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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Surgical Management of Intrahepatic Cholangiocarcinoma: Defining an Optimal Prognostic Lymph Node Stratification Schema

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ABSTRACT

Background. Metastatic disease to the regional lymph node (LN) is a strong predictor of worse long-term outcome after curative-intent resection of intrahepatic cholangiocarcinoma (ICC). The objectives of this study were to assess the prognostic performance of American Joint Committee on Cancer (AJCC)/International Union Against Cancer, 7th edition, N stage, LN ratio (LNR), and log odds of metastatic LN (LODDS) staging criteria in patients with ICC.

Methods. The surveillance, epidemiology, and end results cancer registry was queried to identify 749 patients who underwent surgical resection of ICC during 1988–2011. The Kaplan–Meier method and Cox proportional hazards regression models were used to analyze survival. The relative discriminative abilities of the different LN staging systems were assessed by the Harrell concordance index (c statistic).

Results. Of the 749 patients, 477 (63.7 %) had no LN metastasis, while 272 (36.3 %) had LN metastasis. Patients with LN metastasis had an increased risk of death (hazard ratio 2.42, 95 % confidence interval 1.98–2.95; $P < 0.001$). When assessed using categorical values, LNR (C index 0.620) and LODDS (C index = 0.630) showed a better prognostic performance than the AJCC 7th edition staging system (C index = 0.607). When assessed using continuous values, the LODDS staging system (C index = 0.626) slightly outperformed LNR (C index = 0.621). There was heterogeneity of outcomes among patients with no LN involved (LNR = 0) or all LN involved (LNR = 1), indicating that LODDS may better characterize and stratify outcomes among these groups.

Conclusions. LODDS and LNR showed better prognostic performance than the AJCC 7th edition staging system. When assessed as categorical and continuous variables, LODDS outperformed LNR, especially among those patients with either very low or high LNR.

Similar to other gastrointestinal malignancies, lymph node (LN) status is an important prognostic risk factor for patients with intrahepatic cholangiocarcinoma (ICC).[1–9] How best to define LN status to predict long-term oncologic outcomes has been a topic of increasing interest for many gastrointestinal malignancies, including pancreatic, gastric, and gallbladder cancer.[10–12] Rather than a simple binary designation (i.e., N0 vs. N1), some investigators have proposed that the lymph node ratio (LNR), defined as the ratio of number of metastatic lymph nodes (NMLN) relative to the total number of LN examined (TNLE) may be a better indicator of the impact of LN status on survival after surgery for gastrointestinal malignancies.[13,14] Our group has suggested, however, that LNR may be misleading when used as a prognostic tool for patients who have a whole-number-integer LNR (i.e., 0 or 1).[11,12] Alternatively, several investigators have suggested the log odds of metastatic LN (LODDS), defined as the natural logarithm of the ratio of the probability of a LN to contain metastatic disease versus the probability of a LN to be free of metastatic disease, has prognostic value.[15,16]

The role of routine lymphadenectomy for ICC is controversial. Lymphadenectomy is performed in only approximately half of patients who undergo resection for

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ICC, even at high-volume tertiary hepatobiliary centers.[17] When lymphadenectomy is performed, the overall number of LN collected tends to be relatively low, with a reported median of 2–4 LN evaluated.[17,18] Currently, there is a lack of data on the prognostic performance of various LN staging systems for patients undergoing resection of ICC.[14,19–22] Virtually no data exist on the impact of TNLE, LNR, and LODDS because no study has examined the relative clinical value or prognostic performance of these different LN staging systems for ICC. Therefore, the objective of the current study was to define the relationship among TNLE, NMLN, LNR, and LODDS in a large cohort of patients with ICC. Specifically, we sought to define the prognostic performance of various LN staging schemas among patients undergoing resection of ICC using both nationally representative United States data from the surveillance, epidemiology, and end results (SEER) database.

MATERIALS AND METHODS

Data Sources and Samples

Using the SEER cancer registry database, all patients who underwent liver-directed therapy for ICC between 1988 and 2011 were identified. Using the International Classification of Disease for Oncology, 3rd edition (ICD-O-3), primary site code for liver (22.0), along with the histology code for cholangiocarcinoma (8160), the primary site code for intrahepatic bile duct (22.1), the histology codes for malignant neoplasm (8000), malignant tumor cells (8001), carcinoma (8010), undifferentiated carcinoma (8020), adenocarcinoma (8140), and cholangiocarcinoma (8160) with behavior code (3-malignant tumor), 10,126 patients with ICC were identified.[18] Only patients with microscopically confirmed primary ICC who underwent curative-intent surgery or regional lymphadenectomy and who had data on TNLE and NMLN were included ($n = 749$).

Statistical Analysis

Summary statistics were reported as frequencies with percentages or median values with interquartile ranges (IQR), as appropriate. Standard demographic and clinicopathologic data including age, sex, race, diagnosis year, tumor grade, tumor size, TNLE, NMLN, American Joint Committee on Cancer (AJCC), 7th edition, tumor, node, metastasis classification system classification, and information on cancer-directed surgery were collected. Data on cancer-directed therapy were identified using surgery of primary site codes and site-specific surgery codes for the SEER data set. Information regarding vital status and survival months was collected for all patients.

The LNR was defined as the ratio of the NMLN and the TNLE.[23] The log odds of positive lymph nodes (LODDS) was defined as $\log[(\text{NMLN} + 0.5)/(\text{TNLE} - \text{NMLN} + 0.5)]$.[15] The strata for LNR and LODDS were determined by comparing disease-specific survival (DSS) rates according to LNR and LODDS with an interval of 0.1 and 0.5, respectively. Patients with similar prognosis (log-rank statistic) were then combined. Patients with metastatic LN were classified on the basis of the following intervals: rN0, $\text{LNR} = 0$; rN1, $0 < \text{LNR} \leq 0.5$; and rN2, $0.5 < \text{LNR} \leq 1.0$. LODDS were partitioned into the following categories, LODDS1, $\text{LODDS} \leq 1.5$; LODDS2, $\leq 1.5 < \text{LODDS} \leq 1.0$; LODDS3, $-1.0 < \text{LODDS} \leq 0$; and LODDS4, $0 < \text{LODDS}$. Finally, the impact of TNLE on prognosis was determined using different TNLE cutoff points (≤ 3 and >3 LN).

DSS estimates for the entire study population were estimated by the Kaplan–Meier method calculated from the date of diagnosis to the date of last follow-up or death; differences in survival were examined by the log-rank test. Univariate and multivariate Cox proportional hazard regression models were constructed. Relative risks were presented as hazard ratios (HRs) with 95 % confidence intervals (CIs). Kaplan–Meier estimates of survival and Cox proportional hazards models were used to explore differences in survival.[15,23] The relative discriminative abilities of the LNR and LODDS system were assessed using the Akaike information criterion (AIC) and the Harrell concordance index (c statistic). Lower AIC values indicate a better fit of the model, while a value of $c = 0.5$ indicates no predictive ability compared to chance alone and a value of one indicates perfect discrimination.[24,25] All analyses were carried out by Stata software, version 12.0 (StataCorp, College Station, TX). All tests were two-sided, and a P value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics and Impact on Overall Survival

A total of 749 ICC patients who underwent cancer-directed therapy and who met the inclusion criteria were identified from the SEER cancer registry (Table 1). The median age among the entire cohort was 61 years (IQR 51–70 years). On pathology, most tumors were T1 or T2 ($n = 178$, 38.9 % and $n = 99$, 21.7 %, respectively), while fewer patients had T3 or T4 disease ($n = 114$, 24.9 % and $n = 66$, 14.4 %, respectively). Almost one-third of patients had LN metastasis ($n = 272$, 36.3 %), with a median

TABLE 1 Characteristics of 749 patients with intrahepatic cholangiocarcinoma from surveillance, epidemiology, and end results database

Characteristic	Value
Male sex	351 (46.9)
White race	609 (81.3)
Age (years), median (IQR)	61 (51–70)
Year of diagnosis	105 (14.0)
1988–1997	180 (24.0)
1998–2003	464 (61.9)
2004–2010	
Grade ($n = 605$)	
Well differentiated	72 (11.9)
Moderately differentiated	315 (52.1)
Poorly differentiated	202 (33.4)
Undifferentiated	16 (2.6)
Tumor size, cm, median (IQR)	5.5 (3.2–8.2)
T stage ($n = 457$)	
T1	178 (38.9)
T2	99 (21.7)
T3	114 (24.9)
T4	66 (14.4)
N stage	
N0	477 (63.7)
N1	272 (36.3)
No. of lymph nodes collected, [median] (range)	2 [1, 4] (1–36)
No. of lymph nodes metastases, [median] (range)	0 [0, 1] (0–10)
LNR, median (range)	0 (0–0.5)
LODDS, median (range)	−1.1 [−1.9, 0] (−4.3–2.7)
LNR classification	
rN0	477 (63.7)
rN1	121 (16.2)
rN2	151 (20.2)
LODDS classification	
LODDS 1	290 (38.7)
LODDS 2	228 (30.4)
LODDS 3	80 (10.7)
LODDS 4	151 (20.2)
Radiotherapy	181 (24.2)
Preoperative	14 (7.7)
Postoperative	150 (82.9)
Pre- and postoperative	1 (0.5)
Intraoperative	3 (1.7)
Unknown	13 (7.2)
Resection	615 (66.7)

Data are presented as *n* (%) unless otherwise indicated

IQR interquartile range, *LNR* lymph node ratio, *LODDS* lymph node basin, log odds

TNLE of 2 (IQR 1–4; range 1–36). The number of TNLE changed over time ($P < 0.001$) from a median of 1 LN (IQR 1–3) in 1988–1997 to 2 LN (IQR 1–4) in 1998–2011. Only 1 LN was collected in 293 patients (39.1 %), 2 LN in 129 (17.2 %), 3 LN in 101 (13.5 %), and more than 3 LN in 226 (30.2 %). Among those patients with LN metastasis, a median number of 3 LN (IQR 1–6; range 1–26) was involved. The median LNR and LODDS were 0 (IQR 0–0.5) and −1.1 (IQR −1.9–0; range −4.3–2.7), respectively.

The 1-, 3-, and 5-year DSS was 74.5, 44.3, and 31.6 %, respectively; median survival was 28 months (95 % CI 24–33 months). In examining the entire cohort, several clinical and pathologic factors were associated with worse DSS including increasing tumor size (HR 1.01, 95 % CI 1.00–1.01; $P < 0.001$), tumor grade (reference, well to moderately differentiated; poorly to undifferentiated HR 1.76, 95 % CI 1.42–2.19) T stage (T2: HR 2.14, 95 % CI 1.43–3.21; T3: HR 2.29, 95 % CI 1.55–3.38; T4: HR 3.25, 95 % CI 2.09–5.05; all $P < 0.001$), and LN metastasis (HR 2.42, 95 % CI 1.98–2.95) (all $P < 0.001$).

Impact of TNLE and NMLN on Prognosis

Both TNLE and NMLN were associated with long-term prognosis. Among patients with no LN metastasis, the risk of death decreased for each negative node examined up to three LN examined (HR 0.79, 95 % CI 0.65–0.97; $P = 0.03$). After four TNLE, the effect on survival for additional LN examined was negligible. For example, N0 patients who had ≤ 3 TNLE had a median 3- and 5-year survival of 46 months, 56.3 and 42.3 % versus 51 months, 57.5 and 39.2 % among patients who had >3 nodes examined ($P = 0.94$).

The NMLN also affected prognosis. Of the 272 patients who had N1 disease, the NMLN was 1 ($n = 162$; 59.6 %), 2 ($n = 49$; 18.0 %), 3 ($n = 25$; 9.2 %), or ≥ 4 ($n = 36$; 13.2 %). When modeled as a continuous variable, NMLN was associated with DSS (HR 1.26, 95 % CI 1.19–1.34 per additional LN metastasis); patients with ≥ 3 NMLN had a particularly high risk of DSS compared to patients who had only 1 NMLN (HR 1.47, 95 % CI 1.05–2.07; $P = 0.03$).

Performance of LNR and LODDS

Initial performance of LNR and LODDS was evaluated. The 5-year DSS according to the different LNR categories was nR0 41.8 %, nR1 22.9 %, and nR2 8.2 % (Fig. 1a), while 5-year DSS stratified by LODDS categories was LODDS1 43.3 %, LODDS2 37.2 %, LODDS3 21.0 %, and LODDS4 8.2 % (Fig. 1b). When assessed using the established categorical cutoff values, LODDS was noted to have a

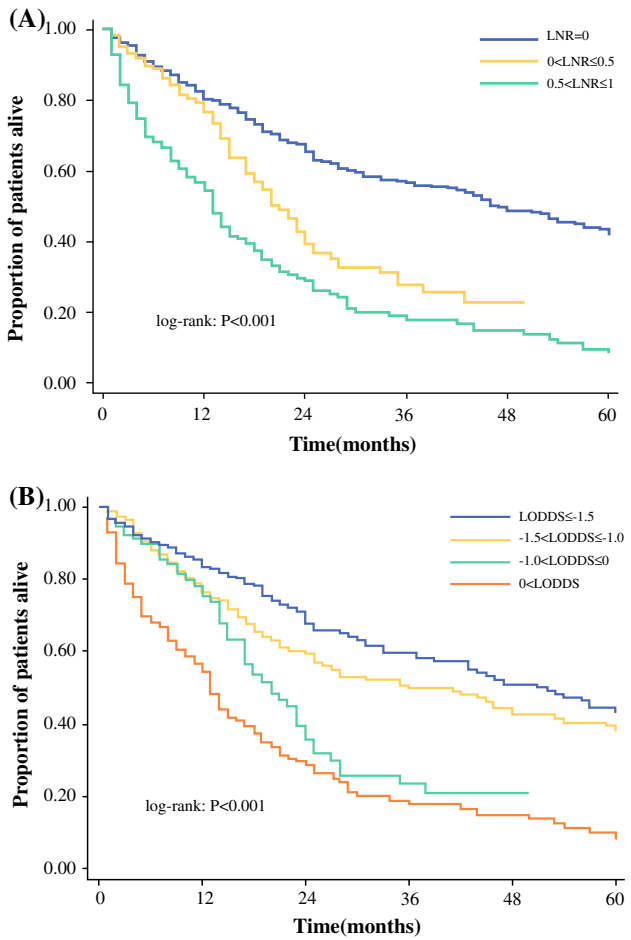

FIG. 1 Kaplan–Meier curves for DSS stratified by LN categories based on **a** LNR and **b** LODDS

somewhat better prognostic performance (C index = 0.630; AIC = 4692.66) than LNR (C index = 0.620; AIC = 4691.89) and AJCC 7th edition nodal staging (C index = 0.607; AIC = 4702.02). When stratified by TNLE (≤3 vs. >3 LN), LODDS performed better among patients who had ≤3 TNLE (C index = 0.632; AIC = 3108.02) compared to LNR (C index = 0.612; AIC = 3110.37) or AJCC nodal staging (C index = 0.603; AIC = 3114.43). In contrast, LNR performed slightly better among patients with >3 TNLE (LNR: C index = 0.642; AIC = 1096.54 vs. LODDS: C index = 0.632; AIC = 1098.40 vs. AJCC: C index = 0.614: AIC = 1100.58).

Examining each scoring system as continuous variables was then performed to further assess the discriminatory ability of LNR and LODDS. LODDS (C index = 0.626; AIC = 4702.67) again tended to have more discrimination than LNR (C index = 0.621; AIC = 4695.05) (Table 2). In multivariable analysis, the Cox proportional hazard model with LODDS (C index = 0.679) had slightly higher discriminating performance compared to LNR (C index = 0.676) or N stage (C index = 0.673) even after adjusting for other prognostic factors such as size, T stage, and grade of tumors ($P < 0.001$). When stratified by TNLE, LODDS as a continuous prognostic factor (C index = 0.631; AIC = 3109.41) was better than LNR (C index = 0.613; AIC = 3109.24) among patients with low TNLE. However, among patients with >3 LN examined, LNR (C index = 0.644; AIC = 1094.63) performed better than LODDS (C index = 0.629; AIC = 1095.64). When stratified by tumor stage, the prognostic performance of LODDS (C index = 0.606; AIC = 844.78) was slightly better than LNR (C index = 0.599; AIC = 843.33) among patients with advanced stage (T3/T4) tumors, while LNR (C index = 0.649; AIC = 894.13) outperformed LODDS (C index = 0.623; AIC = 900.99) among patients with earlier stage (T1/T2) disease. Also, when stratified by tumor grade, LODDS performed better than LNR among patients with well/moderately differentiated tumors (LODDS C index = 0.612; AIC = 1910.17 vs. LNR C index = 0.600; AIC = 1907.59) and those with poorly/undifferentiated tumors (LODDS C index = 0.636; AIC = 1301.95 vs. LNR C index = 0.633; AIC = 1299.93).

Scatter plots were created to evaluate the relationship between TNLE, NMLN, LNR, and LODDS (Figs. 2, 3). As noted in Fig. 2, LODDS increased with increasing NMLN, with a high correlation between LODDS and NMLN ($r = 0.60$). Similarly, LODDS increased with increasing LNR, suggesting a strong overall correlation between these two nodal staging systems ($r = 0.90$) (Fig. 3). Although LNR and LODDS correlated, the data demonstrated that this correlation was not linear. In particular, LODDS values increased slowly when LNR values were in between ~0.2 and 0.8, while LODDS values were very heterogeneous among patients with no LN metastasis (LNR = 0) and among patients with metastatic disease in all LN examined (LNR 1). Specifically, LODDS values ranged between −4.29 and −1.10 among patients with no LN metastasis and 1.10 and 2.71 among patients who had a metastasis in every LN. In essence, while many patients with either a LNR of 0 or 1 seemed to have the same prognosis as estimated by LNR, LODDS revealed a significant amount of residual heterogeneity with regard to prognosis. For example, among patients with a LNR of 0 or 1, 5-year DSS still ranged from 31.1 to 100 % and 2.4 to 39.7 %, respectively. In contrast, LODDS had a better ability to discriminate prognosis among patients with an LNR of 0 or 1 (Fig. 3).

DISCUSSION

Although complete surgical resection remains the treatment of choice for patients with ICC, the prognosis of

TABLE 2 Univariate analysis for overall prognostic performance of node staging schemes for intrahepatic cholangiocarcinoma

Node staging scheme	Discriminatory capacity		LN examined (≤3 LN)		LN examined (>3 LN)	
	Harrell's C	AIC	Harrell's C	AIC	Harrell's C	AIC
AJCC 7th	0.607	4702.02	0.603	3114.43	0.614	1100.58
LNR continuous	0.621	4695.05	0.613	3109.24	0.644	1094.63
LODDS continuous	0.626	4702.67	0.631	3109.41	0.629	1095.64
LNR classification	0.620	4691.89	0.612	3110.37	0.642	1096.54
LODDS classification	0.630	4692.66	0.632	3108.02	0.632	1098.40

Lower AIC values indicate a better fit of the model; a value of $c = 0.5$ indicates no predictive ability compared to chance alone, whereas a value of 1 indicates perfect discrimination

LN lymph node, *AIC* Akaike information criterion, *AJCC* American Joint Committee on Cancer, *LNR* lymph node ratio, *LODDS* log odds of metastatic LN

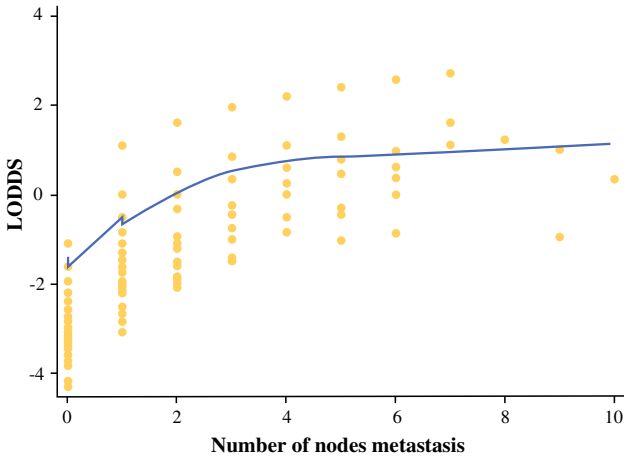

FIG. 2 Distribution of LODDS versus number of node metastases

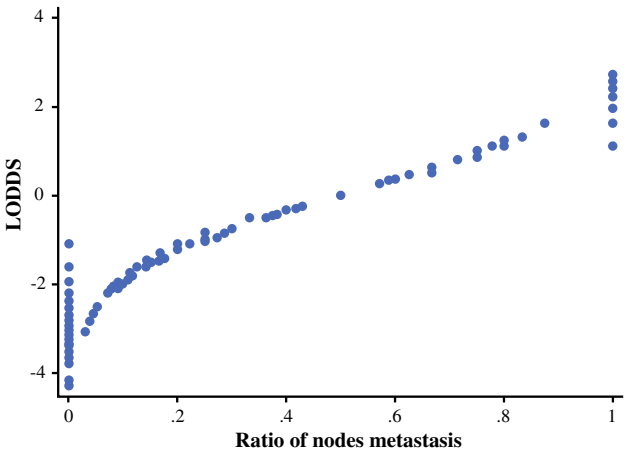

FIG. 3 Distribution of LODDS versus LNR

ICC remains unfavorable, with 5-year survival ranging from 20 to 40 %.[17] Several studies that have reported that metastatic nodal disease is associated with worse survival.[13,18,26–29] However, there is currently no standard approach to assessing regional nodal information.[17,18] Accurate staging information is critical to both patients and physicians to determine prognosis, as well as to plan the intensity of postoperative surveillance. The 7th edition of the AJCC staging manual stratifies patients on the basis of the presence or absence of regional LN metastasis; however, the chance of discovering a nodal metastasis depends on the TNLE.[30] As such, staging systems such as LNR and LODDS have been proposed as alternative means to interpret LN data.[15,23] This study is important because it is the first to evaluate the prognostic ability of LNR and LODDS relative to AJCC LN staging among patients with ICC. Specifically, using a population-based U.S. cohort of patients with ICC, we demonstrated that both LNR and LODDS staging systems showed superior prognostic discriminatory ability compared to the AJCC 7th LN staging system. In particular, we noted that LNR performed better when >3 LN were examined, while LODDS performed better among patients who had ≤3 LN examined. These data may be particularly important given that the median number of TNLE for patients with ICC was 2. Furthermore, the data strongly suggest that a LNR of 0 or 1 may fail to provide accurate information for patients with ICC.[11,12]

In a recent meta-analysis, LN metastasis has been noted to be associated with increased risk of death in pool data (HR 2.09, 95 % CI 1.80–2.43).[9] Similarly, in the current study, we noted a similar relative risk of death associated with LN metastasis (HR 2.42, 95 % CI 1.98–2.95; $P < 0.001$). Furthermore, we noted that the NMLN was associated with prognosis with a 26 % increased risk of death per each additional LN metastasis. Recently, LNR and LODDS have been proposed as potential better prognostic tools to examine the impact of LN metastasis.[15,23] The superior performance of LNR and LODDS has been demonstrated in cancers such as colorectal and gastric cancer.[16,19,20,23,30–32] In patients with ICC, however, there are few data on various LN staging systems.[13,33] In

particular, the prognostic performance of LODDS has not been previously examined. In the current study, we noted that although AJCC, LNR, and LODDS all were associated with long-term outcome, LNR and LODDS outperformed the AJCC staging system. Furthermore, LODDS was generally the best prognostic LN staging system, outperforming both AJCC and LNR. Importantly, in a disease where the TNLE is commonly ≤3 LN, LODDS performed the best among patients with low TNLE (Table 2). Several previous studies have shown the superiority of LODDS in patients with tumors other than ICC.[15,34] As demonstrated in the current study, an advantage of LODDS is the potential to transform LN into natural logarithm so as to better discriminate patients with an LNR of 0 or 1. LODDS is not directly correlated with TNLE or NMLN and therefore may be a better prognostic indicator than LNR among patient with a low number of LN examined. Although several studies have demonstrated that LNR had good discriminatory ability, LNR may be affected by the TNLE. For instance, among patients with all nodes involved (LNR = 1), the prognosis may be substantially different in patients who have five LN metastasis out of five LN examined versus one LN metastasis out of one LN examined. We noted, however, that LODDS better demonstrated the heterogeneous prognosis of patients with LNR 0 or 1 (Fig. 2).

Our study had several limitations. The SEER registry does not provide clinical data on perioperative chemotherapy or treatment rationale. However, our aim was to examine lymphadenectomy and compare different LN staging systems. The SEER registry does provide accurate information on number of LN retrieved and the status of regional LN.

In conclusion, our data suggest that LODDS and LNR are both better predictors of survival after curative intent resection in patients with ICC that the current AJCC nodal staging. Furthermore, while LNR performed well among patients who had >3 LN examined, LODDS was better at determining prognosis among patients with ≤3 LN examined. Furthermore, LODDS was better at displaying the heterogeneity of prognosis of patients with a LNR of 0 or 1. For the majority of patients undergoing resection of ICC with a low TNLE, LODDS should be the nodal staging system of choice.

CONFLICT OF INTEREST The authors declare no conflict of interest.

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