	0.917–1.773	0.149	1.562	1.223–1.995	<0.001
Vaginal margin						
Negative	1(Ref)	-	-	1(Ref)	-	-
Positive	1.090	0.731–1.626	0.673	1.324	0.987–1.777	0.061
Para-aortic lymph node			0.180			0.428
Negative	1(Ref)	-	-	1(Ref)	-	-
Positive	1.042	0.567–1.917	0.894	1.261	0.842–1.889	0.261
Unremoved	1.448	1.103–1.981	0.080	1.110	0.914–1.348	0.295

LNR Lymph node ratio, nMLN Number of metastatic lymph nodes, PSM Propensity score matching, QM Querleu-Morrow

correlated with a worse 5-year DFS ($P=0.035$) but not OS ($P=0.174$) compared to cervical stromal invasion $\leq 1/2$, while unknown cervical stromal invasion did not affect either 5-year OS or DFS ($P>0.05$). Positive parametrial involvement correlated with worse 5-year OS and DFS ($P<0.05$) when compared to negative parametrial involvement. Moreover, before and after PSM there were no effects of age, lymphovascular space invasion,

vaginal margin, or para-aortic lymph node metastasis on either 5-year OS or DFS ($P>0.05$) (Table 4).

Comparison of oncological outcomes in LNR ≤ 0.11 and LNR > 0.11 groups

The Kaplan–Meier analysis revealed significant differences in survival between the LNR ≤ 0.11 and LNR > 0.11 groups as follows: OS: 81.9% vs 70.6%, $P<0.001$, and DFS:

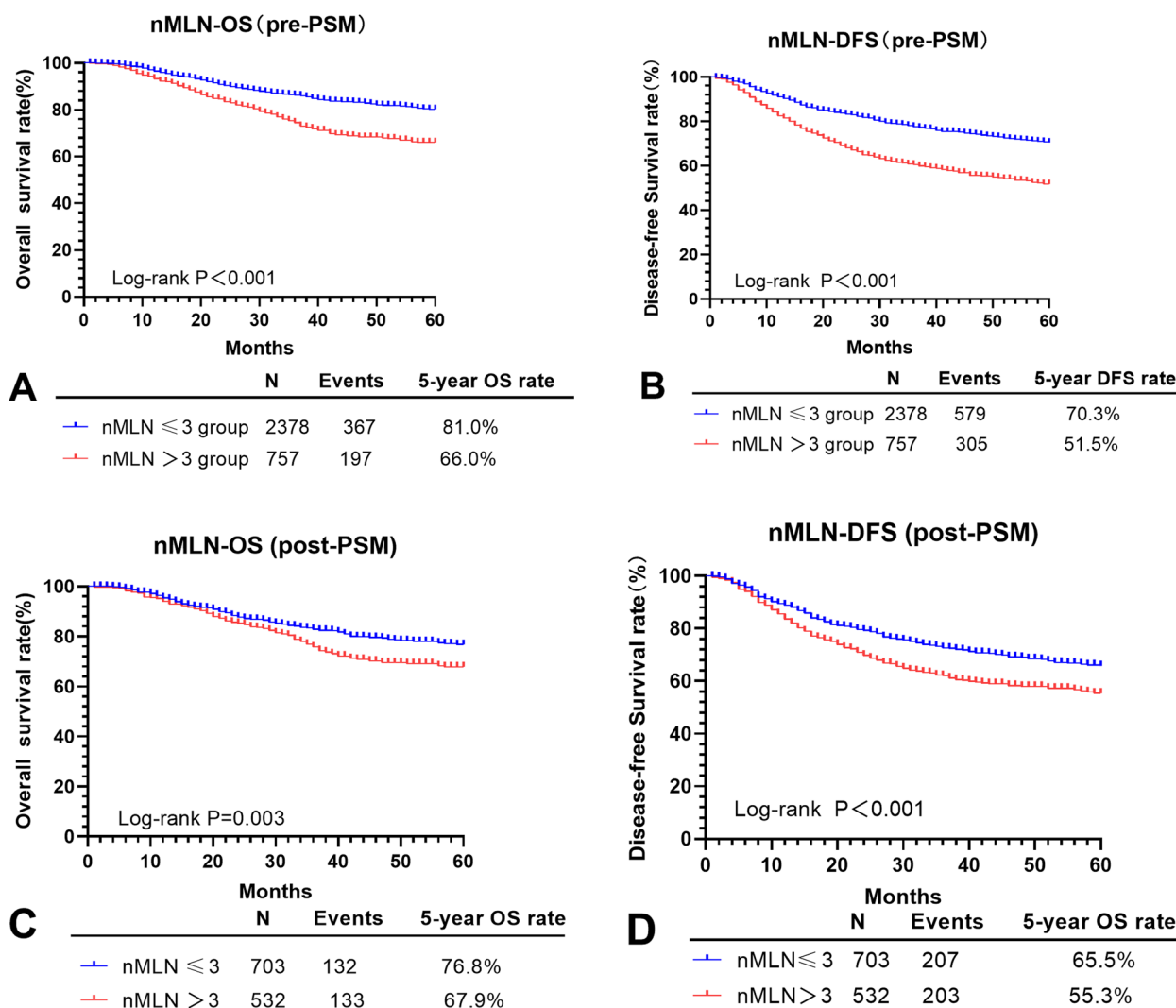


Fig. 2 OS and DFS of the patients in the nMLN ≤ 3 and nMLN > 3 groups

72.3% vs 57.9%, $P < 0.001$ (pre-PSM); OS: 82.5% vs 76.9%, $P = 0.010$; and DFS: 72.8% vs 65.1%, $P = 0.002$ (post-PSM) (Fig. 3).

After PSM, the HRs for lower survival for the LNR > 0.11 group were as follows, OS: 1.407, 95% CI: 1.103–1.794, $P = 0.006$, and DFS: 1.347, 95% CI: 1.110–1.633, $P = 0.002$. While adenocarcinoma correlated with a worse 5-year OS and DFS compared to squamous cell carcinoma ($P = 0.001$ and 0.110, respectively), adenosquamous cell carcinoma did not affect either the 5-year OS or DFS ($P > 0.05$). Tumor diameter > 4 cm correlated with a worse 5-year OS and DFS ($P = 0.013$ and 0.012, respectively) compared to tumor diameter ≤ 4 cm, while unknown tumor diameter did not affect either the 5-year OS or DFS ($P > 0.05$). Compared to cervical stromal invasion ≤ 1/2, cervical stromal invasion > 1/2 correlated with a worse 5-year OS and DFS ($P = 0.008$ and 0.001,

respectively), while unknown cervical stromal invasion did not affect either 5-year OS or DFS ($P > 0.05$). Positive parametrial involvement correlated with a worse 5-year OS and DFS ($P = 0.025$ and 0.001, respectively) compared to negative parametrial involvement. Compared to negative vaginal margins, positive vaginal margins correlated with a worse 5-year DFS ($P = 0.012$) but not with OS ($P = 0.889$). Additionally, before and after PSM there were no effects of age, nMLN, hysterectomy type, lymphovascular space invasion, or para-aortic lymph node metastasis on either 5-year OS or DFS ($P > 0.05$) (Table 5).

Discussion

Summary of main results

Metastatic lymph node is a poor prognostic indicator for CC [2–5]. The current study determined the impact of nMLN and LNR on survival outcomes in patients

Table 4 Cox multivariate survival analysis of patients in the nMLN ≤ 3 and nMLN > 3 groups (post-PSM)

Variables	5-year OS			5-year DFS		
	HR	95%CI	P	HR	95%CI	P
Age(years)	1.009	0.995–1.022	0.215	1.002	0.991–1.013	0.695
nMLN						
≤ 3	1(Ref)	-	-	1(Ref)	-	-
> 3	1.411	1.108–1.798	0.005	1.428	1.175–1.735	< 0.001
LNR						
≤ 0.11	1(Ref)	-	-	1(Ref)	-	-
> 0.11	2.168	1.096–4.287	0.026	1.436	0.917–2.249	0.114
Histological type			0.074			0.108
Squamous cell carcinoma	-	1(Ref)	-	-	-	-
Adenocarcinoma	1.377	0.911–2.080	0.129	1.385	1.004–1.910	0.047
Adenosquamous cell carcinoma	1.799	0.984–3.414	0.073	1.278	0.715–2.286	0.408
Hysterectomy type			0.055			0.087
Type QM-B	1(Ref)	-	-	1(Ref)	-	-
Type QM-C1	0.900	0.124–6.532	0.917	1.429	0.353–5.791	0.617
Type QM-C2	1.329	1.021–1.729	0.034	1.293	1.044–1.601	0.019
Unknown	0.457	0.168–1.241	0.124	0.845	0.478–1.492	0.561
Tumor diameter(cm)			0.094			0.066
≤ 4	1(Ref)	-	-	1(Ref)	-	-
> 4	1.320	1.020–1.708	0.035	1.232	1.000–1.516	0.050
Unknown	1.284	0.801–2.056	0.299	1.380	0.995–1.993	0.086
Lymphovascular space invasion						
Negative	1(Ref)	-	-	1(Ref)	-	-
Positive	1.280	0.998–1.643	0.052	0.960	0.782–1.179	0.699
Cervical stromal invasion			0.340			0.076
$\leq 1/2$	1(Ref)	-	-	1(Ref)	-	-
$> 1/2$	1.287	0.895–1.851	0.174	1.367	1.023–1.828	0.035
Unknown	1.057	0.565–1.978	0.862	1.083	0.662–1.773	0.751
Parametrial involvement						
Negative	1(Ref)	-	-	1(Ref)	-	-
Positive	1.772	1.111–2.825	0.016	1.805	1.245–2.618	0.002
Vaginal margin						
Negative	1(Ref)	-	-	1(Ref)	-	-
Positive	0.724	0.336–1.561	0.410	0.985	0.571–1.700	0.958
Para-aortic lymph node			0.198			0.511
Negative	1(Ref)	-	-	1(Ref)	-	-
Positive	1.848	0.538–6.345	0.329	1.612	0.633–4.108	0.317
Unremoved	1.480	0.951–2.302	0.082	1.141	0.837–1.556	0.403

LNR Lymph node ratio, nMLN number of metastatic lymph nodes, PSM Propensity score matching, QM Querleu-Morrow

with FIGO 2018 stage IIICp CC. We demonstrated that nMLN > 3 indicated a worse prognosis than nMLN ≤ 3 , while LNR > 0.11 was a poor prognostic indicator compared to LNR ≤ 0.11 .

Predictive value of the nMLN and LNR

The LN staging system based on nMLN has been extensively applied to breast, gastric, and rectal carcinomas

[21]. In CC, high nMLN is negatively correlated with prognosis [7–15]. While cut-off values for nMLN ranging from ≥ 2 to > 5 have been reported [10, 12–15], the optimal cut-off value is still being explored. Several studies have demonstrated that the prognosis of patients with only one metastatic lymph node was comparable to that of those without metastatic lymph nodes [12–14]. However, patients with ≥ 2 metastatic lymph nodes had

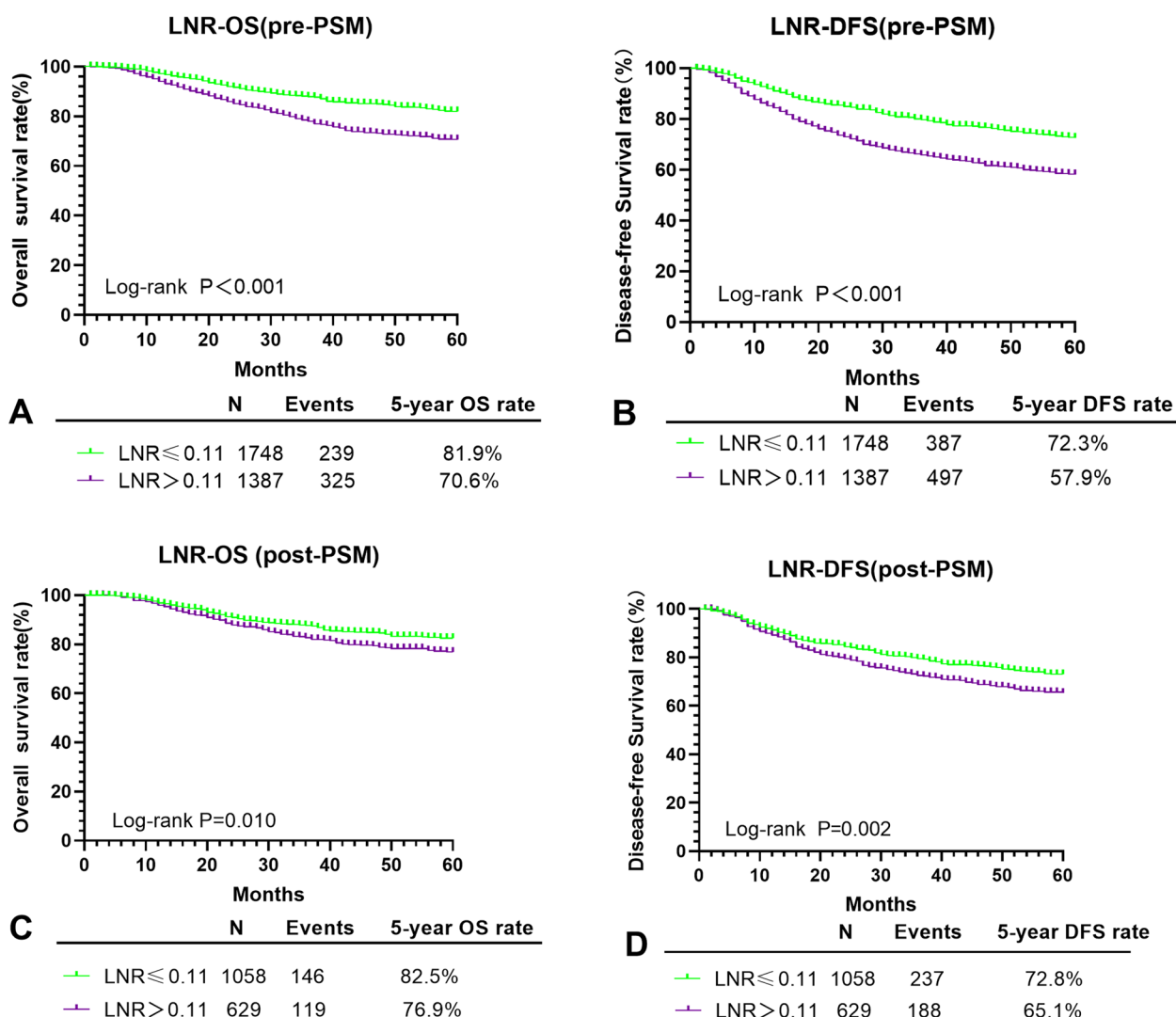


Fig. 3 OS and DFS of the patients in LNR ≤ 0.11 and LNR > 0.11 groups

poorer survival than those without an metastatic lymph node (87% vs 61%, $P < 0.001$) [14] and a worse 5-year DFS than those with 1–2 metastatic lymph nodes (54.7% vs 78.1%, $P = 0.006$) [10]. A 10-year multi-center study by Kwon et al. in Korea included 249 patients with FIGO 2009 stages IB–IIA CC, all of whom underwent radical hysterectomy with pelvic \pm para-aortic lymphadenectomy [7]. All patients had pathologically confirmed metastatic lymph node and underwent postoperative standardized adjuvant therapy. The mean number of removed LNs was 26 (range, 4–85), and the Evaluate Cut Points application was used to determine the cut-off values. Kwon et al. found that nMLN > 3 , lymphovascular space invasion, and non-squamous cell carcinoma were risk factors for poor distant metastasis-free survival and DFS in early-stage CC, while there was no significant survival difference between patients without an metastatic lymph node

and those with 1–3 metastatic lymph nodes [7]. Olthof et al. studied CC patients (FIGO 2009 stages IA2–IIA1) with metastatic lymph nodes diagnosed after radical hysterectomy and pelvic lymphadenectomy and demonstrated that nMLN ≥ 4 was independently associated with poor survival [15]. Another study by Inoue and Morita included CC patients (FIGO 2009 stages IB–IIB) with pathologically confirmed metastatic lymph node after radical hysterectomy and bilateral pelvic lymphadenectomy [12]. They concluded that the nMLN was a better prognostic factor than the presence of metastatic lymph node, with 5-year OS of 81%, 41%, and 23% in patients with 1, 2–3, and ≥ 4 metastatic lymph nodes, respectively ($P < 0.001$). Patients with ≥ 4 metastatic lymph nodes had markedly lower survival rates than those without any metastatic lymph node. Consistent with the studies by Kwon et al., Olthof et al., and Inoue and Morita, we

Table 5 Cox multivariate survival analysis of patients in the LNR ≤ 0.11 and LNR > 0.11 groups (post-PSM)

Variables	5-year OS			5-year DFS		
	HR	95%CI	P	HR	95%CI	P
Age(years)	1.011	0.996–1.025	0.149	1.008	0.997–1.020	0.141
nMLN						
≤ 3	1(Ref)	-	-	1(Ref)	-	-
> 3	0.945	0.459–1.947	0.879	1.334	0.831–2.144	0.233
LNR						
≤ 0.11	1(Ref)	-	-	1(Ref)	-	-
> 0.11	1.407	1.103–1.794	0.006	1.347	1.110–1.633	0.002
Histological type			0.004			0.032
Squamous cell carcinoma	1(Ref)	-	-	1(Ref)	-	-
Adenocarcinoma	1.860	1.289–2.683	0.001	1.500	1.104–2.039	0.010
Adenosquamous cell carcinoma	1.322	0.650–2.687	0.441	1.192	0.669–2.126	0.551
Hysterectomy type			0.055			0.784
Type QM-B	1(Ref)	-	-	1(Ref)	-	-
Type QM-C1	0.749	0.104–5.390	0.774	0.412	0.058–2.947	0.377
Type QM-C2	1.041	0.793–1.367	0.772	1.041	0.840–1.290	0.716
Unknown	0.560	0.205–1.525	0.257	0.900	0.487–1.664	0.737
Tumor diameter(cm)			0.023			0.020
≤ 4	1(Ref)	-	-	1(Ref)	-	-
> 4	1.383	1.072–1.785	0.013	1.297	1.060–1.587	0.012
Unknown	1.537	0.951–2.484	0.079	1.420	0.969–2.081	0.072
Lymphovascular space invasion						
Negative	1(Ref)	-	-	1(Ref)	-	-
Positive	1.089	0.839–1.414	0.520	0.849	0.687–1.049	0.130
Cervical stromal invasion			0.029			0.006
$\leq 1/2$	1(Ref)	-	-	1(Ref)	-	-
$> 1/2$	1.729	1.151–2.598	0.008	1.639	1.208–2.223	0.001
Unknown	1.771	0.958–3.275	0.068	1.405	0.855–2.310	0.180
Parametrial involvement						
Negative	1(Ref)	-	-	1(Ref)	-	-
Positive	1.720	1.071–2.760	0.025	1.859	1.291–2.678	0.001
Vaginal margin						
Negative	1(Ref)	-	-	1(Ref)	-	-
Positive	1.047	0.548–2.003	0.889	1.736	1.127–2.675	0.012
Para-aortic lymph node			0.257			0.899
Negative	1(Ref)	-	-	1(Ref)	-	-
Positive	0.926	0.213–4.029	0.918	1.245	0.491–3.157	0.645
Unremoved	1.431	0.913–2.243	0.118	1.023	0.753–1.391	0.883

LNR Lymph node ratio, nMLN Number of metastatic lymph nodes, PSM Propensity score matching, QM Querleu-Morrow

found that the nMLN > 3 group had a poorer prognosis than the nMLN ≤ 3 group [7, 12, 15]. All these studies included patients with similar stages of CC. While our study included patients with FIGO 2009 stages IA-IIB CC, Kwon et al., Inoue et al., and Olthof et al. studied those with FIGO 2009 stages IB-IIA, FIGO 2009 stages IB-IIB, and FIGO 2009 stages IA2-IIA1 CC [7, 12, 15]. Additionally, patients in all the studies underwent radical

hysterectomy with pelvic \pm para-aortic lymphadenectomy. Finally, the metastatic lymph nodes were diagnosed through postoperative pathological confirmation in all these studies. These factors also account for the inconsistent results from other studies.

The LNR is the ratio of the nMLN to the total number of removed LNs, which avoids the effects of confounding factors [29]. LNR is a newly validated predictor of CC,

however, the exact cut-off value for LNR remains unclear, with the values reported in the literature ranging from 0.05 to 0.2 [11, 15, 18–20, 23–26]. In a study by Aslan et al. [19] that included 138 patients with stage IIIC1 and 47 with stage IIIC2 CC, patients with $LNR < 0.05$ had better 5-year OS and DFS than those with $LNR \geq 0.05$ (OS: 80.6% vs 61.2%, $P=0.007$; DFS: 78.2% vs 48.4%, $P<0.001$). However, 23.2% of the patients underwent para-aortic lymphadenectomy, which limited the number of removed LNs (pelvic LNs > 10 and para-aortic LNs > 5). In another study on FIGO 2009 stage I or II CC, Fleming et al. [20] demonstrated that $LNR > 0.066$ was associated with poorer progression-free survival, whereas $LNR > 0.076$ was associated with poorer OS. However, only 95 patients were included in the study. Similar results were reported by Li et al. $LNR \geq 0.08$ was an independent prognostic factor for OS ($P=0.001$) [24]. Their study included 273 patients with FIGO 2018 stage IIICp CC; only a few received postoperative adjuvant therapy. Another study reported that CC patients with $LNR > 0.2$ had a 2.56-fold higher risk of poor OS and a 2.404-fold higher risk of poor DFS than those with $LNR < 0.2$ [18]. Their study, which included 198 squamous cell carcinoma patients (42.4% of whom without postoperative adjuvant therapy), showed that the LNR had a higher predictive value than the cervical stromal invasion depth [18]. Several studies have reported cut-off values of LNR comparable to the value (0.11) in the current study [11, 15, 23, 25]. In a study including 80 patients with CC and metastatic lymph nodes (FIGO 2009 stages IIB to IVA) who underwent concurrent platinum-based radiotherapy after surgical staging, Polterauer et al. [23] concluded that $LNR > 0.1$ was an independent factor associated with poor DFS and OS ($P=0.01$). Chen et al. [25] studied 120 CC patients with metastatic lymph nodes (FIGO 2009 stages IA2 to IIB) and found that patients with $LNR > 0.1$ had markedly poorer 5-year OS than those with $LNR \leq 0.1$ (42.9% and 11.8%, respectively). In addition, as a prognostic evaluator, LNR was verified to be superior to nMLN. In Chen's study, 75% of the patients received neoadjuvant chemotherapy before surgery. Guo et al. [11] showed that for squamous cell carcinoma patients with FIGO 2018 stage IIIC CC (928IIIC1/97IIIC2), the $LNR > 0.16$ was an independent risk factor. The stage was confirmed by radical abdominal hysterectomy, pelvic lymphadenectomy, bilateral salpingo-oophorectomy, and para-aortic lymphadenectomy. Additionally, Olthof et al. [15] found that $LNR \geq 0.177$ was associated with a poorer 5-year OS compared with $LNR < 0.177$.

The accuracy of imaging such as computed tomography, magnetic resonance imaging, and positron emission tomography for the diagnosis of metastatic lymph node requires further improvement [30]. The sensitivity and

specificity of computed tomography were 57% and 91%, magnetic resonance imaging were 52% and 94%, and positron emission tomography were 66% and 97%, respectively [31]. Therefore, pathological confirmation appears to be the most accurate criterion for assessing LN status [32]. Meanwhile, laparoscopic treatment of CC has shown that minimally invasive radical hysterectomy has a worse prognosis than open surgery [33]. Therefore, only patients who underwent open surgery and had pathologically confirmed metastatic lymph node were included in the current study. Currently, there is no definitive opinion on the minimum number of LNs that should be removed during lymphadenectomy. In 2009, the European Organization for Research and Treatment of Cancer proposed a standard of 11 LNs to be removed during surgery for CC [34]. However, according to the European Society of Gynecologic Oncology Quality Indicators for the Management of Cervical Cancer Surgery, there is no specific recommendation regarding the number of LNs to be removed during lymphadenectomy [35]. Therefore, the number of LNs removed was not limited in this study. Theoretically, the higher the number of examined LNs, the higher the value of the assessment of LN status [36]. The number of examined metastatic lymph nodes positively correlates with the number of removed LNs [7, 37]. Therefore, inconsistencies in the cut-off values of nMLN and LNR may be due to the diagnosis of metastatic lymph node and number of removed LNs.

Predictive value of other prognostic predictors

The prognostic risk factors for CC include both high-risk and intermediate-risk factors. Pelvic LN metastasis, parametrial involvement, and positive vaginal margin represent the main high-risk factors, while the intermediate-risk ones include lymphovascular space invasion, deep cervical stromal invasion, and tumor diameter > 4 cm [38, 39]. A meta-analysis by Huang et al. [39] demonstrated a significant association between deep cervical stromal invasion, parametrial involvement, lymphovascular space invasion, tumor diameter, age, and pelvic LN metastasis. A report by Salvo et al. [40] disputed this, claiming that only the effect of metastatic LN was considered in cases of stage IIIC diseases, without any consideration given to factors such as tumor diameter or parametrial, vaginal, and ovarian invasion. The present study revealed that, in addition to nMLN and LNR, adenocarcinoma, adenosquamous cell carcinoma, lymphovascular space invasion, tumor diameter > 4 cm, cervical stromal invasion $> 1/2$, positive vaginal margin, and positive parametrial involvement were significant prognostic predictors—which is in agreement with the results of the above two studies.

The most common CC tissue type is squamous carcinoma (75%), followed by adenocarcinoma (10–25%), with other types (including adenosquamous carcinoma) being far less frequent (<5%) [41]. Hence, we were only able to analyze small number of adenosquamous carcinoma cases in this study. Some studies have suggested that tissue type correlates with prognosis [42–45]. Nakanishi et al. and Kodama et al. [44, 45] both demonstrated that LN metastasis can influence outcomes, being associated with a significantly worse prognosis for adenocarcinoma than for squamous cell carcinoma. A study on stage IIIC disease also showed that the prognoses of adenocarcinoma and adenosquamous cell carcinoma were worse than that of squamous carcinoma [43]. In this study, both adenocarcinoma (OS HR: 1.590, 95% CI: 1.226–2.063, $P < 0.001$; DFS HR: 1.498, 95% CI: 1.217–1.845, $P < 0.001$) and adenosquamous cell carcinoma (OS HR: 1.779, 95% CI: 1.177–2.690, $P = 0.006$) had worse prognoses than squamous cell carcinoma before PSM. After PSM only adenocarcinoma had a worse prognosis than squamous carcinoma (DFS HR: 1.385, 95% CI: 1.004–1.910, $P = 0.047$ in the $nMLN \leq 3$ and $nMLN > 3$ groups; OS HR: 1.860, 95% CI: 1.289–2.683, $P = 0.001$; DFS HR: 1.500, 95% CI: 1.104–2.039, $P = 0.010$ in the $LNR \leq 0.11$ and $LNR > 0.11$ groups), which may be related to the lower number of adenosquamous cell carcinoma cases in these groups after PSM.

Lymphovascular space invasion manifests as one or more clusters of tumor cells in the interstitial space (ie., the lymphatic or vascular interstitial space) surrounded by endothelial cells, suggesting invasion of tumor cells into blood and lymphatic vessels. These tumor cells may spread and implant at other sites throughout surrounding blood or lymphatic vessels, leading to tumor metastasis. However, current studies on the relationship between lymphovascular space invasion and prognosis are conflicting. Kwon et al. and Widschwendter et al. both showed that lymphovascular space invasion strongly correlated with LN metastasis and resulted in a poor prognosis in cases of CC [7, 22]. However, a study by Wang et al. [46] reported that this phenomenon was an independent predictor of pelvic LN metastasis, but that there is currently no evidence to suggest that it can guide early-stage CC prognosis. However, that study also included cases without metastatic LN. In this study, lymphovascular space invasion correlated with lower OS (OS HR: 1.283, 95% CI: 1.080–1.524, $P = 0.005$) before PSM, but not afterward. Therefore, the relationship between lymphovascular space invasion and prognosis in stage IIIC merits further investigation through prospective studies.

Tumor size was found to be positively associated with pelvic LN metastasis, as a tumor diameter of >4 cm increased the rate of pelvic LN metastasis by as much as

as 43.5%. Tumor diameter was also found to correlate significantly with prognosis [47]. In their study, Park et al. confirmed that a tumor diameter of >4 cm had a significant impact on patient prognoses [48]. In this study, a tumor diameter of >CI: 1.1111–2.8254 cm was associated with poorer prognosis (OS HR: 1.408, 95% CI: 1.183–1.675, $P < 0.001$; DFS HR: 1.365, 95% CI: 1.187–1.569, $P < 0.001$ pre-PSM; post-PSM, in the $nMLN \leq 3$ and $nMLN > 3$ groups, OS HR: 1.320, 95% CI: 1.020–1.708, $P = 0.035$; in the $LNR \leq 0.11$ and $LNR > 0.11$ groups, OS HR: 1.383, 95% CI: 1.072–1.785, $P = 0.013$; DFS HR: 1.297, 95% CI: 1.060–1.587, $P = 0.012$). It is therefore possible that increased tumor size correlates with increased risk of parametrial involvement and LN metastasis, as well as decreased survival [49].

Paracervical lymphoid tissue is abundant. The paracervix represents the first site of extracervical dissemination, and parametrial involvement tends to lead to LN metastasis. Nanthamongkolkul et al. suggested that deep parametrial involvement and deep cervical stromal invasion correlated with LN metastasis, resulting in a decreased survival rate [50, 51]. This study also found that positive parametrial involvement correlated with poorer prognoses (DFS HR: 1.562, 95% CI: 1.223–1.995, $P < 0.001$ pre-PSM; post-PSM, in the $nMLN \leq 3$ and $nMLN > 3$ groups, OS HR: 1.772, 95% CI: 1.1111–2.825, $P = 0.016$; DFS HR: 1.805, 95% CI: 1.245–2.618, $P = 0.002$; in the $LNR \leq 0.11$ and $LNR > 0.11$ groups, OS HR: 1.720, 95% CI: 1.071–2.760, $P = 0.025$; DFS HR: 1.859, 95% CI: 1.291–2.678, $P = 0.001$). A cervical stromal invasion of >1/2 also correlated with poorer prognosis compared to $\leq 1/2$ (OS HR: 1.738, 95% CI: 1.313–2.301, $P < 0.001$; DFS HR: 1.581, 95% CI: 1.278–1.957, $P < 0.001$ pre-PSM; post-PSM, in the $nMLN \leq 3$ and $nMLN > 3$ groups, DFS HR: 1.367, 95% CI: 1.023–1.828, $P = 0.035$; in the $LNR \leq 0.11$ and $LNR > 0.11$ groups, OS HR: 1.729, 95% CI: 1.151–2.598, $P = 0.008$; DFS HR: 1.639, 95% CI: 1.208–2.223, $P = 0.001$).

Surgical staging of CC is currently based on Querleu-Morrow (QM) staging, which is divided into four major categories: A, B (B1, B2), C (C1, C2), and D (D1, D2). The standard surgical procedure for CC is radical hysterectomy accompanied by possible pelvic and para-aortic lymphadenectomy. Radical hysterectomies are staged according to QM as type QM-C2. Type QM-C2 hysterectomies involve the removal of the entire parametrium and pelvic autonomic nerves, which can lead to significant complications [52]. In contrast, type QM-B hysterectomies involve relatively narrow resections that may reduce complications, potentially with similar therapeutic outcomes to those of type QM-C [53]. A study by Chen et al. [54], which analyzed data from 9135 CC cases, showed that, before PSM, patients who underwent type QM-C2 hysterectomies had lower 5-year OS

(89.5 vs 92.0%, HR: 1.393) and DFS (84.3 vs 87.4%, HR: 1.342) rates compared to those who underwent type QM-B ones. After PSM, there was no difference in OS between the two groups, but the 5-year DFS was lower in the patients who underwent type QM-C2 procedures (82.1 vs 84.8%, HR: 1.144). Therefore, type Q-MB hysterectomies may be useful for the treatment of stage IA1 (lymphovascular space invasion)-IIA2 CCs. In this study, only patients in the $nMLN \leq 3$ and $nMLN > 3$ groups who underwent type QM-C2 hysterectomies had poorer prognoses than those who had type QM-B procedures, after PSM (OS HR: 1.329, 95% CI: 1.021–1.729, $P=0.034$; DFS HR: 1.293, 95% CI: 1.044–1.601, $P=0.019$). That study by Chen et al. included patients without LN metastasis, whereas all patients in the present study had LN metastasis, which may explain the differences in the results obtained between the two studies. Whether type QM-B hysterectomy procedures can be effectively used to treat stage IIIC malignancies merits further exploration.

Strengths and weaknesses

The strength of the current study is that it includes real-world data using a large sample size from a developing country with a high prevalence of CC. In addition, we accurately calculated the cut-off values using ROC curves. The effect of intra-group baseline differences was reduced using the statistically accepted PSM. However, due to the retrospective nature of the analysis, the current study has certain limitations. First, retrospective studies do not allow for rigorous screening of study subjects, resulting in significant population heterogeneity in the study cohort. Second, all patients in this study received standard postoperative adjuvant therapy; however, detailed adjuvant regimens, drug doses, and radiation doses were not differentiated. All of these factors may have had an impact on survival rates. Third, inter-institutional heterogeneity might exist, especially in surgical techniques, despite the two institutions sharing training programs for gynecologic oncologists. Finally, the high number of cases without para-aortic lymphadenectomy and the lack of metastasis-related information such as metastatic lesions, para-aortic or pelvic topography, type of LN metastasis (size, micrometastasis) etc., as well as the lack of detailed protocols for the evaluation of LN by the pathologists and information on the status of HPV infection may have led to some bias in our results.

Implications for practice and future research

In conclusion, for patients with FIGO 2018 stage IIICp CC, $nMLN > 3$ and $LNR > 0.11$ appeared to be associated with inferior oncological outcomes. In clinical

practice, patients with FIGO 2018 stage IIICp CC need to be staged and appropriately treated to stratify the survival risk according to the impact of the $nMLNs$ and LNR . A multi-center, large-sample prospective study is needed to further confirm the results of the current study.

Conclusions

Patients with $nMLN > 3$ have a worse prognosis than those with $nMLN \leq 3$, while patients with $LNR > 0.11$ have a poorer prognosis than those with $LNR \leq 0.11$. Treatment and management of patients with FIGO 2018 stage IIICp CC need to be differentiated by $nMLN$ and LNR .

Abbreviations

ARH	Abdominal radical hysterectomy
CC	Cervical cancer
CI	Confidence intervals
DFS	Disease-free survival
FIGO	International Federation of Gynecology and Obstetrics
HR	Hazard ratio
LN	Lymph node
LNR	Lymph node ratio
$nMLN$	Number of metastatic lymph nodes
OS	Overall survival
PSM	Propensity score matching
QM	Querleu-Morrow
ROC	Receiver operating characteristic

Supplementary Information

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Supplementary Material 1.

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Registry and the registration No. of the Study/Trial

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Authors' contributions

All authors approved the final version of the study. Yanna Ye and Rui Lian contributed equally to the work. Yanna Ye conceptualized, engineered, and monitored the study, construed data, and formulated and amended the manuscript. Rui Lian conceived and implemented the literature search, performed the data analysis and interpretation, and developed and refined the manuscript. Zhiqiang Li conceptualized and engineered the study, and gathered and explained the data. Xiaolin Chen explained the data and developed and refined the manuscript. Yahong Huang conducted the documentation search, analyzed and interpreted data, and drew graphs and figures. Jilong Yao and Anwei Lu provided resources, performed the data analysis and interpretation, and validation and participated in writing the original draft of the manuscript. Jinghe Lang orchestrated this study. Ping Liu and Chunlin Chen conceived of, designed, and supervised the study. All authors contributed to editorial changes in the manuscript.

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Availability of data and materials

Data supporting the findings of this study are available upon request from the corresponding authors. The data are not publicly available because of privacy and ethical restrictions. These data are also related to unpublished studies. However, these data involve privacy issues for some patients and are not publicly shared.

Declarations**Ethics approval and consent to participate**

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki of 1964. And it was approved by the Ethics Committee of the Nanfang Hospital of Southern Medical University (approval number NFEC-2017-135), who deemed that written informed consent was not necessary owing to the retrospective nature of the research and the concealment of patient information.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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