Journal of Cancer Research and Clinical Oncology (2025) 151:107
https://doi.org/10.1007/s00432-025-06148-3

RESEARCH

Should lymphadenectomy be recommended in radical surgery of intrahepatic cholangiocarcinoma patients? A retrospective study

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Received: 4 December 2024 / Accepted: 20 February 2025 / Published online: 12 March 2025

Abstract

Purpose Intrahepatic cholangiocarcinoma (ICC) is an extremely deadly cancer with high recurrence incidence, particularly in patients with lymph node metastasis (LNM). The necessity of lymphadenectomy including lymph node biology (LNB) and dissection (LND) during ICC radical surgery remains debate.

Methods We retrospectively analyzed the patients diagnosed with ICC and underwent radical surgery at the Cancer Hospital of the Chinese Academy of Medical Sciences from 2012 to 2023.

Results A total of 308 ICC patients were involved in this study. $pLNM^+$ group had poorer OS ($P<0.0001$) and poorer DFS ($P<0.0001$) compared with $pLNM^-$ group. Compared to the LN^- group, LN^+ group exhibited worse OS ($P=0.038$) and worse DFS ($P=0.003$). After PSM and IPTW, compared with LN^- group, LNB exhibited longer operation time (IPTW: $P=0.0024$) and longer hospitalization days (IPTW: $P=0.0112$) with no significant differences in complications, DFS, and OS. Compared with LN^- group, LND group had no better DFS and OS, only more complications (IPTW: $P=0.0191$), longer operation time (all $P<0.001$), higher risk of bleeding (all $P<0.05$), transfusion (IPTW: $P=0.014$) and longer hospitalization days (IPTW: $P=0.0044$). Compared with LNB group, LND had longer operation time ($P=0.0227$), higher risk of bleeding ($P=0.017$) and transfusion ($P=0.0321$), and more postoperative complications ($P=0.0425$), with no difference in DFS and OS.

Conclusion Lymphadenectomy does not necessarily provide long-term survival or recurrence benefits. LND only achieves the effect of LNB while negatively affects postoperative recovery without survival benefit for ICC patients. LNB can be performed for accurate pathological staging while not all patients may require LND based on their specific circumstances.

Keywords Intrahepatic cholangiocarcinoma · Inverse probability of treatment weighted analysis · Hepatology · Lymph node biology · Lymph node dissection · Propensity score matching analysis

Abbreviations

AFP	Alpha fetoprotein
AJCC	American joint committee on cancer
BMI	Body mass index
CA199	Carbohydrate antigen 19–9
CEA	Carcinoembryonic antigen
DFS	Disease-free survival
HIAC	Hepatic arterial infusion chemotherapy
ICC	Intrahepatic cholangiocarcinoma
IPTW	Inverse probability of treatment weighted analysis
MRI	Magnetic resonance imaging
LN	Lymph node
LNB	Lymph node biology
LNM	Lymph node metastasis
LND	Lymph node dissection
LR	Liver resection
OS	Overall survival
PSM	Propensity score matching analysis
PTCD	Percutaneous transhepatic cholangial drainage

Introduction

Intrahepatic cholangiocarcinoma (ICC) is one of the most fatal malignant tumors around the world, accounting for 5% to 30% of all primary liver cancers (Lee and Chun 2018).

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The risks of ICC include infections (eg., HBV, HCV and Epstein-Barr virus), bad lifestyle (eg., alcohol consumption and smoking), metabolic and genetic risk factors (Massarweh and El-Serag 2017). The onset of ICC is insidious. Many ICC patients have no special symptoms in the early stage and enter the advanced stage once discovered (Chen et al. 2023). Despite the development of a series of new treatment strategies and progress over the past few decades, the prognosis of ICC remains dismal.

Liver resection (LR) or radical surgery is the mainstay of treatment, but only a minority of patients (15%) are candidates for surgery (Roy et al. 2021). The tumor recurrence rate in LR is high (50–70%), (Rhee et al. 2023). the current 5-year overall survival (OS) rate after LR is only 25–40% (Mazzaferro et al. 2020) How to increase the survival rate and reduce the recurrence rate of LR needs further study. LNM is strongly associated with high recurrent rate and poor prognosis in ICC (Kim et al. 2022b). Lymphadenectomy is important method for the precise pathological diagnosis of LNM during the LR in ICC including lymph node biology (LNB) and lymph node dissection (LND) (Yoh et al. 2018). However, the benefits and indications for lymphadenectomy remain unclear. Whether lymphadenectomy can be used as a routine intraoperative resection during LR remains a source of debate (Zhang et al. 2018). Whether lymphadenectomy has the potential to reduce the risk of locoregional recurrence, and the uncertainty about the survival benefit and postoperative complications have been the focus of controversy (Zhou et al. 2019). In this article, we retrospectively analyzed the patients who were diagnosed with ICC and underwent surgical treatment at the Cancer Hospital of the Chinese Academy of Medical Sciences from 2012 to 2023. The purpose of this article is to explore whether ICC patients benefit from lymphadenectomy and whether lymphadenectomy should be recommended in operable ICC patients.

Methods

Patients and follow-up

This retrospective study collected and analyzed the original clinical data of patients diagnosed with ICC and underwent radical surgery at the Cancer Hospital of the Chinese Academy of Medical Sciences from January 2012 to January 2023. This study was approved by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (Approval number: 21/315–2986). All research was conducted in accordance with both the Declarations of Helsinki and Istanbul. The "radical surgery" of ICC is defined as: adhering to the principles of R0 resection and preserving an adequate volume of functionally viable residual liver, completely removing all tumor lesions detectable preoperatively and intraoperatively, and having tumor-free margins confirmed by histopathological examination; if tumor directly invades organs/tissues, histopathological confirmation of negative margins post-combined resection is needed; there should be no extrahepatic distant metastasis or major vascular invasion (Zhang et al. 2024a, b). Patients meet the following conditions are included in the criteria: (1) who were diagnosed with ICC by postoperative pathological diagnosis; (2) who undergoing liver tumor resection; (3) who were able to receive regular follow-up visits. Patients meet the following conditions were excluded from this study: (1) who were mixed with hepatocellular carcinoma or other malignant tumors, (2) who were with distant metastasis including distant LNM, (3) who were dead in one month, (4) who were lost to follow-up.

Our last follow-up for all patients were in February 2024, all patients with the minimum follow-up time of 1 year. The definition of the follow-up was: patients were followed up every 3 months in the first 2 years after surgery, and every 6 months thereafter. For cases that cannot return to the hospital for reexamination, follow-up was conducted via phone or WeChat. Patients who were follow-up lost were excluded from this study. The examination items included blood routine, biochemistry, tumor markers (carcinoembryonic antigen (CEA), Alpha fetoprotein (AFP), and Carbohydrate antigen 19–9 (CA199)), CT or enhanced MRI examination. If recurrence was suspected, enhanced CT and MRI, puncture biopsy and further treatment were performed.

Grouping and definition

Lymphadenectomy containing LNB and LND was defined as the LNs were resected during the operation. ICC patients without under lymphadenectomy was involved in LN^- group. LN^+ group was defined as the patients whose lymphadenectomy was performed during the operation, the number of resected LNs were collected. LN^+ group was divided into pathological LNM^+ ($pLNM^+$) group and $pLNM^-$ group according to the postoperative pathology: whether LNM was confirmed in the resected LNs. LN^+ group was also divided into the LNB group and LND group according to the definition of LNB and LND: (1) LNB was defined as the biopsy of suspiciously swollen LNs during surgery, the number of LNs resected during surgery is less than 6 without systematic dissection of LNs. Its main purpose is to diagnose and determine the patient's T stage. (2) LND was defined as the systematic dissection of LNs according to the AJCC standards, referring to the removal of any LNs that may be affected by the tumor completely from specific areas of the body for diagnostic and therapeutic reasons, scoping to at least the second station and the resection of at least 6 or more LNs (Lluís et al. 2023; Zhang et al. 2024a,

b), including hepatic artery LN (NO.8 station), hepatoduodenal ligament LN (NO.12 station), posterior pancreatic LN (NO.13 station) and LNs based on the location of the primary ICC tumor (Ke et al. 2021; Lluís et al. 2023).

Data collections and definitions

We collected the following data of indicators from the medical record writing system: (1) Sex. (2) Age was defined as the initial diagnostic age, patients over 65 years old are defined as elderly patients. (3) Body mass index (BMI): whose BMI over 25 were defined as overweight. (4) Hepatobiliary history, such as gallbladder surgery, percutaneous transhepatic cholangial drainage (PTCD), and interventional surgery for hemangioma. (3) Neoadjuvant treatment, including neoadjuvant chemoradiotherapy, targeted or immunotherapy, interventional or other therapy. (4) HBV infection, determined by the five quantitative hepatitis B tests. (5) Preoperative patient serum tumor marker: CEA, AFP, CA199 levels. Since the data of the "CEA", "CA199", and "AFP" were extremely different (range between 1 and 100,000), we took the Log2 logarithm of these three to reduce the huge differences between patients to facilitate subsequent PSM and IPTW analysis. (6) Enlarged LNs: preoperative imaging CT or MRI diagnosis that the diameter of LN minor axis around the liver is over 10 mm with or without central necrosis or inhomogeneous enhancement (Ke et al. 2021).

Besides, we collect the following data through the surgical system: (1) Lymphadenectomy, as the definition in above in Sect. "Grouping and definition" *Grouping and definition*. (2) Operation time, refers to the time between the first incision and the final incision. (3) Bleeding, refers to the amount of blood loss during the operation, estimated by the surgeon referring to the amount of suction. (4) Transfusion, refers to the amount of blood transfused during surgery, which can be precisely calculated in the transfusion record.

In addition, we reviewed the pathology reports following the standard postoperative pathology procedures: (1) LNM, refers to whether tumor cell infiltration was found in the resected LNs. (2) T stage, according to the latest AJCC surgical pathological staging (Meng et al. 2017). (3) Microvascular invasion, refers to the invasion of the portal vein, portal artery, hepatic vein, or capsule blood vessels of liver tissue adjacent to the tumor margin. (Kim et al. 2024) (4) Liver capsule invasion, refers to the tumor tissue cells were detected in Glisson capsule. (5) Differentiation, refers to the degree of differentiation of tumor tissue, divided into highly differentiated, moderately differentiated, and poorly differentiated groups. (6) Lymphocyte invasion: refers to the abnormal proliferation and aggregation of lymphocytes in tissues and organs, forming invasive lesions. (7) Tumor number. (8) Tumor size, we took a cut-off of 4 cm, and masses larger than 4 cm were called large tumors.

Meanwhile, we collected the postoperative and outcome data: (1) Postoperative hospitalization day. (2) Total postoperative hospitalization day. (3) Postoperative complication, refers to the complications during hospitalization after surgery, including biliary fistula, infection, liver failure, liver hemorrhage, renal failure, hepatic encephalopathy, atelectasis. (4) Post treatment, including the chemotherapy, radiotherapy, hepatic arterial infusion chemotherapy (HIAC), targeted therapy, and immunotherapy. (5) Recurrence, refers to either a new lesion with ICC radiological features, or with distant metastasis radiological features. The site and time of recurrence or metastasis were collected. Disease-free survival (DFS) was defined as the duration from the date of surgery to tumor recurrence or metastasis. (6) Survival: the final outcome of the patients, refers to whether the patients were currently in a state of survival or death to the last follow-up time. OS was calculated from the date of surgery to the date of death or the last follow-up.

PSM and IPTW analysis

In our study, we meticulously selected indicators that were theoretically causally related to prognosis and incorporated them into the PSM and IPTW analysis. To ensure the robustness of our variable selection, we conducted univariate COX analysis to identify variables related to prognosis, screening out variable factors with P values less than 0.1 through R software (version: R4.4.0, https://www.R-project.org/, Vienna, Austria). Subsequently, these factors were included in multivariate COX analysis to further confirm their independent association with survival. The variables that maintained a P value of less than 0.1 after multivariate COX analysis were then selected as the covariates for both the PSM and IPTW analyses. In addition to the results screened by the COX analysis, we also consider the indicators with significant Standardized Mean Difference (SMD) variations as covariates that need to be adjusted between the two groups. The purpose was to ensure the quality of matching, ensuring that those groups were balanced on these prognostic factors after matching.

During both PSM and IPTW analysis, propensity scores are calculated using multivariate Logistic regression, with treatment assignment (LNB or LND) as the dependent variable and potential confounders as independent variables. Multivariate Logistic regression analysis estimates the probability of treatment based on these covariates, thus generating propensity scores for matching. During PSM analysis, patients were matched 1:1 by propensity scores based on the results of the covariates of multivariate COX analysis by using SPSS Statistics software (version: IBM SPSS Statistics 26, https://www.ibm.com/support/pages/downloading-ibm-spss-statistics-26) with a 1:1 nearest neighbor matching algorithm. The matching tolerance was set to 0.02

without replacement. This approach was chosen to ensure that the treatment and control groups were well-matched on the selected prognostic factors, thereby enhancing the quality of the matching process. Regarding the IPTW method, we calculated the probability value for each individual using the multivariate Logistic regression analysis. Based on these probability values, we then calculated the weights for each individual. For individuals in the treatment group (LNB or LND group), their weight is 1/individual probability value; for individuals in the control group (LN^- group), their weight is 1/(1-individual probability value). Utilizing these weights, we re-weighted each individual, and subsequently applied the weighted data to estimate the causal effect. To assess the balance achieved through PSM and IPTW, we considered SMDs below 0.10 to indicate adequate covariate balance, with differences below 0.20 considered acceptable. This metric allowed us to evaluate the effectiveness of our matching and weighting procedures in creating balanced groups on the prognostic factors.

Statistical analysis

We used R software and SPSS Statistics software for data analysis and graphing. We used the "survival" and "survminer" packages to perform univariate and multivariate COX analysis and drawing KM curves. Continuous variables are reported as mean ± SD, or median and IQR, depending on whether they conform to normal distribution. For continuous variables that conform to the normal distribution, we used the independent sample t test. For continuous variables that do not conform to the normal distribution, The Kruskal–Wallis or Mann–Whitney U test were used. The chi-square or Fisher's exact test were used to test categorical variables, and the ANOVA test were used to test the three groups of continuous variables. Statistical significance was defined as a two-sided P value < 0.05.

Results

Clinical characteristics of ICC patients included in the study

The flowchart of this study was described in Fig. 1. 370 patients who were diagnosed ICC and under radical surgery, and we excluded the following total 62 patients: 31 patients who had HCC (mixed carcinoma), 4 patients who were death within 1 month, 11 patients who had distant metastasis, and 16 patients who were follow-up lost. Finally, a total of 308 patients were included (Table 1). Our loss to follow-up rate was controlled within 5%. Among them, 225 (73.1%) patients underwent lymphadenectomy, of which 115 patients underwent LNB and 110 underwent LND, and postoperative pathology proved that 78 patients had LNM. 52 (16.9%) patients experienced postoperative complications. Specifically, according to the Clavien-Dindo classification, 7(13.5%) patients had Grade I complications, 18 (34.6%) patients had Grade II complications, 20 (38.5%) patients had Grade III complications, and 7 patients (13.5%) had Grade IV complications. All complications were managed according to standardized protocols, and there were no postoperative deaths. In addition, 133 (43.1%) patients received adjuvant treatment after surgery, mainly chemotherapy (63.2%), radiotherapy (24.6%), and HIAC treatment (9.8%). 200 patients experienced postoperative recurrence; the ICC tumor recurrence rate reached 64.9%. The 1-year DFS rate was 52.9%, the 3-year DFS rate was 20.5%, and the 5-year DFS rate was 13.6%. The main site of recurrence were primary tumors site and liver metastasis (72.5%), retroperitoneal metastasis (13%), lung metastasis (7.5%), and bone metastasis (3.5%). The survival rate is extremely poor, with 1-year survival rate of 75.3%, 3-year survival rate of 34.7%, and 5-year survival rate of 22.4%.

Patients underwent lymphadenectomy had worse postoperative outcomes and poorer prognosis before PSM and IPTW

According to the group definition, 83 patients were in the LN^- group, 115 patients were in the LNB group, and 110 patients were in the LND group. The comparison of the baseline of the three groups was shown in Table 1. The comparison of the baseline of the LN^- and LN^+ groups was shown in Supplementary Table 1. LN^+ group had a higher T stage ($\chi^2 = 16.86$, $P = 0.0008$) and more lymphocyte infiltration ($\chi^2 = 7.078$, $P = 0.008$), which were associated with worse prognosis. Operation time is an important indicator to measure the difficulty of surgery (Xi et al. 2022), the operation time of LN^+ group was significantly longer than that of LN^- group (273.680 ± 89.936 min vs. 220.711 ± 90.423 min, $P < 0.0001$), indicating the difficulty of operation was corresponding significantly increased. At the same time, the patient's bleeding risk (LN^- vs. LN^+ (rank mean):119.7 vs. 167.35, $P < 0.0001$) and blood transfusion risk (LN^- vs. LN^+ (rank mean):141 vs. 159.5, $P = 0.022$) in the LN^+ groups were significantly higher than those in the LN^- group. The postoperative hospitalization days (7.819 ± 3.073 days vs. 10.778 ± 5.746 days, $P < 0.0001$) and total hospitalization days (14.012 ± 5.230 days vs.17.316 ± 7.637 days, $P = 0.0003$) in the LN^+ groups were significantly longer than those in the LN^- group. The risk of postoperative complications (LN^- vs. LN^+: 7.23% vs. 20.44%, $\chi^2 = 7.546$, $P = 0.01$) in the LN^+ groups were significantly higher than that in the LN^- group. In addition, the prognostic survival rate (5-year OS rate: LN^- vs. LN^+: 25.3% vs. 21.3%, $\chi^2 = 4.288$, $P = 0.038$) and DFS rate (5-year DFS rate: LN^- vs. LN^+:

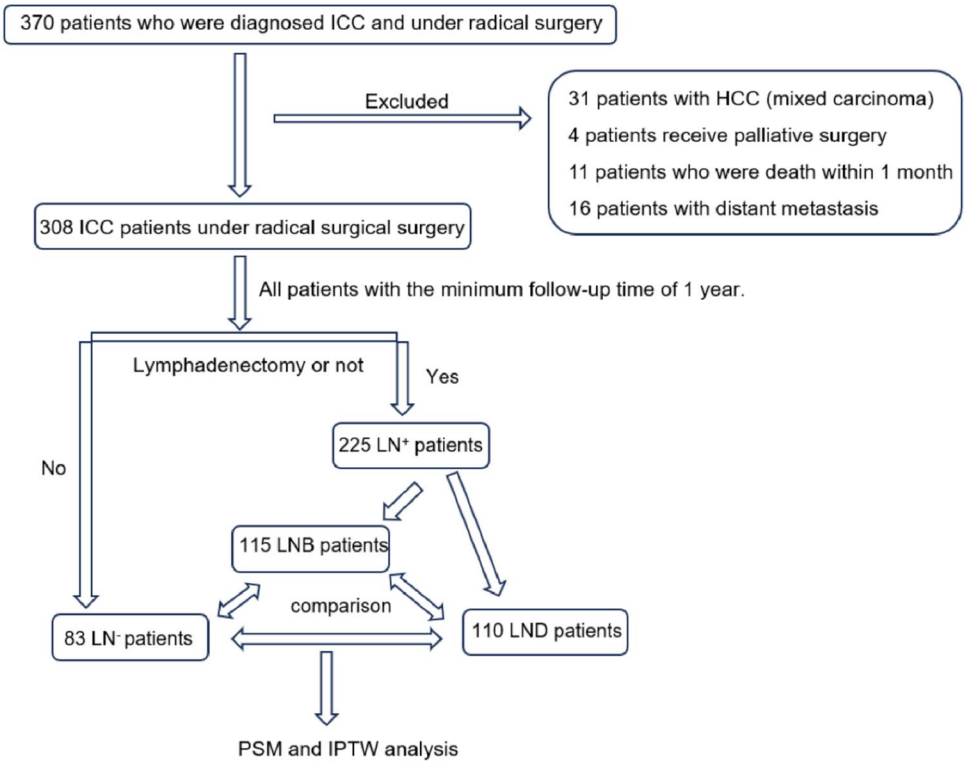

Fig. 1 flowchart of the study. 370 patients who were diagnosed ICC and under radical surgery were involved in our retrospective study. Among them, 31 patients had mixed carcinoma, 7 patients received palliative surgery, 4 patients were death within 1 month, 4 patients had distant metastasis, and 16 patients were follow-up lost. Those 62 patients were excluded in our study. All the 308 patients were followed-up and with the minimum follow-up of 1 year. According to whether the lymphadenectomy was performed during surgery, 83 patients were included into LN- groups, and 225 patients were included into LN + group. Then 110 patients with the resection of at least 6 or more LNs including hepatododenal ligament LN and parahepatic artery LN were included into LND group, and the other 115 patients were included into LNB group. *DFS* disease-free survival; *HCC* Hepatocellular carcinoma; *ICC* Intrahepatic cholangiocarcinoma; *IPTW* inverse probability of treatment weighted analysis; *LN* lymph node; *LNB* lymph node biology; *LND* lymph node dissection; *PSM* propensity score matching analysis

19.3% vs. 11.6%, $\chi^2 = 9.903$, $P = 0.003$) of the LN^+ group were significantly lower than that of the LN^- group (Fig. 2A and B), LN^+ patients had a worse prognosis, contrary to the conclusions of many previous studies. In addition, the LN^- group has the best outcome compared with LNB and LND group (Fig. 2C and D), especially in the DFS rate ($\chi^2 = 11.333$, $P = 0.003$).

LNM is an extremely poor prognosis risk factor in ICC patients

According to the pathology reports, we divided the ICC patients into $pLNM^+$ group, $pLNM^-$ group and LN^- group (the patients without performing the lymphadenectomy). After KM analysis, we found that $pLNM^+$ group had extremely poor prognosis compared with $pLNM^-$ and LN^- group (Fig. 3). In $pLNM^+$ group, the 5-year OS rate was only 7.7%, no patients survived longer than 6 years, the median OS time was only 17 months, which appeared to be extremely lower than that in the $pLNM^-$ and LN^- groups (median OS time: $pLNM^+$ vs. $pLNM^-$ vs. LN^-: 17 months vs. 57 months vs. 54 months, $P < 0.0001$). In addition, almost all the $pLNM^+$ patients recurred within 5 years. The median DFS time was only 7 months, extremely lower than other groups (median DFS time: $pLNM^+$ vs. LN^- vs. $pLNM^-$: 7 months vs. 20 months vs. 42 months, $P < 0.0001$).

Univariate and multivariate COX analysis were performed to find the covariates for propensity score calculation of the PSM and IPTW.

By using R 4.3.3, we performed the univariate and multivariate COX analysis of OS and survive (Table 2). After Univariate COX analysis, the P value of the "hepatobiliary history ($P = 0.034$)", "CEA(log2) ($P < 0.0001$)", "CA199(log2) ($P < 0.0001$)", "HBV infection ($P = 0.068$)", "Imaging ($P = 0.052$)", "Surgical approach ($P = 0.018$)", "T ($P < 0.0001$)", "liver capsule invasion ($P = 0.022$)", "lymphocyte invasion ($P = 0.007$)" were all less than 0.1, thus we used those baseline characteristics to perform the

Table 1 The baseline characteristics of the LN⁻, LNB and LND groups

	Level	Overall	LN⁻	LNB	LND	*P* value
n		308	83	115	110	
Sex (%)	Male	185 (60.06)	53 (63.86)	67 (58.26)	65 (59.09)	0.7059
	Famale	123 (39.94)	30 (36.14)	48 (41.74)	45 (40.91)	
Age (%)	≤65 years	234 (75.97)	60 (72.29)	88 (76.52)	86 (78.18)	0.6281
	>65 years	74 (24.03)	23 (27.71)	27 (23.48)	24 (21.82)	
BMI (%)	≤25	178 (57.79)	39 (46.99)	69 (60.00)	70 (63.64)	0.0566
	>25	130 (42.21)	44 (53.01)	46 (40.00)	40 (36.36)	
Hepatobiliary history (%)	Yes	20 (6.49)	6 (7.23)	9 (7.83)	5 (4.55)	0.5776
	No	288 (93.51)	77 (92.77)	106 (92.17)	105 (95.45)	
Neoadjuvant treatment (%)	No	282 (91.56)	80 (96.39)	103 (89.57)	99 (90.00)	0.1792
	Yes	26 (8.44)	3 (3.61)	12 (10.43)	11 (10.00)	
HBV infection (%)	Yes	159 (51.62)	51 (61.45)	54 (46.96)	54 (49.09)	0.1058
	No	149 (48.38)	32 (38.55)	61 (53.04)	56 (50.91)	
Enlarged LNs (%)	Yes	163 (52.92)	38 (45.78)	57 (49.57)	68 (61.82)	0.0575
	No	145 (47.08)	45 (54.22)	58 (50.43)	42 (38.18)	
Surgery approach (%)	Laparotomy	239 (77.60)	41 (49.40)	97 (84.35)	101 (91.82)	<0.0001
	Laparoscopy	69 (22.40)	42 (50.60)	18 (15.65)	9 (8.18)	
CEA (median [IQR])		1.38 [0.68, 2.10]	1.07 [0.59, 1.97]	1.43 [0.77, 2.14]	1.43 [0.87, 2.18]	0.119
AFP (median [IQR])		1.68 [1.14, 2.39]	1.63 [1.29, 2.42]	1.72 [1.07, 2.34]	1.70 [1.14, 2.43]	0.7997
CA199 (median [IQR])		5.58 [3.76, 8.75]	4.29 [3.10, 6.79]	6.04 [3.89, 9.07]	6.09 [4.20, 9.07]	0.0022
T stage (%)	T1	149 (49.68)	54 (65.06)	56 (48.70)	39 (35.45)	<0.0001
	T2	108 (35.06)	25 (30.12)	40 (34.78)	43 (39.09)	
	T3	33 (9.74)	3 (3.61)	12 (10.43)	18 (16.36)	
	T4	18 (5.52)	1 (1.20)	7 (6.09)	10 (9.09)	
Liver capsule invasion (%)	Yes	205 (66.56)	53 (63.86)	71 (61.74)	81 (73.64)	0.1389
	No	103 (33.44)	30 (36.14)	44 (38.26)	29 (26.36)	
Microvascular invasion (%)	Yes	108 (35.06)	24 (28.92)	39 (33.91)	45 (40.91)	0.2127
	No	200 (64.94)	59 (71.08)	76 (66.09)	65 (59.09)	
Differentiation (%)	Low	175 (56.82)	47 (56.63)	65 (56.52)	63 (57.27)	0.8075
	Middle	126 (40.91)	35 (42.17)	48 (41.74)	43 (39.09)	
	High	7 (2.27)	1 (1.20)	2 (1.74)	4 (3.64)	
Lymphocyte invasion (%)	Yes	146 (47.40)	29 (34.94)	55 (47.83)	62 (56.36)	0.0128
	No	162 (52.60)	54 (65.06)	60 (52.17)	48 (43.64)	
Tumor number (%)	1	244 (79.22)	89 (77.39)	85 (77.27)	70 (84.34)	0.662
	2	(13.96)	16 (13.91)	16 (14.55)	11 (13.25)	
	3	15 (4.87)	7 (6.09)	6 (5.45)	2 (2.41)	
	4	6 (1.95)	3 (2.61)	3 (2.73)	0 (0.00)	
Size group (%)	≤4 cm	119 (38.64)	37 (44.58)	48 (41.74)	34 (30.91)	0.1068
	>4 cm	189 (61.36)	46 (55.42)	67 (58.26)	76 (69.09)	
Post treatment (%)	Yes	133 (43.18)	25 (30.12)	56 (48.70)	52 (47.27)	0.0188
	No	175 (56.82)	58 (69.88)	59 (51.30)	58 (52.73)	
Operation time (mean (SD), min)		259.41 (92.95)	220.71 (90.42)	256.23 (78.68)	291.923 (97.42)	<0.0001
bleeding (median [IQR], ml)		200.00 [100.00, 462.50]	100.00 [50.00, 200.00]	200.00 [100.00, 475.00]	300.00 [100.00, 600.00]	<0.0001
Transfusion (median [IQR], ml)		0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 675.00]	0.006

Table 1 (continued)

	Level	Overall	LN^-	LNB	LND	*P* value
Postoperative hospitalization day (mean (SD), days)		9.98 (5.32)	7.82 (3.07)	10.41 (6.21)	11.16 (5.22)	< 0.0001
Total hospitalization day (mean (SD), days)		16.43 (7.21)	14.01 (5.23)	17.11 (8.18)	17.53 (7.05)	0.0014
Complication Grade (%)	No	256 (83.12)	77 (92.77)	99 (86.09)	80 (72.73)	0.005
	I and II	25 (8.12)	3 (3.61)	7 (6.09)	15 (13.64)	
	III and IV	27 (8.77)	3 (3.61)	9 (7.83)	15 (13.64)	

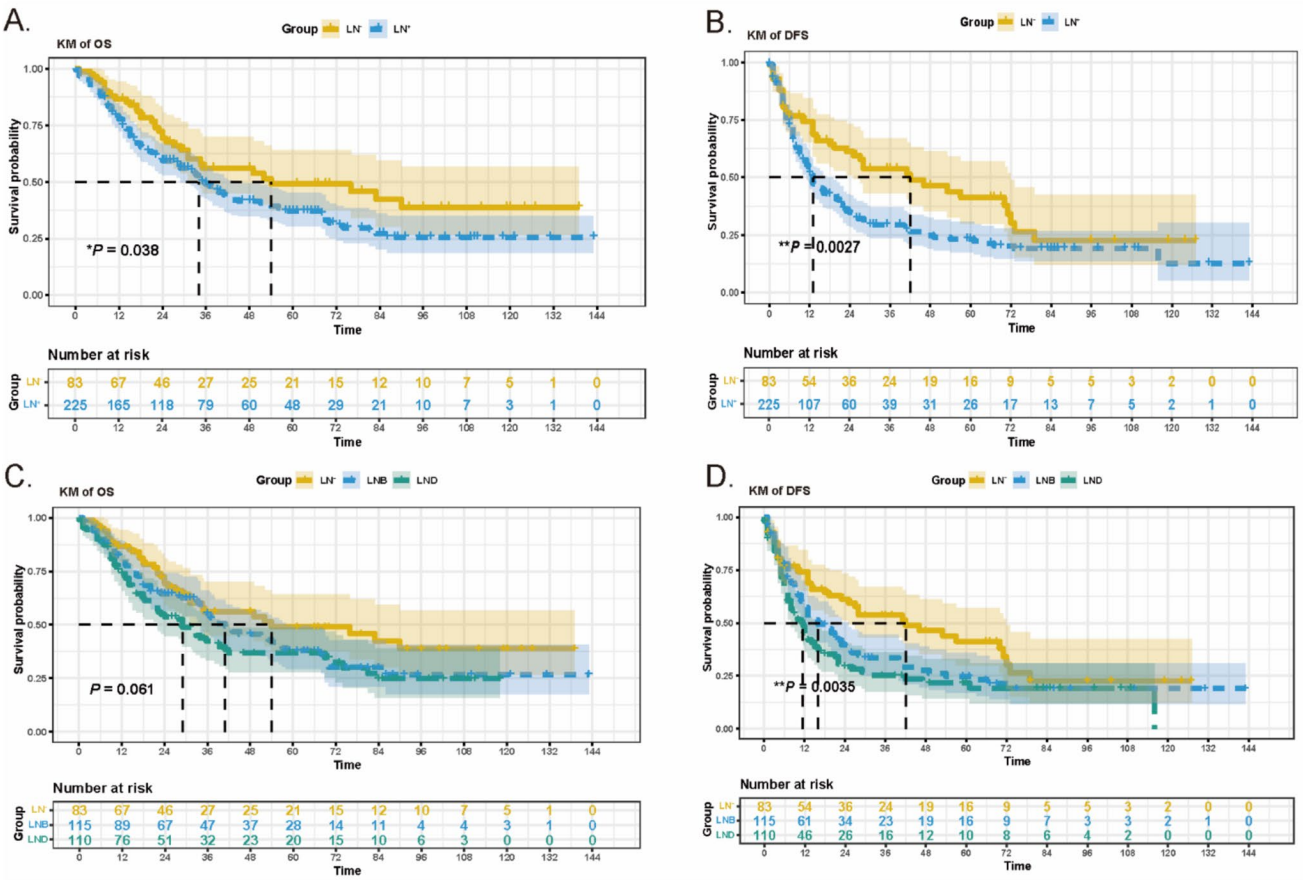

Fig. 2 The KM analysis of OS and DFS before PSM and IPTW. **A** The comparison of KM analysis of OS between LN^- and LN^+ group. Compared with LN^- group, LN^+ group had poorer outcomes ($P = 0.038$). **B** The comparison of KM analysis of DFS between LN^- and LN^+ group. Compared with LN^- group, LN^+ group had and higher recurrence rate ($P = 0.0027$). **C** The comparison of KM analysis of OS between LN^-, LNB and LND groups. With increased lymph node dissection, the prognosis gradually becomes poorer, although there was no significant difference in OS between those three groups ($P = 0.06$). **D** The comparison of KM analysis of DFS between LN^-, LNB and LND groups. The LND group had the worst DFS, and there was significant statistical difference between the three groups ($P = 0.0035$). *DFS* disease-free survival; *LN* lymph node; *LNB* lymph node biology; *LND* lymph node dissection; *OS* overall survival

multivariate COX analysis. After multivariate COX analysis, we found that the P value of "hepatobiliary history ($P = 0.0194$)", "CEA(Log2) ($P < 0.0001$)", "CA199(Log2) ($P = 0.0081$)", "T stage ($P < 0.0001$)", "lymphocyte invasion ($P = 0.0459$)", "liver capsule invasion ($P = 0.0552$)", "surgery approach ($P = 0.0675$)" were less than 0.1, thus we included those confounding factors as covariates in the calculation of the propensity score for both PSM and IPTW analyses. In addition, in the LNB and LN^- groups, the SMD of "post treatment" between the two groups was extremely unbalanced (Fig. 4A). Similarly, in the

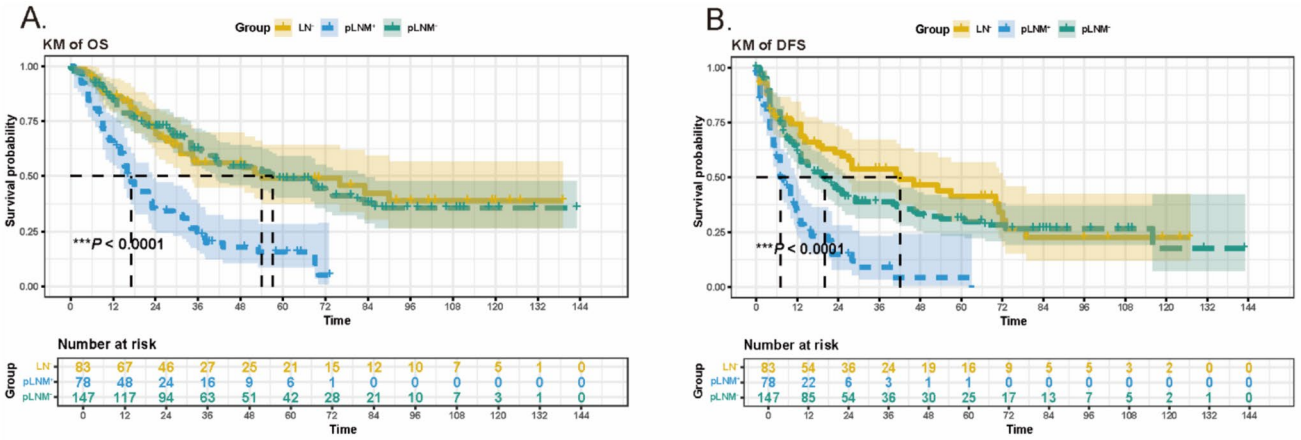

Fig. 3 The KM analysis of OS and DFS between LN⁻, pLNM⁻, and pLNM⁺ group. **A** The KM analysis of OS between those three groups. The pLNM⁺ had the worst OS ($P < 0.0001$). **B** The KM analysis of DFS between those three groups. The pLNM⁺ still had the worst DFS ($P < 0.0001$). *DFS* disease-free survival; *LN* lymph node; *LNM* lymph node metastasis; *OS* overall survival

Table 2 The results of the univariate and multivariate COX analysis about OS and survival

	Univariate COX			Multivariate COX		
Characteristics	HR	CI	*P* value	HR	CI	*P* value
Age (> 65 years)	0.79	0.54–1.15	0.212			
sex	0.82	0.6–1.11	0.2			
BMI (> 25)	1.18	0.87–1.6	0.291			
Hepatobiliary history	1.75	1.04–2.93	**0.034** *	1.88	1.11–3.18	**0.01944***
Neoadjuvant treatment	1.18	0.71–1.98	0.527			
CEA (Log2)	1.36	1.24–1.5	**1.00E–04*****	1.26	1.13–1.41	**4E–05*****
AFP (Log2)	1.05	0.95–1.16	0.303			
CA199 (Log2)	1.16	1.1–1.21	**1.00E–04*****	1.07	1.02–1.13	**0.00812****
HBV infection	1.33	0.98–1.8	0.068	1.08	0.79–1.48	0.6157
Enlarged LNs	0.74	0.54–1	0.052	0.97	0.70–1.35	0.87175
Surgery approach	0.58	0.36–0.91	**0.018**	0.64	0.40–1.03	**0.06746**
Tumor number	1.21	0.9–1.62	0.208			
T stage	1.48	1.27–1.72	**< 0.0001*****	1.33	1.13–1.57	**7E–04*****
Size max (> 4 cm)	1.1	0.8–1.5	0.561			
Liver capsule invasion	0.67	0.48–0.94	**0.022***	0.714	0.50–1.01	**0.055**
Microvascular invasion	0.84	0.61–1.15	0.273			
differentiation	0.82	0.62–1.08	0.163			
Lymphocyte invasion	0.66	0.48–0.89	**0.007****	0.73	0.53–0.99	**0.04593***
Post treatment	0.86	0.64–1.17	0.345			

The bold data refers to the covariates we selected for the PSM and IPTW analyses

LND and LN⁻ groups, the SMDs of "post treatment" and "enlarged LNs" between the two groups were also very large (Fig. 4C). Thus, we included these variables in the matching covariates of the LN⁻ and LND groups.

LNB increased the operation time and post hospitalization days without increasing bleeding, transfusion, complications and prognosis compared with LN⁻ group.

During PSM analysis between LNB and LN⁻ group, we used a matching tolerance of 0.02, and finally successfully matched 55 pairs of patients on a 1:1 basis. After PSM and IPTW, those previously unbalanced baselines

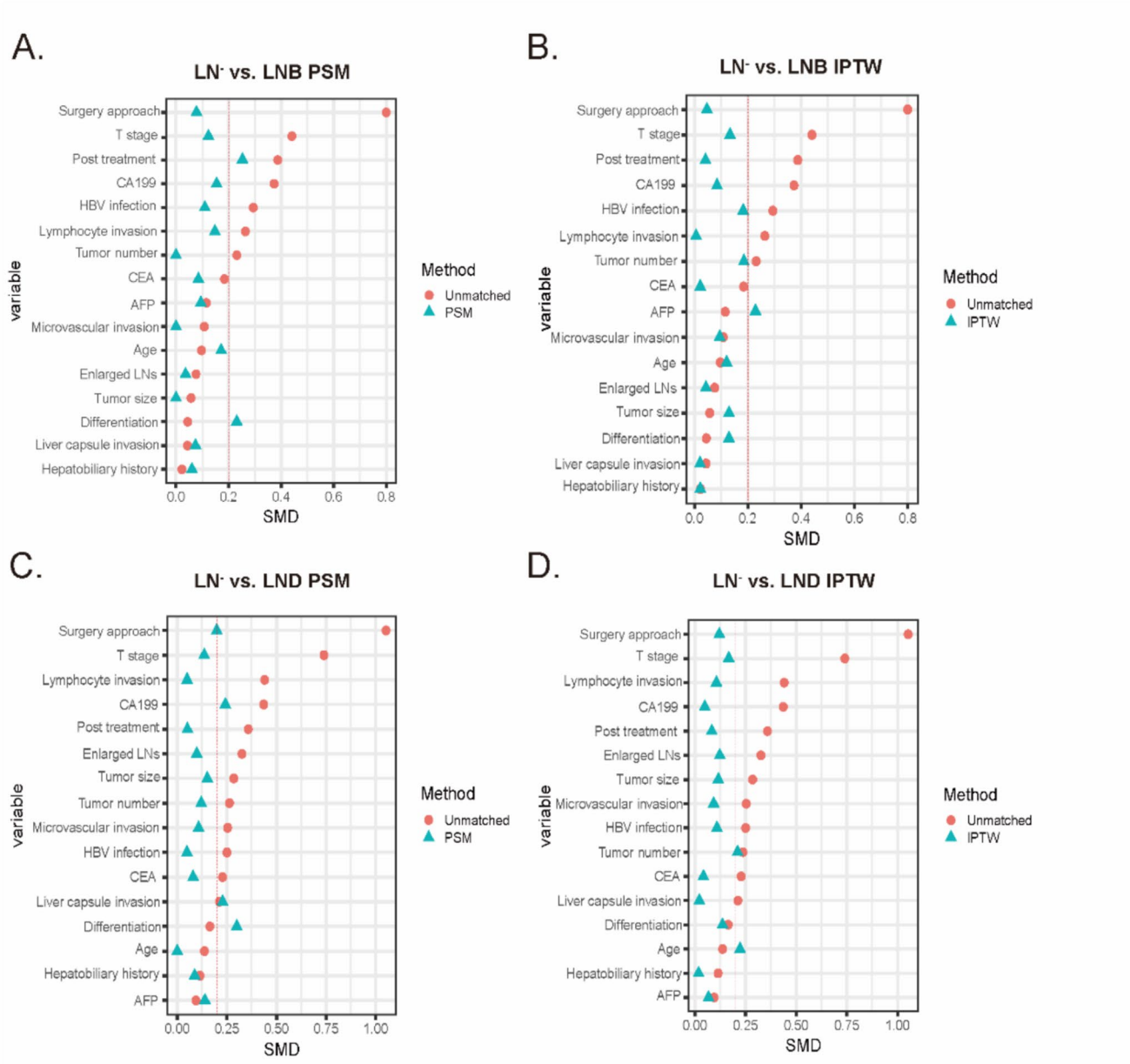

Fig. 4 The evaluation of the SMD in PSM and IPTW. **A** The evaluation of the PSM in LN^- and LNB group. **B** The evaluation of the IPTW in LN^- and LNB group. **C** The evaluation of the PSM in LN^- and LND group. **D** The evaluation of the IPTW in LN^- and LND group. We set the cutoff value for SMD at 0.2, and the results showed that most of the confounding factors have been well adjusted after PSM and IPTW. *DFS* disease-free survival; *IPTW* inverse probability of treatment weighted analysis; *LN* lymph node; *LNB* lymph node biology; *LND* lymph node dissection; *PSM* propensity score matching analysis

have been unified (Table 3, Fig. 4A and B). After PSM and IPTW, the operation time of LNB is still significantly longer than that of the LN^- group (LN^- vs. LNB: PSM: 225.60 ± 94.37 min vs.251.56 ± 77.36 min, $P = 0.1175$; IPTW: 221.52 ± 83.63 min vs.264.48 ± 80.24 min, $P = 0.0024$), with longer postoperative hospitalization days (LN^- vs. LNB: PSM: 8.22 ± 3.39 days vs. 9.58 ± 5.05 days, $P = 0.0994$; IPTW: 8.12 ± 3.22 days vs.10.70 ± 6.94 days, $P = 0.0112$) and total hospitalization days (LN^- vs. LNB: IPTW: 14.49 ± 5.09 days vs.17.42 ± 9.23 days, $P = 0.0346$). At the same time, we found that there was no significant difference in the risk of bleeding (PSM: $P = 0.4087$, IPTW: $P = 0.4471$) and blood transfusion (PSM: $P = 0.6327$, IPTW: $P = 0.6971$), and there was no significant difference in postoperative complications (PSM: $P = 0.7881$, IPTW: $P = 0.3892$). By using KM analysis, we found that LNB had no effect on the prognosis

Table 3 The comparison of LN^- and LNB before and after PSM or IPTW

	Before PSM and IPTW					After PSM				After IPTW			
	Level	Overall	LN^-	LNB	P value	Overall	LN^-	LNB	P value	Overall	LN^-	LNB	*P* value
N		198	83	115		110	55	55		402.04	199.91	202.1	
Hepatobiliary history (%)	Yes	15(7.58%)	6(7.23%)	9(7.83%)	1	11 (10.00)	5 (9.09)	6 (10.91)	1	368.87 (91.75)	182.82 (91.45)	186.05 (92.05)	0.8954
	No	183(92.42%)	77(92.77%)	106 (92.17)		99 (90.00)	50 (90.91)	49 (89.09)		33.17 (8.25)	17.10 (8.55)	16.08 (7.95)	
Enlarged LNs (%)	Yes	95 (47.98)	38 (45.78)	57 (49.57)	0.7029	53 (48.18)	26 (47.27)	27 (49.09)	1	198.77 (49.44)	96.66 (48.35)	102.10 (50.51)	0.8098
	No	103 (52.02)	45 (54.22)	58 (50.43)		57 (51.82)	29 (52.73)	28 (50.91)		203.28 (50.56)	103.25 (51.65)	100.03 (49.49)	
CEA (median [IQR])		1.29 [0.68, 2.10]	1.07 [0.59, 1.96]	1.43[0.77, 2.14]	0.0986	1.20 [0.68, 1.95]	1.14 [0.59, 2.19]	1.20 [0.72, 1.79]	0.7513	1.26 [0.77, 2.10]	1.21 [0.70, 2.23]	1.32 [0.77, 1.95]	0.9096
CA199 (median [IQR])		5.17 [3.58, 8.23]	4.29 [3.10, 6.79]	6.04 [3.89, 9.07]	0.0039	5.02 [3.48, 8.08]	4.59 [3.06, 7.20]	5.14 [3.79, 8.18]	0.2636	5.24 [3.41, 8.35]	4.86 [3.07, 8.31]	5.56 [3.72, 8.24]	0.6897
Surgery approach (%)	Laparotomy	138 (69.70)	41 (49.40)	97 (84.35)	<0.0001	76 (69.09)	39 (70.91)	37 (67.27)	0.8365	277.50 (69.02)	140.17 (70.11)	137.33 (67.94)	0.7881
	Laparoscopy	60 (30.30)	42 (50.60)	18 (15.65)		34 (30.91)	16 (29.09)	18 (32.73)		124.55 (30.98)	59.75 (29.89)	64.80 (32.06)	
T stage (%)	T1	110 (55.56)	54 (65.06)	56 (48.70)	0.0376	71 (64.55)	37 (67.27)	34 (61.82)	0.9367	222.92 (55.45)	106.49 (53.27)	116.43 (57.60)	0.9164
	T2	65 (32.83)	25 (30.12)	40 (34.78)		31 (28.18)	14 (25.45)	17 (30.91)		126.47 (31.46)	64.19 (32.11)	62.28 (30.81)	
	T3	15 (7.58)	3 (3.61)	12 (10.43)		6 (5.45)	3 (5.45)	3 (5.45)		31.17 (7.75)	15.82 (7.91)	15.35 (7.59)	
	T4	8 (4.04)	1 (1.20)	7 (6.09)		2 (1.82)	1 (1.82)	1 (1.82)		21.49 (5.35)	13.41 (6.71)	8.08 (4.00)	
Differentiation (%)	Low	112 (56.57)	47 (56.63)	65 (56.52)	0.9545	58 (52.73)	27 (49.09)	31 (56.36)	0.4838	197.48 (49.12)	91.96 (46.00)	105.52 (52.20)	0.6885
	Middle	83 (41.92)	35 (42.17)	48 (41.74)		51 (46.36)	27 (49.09)	24 (43.64)		200.10 (49.77)	105.97 (53.01)	94.13 (46.57)	
	High	3 (1.52)	1 (1.20)	2 (1.74)		1 (0.91)	1 (1.82)	0 (0.00)		4.47 (1.11)	1.99 (1.00)	2.48 (1.23)	
Liver capsule invasion (%)	Yes	124 (62.63)	53 (63.86)	71 (61.74)	0.8769	66 (60.00)	34 (61.82)	32 (58.18)	0.8457	254.68 (63.35)	127.66 (63.86)	127.02 (62.84)	0.9044
	No	74 (37.37)	30 (36.14)	44 (38.26)		44 (40.00)	21 (38.18)	23 (41.82)		147.36 (36.65)	72.26 (36.14)	75.11 (37.16)	
Lymphocyte invasion (%)	Yes	84 (42.42)	29 (34.94)	55 (47.83)	0.096	46 (41.82)	21 (38.18)	25 (45.45)	0.562	163.42 (40.65)	81.58 (40.81)	81.84 (40.49)	0.9706
	No	114 (57.58)	54 (65.06)	60 (52.17)		64 (58.18)	34 (61.82)	30 (54.55)		238.62 (59.35)	118.33 (59.19)	120.29 (59.51)	

Table 3 (continued)

	Before PSM and IPTW					After PSM				After IPTW			
	Level	Overall	LN^-	LNB	P value	Overall	LN^-	LNB	P value	Overall	LN^-	LNB	*P* value
Post treatment (%)	Yes	81 (40.91)	25 (30.12)	56 (48.70)	0.0133	37 (33.64)	15 (27.27)	22 (40.00)	0.226	238.94 (59.43)	116.75 (58.40)	122.19 (60.45)	0.8176
	No	117 (59.09)	58 (69.88)	59 (51.30)		73 (66.36)	40 (72.73)	33 (60.00)		163.10 (40.57)	83.16 (41.60)	79.94 (39.55)	
Operation time (mean (SD), min)		241.34 (85.41)	220.71 (90.42)	256.22 (78.68)	0.0036	238.58 (86.87)	225.60 (94.37)	251.56 (77.36)	0.1175	243.12 (84.51)	221.52 (83.63)	264.48 (80.24)	0.0024
bleeding (median [IQR], ml)		150.00 [85.00, 400.00]	100.00 [50.00, 200.00]	200.00 [100.00, 475.00]	0.0057	100.00 [50.00, 300.00]	100.00 [50.00, 200.00]	100.00 [90.00, 300.00]	0.4087	100.00 [50.00, 300.00]	100.00 [50.00, 242.10]	200.00 [100.00, 300.00]	0.4471
transfusion (median [IQR], ml)		0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.2269	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.6327	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.6971
Post days (mean (SD), days)		9.32 (5.28)	7.82 (3.07)	10.41 (6.21)	0.0006	8.90 (4.34)	8.22 (3.39)	9.58 (5.05)	0.0994	9.42 (5.56)	8.12 (3.22)	10.70 (6.94)	0.0112
All days (mean (SD), days)		15.81 (7.25)	14.01 (5.23)	17.11 (8.18)	0.0028	15.42 (6.51)	14.82 (5.71)	16.02 (7.23)	0.3361	15.969 (7.590)	14.49 (5.09)	17.42 (9.23)	0.0346
Complication Grade (%)	No	176 (88.89)	77 (92.77)	99 (86.09)	0.3268	100 (90.91)	50 (90.91)	50 (90.91)	0.7881	361.02 (89.80)	186.27 (93.17)	174.76 (86.46)	0.3892
	I and II	10 (5.05)	3 (3.61)	7 (6.09)		7 (6.36)	3 (5.45)	4 (7.27)		23.21 (5.77)	8.10 (4.05)	15.11 (7.48)	
	III and IV	12 (6.06)	3 (3.61)	9 (7.83)		3 (2.73)	2 (3.64)	1 (1.82)		17.81 (4.43)	5.55 (2.78)	12.26 (6.07)	

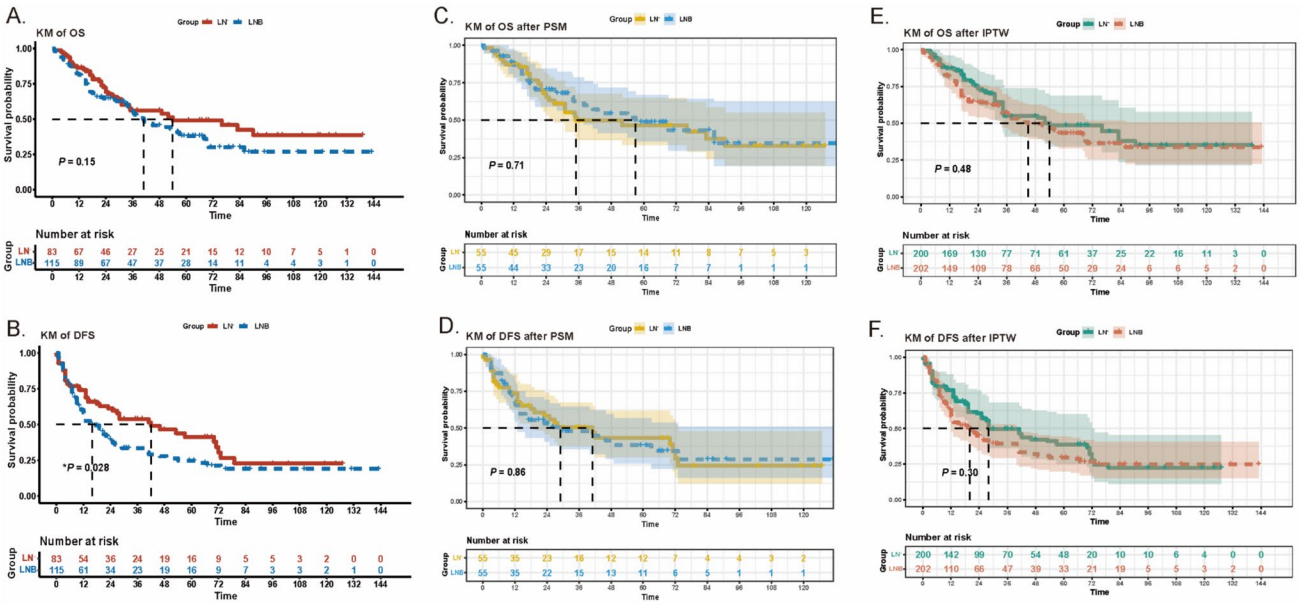

Fig. 5 The KM analysis of OS and DFS in LN⁻ and LNB group. **A**, **B** Before PSM, the OS of the LNB group was slightly lower than that of the LN⁻ group without significant difference ($P=0.15$). The DFS of the LNB group was significantly lower than that of the LN⁻ group ($P=0.028$). (C, D): After IPTW, there was no significant statistical difference in OS ($P=0.71$) or DFS ($P=0.86$) between the two groups; **E**, **F** After PSM, there was no significant statistical difference between the two groups in OS ($P=0.48$) or DFS ($P=0.30$). *DFS* disease-free survival; *LN* lymph node; *LNB* lymph node biology; *OS* overall survival

(Fig. 5), no matter on OS (PSM: $P=0.71$, IPTW: $P=0.48$) or DFS (PSM: $P=0.86$, IPTW: $P=0.30$).

LND group showed worse intra and postoperative outcomes and does not bring survival benefit to patients compared with LN⁻ group

After using PSM, 41 pairs of patients were successfully matched 1:1 basis, and there was no statistical difference in the above baseline factors. After PSM and IPTW, those previously unbalanced baselines have been unified (Table 4, Fig. 4C and D). Compared with LN⁻ group, LND group had no better DFS (Fig. 6, PSM: $P=0.56$, IPTW: $P=0.075$) and OS (PSM: $P=0.99$; IPTW: $P=0.33$), only more complications (IPTW: $P=0.0191$), longer operation time (LN⁻ vs. LND: PSM: 214.59 ± 73.61 min vs. 274.81 ± 83.48 min, $P=0.0009$; IPTW: 222.51 ± 79.26 vs.284.33 ± 88.59, $P<0.0001$), higher risk of bleeding (PSM: $P=0.0264$; IPTW: $P=0.005$) and transfusion (IPTW: $P=0.014$), longer postoperative hospitalization days (before: $P<0.0001$; PSM: $P=0.2709$; IPTW: $P<0.0001$) and longer total hospitalization days (before: $P=0.0002$; PSM: $P=0.516$; IPTW: $P=0.0191$).

LND causes worse postoperative outcomes compared with LNB group

115 patients were included in the LNB group and 110 patients were in the LND group. The comparison of the baseline characteristics of the LNB group and LND group can be seen in Table 5. There was no significant difference in preoperative and intraoperative characteristics between the two groups at baseline, thus it was no need for PSM or IPTW to adjust the baseline levels between the two groups. The operation time of LND was significantly longer than that of the LNB group (LNB vs. LND: 256.23 ± 78.68 min vs. 291.93 ± 97.42 min, $P=0.0027$), the difficulty of the operation was significantly increased. At the same time, the bleeding risk ($P=0.017$) and blood transfusion risk ($P=0.0321$) of patients in the LND group were significantly higher than those in the LNB group. Although the postoperative hospitalization days (LNB vs. LND: 10.41 ± 6.21 days vs.11.16 ± 5.22 days, $P=0.3256$) and total hospitalization days (LNB vs. LND: 17.11 ± 8.18 days vs. 17.53 ± 7.05 days, $P=0.6852$) of the LND group were not significantly different from those of the LNB group, the incidence of postoperative complications in the LND group was significantly higher than LNB group (LNB vs. LND: 13.91% vs. 27.27%, $P=0.0204$). There was no significant statistical difference in the prognostic OS rate ($P=0.28$) and postoperative DFS rate ($P=0.14$) of LNB and LND group (Fig. 7A and B). 34/115 (29.57%) of LNB group patients were diagnosed as "pLNM⁺", while 44/110 (40.00%) of LND group patients were diagnosed as "pLNM⁺" with no significant difference between those two groups (Table 5, $P=0.1326$). There was no difference between OS ($P=0.51$) and DFS ($P=0.14$) of patients with pLNM⁺ following LND and LNB (Fig. 7C

Table 4 The comparison of LN^- and LND before and after PSM and IPTW

Group	Level	Before PSM and IPTW				After PSM				After IPTW			
		overall	LN^-	LND	P value	Overall	LN^-	LND	P value	Overall	LN^-	LND	*P* value
n		193	83	110		82	41	41		377.4	192.8	184.6	
Hepatobiliary history (%)	No	182 (94.30)	77 (92.77)	105 (95.45)	0.6294	75 (91.46)	37 (90.24)	38 (92.68)	1	356.76 (94.53)	181.87 (94.33)	174.89 (94.74)	0.9087
	Yes	11 (5.70)	6 (7.23)	5 (4.55)		7 (8.54)	4 (9.76)	3 (7.32)		20.63 (5.47)	10.93 (5.67)	9.70 (5.26)	
Enlarged LNs (%)	Yes	106 (54.92)	38 (45.78)	68 (61.82)	0.0384	38 (46.34)	18 (43.90)	20 (48.78)	0.8247	204.69 (54.24)	110.34 (57.23)	94.35 (51.12)	0.5487
	No	87 (45.08)	45 (54.22)	42 (38.18)		44 (53.66)	23 (56.10)	21 (51.22)		172.70 (45.76)	82.46 (42.77)	90.24 (48.88)	
CEA (median [IQR])		1.32 [0.69, 2.10]	1.07 [0.59, 1.96]	1.43 [0.87, 2.18]	0.049	1.32 [0.49, 2.10]	1.14 [0.59, 2.10]	1.38 [0.38, 2.07]	0.9003	1.38 [0.68, 1.96]	1.23 [0.77, 2.05]	1.38 [0.59, 1.92]	0.814
CA199 (median [IQR])		5.26 [3.64, 8.63]	4.29 [3.10, 6.79]	6.09 [4.20, 9.07]	0.001	5.19 [3.47, 7.46]	4.59 [3.07, 7.13]	5.700 [4.12, 7.51]	0.1519	6.02 [3.79, 9.71]	6.00 [3.51, 10.35]	5.99 [4.12, 9.09]	0.84
Surgery approach (%)	Laparotomy	142 (73.58)	41 (49.40)	101 (91.82)	<0.0001	69 (84.15)	36 (87.80)	33 (80.49)	0.5454	289.49 (76.71)	143.09 (74.22)	146.39 (79.31)	0.57
	Laparoscopy	51(26.42)	42 (50.60)	9 (8.18)		13 (15.85)	5 (12.20)	8 (19.51)		87.90 (23.29)	49.70 (25.78)	38.20 (20.69)	
T stage (%)	T1	93 (48.19)	54 (65.06)	39 (35.45)	0.0001	50 (60.98)	25 (60.98)	25 (60.98)	0.945	180.14 (47.73)	91.44 (47.43)	88.70 (48.05)	0.9116
	T2	68 (35.23)	25 (30.12)	43 (39.09)		23 (28.05)	12 (29.27)	11 (26.83)		118.72 (31.46)	55.71 (28.89)	63.01 (34.13)	
	T3	21 (10.88)	3 (3.61)	18 (16.36)		6 (7.32)	3 (7.32)	3 (7.32)		53.61 (14.21)	32.14 (16.67)	21.47 (11.63)	
	T4	11 (5.70)	1 (1.20)	10 (9.09)		3 (3.66)	1 (2.44)	2 (4.88)		24.92 (6.60)	13.50 (7.00)	11.41 (6.18)	
Differentiation(%)	Low	110 (56.99)	47 (56.63)	63 (57.27)	0.5505	42 (51.22)	21 (51.22)	21 (51.22)	0.349	199.73 (52.93)	99.81 (51.77)	99.92 (54.13)	0.703
	Middle	78 (40.41)	35 (42.17)	43 (39.09)		38 (46.34)	20 (48.78)	18 (43.90)		171.39 (45.41)	91.23 (47.32)	80.15 (43.42)	
	High	5 (2.59)	1 (1.20)	4 (3.64)		2 (2.44)	0 (0.00)	2 (4.88)		6.27 (1.66)	1.75 (0.91)	4.52 (2.45)	
Liver capsule invasion (%)	Yes	134 (69.43)	53 (63.86)	81 (73.64)	0.1928	62 (75.61)	29 (70.73)	33 (80.49)	0.4404	269.70 (71.47)	138.72 (71.95)	130.99 (70.96)	0.914
	No	59 (30.57)	30 (36.14)	29 (26.36)		20 (24.39)	12 (29.27)	8 (19.51)		107.68 (28.53)	54.08 (28.05)	53.60 (29.04)	
Lymphocyte invasion (%)	Yes	91 (47.15)	29 (34.94)	62 (56.36)	0.005	33 (40.24)	16 (39.02)	17 (41.46)	1	179.25 (47.50)	86.58 (44.91)	92.67 (50.20)	0.632
	No	102 (52.85)	54 (65.06)	48 (43.64)		49 (59.76)	25 (60.98)	24 (58.54)		198.14 (52.50)	106.21 (55.09)	91.93 (49.80)	

Table 4 (continued)

Group	Level	Before PSM and IPTW				After PSM				After IPTW			
		overall	LN^-	LND	P value	Overall	LN^-	LND	P value	Overall	LN^-	LND	*P* value
Post treatment (%)	Yes	77 (39.90)	25 (30.12)	52 (47.27)	0.0238	53 (64.63)	27 (65.85)	26 (63.41)	1	148.98 (39.48)	72.27 (37.48)	76.71 (41.56)	0.6977
	No	116 (60.10)	58 (69.88)	58 (52.73)		29 (35.37)	14 (34.15)	15 (36.59)		228.41 (60.52)	120.53 (62.52)	107.88 (58.44)	
Operation time (mean (SD), min)		261.30 (100.65)	220.71 (90.42)	291.93 (97.42)	< 0.0001	244.70 (83.87)	214.59 (73.61)	274.81 (83.48)	0.0009	252.75 (89.28)	222.51 (79.26)	284.33 (88.59)	< 0.0001
Bleeding (median [IQR], ml)		200.00 [100.00, 400.00]	100.00 [50.00, 200.00]	300.00 [100.00, 600.00]	< 0.0001	200.00 [100.00, 400.00]	100.00 [50.00, 300.00]	300.00 [100.00, 500.00]	0.0264	100.00 [50.00, 400.00]	100.00 [50.00, 200.000]	257.16 [100.00, 500.00]	0.005
Transfusion (median [IQR], ml)		0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 675.00]	0.0032	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.3426	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 88.58]	0.014
Post days (mean (SD), days)		9.73 (4.72)	7.82 (3.07)	11.16 (5.22)	< 0.0001	9.13 (3.29)	8.732 (3.46)	9.54 (3.10)	0.2709	9.33 (4.02)	8.13 (2.94)	10.59 (4.59)	< 0.0001
All days (mean (SD), days)		16.02 (6.55)	14.01 (5.23)	17.53 (7.05)	0.0002	15.34 (4.70)	15.68 (5.27)	15.00 (4.09)	0.5141	15.77 (5.74)	14.53 (4.67)	17.06 (6.45)	0.0044
Complication Grade (%)	No	157 (81.35)	77 (92.77)	80 (72.73)	0.0019	73 (89.02)	38 (92.68)	35 (85.37)	0.516	319.55 (84.67)	180.11 (93.42)	139.44 (75.54)	0.0191
	I and II	18 (9.33)	3 (3.61)	15 (13.64)		5 (6.10)	2 (4.88)	3 (7.32)		34.01 (9.01)	7.96 (4.13)	26.05 (14.11)	
	III and IV	18 (9.33)	3 (3.61)	15 (13.64)		4 (4.88)	1 (2.44)	3 (7.32)		23.83 (6.31)	4.73 (2.45)	19.10 (10.35)	

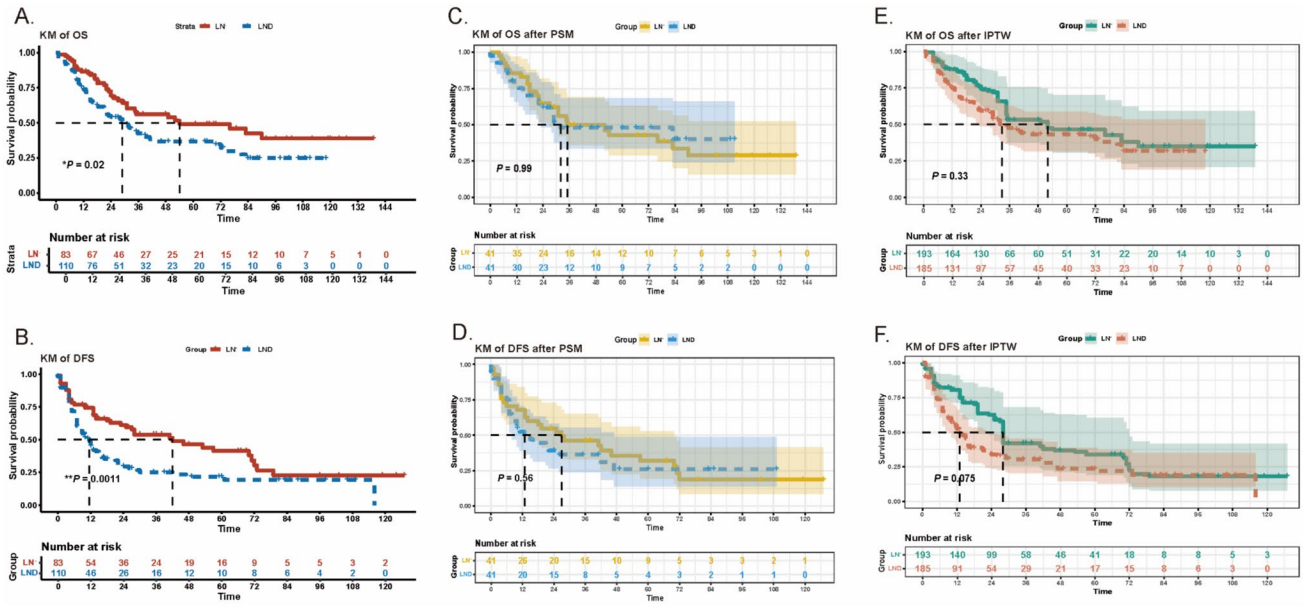

Fig. 6 The KM analysis of LN^- and LND group. **A**, **B** Before PSM, the OS ($P=0.22$) and the DFS ($P=0.0011$) of the LND group were significantly lower than that of the LN^- group. **C**, **D** After PSM, there was no significant statistical difference between the two groups in OS ($P=0.99$) or DFS ($P=0.56$). **E**, **F** After IPTW, there was no significant statistical difference in OS ($P=0.33$) or DFS ($P=0.075$) between the two groups. *DFS* disease-free survival; *IPTW* inverse probability of treatment weighted analysis; *LN* lymph node; *LND* lymph node dissection; *OS* overall survival; *PSM* propensity score matching analysis

and D) and no difference between OS ($P=0.78$) and DFS ($P=0.7$) of patients with $pLNM^-$ following LND and LNB (Fig. 7E and F).

Discussion

ICC is a highly malignant tumor with poor prognosis, only a small number of ICC patients (10%−15%) are suitable for surgical treatment (Roy et al. 2021). Even with surgical treatment, ICC is still associated with high recurrence and poor survival outcomes. In our study, the ICC tumor recurrence rate reached an astonishing 64.9%, and the 5-year DFS rate was only 13.6%. The survival rate was extremely poor, 5-year survival rate was only 22.4%. Consistent with previous studies, *Jeong, J.* et al. demonstrated that more than 50% of ICC patients developed disease progression within 20 months after radical surgery, and the 5-year OS rate was between 30 and 35% (Jeong et al. 2022). *Mazzaferro, V.* et al. reported that 50–70% of the patients developed recurrence after a median of 26 months. The median OS after radical surgery was 40 months, and the 5-year OS rate was 25–40% (Mazzaferro et al. 2020). LNM is an independent risk factor for poor prognosis after surgical resection as the *result 3.3* described. Consistent with previous study, up to 45–65% of ICC patients found LNM at the time of clinical diagnosis (Sposito et al. 2022). The 5-year OS of pN0 patients was 35–50%, while that of pN1 patients was only 0–20% (Navarro et al. 2020). Once LNM was confirmed, the median survival time after radical surgery decreased to 15–20 months, and the 5-year OS rate decreased to 15% (Hyder et al. 2014). ICC does have a poor prognosis, especially the patients with LNM.

However, there is currently no international consensus guideline on the lymphadenectomy, which is precisely why lymphadenectomy remains a controversial procedure. The majority of surgeons followed these general criteria: (1) preoperative imaging findings of metastatic LNs; (2) intraoperative exploration revealing enlarged or suspicious LNs. Whether lymphadenectomy is beneficial to patients has indeed been a highly controversial topic. In our retrospective study, compared with LN^- group, the OS ($P=0.038$) and DFS ($P=0.0027$) of the LN^+ group were significantly lower before PSM and IPTW. The LND group has a worse prognosis, which is contrary to various previous studies that LND could promote the long-term survival (Chen et al. 2022; Ke et al. 2021; Kim et al. 2019). After the baseline comparison, we found that those confounding factors affected the prognosis. Firstly, the LN^+ group had a higher T stage ($P=0.0008$). The higher the T stage, the worse the prognosis (Huang et al. 2021; Sun et al. 2021). The higher T stage means the larger tumor diameter, more multiple tumors, or higher probability of vascular invasion, (Zhang et al. 2021) which could be roughly judged by the doctor from a macro perspective during the operation. Thus, the higher the tumor stage, the more likely doctors will choose to perform LNB for accurate

Table 5 The baseline characteristics of the LNB group and LND group

	Level	Overall	LNB	LND	*P* value
n		225	115	110	
Hepatobiliary history (%)	No	211 (93.78)	106 (92.17)	105 (95.45)	0.4579
	Yes	14 (6.22)	9 (7.83)	5 (4.55)	
Enlarged LNs (%)	Yes	125 (55.56)	57 (49.57)	68 (61.82)	0.0864
	No	100 (44.44)	58 (50.43)	42 (38.18)	
CEA (median [IQR])		1.43 [0.77, 2.17]	1.43 [0.77, 2.14]	1.43 [0.87, 2.18]	0.7695
CA199 (median [IQR])		6.06 [4.07, 9.09]	6.04 [3.89, 9.07]	6.09 [4.20, 9.07]	0.7047
Surgery approach (%)	Laparotomy	198 (88.00)	97 (84.35)	101 (91.82)	0.1289
	Laparoscopy	27 (12.00)	18 (15.65)	9 (8.18)	
T stage (%)	T1	95 (42.22)	56 (48.70)	39 (35.45)	0.1893
	T2	83 (36.89)	40 (34.78)	43 (39.09)	
	T3	30 (13.33)	12 (10.43)	18 (16.36)	
	T4	17 (7.56)	7 (6.09)	10 (9.09)	
Differentiation (%)	Low	128 (56.89)	65 (56.52)	63 (57.27)	0.6499
	Middle	91 (40.44)	48 (41.74)	43 (39.09)	
	High	6 (2.67)	2 (1.74)	4 (3.64)	
Liver capsule invasion (%)	Yes	152 (67.56)	71 (61.74)	81 (73.64)	0.0779
	No	73 (32.44)	44 (38.26)	29 (26.36)	
Lymphocyte invasion (%)	Yes	117 (52.00)	55 (47.83)	62 (56.36)	0.251
	No	108 (48.00)	60 (52.17)	48 (43.64)	
Post treatment (%)	No	117 (52.00)	59 (51.30)	58 (52.73)	0.9362
	Yes	108 (48.00)	56 (48.70)	52 (47.27)	
$pLNM^+$ (%)	No	147 (65.33)	81 (70.43)	66 (60.00)	0.1326
	Yes	78 (34.67)	34 (29.57)	44 (40.00)	
Operation time (mean (SD), min)		273.68 (89.94)	256.23 (78.68)	291.93 (97.42)	0.0027
Bleeding (median [IQR], ml)		200.00 [100.00, 500.00]	200.00 [100.00, 475.00]	300.00 [100.00, 600.00]	0.017
Transfusion (median [IQR], ml)		0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 675.00]	0.0321
Post days (mean (SD), days)		10.78 (5.75)	10.41 (6.21)	11.16 (5.22)	0.3256
All days (mean (SD), days)		17.32 (7.64)	17.113 (8.18)	17.53 (7.05)	0.6852
Complication Grade (%)	No	179 (79.56)	99 (86.09)	80 (72.73)	0.0425
	I and II	22 (9.78)	7 (6.09)	15 (13.64)	
	III and IV	24 (10.67)	9 (7.83)	15 (13.64)	

staging or LND to prevent metastasis, making it easier for patients with higher T stages to undergo lymphadenectomy, leading higher T stage in LN^+ group. In addition, the LN^+ group had higher CEA level (LN- vs. LN^+: 1.07 [0.59, 1.96] vs.1.43 [0.77, 2.17], $P=0.041$) and CA199 level (LN- vs. LN^+: 4.29 [3.10, 6.80] vs.6.06 [4.07, 9.09], $P=0.0005$), which indicate the overloading tumor cells, greater risk of LNM, greater risk of distant metastasis, and poor prognosis (Li et al. 2022). In postoperative pathology, the tumor tissue of the LN^+ group had higher lymphocyte infiltration ($P=0.008$), also indicates a worse prognosis (Galun et al. 2018). 30.12% LN^- patients received the postoperative adjuvant therapy, lower than the LN^+ group (48%, $P=0.0073$). The postoperative adjuvant therapy may improve the prognosis that was another confounding factor contributing to the better survival rate of LN^- group. These confounding factors together led to better OS and DFS in the LN^- group than in the LN^+ group.

Therefore, we urgently needed to adjust these confounding factors. After univariate and multivariate COX analysis and SMD analysis, we actively selecting indicators that theoretically have a causal relationship with prognostic indicators and including them in the PSM and IPTW analysis, the results are easier to interpret, and the problem of model failure due to too many variables is avoided, improving the accuracy and reliability of the study. PSM is a classical method to reduce the confounding effect in the retrospective study (Lee et al. 2022). PSM showed robust matching effect, greatly eliminate the influence of endogenous factors as indicated in the observational study (Benedetto et al. 2018). However, there is sample size loss caused by non-pairing in the process of "finding paired samples". In our

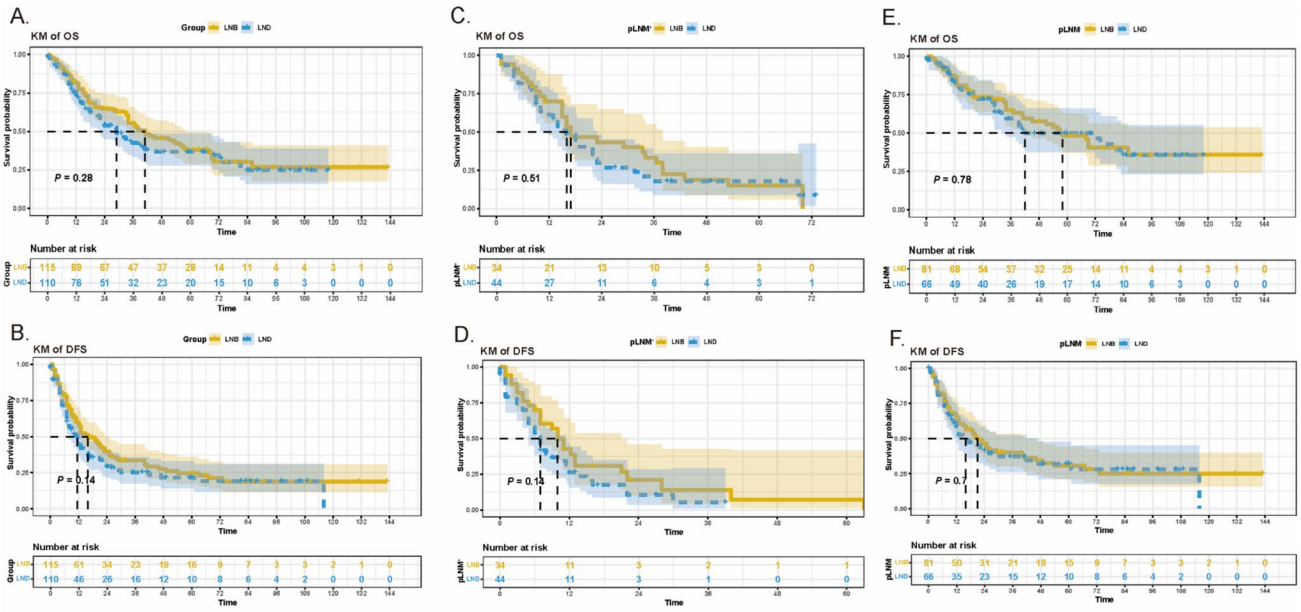

Fig. 7 The KM analysis of LNB and LND group. **A** The comparison of KM analysis of OS between LNB and LND group ($P=0.28$). **B** The comparison of KM analysis of DFS between LNB and LND group ($P=0.14$). **C** The comparison of KM analysis of OS between $pLNM^+$ LNB and $pLNM^+$ LND group ($P=0.51$). **D** The comparison of KM analysis of DFS between $pLNM^+$ LNB and $pLNM^+$ LND group ($P=0.14$). **E** The comparison of KM analysis of OS between $pLNM^-$ LNB and $pLNM^-$ LND group ($P=0.78$). **F** The comparison of KM analysis of DFS between $pLNM^-$ LNB and $pLNM^-$ LND group ($P=0.7$). *DFS* disease-free survival; *LN* lymph node; *LNM* lymph node metastasis; *LNB* lymph node biology; *LND* lymph node dissection; *OS* overall survival

study, we included 7 covariates that needed to be adjusted during PSM, resulting in a drastically reduction of patients included, although it further eliminated the influence of irrelevant variables. Only 55 pairs (110 in total) of patients were involved after PSM between LN^- and LNB group, the data loss ratio reached 44.4%. Only 41 pairs (82 in total) of patients were involved after PSM between LN^- and LND group with the data loss ratio of 57.5%. At the same time, IPTW is a rising statistical method without causing data loss (Austin & Stuart 2015). IPTW has been used by various ICC research fields to adjust the confounding factors on the basis of maintaining the sample size (Ke et al. 2023; Sposito et al. 2023).

After univariate and multivariate COX analysis, we involved those seven confounding factors ("hepatobiliary history", "CEA(Log2)", "CA199(Log2)", "T stage", "lymphocyte invasion", "liver capsule invasion", "surgery approach") as the covariates of PSM and IPTW. As discussed above, "CEA", "CA199", "T stage", "lymphocyte invasion" have significant influence on the prognosis in ICC patients. Although the there was no significant difference of "hepatobiliary history" between those three groups, ICC patients with a history of hepatobiliary may have a worse prognosis since the certain damage has caused to bile duct cells, (Lurje et al. 2023) thus it is necessary to be involved into adjusted factor. In addition, we found that the P value of "liver capsule invasion ($P=0.0552$)", "surgery approach ($P=0.0675$)" were close to 0.05 and may have an uncertain impact on prognosis. Previous research has shown the invasion of liver capsule caused worse survival rate, (Zhou et al. 2020) and the laparoscopic surgery leads to better short-term outcomes in ICC patients, (Zhao et al. 2023). According to statistical principles of PSM and IPTW, researchers can determine the threshold of the including P value of PSM and IPTW between 0.05 and 0.1 based on actual clinical conditions. Therefore, we finally included the factors with the P value of multivariate COX analysis less than 0.1 as the covariates of PSM and IPTW. These seven confounding factors have been well adjusted after PSM and IPTW (Fig. 4).

As described in *results 3.4*, compared with LN^- group, LNB group only increased the operation time and postoperative or total hospitalization time after PSM and IPTW, without increasing the complication or risk of bleeding or risk of transfusion. Due to the inaccuracy of preoperative imaging in predicting LNM, LNM staging was inaccurate in up to 40% of ICC patients, (Tsilimigras et al. 2021) LNB is of great significance in the diagnosis of LNM. LNB as the gold standard for pathological diagnosis of LNM, provides accurate nodal staging and enables precise pathological staging for ICC patients (Sposito et al. 2023). In our study, the NO.8 LN (the common hepatic artery LN) and NO.12 LN (the hepatoduodenal ligament LN) were firstly dissected to achieve the accurate staging during LNB. Previous researches showed that 4 or more LNs are sufficient to obtain

accurate staging, (Chen et al. 2021). and the No.12 LN and No.8 LN must be included during the LNB for accurate staging since those two are the highest risk areas for LNM (Kang et al. 2021; Kim et al. 2022a). Accurate nodal staging could predict and guide the postoperative adjuvant treatment to achieve better prognosis (Ke et al. 2021). Although LNB also prolongs the operation time and hospitalization days compared with LN^- group, in view of the fact that LNB can bring more accurate pathological staging guides subsequent treatment, these adverse events are acceptable. In addition, no-LND may lead to the omission of LNM and inaccurate staging of ICC, LNB can significantly make up for these two shortcomings.

To assess whether LNB is sufficient for lymphadenectomy, we evaluated the possibility of missing positive LNs in *results 3.6*. The results showed that 29.57% of LNB group patients were diagnosed as "$pLNM^+$", while 40.00% of LND group patients were diagnosed as "$pLNM^+$". The LNB group was 10 percentage points lower than the LND group, suggesting that there may be difference suggests a potential underestimation of $pLNM^+$ in the LNB group, LNB may have a possible 25% LN positive missing rate. However, a Chi-square test showed there was no significant difference in the proportion of $pLNM^+$ between those two groups ($P=0.1326$). This indicates that, statistically, the difference in $pLNM^+$ rates is not significant, and the observed difference could be due to random variation. To determine whether the underestimation of $pLNM^+$ in the LNB group affects survival outcomes, we compared the prognosis of patients with $pLNM^+$ following LND and LNB. The results showed no difference between OS ($P=0.51$) and DFS ($P=0.14$) of patients with $pLNM^+$ following LND and LNB (Fig. 7C and D). This suggests that even if there is a 25% underestimation of $pLNM^+$ in the LNB group, it does not significantly impact the survival outcomes. Similarly, we compared the prognosis of patients with $pLNM^-$ following LND and LNB. The results again showed no difference between OS ($P=0.78$) and DFS ($P=0.7$) of patients with $pLNM^-$ following LND and LNB (Fig. 7E and F). This further supports the reliability of LNB in prognostic assessment and indicates that the potential missing of positive lymph nodes in LNB is acceptable. LNB is comparable to LND, indicating that the prognostic impact of $pLNM^-$ is reliable, and the potential missing of LNMs in LNB is acceptable, suggesting that LNB can achieve the same effect as LND.

LND is still under debated due to it increases the difficulty of surgery, adverse effects on postoperative recovery, and uncertainty about prognosis (Lee et al. 2020; Zhou et al. 2019) Although some centers indicated that LND could promote the long-term outcomes and prognosis of ICC patients, (Chen et al. 2022; Ke et al. 2021; Kim et al. 2019; Yoh et al. 2019) many centers including our center did not find the benefit of LND to the therapeutic effect, the OS or DFS was not significant improved after LND (Hu et al. 2021; Li et al. 2013; Zhou et al. 2019; Zhu et al. 2023). In our center, we strictly followed the standard of LND steps and resection range defined by AJCC, (Kim et al. 2019) at least 6 LNs including the NO.12 LN and NO.8 LN were dissected. However, review of LND showed that the implementation rate of LND in major hepatobiliary surgery centers in the world ranges from 26.9 to 100%, only 10% of ICC patients receive the adequate LND (Lluís et al. 2023). In addition, many centers do not strictly follow the AJCC guidelines for LND, the mode and steps of LND vary from center to center, depending on the experience of the surgeon. Those contributes to the different or even completely opposite conclusions eventually lead to the debate of LND.

The original purpose of LND is to accurately stage and prevent suspicious LNM to reduce the risk of recurrence and achieve a better prognosis. However, due to the high complexity and variability of lymphatic system around the liver, (Morine & Shimada 2015) it is impossible for us to comprehensively dissect all the LNs around the liver. Although we dissected the most suspicious LNs that may develop LNM such as NO.12 and NO.8 LNs, (Kang et al. 2021) the other LNs still have the probability of developing LNM. In addition, LNM is a systemic disease (D. Y. Li et al. 2013). Researches have proved that LNM in ICC can directly spread to distant regional LNs through the multidirectional lymphatic pathways connected to the systemic lymphatic system (Li et al. 2013). LND performed on ICC patients who are confirmed to have LNM may still only be LN sampling in a broad sense and cannot achieve the dissection effect only the LNB effect. Therefore, it is not surprising that LND does not achieve the original expected prognosis. Furthermore, LND is associated with increased post-operative morbidity (Zhou et al. 2019). As described in *Results 3.5,* after adjusting the confounding factors by using PSM and IPTW, compared with LN^- group, LND significantly increased the operation time, the risk of post-operative complications bleeding, transfusion, prolong the total and postoperative hospitalization days, which were consistent with previous studies (Yoh et al. 2019). Previous studies indicated that the incidence of complications increases significantly after LND in patients with cirrhosis (Bagante et al. 2018). ICC patients with cirrhosis need to be more careful to perform LND. LNB can provide almost the same information about staging as LND, but significantly reduces post-operative morbidity (Choi et al. 2009). As described in *Results 3.6,* compared with LND, LNB shortens surgery time with minimal impact on operative duration and avoid the increased risk of bleeding, blood transfusion, and postoperative complications. In addition, according to the AJCC staging (Chun et al. 2018; Lee and Chun 2018), among the four types of biliary system tumors (ICC, gallbladder cancer, hilar cholangiocarcinoma, and

distal cholangiocarcinoma), only ICC has an N stage of N1. The other three types are divided into N1 and N2, and they are collectively classified as extrahepatic cholangiocarcinoma. Once there are positive LNs detected in ICC, the N stage is determined without emphasizing the number of positive LNs. LNB is already sufficient for pathological staging, and LND is not necessary for further accurate staging. Therefore, LNB is more recommended compared with LND for accurate pathological stage and more beneficial for patients.

For the future outlook, since LNB is superior to LND and bring more benefits to patients, we will promote LNB more preferentially than LND during radical surgery of ICC in clinical work. In addition, LNM plays such important role in the prognosis of ICC patients, if LNM can be accurately determined before surgery by imaging, then targeted lymphadenectomy can be performed. However, the radiographic LNM staging was inaccurate in up to 40% of ICC patients (Tsilimigras et al. 2021). In the future we propose to establish the muti-imaging omics to build the models to improve the accuracy of preoperative LNM judgment as well as the early recurrence in ICC patients. At the same time, sentinel lymph node biopsy (SLNB) is worth further research. SLN refers to the first station of lymphatic reflux in the organ and the first LNs where LNM occurs (Kurochkin et al. 2022). Like other cancers such as breast cancer and endometrial cancer, SLNB provides a highly reliable method to achieve the accurate staging and is a potential solution to significantly reduce the negative impact of lymphadenectomy in ICC patients (Yasukawa et al. 2021). Although few studies have been performed on SLNB due to the complexity of the hepatic lymphatic system, it will be a major breakthrough in the field of ICC once successful.

In our study, we collected all the eligible ICC patients in this center over the past ten years. As the top cancer hospital in China, the surgical procedures were strictly carried out in accordance with standard procedures, many operation variables were controlled. By using both PSM and IPTW methods, the confounding factors were also well controlled. At the same time, this study was one of the few retrospective studies on LND, and we have reached a conclusion different from enormous previous literatures, providing a solid theoretical basis for opposing the removal of LND. There are still some limitations in our study. As a retrospective study, our articles inevitably face recall bias and choice bias. Furthermore, the single-center characteristics of our study limit the universality of the results. This is a single-center retrospective study with geographical limitations in China and relatively small sample size. The control of variables in retrospective study is far inferior to that in prospective studies, and the loss to follow-up bias is still exist. This article proposes and highlights the LNB, while standardized LNB needs to be further developed in the future.

Concluding remarks

LNM is an extremely poor prognosis risk factor for ICC patients. Lymphadenectomy does not necessarily provide long-term benefits, and not all patients may require LND based on their specific circumstances. LND can only achieve the effect of LNB while negatively affects postoperative recovery with no survival benefit for ICC patients. LNB enables precise pathological staging, with minimal impact on operative duration and postoperative recovery, avoiding increased risk of bleeding, blood transfusion, and postoperative complications. However, standardizing LNB still needs further clinical research.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00432-025-06148-3.

Acknowledgements Fundings: Liming Wang is supported by the CAMS Innovation Fund for Medical Sciences (CIFMS), 2022-I2M-C&T-B-062.

Author contributions Ruoyu Zhang and Dayong Cao: data collection, data analysis, the original draft preparation, tables, and figures production, with the help of Min Yang, Jiajun Wang, Feng Ye, and Ning Huang; Liming Wang, Bo Chen and Liu Mei: conceptualization, review and critical revision; all authors: literature search, review, commentary, and final approval of the manuscript.

Funding Liming Wang is supported by the CAMS Innovation Fund for Medical Sciences (CIFMS), 2022-I2M-C&T-B-062.

Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval This study was approved by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (Approval number: 21/315–2986). All research was conducted in accordance with both the Declarations of Helsinki and Istanbul.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Clinical trial registration Not applicable.

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