Original Article

Lymph node ratio predicts prognosis in patients with surgically resected invasive pancreatic cystic neoplasms

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Background: In current days, the prevalence of pancreatic cystic neoplasms (PCN) is on the rise. Lymph node ratio (LNR) has emerged as a promising prognostic factor in pancreatic adenocarcinoma (PDAC). However, the prognostic value of LNR in patients with invasive PCN remains unknown.

Methods: We used Surveillance, Epidemiology, and End Results (SEER) database to retrieve the baseline characteristics and clinical tumor variables of patients diagnosed with PCN between 1988 and 2014. Survival analyses were performed using the Kaplan-Meier method. Univariate and multivariate analyses were performed to identify factors associated with patient prognosis.

Results: A total of 10,656 PCN cases were initially identified. Based on our exclusion criteria, our analyses included data from 1246 cases, of which 479 were patients with lymph node involvement. Patients with high LNR had shorter overall survival (OS) than patients with low LNR (median OS, 13 *vs.* 21 months; P=0). Our univariate and multivariate analyses identified LNR (P=0) and grade (P=0.010) as independent prognostic factors in patients with invasive PCN.

Conclusions: Our findings suggest that LNR is a reliable, independent prognostic factor in patients with invasive PCN, strongly associated with OS and cancer-specific survival (CSS). LNR may represent a promising prognostic factor alternative to the AJCC (the American Joint Committee on Cancer) N stage in patients with node-positive PCN.

Keywords: Pancreatic cystic neoplasms (PCNs); Lymph node ratio (LNR); SEER database

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Introduction

The prevalence of pancreatic cystic neoplasms (PCNs) is on the rise (1). Although the current AJCC (the American Joint Committee on Cancer) lymph node (N) staging guidelines take into account lymph node involvement, it does not consider the number of lymph nodes removed or the fraction of the positive nodes.

Lymph node ratio (LNR) is a measure of the number of positive regional lymph nodes (RNP) relative to the number of regional nodes examined (RNE). For pancreatic ductal

adenocarcinoma (PDAC) patients with metastatic lymph nodes, LNR appears to be associated with prognosis (2-7). Moreover, in a single-center retrospective study, Partelli *et al.* (8) found that high LNR was associated with poor prognosis in patients with invasive intraductal papillary mucinous neoplasms (IPMN). However, the prognostic value of LNR in patients with invasive PCN remains unknown.

The aim of this study is to evaluate the relationship between LNR and the survival of patients with intraductal papillary mucinous neoplasms (IPMN), mucinous cystic neoplasms (MCN), serous cystadenomas (SCN), and solid pseudopapillary neoplasms (SPN), which are the most common types of invasive PCN (9,10).

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-1355).

Methods

Patients

Data from PCN patients (including IPMN, SPN, MCN, and SCN) from 1988 to 2014 were obtained from the publicly available Surveillance, Epidemiology, and End Results (SEER) database using SEER Stat software (version 8.3.4) (https://seer.cancer.gov/).

Patients were diagnosed with invasive IPMN, SPN, MCN, and SCN based on pancreatic location and the International Classification of Disease for Oncology, 3rd Edition (ICD-O-3) histological classification. The following data were retrieved from the SEER database: baseline demographic characteristics (age, diagnosis year, race, sex, and marital status), clinical tumor variables (tumor location, tumor size, histological types, RNE, RNP, metastasis, and grade), surgical procedures (total pancreatectomy or other) and survival time (from diagnosis to last follow - up or the date of death). Living patients or those lost to follow-up were right-censored for the overall survival (OS) analysis. Patients whose death was not related to PCN were right-censored for the cancer-specific survival (CSS) analysis. The LNR was defined as the number of RNP divided by the number of RNE (RNP/RNE). The detailed process of data extraction is shown in *Figure 1*. Since only one SCN case remained based on our exclusion criteria, MCN and SCN cases were grouped together. The relationships between LNR and survival outcomes were analyzed for the entire cohort, node-negative cases, and node-positive cases.

Continuous variables were reported using median with 25th and 75th percentiles. Kaplan-Meier method, log-rank test, likelihood ratio test, and Cox proportional hazard models were used in univariate and multivariate analysis as appropriate to investigate the associations between the endpoints and the risk factors. Continuous variables, such as the year of diagnosis and RNE, were divided into four equal-sized groups based on numbers of patients and the prior studies (11). Age at diagnosis was split into two groups by 65 years.

Survival analysis of patients grouped according to tumor size, defined using the pancreatic cancer AJCC T stage (8^{th} edition), was performed using the Kaplan-Meier method (*Figure S1*). Regional lymph node staging was based on the AJCC N staging (8^{th} edition) system. RNP and LNR cases were divided into three groups: patients without lymph node involvement and two equal-sized groups of patients with lymph node involvement. Cases were groups based on the LNR as follows: LNR A, no nodal involvement; LNR B, ≤20%, and LNR C, >20% (*Table 1*).

Statistical analysis

Continuous variables were compared using the Student's *t*-test, whereas categorical variables were compared using the Chi-square test. OS and CSS survival analyses were performed using the Kaplan-Meier method, and comparisons were performed using the log-rank test. Multivariate regression analysis was performed using the Cox proportional hazards model and a backward-elimination procedure with all possible confounders. Factors that demonstrated statistically significant ($P<0.05$) association with OS were included in the final analysis. All statistical analyses were performed using the SPSS software (version 20.0, SPSS Inc., Chicago, IL, USA). All P values are 2-sided; P values <0.05 were considered statistically significant.

Results

Demographic and tumor characteristics of the study population

Data from 1,246 patients who met the inclusion criteria were included in this study (*Figure 1*). The baseline patient characteristics and tumor features are summarized in *Table 2*. More than 60% of patients (n=767) had no regional lymph node involvement (N0) and 38% (n=479) had at least one

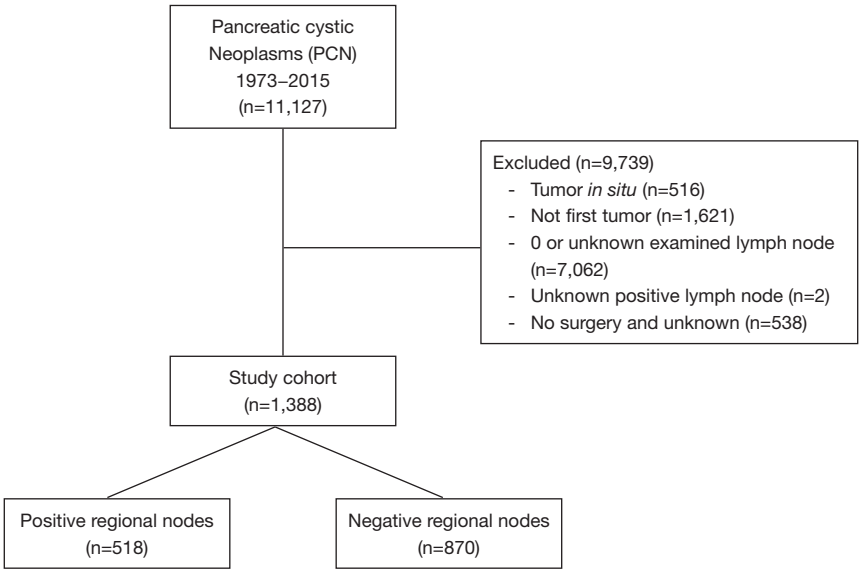

Figure 1 Schematic representation of data extraction from the SEER database. SEER: Surveillance, Epidemiology, and End Results database.

Table 1 Grouping of continuous variables

Variable	Group
LNR Group	0
	≤20%
	>20%
Year interval	1998–2004
	2005–2009
	2010–2014
Age group	≤65
	>65
RNE	1–5
	6–10
	11–16
	≥17
RNP	0
	1–2
	≥3

LNR, lymph node ratio; RNP, the number of positive regional lymph nodes; RNE, regional nodes examined.

positive lymph node. The median number of positive lymph nodes in LNR B and LNR C groups was one and four lymph nodes, respectively. There were no significant differences in the baseline characteristics of patients in groups LNR B and LNR C. A high LNR was associated with poor patient survival (median survival time, 13 *vs.* 21 months; P=0), lower RNE (median, 11 *vs.* 15 nodes; P=0), and a higher number of positive lymph nodes (median, 4 *vs.* 1 node; P=0). Since the characteristics of different invasive PCN types might vary, we also compared the patient characteristics and pathological findings, including lymph node status, for each PCN type (*Table 3*).

Kaplan-Meier survival analysis

The results of Kaplan-Meier survival analyses are shown in *Figure 2*. There were remarkable differences in the OS and CSS among the different LNR groups. However, the survival of patients with N1 and N2 stage cancer did not differ significantly, suggesting that LNR may be a better prognostic indicator than the AJCC N stage for PCN patients with regional lymph nodes involvement. High RNE was associated with longer survival time in RNP patients but not in the entire cohort (*Figure 3*). Furthermore, there was an inverse association between RNE and LNR (*Tables 2*,*3*).

Univariate and multivariate survival analysis

To further investigate the impact of RNE, RNP, and LNR on prognosis, we conducted univariable and multivariable

Table 2 Demographic and tumor characteristics of the study populations

	LNR			Total	P (LNR B *vs.* LNR C)	P total
	A	B	C			
Patients	767	239	240	1,246		
Age	64 [55–72]	66 [58–73]	64 [54–72]	63 [50–72]	0.069	0.005
RNE	22 [16–30]	15 [10–22]	11 [6–17]	9 [4–16]	0.000	0.000
RNP	0	1 [1–2]	4 [2–6]	0 [0–1]	0.000	0.000
LNR (%)	0	10.5 [6.3–14.8]	42.5 [28.6–60]	0 [0–14.3%]	0.000	0.000
Survival months	37 [14–79]	21 [11–37]	13 [6–22]	25 [10–61]	0.000	0.000
Year interval					0.101	0.009
1988–2000	237	82	104	423		
2001–2007	262	79	74	415		
2008–2014	268	78	62	408		
Race					0.944	0.137
White	606	199	202	1007		
Black	68	22	20	110		
Other	93	18	18	129		
Age group					0.061	0.069
≤65	424	133	113	670		
>65	343	106	127	576		
Sex					0.218	0.028
Male	341	116	130	587		
Female	426	123	110	659		
Marital status					0.87	0.483
Married	455	149	152	756		
Other	277	81	80	438		
NA	35	9	8	52		
Histologic type					0.371	0.000
IPMN	530	211	209	950		
MCN/SCN	136	23	29	188		
SPN	101	5	2	108		
Tumor site					0.027	0.000
Pancreatic head	389	150	171	710		
Pancreatic body & tail	245	51	44	340		
Other	28	5	7	40		
Overlapping	52	21	7	80		
NA	53	12	11	76		

Table 2 (*continued*)

Table 2 (*continued*)

	LNR			Total	P (LNR B *vs.* LNR C)	P total
	A	B	C			
Surgery type					0.362	0.553
TP	101	38	32	171		
PP	666	201	208	1,075		
T stage					0.666	0.000
T1	186	28	25	239		
T2	204	87	99	390		
T3	353	113	103	569		
T4	24	11	13	48		
RNE4					0.000	0.000
1–5	235	10	65	310		
6–10	179	58	66	303		
11–16	178	62	58	298		
≥17	175	109	51	335		
RNP2					0.000	0.000
0	767	0	0	767		
1	0	163	77	240		
2	0	76	163	239		
N stage					0.000	0.000
N0	767	0	0	767		
N1	0	220	112	332		
N2	0	19	128	147		
Metastasis					0.136	0.032
M0	542	173	138	853		
M1	27	11	16	54		
NA	198	55	86	339		
Grade					0.368	0.000
Grade I	188	39	31	258		
Grade II	220	97	101	418		
Grade III, IV	81	64	77	222		

LNR, lymph node ratio; RNP, the number of positive regional lymph nodes; RNE, regional nodes examined; LNR A, 0; LNR B, ≤0.2; LNR C, >0.2.

Table 3 Comparison between RNE and the LNR

	RNE			
	1–5 lymph nodes	6–10 lymph nodes	11–16 lymph nodes	≥17 lymph nodes
LNR (%)	50 (25.0–100)	25 (14.3–43.7)	20 (8.3–33.3)	11.1(5.3–23.5)

RNE, regional nodes examined; LNR, lymph node ratio.

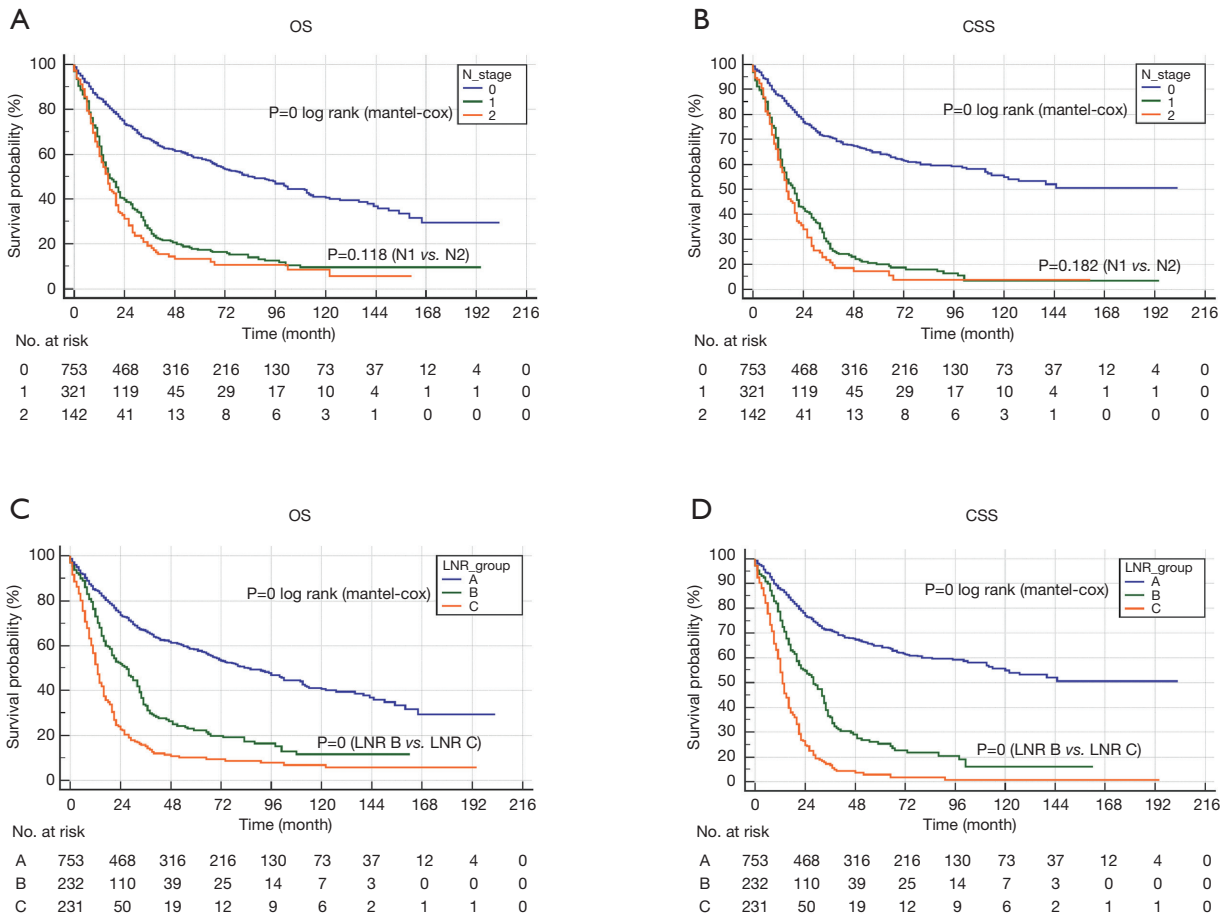

Figure 2 Survival analysis of PCN patients based on the N stage and LNR using the Kaplan-Meier method. (A,B) Compared with node-positive patients, patients with N0 stage exhibited improved OS (P=0) and CSS (P=0). No differences in OS (P=0.118) and CSS (P=0.182) were observed between N1 and N2 patients. (C,D) OS and CSS of PCN patients based on LNR. PCN, pancreatic cystic neoplasms; LNR, Lymph node ratio; OS, overall survival; CSS, cancer-specific survival.

analyses in the entire cohort (*Table 4*) and RNP patients (*Table 5*). The factors significantly associated with OS in univariate analysis were adjusted for multivariate analysis; we identified LNR as a significant factor associated with poor OS, both for RNP patients and the entire cohort. These findings suggest LNR as an independent prognostic factor of poor survival in PCN.

Discussion

Although the prevalence of PCN is on the rise (12), large PCN cohort studies are limited (13), and the factors affecting invasive PCN outcomes remain unclear. In this study, we found that the AJCC N staging could not predict survival in node-positive PCN patients who underwent

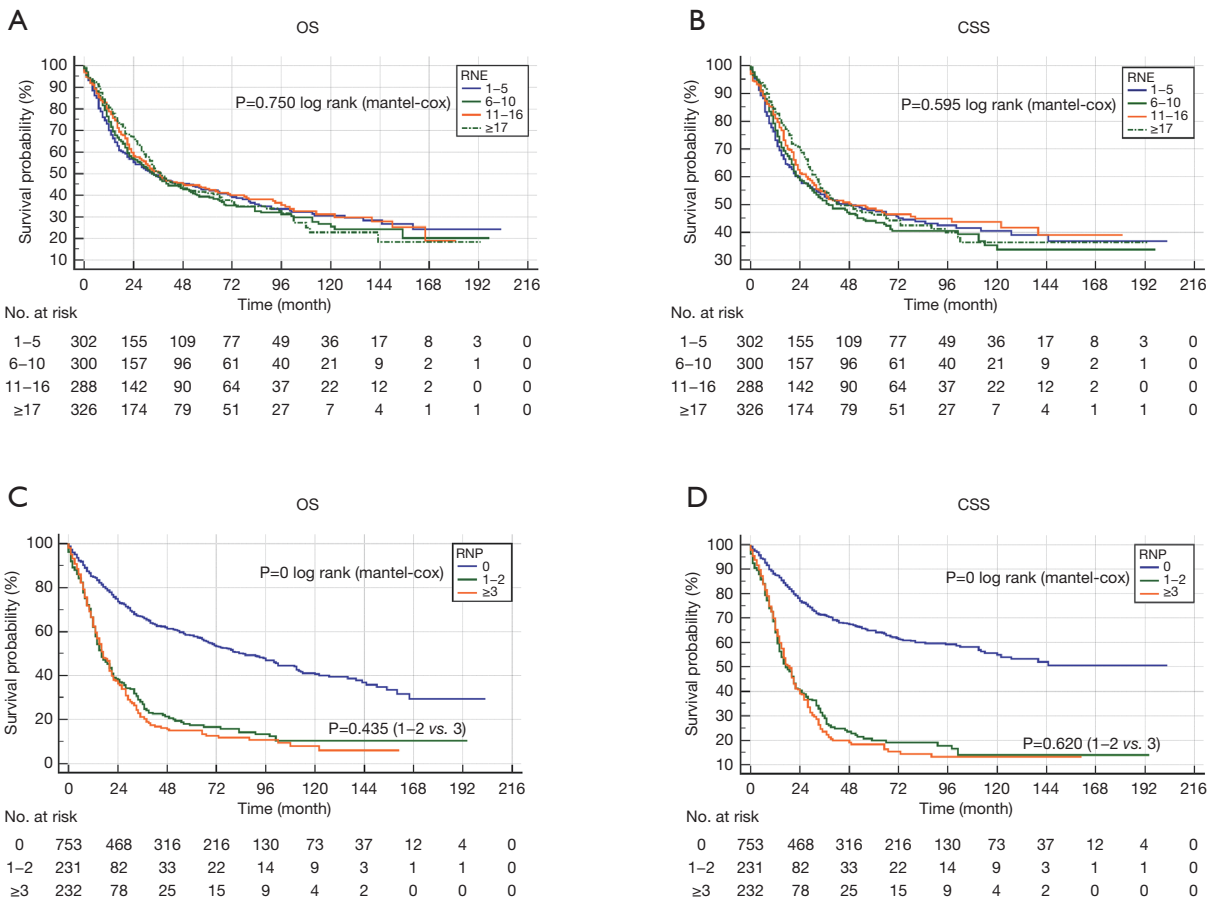

Figure 3 Survival analysis of RNE and RNP group. RNP, the number of positive regional lymph nodes; RNE, regional nodes examined.

surgery (*Figure 2*). Lymph node involvement is one of the main factors predicting survival in various cancers. A large cohort study involving 15,809 PDAC patients demonstrated that combined RNP with RNE predicted survival more accurately than a single factor (3). Studies on gastrointestinal tumors have also shown that LNR is an important prognostic factor (7,14-18). For PDAC patients with N1 disease, LNR also appears to be associated with prognosis (2-6,19). Additionally, a retrospective study demonstrated that LNR was a robust prognostic predictor after invasive IPMN resection (8).

In this study, we analyzed the ability of LNR to predict survival in patients with invasive PCNs. For the entire cohort, univariate and multivariate analyses revealed that higher T stage, metastasis, high tumor grade, and LNR were associated with worse prognosis, corroborating previous findings (13). Intriguingly, RNP and RNE were not independent prognostic factors, even though the AJCC N stage and RNE were previously reported to predict patient outcomes (3,11,20).

In node-positive patients, we found no differences in the survival of patients with N1 and N2 stage disease (*Figure 2*). The 5-year OS of patients with positive lymph nodes was 16.2%, similar to prior studies (11,13). Additionally, the 5-year OS of patients with N1 and N2 stage disease was 17.4% and 13.4%, respectively. Notably, the 5-year OS of patients in LNR B and LNR C groups was 22.2% and 10.3%, respectively. Furthermore, we found profound differences in the survival of patients in the LNR B and LNR C group (*Figure 2*). Univariate and multivariate analyses revealed that LNR was a robust independent prognostic indicator. Importantly, a high LNR was associated with poor survival in patients with invasive PCN, both in the entire cohort and node-positive PCN patients. Compared with the AJCC N stage, LNR provided a more accurate survival prediction in node-positive PCN patients.

Table 4 Univariate and multivariate analysis in all patients

	Univariate analysis				Multivariate analysis			
	P	Hazard ratio	95.0% CI		P	Hazard ratio	95.0% CI	
			Lower	Upper			Lower	Upper
LNR group	0.000				0.000			
LNR A	Ref				Ref			
LNR B	0.000	2.386	2.003	2.842	0.000	2.055	1.591	2.656
LNR C	0.000	4.047	3.413	4.799	0.000	2.970	2.279	3.870
Year interval	0.000							
1998–2000	Ref							
2001–2007	0.000	0.715	0.609	0.840				
2008–2014	0.000	0.553	0.456	0.670				
Race	0.004							
White	Ref							
Black	0.549	0.928	0.726	1.185				
Other	0.001	0.647	0.500	0.836				
Age group	0.000				0.098			
≤65	Ref				Ref			
>65	0.000	1.860	1.614	2.143	0.075	1.203	0.982	1.475
Sex	0.001							
Male	Ref							
Female	0.001	0.784	0.682	0.901				
Histologic type	0.000				0.047			
IPMN	Ref				Ref			
SPN	0.000	0.093	0.050	0.175	0.005	0.059	0.008	0.428
MCN	0.001	0.713	0.582	0.873	0.654	0.929	0.672	1.283
SCN	0.108	0.200	0.028	1.424	0.960	0.002	0.000	0.000
Tumor site	0.002							
Head	Ref							
Body/tail	0.000	0.718	0.606	0.850				
Other	0.433	0.856	0.581	1.262				
Overlapping	0.252	0.839	0.622	1.132				
Surgery	0.764							
TP	Ref							
PP	0.764	1.033	0.836	1.275				

Table 4 (*continued*)

Table 4 (*continued*)

	Univariate analysis				Multivariate analysis			
	P	Hazard ratio	95.0% CI		P	Hazard ratio	95.0% CI	
			Lower	Upper			Lower	Upper
Chemo	0.000				0.001			
No	Ref							
Yes	0.000	1.381	1.200	1.588	0.001	0.677	0.542	0.845
T stage	0.000				0.000			
T1	Ref				Ref			
T2	0.000	1.597	1.292	1.975	0.054	1.363	0.995	1.867
T3	0.039	1.247	1.011	1.537	0.103	1.298	0.949	1.776
T4	0.000	3.745	2.634	5.326	0.000	3.378	2.185	5.223
RNE4	0.668							
1–5	Ref							
6–10	0.626	1.050	0.864	1.275				
11–16	0.767	0.938	0.796	1.184				
≥17	0.470	0.945	0.764	1.132				
RNP	0.000							
0	Ref							
1–2	0.000	2.804	2.376	3.309				
≥3	0.000	3.406	2.845	4.077				
N stage	0.000				0.000			
N0	Ref				Ref			
N1	0.000	2.924	2.501	3.418	0.000	3.686	2.200	5.106
N2	0.000	3.326	2.716	4.072	0.000	2.573	1.901	3.482
Metastasis	0.000				0.000			
M0	Ref				Ref			
M1	0.000	2.977	2.214	4.004	0.000	1.940	1.344	2.800
Grade	0.000				0.000			
I	Ref				Ref			
II	0.000	1.677	1.372	2.050	0.001	1.565	1.197	2.046
III/VI	0.000	2.247	2.247	3.502	0.000	2.074	1.529	2.813

LNR, lymph node ratio; RNP, the number of positive regional lymph nodes; RNE, regional nodes examined; LNR A, 0; LNR B, ≤0.2; LNR C, >0.2; IPMN, intraductal papillary mucinous neoplasms, MCN, mucinous cystic neoplasms, SCN, serous cystadenomas, SPN, solid pseudopapillary neoplasms; TP, total pancreatectomy, PP, Partial pancreatectomy.

Table 5 Univariate and multivariate analysis in node-positive patients

	Univariate analysis				Multivariate analysis			
	P	Hazard ratio	95.0% CI		P	Hazard ratio	95.0% CI	
			Lower	Upper			Lower	Upper
LNR group	0.000				0.000			
LNR B	Ref				Ref			
LNR C	0.000	1.725	1.420	2.096	0.000	1.784	1.379	2.308
Year interval	0.000							
1998–2000	Ref							
2001–2007	0.008	0.739	0.591	0.923				
2008–2014	0.000	0.561	0.432	0.728				
Race	0.316							
White	Ref							
Black	0.940	1.013	0.725	1.416				
Other	0.132	0.751	0.517	1.091				
Age group	0.004							
≤65	Ref							
>65	0.004	1.325	1.092	1.609				
Sex	0.489							
Male	Ref							
Female	0.489	1.070	0.883	1.297				
Marital status	0.446							
Married	Ref							
Other	0.446	1.069	0.901	1.268				
Histologic type	0.208							
IPMN	Ref							
SPN	0.036	0.297	0.095	0.927				
MCN	0.727	1.057	0.775	1.442				
SCN	0.992	0.000	0.000	0.000				
Tumor site	0.494							
Head	Ref							
Body/tail	0.575	1.072	0.841	1.366				
Other	0.295	1.363	0.764	2.430				
Overlapping	0.357	0.812	0.521	1.265				
Surgery	0.831							
TP	Ref							
PP	0.831	0. 970	0.736	1.279				

Table 5 (*continued*)

Table 5 (*continued*)

	Univariate analysis				Multivariate analysis			
	P	Hazard ratio	95.0% CI		P	Hazard ratio	95.0% CI	
			Lower	Upper			Lower	Upper
Chemo	0.000				0.000			
No	Ref				Ref			
Yes	0.000	0.627	0.514	0.763	0.000	0.534	0.402	0.708
T stage	0.005				0.069			
T1	Ref				Ref			
T2	0.101	1.318	0.947	1.835	0.274	1.296	0.814	2.063
T3	0.170	1.262	0.905	1.759	0.237	1.329	0.829	2.130
T4	0.001	2.591	1.538	4.366	0.009	2.320	1.229	4.378
RNE4	0.007							
1–5	Ref							
6–10	0.219	0.830	0.616	1.117				
11–16	0.039	0.727	0.537	0.984				
≥17	0.001	0.616	0.461	0.824				
RNP	0.051							
1–2	Ref							
≥3	0.051	1.214	0.999	1.474				
N stage	0.219							
N1	Ref							
N2	0.219	1.139	.925	1.402				
Metastasis	0.000				0.028			
M0	Ref				Ref			
M1	0.000	2.310	1.538	3.468	0.028	1.706	1.058	2.751
Grade	0.000				0.004			
I	Ref				Ref			
II	0.000	1.759	1.293	2.391	0.002	1.825	1.245	2.674
III/VI	0.000	1.911	1.384	2.639	0.002	1.898	1.264	2.851

LNR, lymph node ratio; RNP, the number of positive regional lymph nodes; RNE, regional nodes examined; LNR B, ≤0.2; LNR C, >0.2; IPMN, intraductal papillary mucinous neoplasms; MCN, mucinous cystic neoplasms; SCN, serous cystadenomas; SPN, solid pseudopapillary neoplasms; TP, total pancreatectomy; PP, partial pancreatectomy.

Neoadjuvant and postoperative adjuvant therapies are widely used to treat pancreatic cancer; however, chemotherapy was not an independent prognostic factor in PCN patients. Due to the high aggressiveness of IPMNs, adjuvant chemotherapy is often recommended (21-31). Nevertheless, no evidence exists to support the benefit of adjuvant treatment in patients with MCN-associated invasive carcinoma (32). Neoadjuvant or postoperative chemotherapy is not routinely used for SPN, as there is no evidence supporting their clinical benefits in SPN patients.

Due to the lack of the corresponding data from the SEER database, we could not analyze the impact of neoadjuvant chemotherapy in patients with invasive PCN. Hence, neoadjuvant chemotherapy is not recommended for patients with locally advanced IPMN- or MCN-associated invasive carcinoma or SPN (33-36). Future studies are required to assess the impact of neoadjuvant therapy on LNR. Although there is no evidence supporting the benefits of palliative chemotherapy for non-resectable or recurrent malignant cystic tumors, palliative chemotherapy is often used in patients with recurrent PCN (37,38).

Werner *et al.* (39) showed that the median survival of pancreatic cancer patients was 25 months. The OS of patients with invasive PCN reported here is considerably shorter than that reported by Werner *et al.* However, in this study, we analyzed data from patients diagnosed between 1988 and 2014, most of which had advanced-stage disease. With the development of novel treatments and diagnostic methods, the prognosis of patients has improved considerably. In this study, we analyzed data from patients who underwent surgery. Given that most patients with small tumors and with no clinical symptoms are treated with conservative therapies, it is likely that many such cases were excluded from our study, contributing to the short OS time. The median age of patients in our study was 64 years, which could also have contributed to the shorter OS time. Moreover, invasive carcinoma has been associated with poor outcomes (40-42). Notably, Schnelldorfer *et al.* (8,43) showed that invasive IPMN was as aggressive as ductal carcinoma.

There are certain limitations to our study. Firstly, this was a retrospective study, and prospective studies are warranted to confirm our findings. Secondly, angioinvasion and perineural invasion are reliable indicators of high PCN invasiveness. Unfortunately, such invasion characteristics were not available in the SEER database. Tumor-free margin status (R0) has been reported to be a strong indicator of curative resection in pancreatic cancer. Moreover, the tumor size of patients withR2 disease could have been inaccurate. These missing variables may have impacted the accuracy and reliability of our findings. Despite these limitations, our study provides a novel insight into the prognostic value of LNR in PCN patients undergoing surgery.

Conclusions

LNR was significantly associated with OS and CSS and was an independent prognostic predictor in patients with invasive PCN. Therefore, LNR may represent a promising prognostic factor alternative to the AJCC N stage in patients with node-positive PCN.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/tcr-20-1355

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-1355). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All data comes from a public database, which removes all patient tags; no ethical approval is required. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Data for this study were obtained from the US NCI SEER database (https://seer.cancer.gov).

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Supplementary

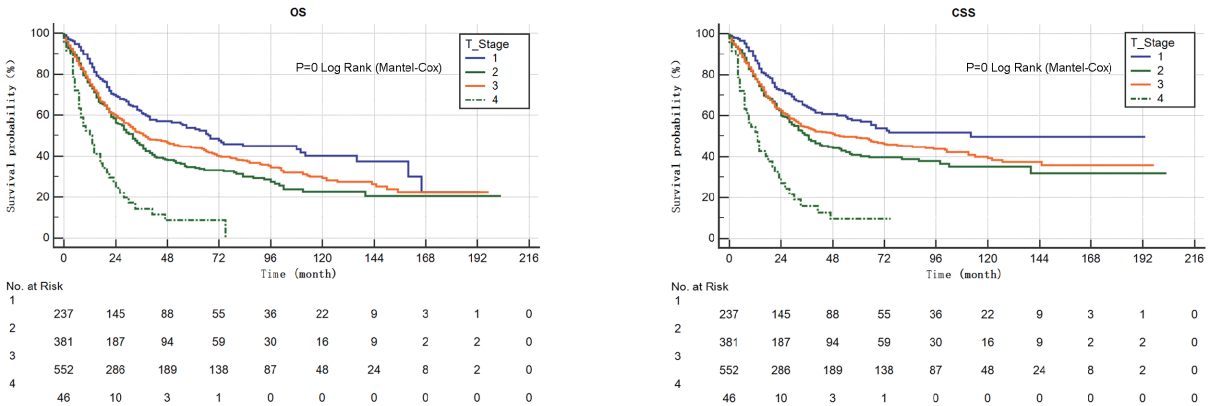

Figure S1 Survival of PCN patients based on the AJCC T stage. PCN, pancreatic cystic neoplasms; AJCC stage, the American Joint Committee on Cancer stage system.