

The Clinical Value of Regional Lymphadenectomy for Intrahepatic Cholangiocarcinoma: Results of A Retrospective Cohort Study

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Abstract

Objective: The aim of this study was to explore the clinical value of lymph node dissection (LND) for intrahepatic cholangiocarcinoma (ICC).

Methods: Clinical and pathological data were collected from 147 ICC patients who attended two tertiary centers over the past 5 years. The patients were classified into two groups: the LND group (group A) and the no-performance LND (NLND) group (group B). Clinical and pathological parameters were compared between the two groups to analyze the impact of LND on the prognosis of ICC patients.

Results: Of the 147 patients, 54.4% (80) received LND and 42.5% (34/80) of these were found to have lymph node metastasis (LNM) in postoperative pathological diagnosis. Patients undergoing LND usually have a larger surgical range, including hemihepatectomy and enlarged hemihepatectomy ($P = 0.001$). LND did not increase postoperative complications (27.5%, $P = 0.354$), but postoperative hospital stays were longer (12.2 ± 6.3 d, $P = 0.005$) in group A compared with group B (20.9% , 9.5 ± 3.5 d). The 5-year survival rates of groups A and B are almost similar (21% vs 29%, $P=0.905$). The overall survival rate of cN0 (diagnosis obtained by imaging) is better than pN1 (diagnosis obtained by histopathology), but lower than pN0. (all $P < 0.05$). Elevated CA19-9 level (HR = 1.764, 95% CI: 1.113 ~ 2.795, $P = 0.016$), vascular invasion (HR = 2.697, 95% CI: 1.103 ~ 6.599, $P = 0.030$), and T staging (HR = 1.848, 95% CI: 1.059 ~ 3.224, $P = 0.031$) were independent risk factors for poor ICC prognosis (all P values > 0.05).

Conclusion: ICC patients with cN0 may have LNM, and the prognosis of LNM patients is usually poor. Our data may support routine lymphadenectomy for ICC.

Introduction

Globally, the overall incidence of intrahepatic cholangiocarcinoma (ICC) is showing an upward trend[1–3]. In recent years, with the development of surgical technology and adjuvant therapy, the surgical resection rate and overall survival rate have improved[3–5]. According to the National Comprehensive Cancer Network guidelines[6], the presence of multiple tumors, extrahepatic lymph node metastasis (LNM), and distant organ metastasis are surgical contraindications for ICC, and tumor resection should only be considered in patients with resectable single tumors, multiple lesions, and/or hilar LNM. Liu and his colleagues[4] suggested that hilar lymph node dissection could not only help clarify the tumor stage, but also reduce the tumor load and prolong the survival time of patients whose tumors could not be resected. Lymph node (LN) status is an important prognostic factor in patients undergoing surgical resection, but the potential clinical value of lymph node dissection (LND) remains controversial. Therefore, we retrospectively analyzed clinical and pathological data from 157 ICC patients over the past 5 years, and assessed the clinical value of LND in improving the prognosis of ICC patients.

Methods

General information and grouping

A retrospective cohort study was conducted. Clinical and pathological data from 219 ICC patients admitted to the Third Affiliated Hospital of Naval Military Medical University ($n = 136$) and the Affiliated Hospital of North Sichuan Medical College ($n = 83$) from January 2013 to February 2018. The TNM staging of ICC was based on the 8th edition of the American Joint Committee on Cancer (AJCC) ICC staging standards. To evaluate the prognostic factors for ICC, we excluded patients with insufficient clinical and/or histopathologic data ($n = 21$), patients for whom potentially curative resection could not be achieved ($n = 33$), those with rare histopathologic subtypes other than adenocarcinoma ($n = 8$), and the patients who only underwent LN sampling ($n = 10$). The remaining 147 patients who underwent macroscopically curative resection comprised the final cohort and were studied in detail. Eighty patients who underwent LND (diagnosis obtained by histopathology) were used as the experimental group (group A). Sixty-seven patients who were suggested no enlarged lymph nodes by imaging examination and did not perform LND (NLND) were used as the control group (group B). This study conformed to the requirements of the Helsinki declaration and all patients and their families provided informed consent prior to surgery.

Surgical Method

Preoperative evaluation and surgical procedures were as follows. Routine preoperative examination was performed and patients with clinically resectable ICC underwent surgical treatment. After laparotomy, exploratory surgery was performed to confirm the absence of visual metastasis. The liver cutting range, parallel liver segmentation, and half liver or extended liver resection were marked to ensure R0 resection as much as possible. Intraoperative hilar occlusion was selective or non-selective, according to the scope and size of liver resection. If the tumor was in the left liver, the LN of the small curved side of the stomach and the hepatic artery and hepatic duodenal ligament would be removed. If the tumor was in the right liver, the LN around the hepatic artery and duodenal ligament and the pancreatic head would be removed. Other tissues and organs locally invaded by the tumor were removed simultaneously. After the operation, the abdominal cavity was rinsed with sterile water and the abdomen was closed after careful inspection for active bleeding and bile leakage.

Observation Parameters And Follow-up Method

We compared the clinical and pathological parameters of group A and B patients and analyzed the risk factors that may affect prognosis. Finally, we explored the effect of LND on the prognosis of patients with different risk factors. Patients were followed up as outpatients or via the telephone to understand their overall postoperative survival. Follow-up began on the day of surgery and ended at death or April 2020.

Statistical Methods

SPSS 22.0 statistical software (IBM, Armonk, NY, USA) was used for data analysis. Numerical data were expressed as median (range). Differences between groups was compared using the Chi square test or Fisher's exact test for categorical variables and ManneWhitney U test for numerical variables. The Kaplan-Meier method was used for survival analysis and a log-rank test was used to analyze survival rates. The multivariable Cox proportional hazards model was used to determine prognostic factors for disease-related deaths. Otherwise, $P < 0.05$ was considered statistically significant.

Results

Clinicopathological characteristics in groups A and B

Of all the patients who received LND (54.4%, 80/147), 42.5% (34/80) were found to have LNM in postoperative pathological diagnosis, with an average of 5 (range 2 ~ 18) LNs. Patients undergoing LND usually have a larger surgical range, including hemihepatectomy and enlarged hemihepatectomy ($P = 0.001$). Compared with group B, patients in group A usually have a longer hospital stay after surgery [(12.2 ± 6.3) d vs (9.5 ± 3.5) d]; $P = 0.009$. There were no significant differences in other clinical or pathological factors between the two groups (Table 1).

Table 1
Comparison of the clinical and pathological features between the group A and B.

Variables	A group(n = 80)	B group(n = 67)	P value
Gender (cases)			
Male	35	26	0.367
Female	45	41	
Age, mean ± SD	57 ± 11	57 ± 11	0.951
CA19-9 (U/ml), [interquartile range (IQR)]	89.4 (25.3 ~ 921.1)	88.2 (16.6 ~ 711.9)	0.817
Hepatitis B(cases)			
Positive	18	23	0.111
Negative	62	44	
Tumor diameter (cm), mean ± SD	6.3 ± 2.7	5.6 ± 2.5	0.833
Number of tumors(cases)			
Single shot	54	44	0.851
Multiple	26	23	
Tumor location(cases)			
Left liver	46	37	0.908
Right liver	26	24	
Bilateral liver	8	6	
Surgery(cases)			
Partial hepatectomy	29	46	0.001
Left hepatectomy	25	13	
Right hepatectomy	6	4	
Enlarged hemihepatectomy	20	4	
Surgical margin(cases)			
R0	76	60	0.211
R1	4	7	
Histological differentiation (cases)			
Well-/Moderate differentiation	67	58	0.663
Poorly differentiated	13	9	

Variables	A group(n = 80)	B group(n = 67)	P value
Vascular invasion (cases)			
Have	8	4	0.374
None	72	63	
Nerve invasion (cases)			
Have	11	7	0.543
None	69	60	
Other invasion* (cases)			
Have	6	5	0.993
None	74	62	
Thrombus (cases)			
Have	9	5	0.436
None	71	62	
Lymph nodes detected, IQR	5 (3 ~ 9)	0	
T Staging(cases)			
T1A	16	21	0.461
T1B	28	20	
T2	18	14	
T3/T4	18	12	
Intraoperative blood loss(mL), IQR	200.0 (200.0 ~ 400.0)	200.0 (100.0 ~ 400.0)	0.233
Intraoperative blood transfusion (cases)			
Have	12	10	0.990
None	68	57	
Postoperative complications**(cases)			
Have	22	14	0.354
None	58	53	
Postoperative hospital stay(d), mean ± SD	12.2 ± 6.3	9.5 ± 3.5	0.009

Variables	A group(n = 80)	B group(n = 67)	P value
*Other invasions: omentum invasion(n = 3), diaphragm invasion(n = 4), gallbladder invasion(n = 1) and hilar bile duct invasion(n = 3).			
**Postoperative complications: bleeding(n = 6), abdominal infection(n = 17), lung infection(n = 3), bile leaka(n = 7), gegastroparesis(n = 2) and liver failure(n = 1).			
Note: The en dash (–) indicates data not shown.			

Follow-up And Survival

Patients were followed up for 87 months. The continuation of 147 ICC patients was analyzed. Cumulative survival rates at 1, 3, and 5 years were 71%, 39%, and 22%, respectively, with a median survival of 23 months. The median survival times for group A and B patients were 25 and 22 months, respectively. The survival rates were not significantly different between the two groups ($\chi^2 = 0.102, P = 0.749$; Fig. 1). Next, we analyzed the impact of pN0, pN1 (diagnosis obtained by histopathology) and cN0 (diagnosis obtained by imaging) on the prognosis of patients. Our results suggest that the overall survival rate of cN0 (NLND) is better than pN1 (LND), but lower than pN0 (LND). (Fig. 2). The median survival time of pN0, pN1, and cN0 were 49.8, 13.3, and 23.3 months, respectively (all $P < 0.05$).

Factors Affecting Patient Prognosis

Table 2 and Table 3 show the analysis results of prognostic risk factors for patients. Univariate analysis suggested that elevated CA19-9 level (hazard ratio [HR] = 2.104, 95% confidence interval [CI]: 1.007 ~ 4.393, $P = 0.048$), the presence of multiple tumors (HR = 3.507, 95% CI: 1.484 ~ 8.287, $P = 0.004$), vascular invasion (HR = 3.145, 95% CI: 1.023 ~ 9.667, $P = 0.045$), and T2-T4 staging (HR = 2.221, 95% CI: 1.046 ~ 4.713, $P = 0.038$) were risk factors for poor ICC prognosis (Table 2). Multivariate analysis suggested that elevated CA19-9 level (HR = 1.764, 95% CI: 1.113 ~ 2.795, $P = 0.016$), vascular invasion (HR = 2.697, 95% CI: 1.103 ~ 6.599, $P = 0.030$), and T staging (HR = 1.848, 95% CI: 1.059 ~ 3.224, $P = 0.031$) were independent risk factors for poor ICC prognosis (Table 3).

Table 2
Univariate analysis for prognostic factors of ICC

Factors	n	Univariate		
		HR	95% CI	P value
CA19-9 (U/ml)				
< 39	48	2.104	1.007 ~ 4.393	0.048
≥ 39	99			
Tumor diameter (cm)				
≤ 5	62	0.938	0.461 ~ 1.909	0.860
> 5	85			
Number of tumors				
Single shot	98	3.507	1.484 ~ 8.287	0.004
Multiple	49			
Surgical margin(cases)				
R0	136	1.304	0.330 ~ 5.156	0.705
R1	11			
Histological differentiation (cases)				
Well-/Moderate differentiation	125	3.140	0.673 ~ 14.641	0.145
Poorly differentiated	22			
Vascular invasion (cases)				
Have	12	3.145	1.023 ~ 9.667	0.045
None	135			
Nerve invasion (cases)				
Have	18	1.548	0.464 ~ 5.161	0.477
None	129			
Thrombus (cases)				
Have	14	0.539	0.143 ~ 2.033	0.362
None	133			
Lymphadenectomy(cases)				
Have	80	1.095	0.545 ~ 2.202	0.799

Factors	n	Univariate		
		HR	95% CI	P value
None	67			
T Staging(cases)				
T1	85	2.221	1.046 ~ 4.713	0.038
T2/T3/T4	62			
Intraoperative blood transfusion (cases)				
Have	22	0.968	0.366 ~ 2.563	0.948
None	125			

Table 3
Multivariate analysis for prognostic factors of ICC

Factors	n	Multivariate		
		HR	95% CI	P value
CA19-9 (U/ml)				
< 39	48	1.764	1.113 ~ 2.795	0.016
≥ 39	99			
Number of tumors				
Single shot	98	1.260	0.731 ~ 2.171	0.406
Multiple	49			
Vascular invasion (cases)				
Have	12	2.697	1.103 ~ 6.599	0.030
None	135			
T Staging(cases)				
T1	85	1.848	1.059 ~ 3.224	0.031
T2/T3/T4	62			

Discussion

ICC patients do not usually show significant clinical symptoms in the early stage of disease. Most patients are found to have locally advanced disease or distant tumor metastasis at the time of diagnosis. Therefore, the tumor resection rate is 20–40%[6]. Surgical resection is the only potentially curative option

for ICC, the 5-year overall survival rate rates range from 25–40% after tumor resection[7]. LNM is an independent prognostic factor for ICC patients[8, 9], with a resection rate of 49–62% and a positive rate of 21–39% of LN[3, 9–12]. The 5-year overall survival rate for patients with LNM is less than 20%[8]. In recent years, some studies have suggested that routine LND can improve the long-term survival of ICC patients[13, 14], but other studies have concluded that LND should only be recommended for patients who are clinically diagnosed as LN-positive[6, 15]. Thus, its clinical value is still questionable. Therefore, we explored the clinical value of LND in patients with ICC who are clinically diagnosed with negative lymph nodes in our study.

French and Japanese scholars performed a multicenter study to compare two matched groups of patients ($n = 56$ each) with clinically node-negative ICC. They performed lymphadenectomy in one group and did not perform this procedure in the other group. The patients who underwent liver resection with lymphadenectomy achieved better 5-year overall survival rate (65% vs 46%, $P = 0.017$) and disease-free survival (34% vs 31%; $P = 0.042$) outcomes compared with patients who underwent liver resection without lymphadenectomy[14]. Furthermore, Kim et al. reached the same conclusion in another propensity score-matched study[13]. Although patients undergoing LND had better survival rates, the present study cannot clearly answer why lymphadenectomy has prognostic importance. Two other studies found that patients who received LND did not have significantly improved recurrence rates, overall survival rate, or recurrence-free survival compared to NLND patients[16, 17].

In our study, it was also found that the overall survival rate of patients receiving LND did not improve compared with NND. We further analyzed the impact of pN0, pN1 and cN0 on the prognosis of patients. The results suggest that the overall survival rate of cN0 is better than pN1, but lower than pN0. ICC patients without lymph node involvement and patients with multiple tumors and LNM may not benefit from LND[18]. Studies have shown that LND can reduce the rate of local recurrence and ensure the thoroughness of the radical treatment to the greatest extent, and it is recommended that patients with no distant metastasis perform LND[13, 19, 20]. The elevated CA19-9 level, vascular invasion, and T staging were independent risk factors for poor ICC prognosis. To clarify tumor stage and to exclude LNM, LND may be useful in patients with the mass-forming (MF) type and the MF-plus-periductal-infiltration type of ICC[21].

Our results suggested that performing LND does not improve prognosis, but 42.5% of patients in the study were found to have LNM in a postoperative pathological assessment. Although regional LNM is also associated with a high recurrence rate after hepatectomy combined with regional LND, it is still possible for approximately 15% of cases to achieve long-term survival[7]. Our study also found that 11% of patients can survive up to 7 years after receiving LND. Patients with LNM usually have a poor prognosis. Once the lymph node is positive by pathological diagnosis, stage I and Ⅱ tumors may be directly classified as stage IIIB (TNM). In addition, the AJCC recommends lymphadenectomy with a minimum of six nodes harvested. Insufficient assessment of lymph node status may lead to inaccurate staging and insufficient application of adjuvant chemotherapy. Adjuvant chemotherapy can improve the

5-year OS rate of ICC patients, which is related to the improvement in survival of patients with positive surgical margins and lymph nodes[22].

Conclusions

LND was more common in patients with tumors located in the left liver and it did not increase the incidence of postoperative complications. 42.5% of patients were found to have LNM in postoperative pathological diagnosis, and patients receiving LND usually have a longer hospital stay. The overall survival time of patients receiving LND is almost similar to that of patients with cN0 (diagnosis obtained by imaging) and no-performance lymphadenectomy. Although the overall survival time of cN0 patients is better than that of pN1 patients, it is significantly lower than that of pN0 patients. Therefore, ICC patients with cN0 may have LNM, and the prognosis of these patients is usually poor. Our data may support routine lymphadenectomy for ICC with the objective of achieving clarified tumor staging and guiding postoperative adjuvant treatment. A limitation of our study is that we did not obtain tumor recurrence data for most of the ICC patients, because this study was retrospective.

Abbreviations

English full name	Abbreviations
intrahepatic cholangiocarcinoma	ICC
lymph node dissection	LND
no-performance LND	NLND
lymph node metastasis	LNM
Lymph node	LN

Declarations

Ethics approval and consent to participate

Our studies have been performed in accordance with the ethical standards as laid down in the Declaration of Helsinki and reviewed and approved by the Clinical Research Ethics Committee of Shanghai Eastern Hepatobiliary Surgery Hospital (Third Affiliated Hospital of Naval Military Medical University), Approval code: EHBHKY2018-02-005.

Consent for publication

All individuals have approved the submitted version and agree to publish our manuscript, including individual details, images and tables.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Facai YANG, Changkang WU, Taian CHEN, Anqi Duan, Jian XU, Zhiyuan BO made substantial contributions to conception and design, and acquisition of data, and analysis and interpretation of data; and

Facai YANG drafted the article; and

Jingdong LI, Yinghe QIU and Bin YI participated in revising it critically for important intellectual content.

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Figures

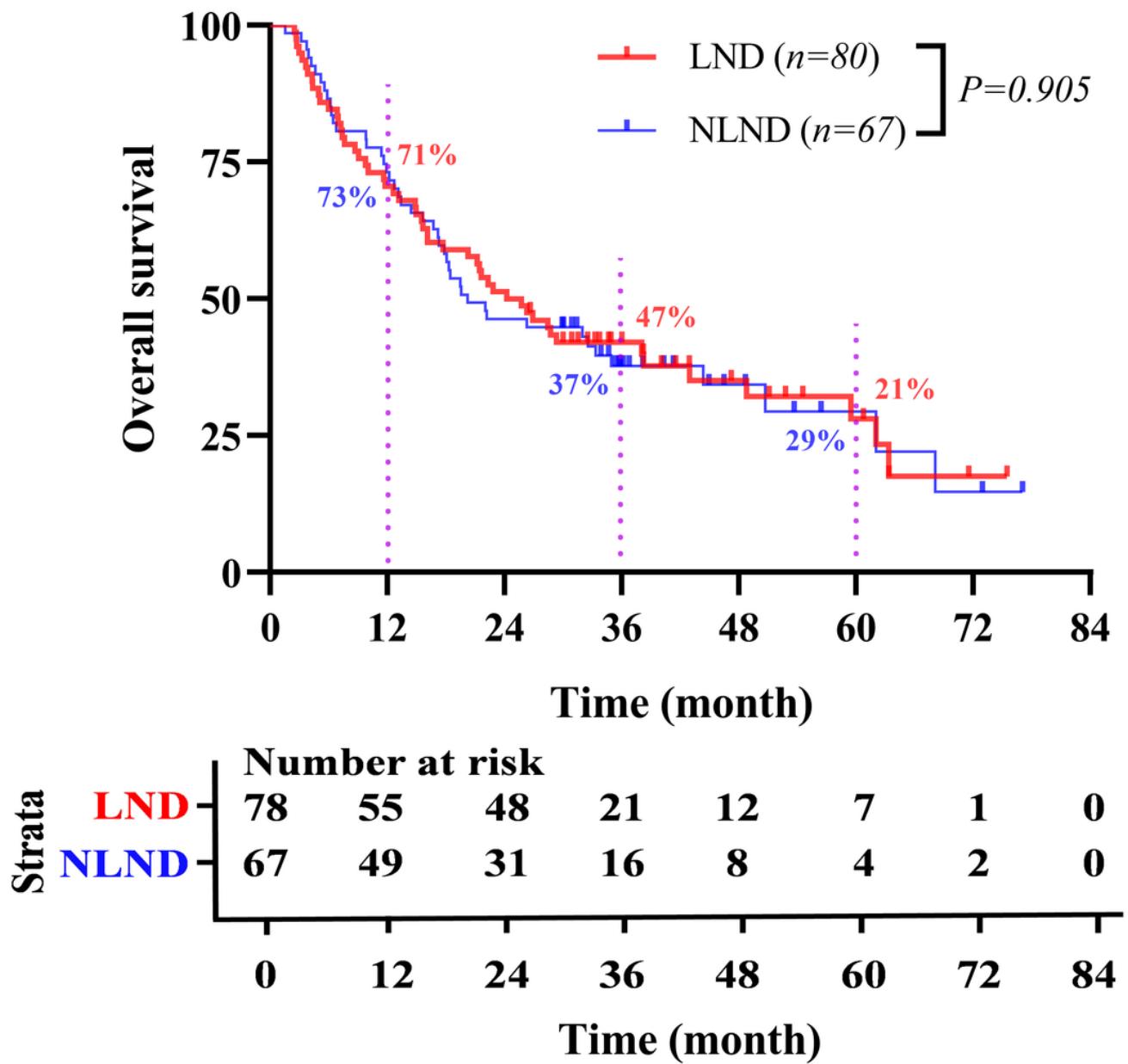


Figure 1

Comparison of the overall survival rates of the patients based LND and no-performance LND (NLND) group. LND: lymph node dissection.

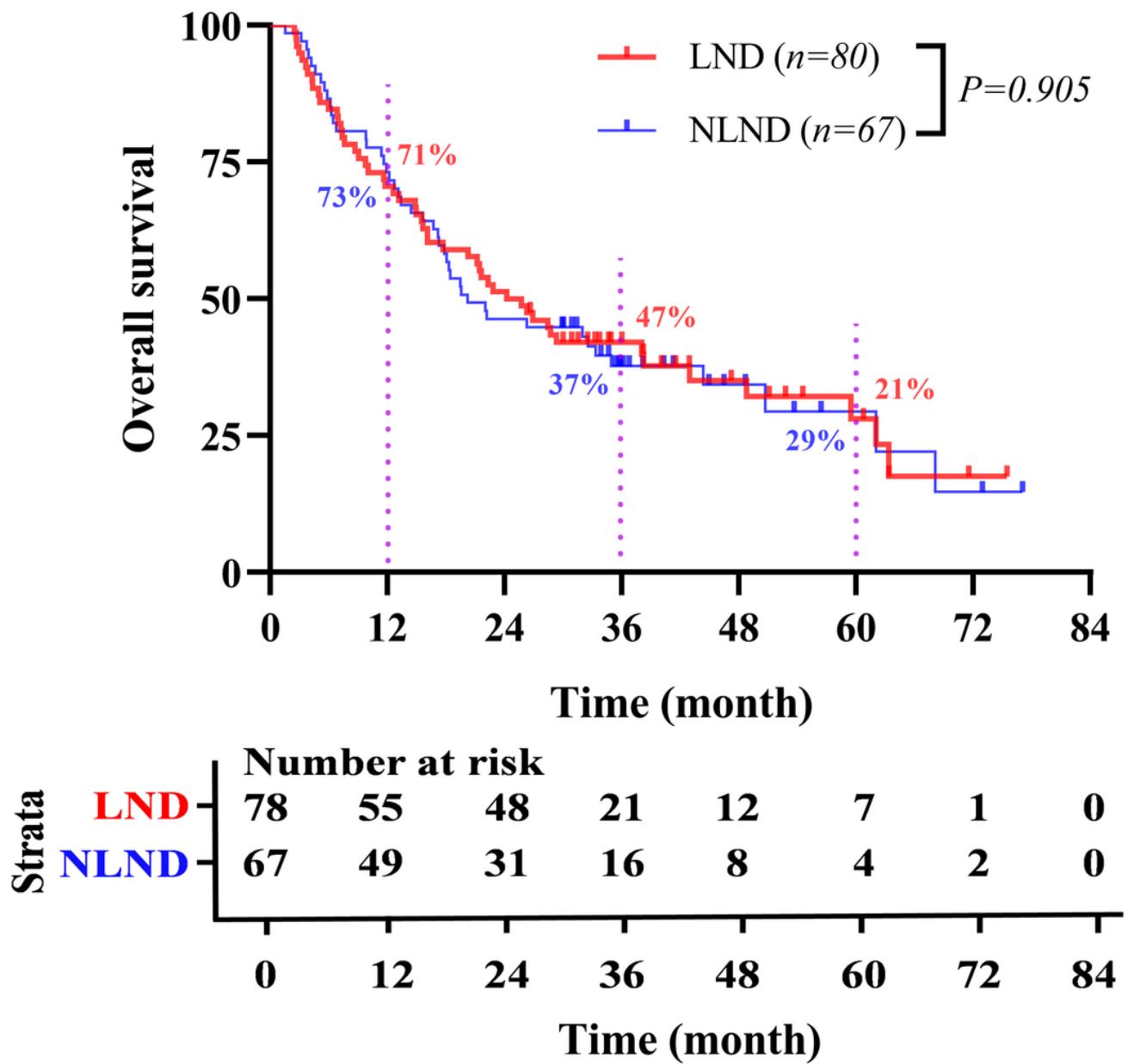


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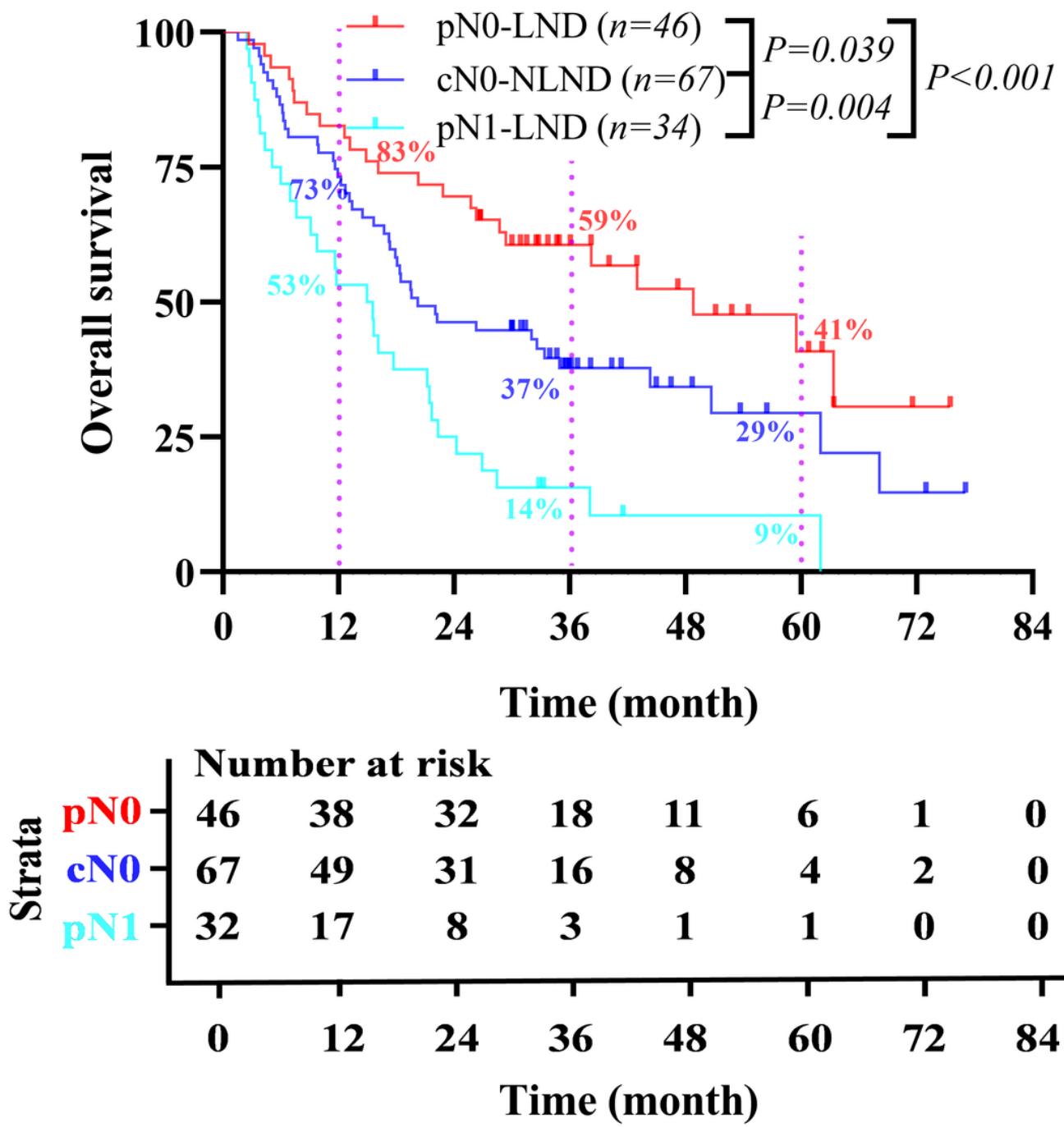


Figure 2

Comparison of the overall survival rates of the patients based lymph node status. pN0, Histopathology examination revealed negative lymph nodes; pN1, Histopathology examination revealed that one or more lymph nodes are positive; cN0, Imaging examination suggested no enlarged lymph nodes.

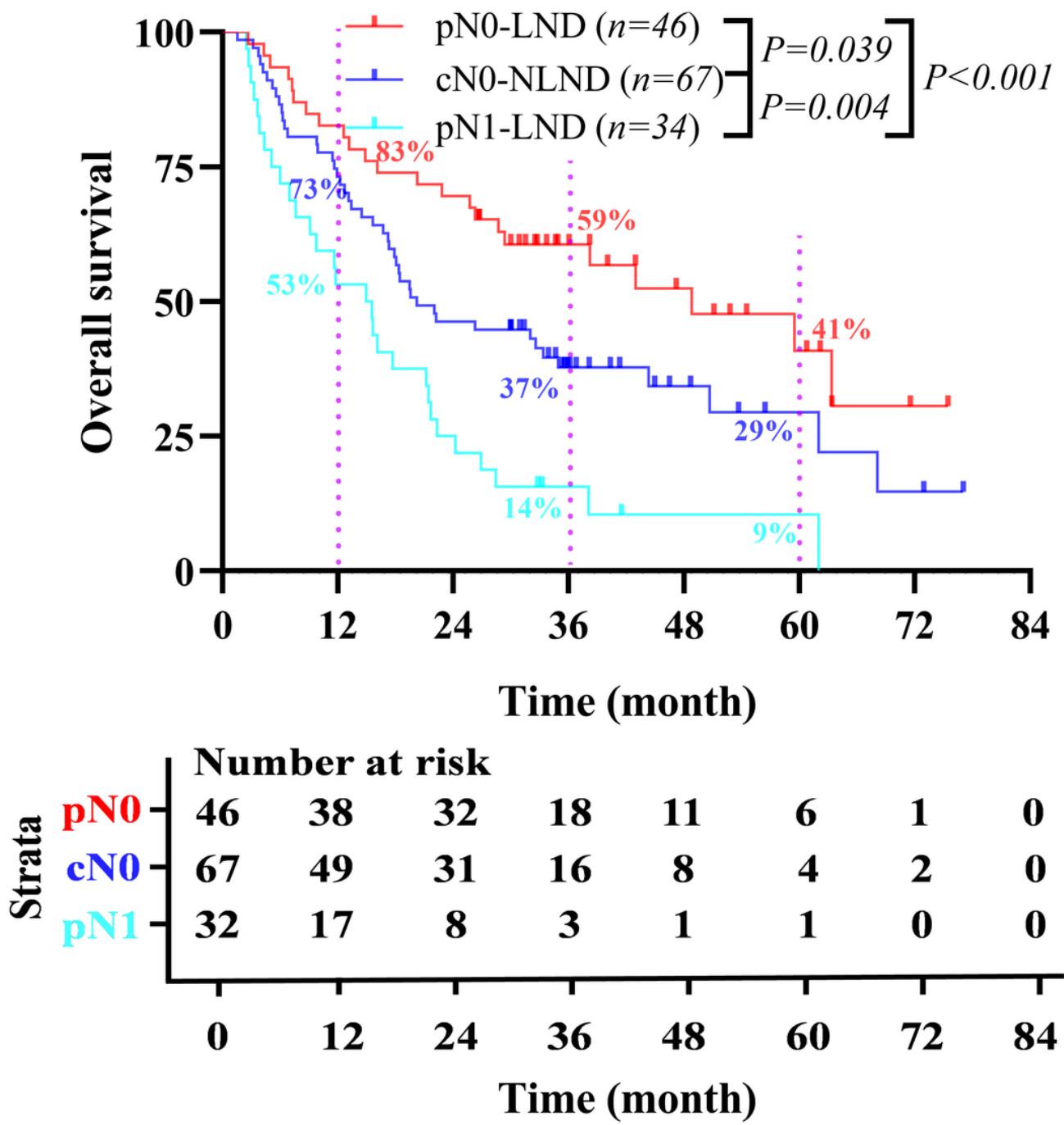


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