Original Article

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Development and validation of a machine-learning model to predict lymph node metastasis of intrahepatic cholangiocarcinoma: A retrospective cohort study

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SUMMARY Lymph node metastasis in intrahepatic cholangiocarcinoma significantly impacts overall survival, emphasizing the need for a predictive model. This study involved patients who underwent curative liver resection between different time periods. Three machine learning models were constructed with a training cohort (2010-2016) and validated with a separate cohort (2019-2023). A total of 170 patients were included in the training set and 101 in the validation cohort. The lymph node status of patients not undergoing lymph node dissection was predicted, followed by survival analysis. Among the models, the support vector machine (SVM) had the best discrimination, with an area under the curve (AUC) of 0.705 for the training set and 0.754 for the validation set, compared to the random forest (AUC: 0.780/0.693) and the logistic regression (AUC: 0.703/0.736). Kaplan-Meier analysis indicated that patients in the positive lymph node group or predicted positive group had significantly worse overall survival (OS: $p < 0.001$ for both) and disease-free survival (DFS: $p < 0.001$ for both) compared to negative groups. An online user-friendly calculator based on the SVM model has been developed for practical application.

Keywords intrahepatic cholangiocarcinoma, hepatectomy, lymph node metastasis, machine learning

1. Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common type of primary liver cancer, accounting for approximately 10-15% of cases, with hepatocellular carcinoma (HCC) being the most prevalent (*1*). Hepatectomy is currently the primary treatment for ICC. However, only a tiny portion of patients with ICC are able to undergo surgery due to the limited availability of effective diagnostic tools (*2*). Even if surgery is undergone, a significant proportion of patients (nearly 20-50%) will suffer from relapse in the 12-24 months following surgery (*3,4*). Certain serological indicators (elevated CA19-9 or positivity for the hepatitis B virus) and pathological features (microvascular invasion (MVI), multifocal tumor, positive margins, *etc.*) are considered to be linked to the prognosis and recurrence of ICC (*5*). Of these factors, positive lymph nodes (LNs) are widely acknowledged as a substantial risk factor for both survival and recurrence. A negative correlation between the quantity of positive LNs and the overall survival rate has been noted (*6*). Hence, having information about the LN status of individuals diagnosed with ICC can yield vital insights into staging and adjuvant strategies.

There is currently a lack of consensus regarding the necessity of performing LN dissection (LND) in patients with ICC. A prominent point of contention about LND is whether it confers a survival advantage. A meta-analysis of 1,377 cases indicated that undergoing routine LND does not provide an advantage in terms of overall survival but is associated with an elevated risk of post-operative mortality (*7*). LN metastases may indicate a widespread metastatic disease rather than local dissemination, therefore diminishing the significance of LND. However, the advocates argue that the unfavorable views of LND are influenced by a bias in that LND is only performed when LN metastasis is suspected, and these patients clearly tend to have a poor prognosis. From a broader perspective, even if LND offers no benefit in terms of prognosis, it can provide precise details regarding the staging of LNs (*8*) and patients pathologically confirmed to have positive LNs should receive adjuvant treatment as soon as possible and be alert to any signs of tumor recurrence. Currently, LND is performed in less than 50% of cases (*9*), and the rate of sufficient LND (≥ 6) has plummeted to less than 20%

(*10*). Consequently, LN status cannot be determined in a large proportion of patients, hindering systematic treatment strategies following surgery. Therefore, several models to predict LN metastasis based on logistic regression, with results visually depicted in nomograms, have emerged (*11-13*). Nevertheless, the low incidence of ICC leads to a relatively limited number of cohorts, thereby restricting the number of included variables. Moreover, models developed with a small sample size are vulnerable to the influence of outliers, inevitably diminishing the accuracy and reliability of the model. Subsequently, machine learning algorithms have been implemented in medical research to address these issues. Random forest (RF), a supervised learning algorithm, creates a sizable number of decision trees and outputs predicted probability or classification by integrating the results from all generated trees (*14*). A variable is assessed and selected at each split in the decision tree, thereby maximize the disparity between the daughter nodes and recursively proceeding until the decision tree reaches maximum extension, thus effectively avoiding the problem of multicollinearity. A support vector machine (SVM) uses support vectors to identify decision surfaces (hyperplane) that maximize the classification margin between different categories (*5*). This algorithm has reduced susceptibility to outliers, hence enhancing the precision of the model.

In brief, the aim of the current study was to construct a model of the LN metastasis utilizing machine learning techniques, including clinical data and pathology information from patients in order to provide a reference for patients who have not undergone LND or who have undergone inadequate LND.

2. Patients and Methods

2.1. Patients

Data were collected on patients who underwent curative-intent hepatectomy and who were diagnosed with ICC pathologically. The data were collected from the hepato-biliary and pancreatic department of West China Hospital, SCU, between the periods of January 2010 to December 2016 and January 2019 to October 2023. Patients lacking complete pathology information, those who did not undergo curative resection, those with concurrent extrahepatic disease, or those with missing follow-up data were excluded from this study. The Ethics Committee of West China Hospital approved this study [Approval No. 2024(343)], which was conducted in accordance with the principles outlined in the Declaration of Helsinki. Due to the retrospective nature of this study, informed consent from the Institutional Review Board was waived. This study has been registered on ClinicalTrials.gov (NCT06290739).

2.2. Included variables and relevant definitions

Demographic, clinicopathological, and serological indicators included sex (male/female); age (continuous); presence of ascites (yes/no); presence of cirrhosis (yes/no); hepatitis B virus, HBV (positive/negative); platelet count, PLT (continuous); total bilirubin, TB (continuous); aspartate aminotransferase, AST (continuous); alanine aminotransferase, ALT (continuous); albumin, ALB (continuous), prothrombin time, PT (continuous); alkaline phosphatase, ALP (continuous); γ-glutamyl transferase, GGT (continuous); α-fetoprotein, AFP (continuous), carcinoembryonic antigen, CEA (negative: < 5 ng/mL, positive: ≥ 5 ng/mL); carbohydrate antigen-199, CA19-9 (< 200 U/mL, ≥ 200 U/mL); tumor number (solitary/multiple); tumor size (continuous); MVI (presence/absent); primary tumor site (right/left); tumor differentiation (poor, moderate to well-differentiated), and LN metastasis (yes/no). The presence of ascites or cirrhosis was comprehensively ascertained with preoperative imaging, intraoperative observations, and pathology. MVI and the degree of differentiation were confirmed by pathology reports. Hilar cholangiocarcinoma, a tumor originating from the caudate lobe, and bilateral lesions were excluded.

2.3. Follow-up

Patients who underwent a hepatectomy from 2010 to 2016 were followed at three-month intervals during the initial two years and then every six months thereafter until the last follow-up (January 2019). Overall survival (OS) refers to the duration between the commencement of surgery and the patient's demise due to any reason. Disease-free survival (DFS) refers to the period of time from the date of surgery until the occurrence of a relapse either within or outside the liver.

2.4. Statistical analyses and model development

Continuous data were expressed as the mean and range, and intergroup comparisons were made using either the Student's *t*-test or Mann-Whitney *U* test, depending on the circumstances. Binary variables were expressed as the frequency (proportion), and differences were tested with the χ^2 test or Fisher's exact test. This study complies with the Transparent Reporting of a multivariable prediction model for individual Prognosis or Diagnosis (TRIPOD) guideline (*15*). The cohort from 2010 to 2016 served as the training set to construct three models: logistic regression (LR), a support vector machine (SVM), and a random forest (RF). Patients who underwent LND from 2019 to 2023 served as the validation set. Least absolute shrinkage and selection operator (LASSO) regression was performed to determine variables that contributed significantly to the model. Subsequently, stepwise regression was performed to simplify the model. Without compromising the goodness of fit of the model, some adjustments to certain variables were empirically made

based on a previous review of the literature. Moreover, optimal hyperparameters for the SVM and RF were determined *via* a 5-fold cross-validation. Ultimately, the hyperparameters for the machine-learning models were as follows: SVM (*Kernel = linear, Cost* = 0.1) and RF (*mtry* = 2; ntree = 132). A receiver operating characteristics (ROC) curve was plotted for each model, and a model with an outperforming area under the curve (AUC) was selected and applied to patients who did not undergo LND. Finally, survival analysis between predicted N1 (LN metastasis) and N0 (without LN metastasis) was graphed *via* a Kaplan-Meier curve and calculated using a log-rank test. A flowchart is shown in Figure 1. The data were analyzed, models were constructed, and outcomes were plotted using the software R (version 4.2.2), (packages: "glmnet," "car," "MASS," "pROC," "survival," "survminer," "e1071," "randomForest," and "shiny").

3. Results

3.1. Patient demographics

A cohort of 271 patients with ICC who underwent LND at various time periods was included this study (Table 1). Of patients with ICC who undergo hepatectomy at this hospital, around 30-40% undergo LND. Figure 2a shows that the rate of LN biopsy was 44.5% (170/382) in the early cohort (2010-2016) and slightly lower at 34.7% (101/291) in the late cohort (2019-2023). However, the rate of adequate LN examination was higher in the later at 36.6% (versus 28.2% in the former), but not significantly so (p = 0.192) (Figure 2b). Overall, the incidence of LN metastasis among individuals who had received LND was 53.5%, with a somewhat greater proportion in the early cohort (56.5%) compared to the late cohort (48.5%), but not significantly (p = 0.253) (Figure 2c). The incidence of liver cirrhosis, the incidence of MVI, the platelet count, and ALT and GGT levels in the validation group were markedly higher than those in the training cohort. In turn, positivity for CEA, multiple lesions, poor differentiation, prothrombin time (PT), and tumor size were significantly greater in the training set.

3.2. Variable screening

The raw dataset consisted of 21 features including demographics (sex, age, ascites, HBV infection, and liver cirrhosis); serological indicators (PLT, PT, TB, ALT, AST, ALB, ALP, GGT, AFP, CEA, and CA19-9), and pathology (tumor size, tumor number, MVI, primary site of the tumor, and tumor differentiation) that needed to be simplified. To streamline the model, control multicollinearity, and remove variables that had minimal impact on the model, LASSO regression was initially performed (Figure 3a). Five-fold cross validation was performed, and the number of variables associated with the minimum value of binomial deviance was incorporated, including a total of 9 parameters: *age*, *platelet count*, *total bilirubin*, *AFP*, *CEA*, *CA19-9*, *tumor number*, *primary tumor site*, and *tumor differentiation*. (Figure 3b). A study has indicated an association between sex and LN metastasis (*16*), but there is no conclusive evidence that the remaining excluded variables are correlated with LN metastasis. The importance of CEA and CA19-9 has been emphasized in numerous studies (*9,17,12*), but other serological indicators have little value in predicting LN status. AFP is a valuable tumor marker for diagnosing HCC and predicting its prognosis, but it has limited utility with regard to ICC. The aggressiveness of a tumor can be associated with tumor size, tumor number, or tumor differentiation. Hence, some pathological features are crucial to predicting the incidence of LN metastasis. MVI is a prognostic marker of HCC recurrence and survival and

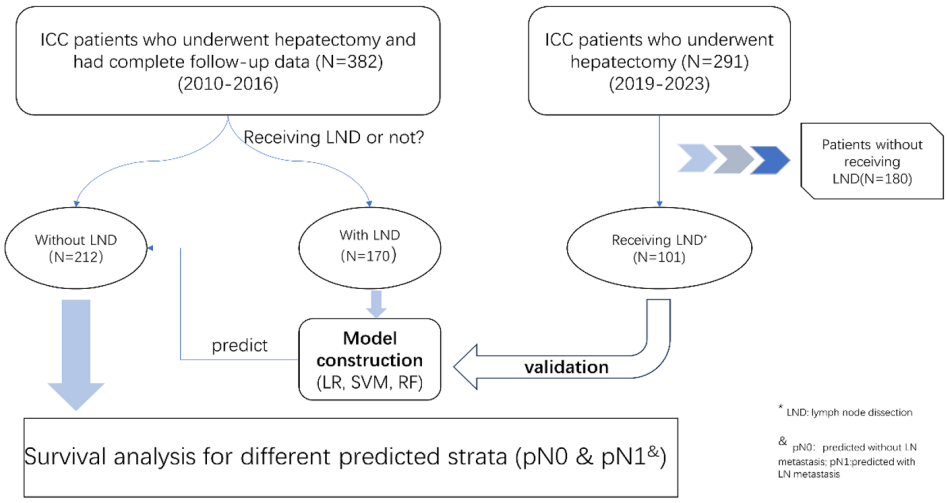

Figure 1. Flowchart for patient screening.

Table 1. Baseline patient characteristics

Cohort	Training set (2010-2016) $N = 170$	Validation set (2019-2023) $N = 101$	*P*-value
Sex (female/male)	87/83	44/57	0.277
Age* (years)	57.20 (20-81)	59.68 (36-84)	0.056
Ascites (no/yes)	142/28	80/21	0.465
HBV (no/yes)	130/40	85/16	0.175
Cirrhosis (no/yes)	158/12	74/27	< 0.001&
PLT (*10^9/L)	183.35 (70-355)	201.67 (54-450)	0.034&
PT (S)	11.62 (9.3-15)	11.13 (9-25)	0.004&
TB (μmol/L)	23.07 (3.8-544)	25.34 (4-358)	0.733
ALT (IU/L)	46.30 (4-620)	70.53 (9-912)	0.036&
AST (IU/L)	45.27 (14-831)	58.41 (15-748)	0.185
ALB (g/L)	42.13 (23.7-50)	42.18 (25-51)	0.937
ALP (IU/L)	169.15 (45-1482)	173.71 (49-979)	0.820
GGT (IU/L)	159.54 (11-1971)	248.54 (10-3928)	0.038&
AFP (ng/ml)	48.60 (0.7-4035)	22.88 (1-1210)	0.482
CEA (<5/≥5 ng/mL)	111/59	81/20	0.013&
CA19-9 (<200/≥200 U/mL)	89/81	64/37	0.101
Tumor number (solitary/multiple)	74/96	86/15	< 0.001&
Tumor size (cm)	6.64 (1-17)	5.64 (2-14)	0.002&
MVI (no/yes)	146/24	63/38	< 0.001&
Primary site of the tumor (right/left)	67/103	35/66	0.514
Tumor differentiation (poor/moderate to well-differentiated)	132/38	50/51	< 0.001&
Lymph node status (negative/positive)	74/96	52/49	0.253
TNLE# (<6/≥6)	122/48	64/37	0.192

*Continuous variables were expressed as the mean (range); #TNLE: total number of lymph nodes examined; &significant difference.

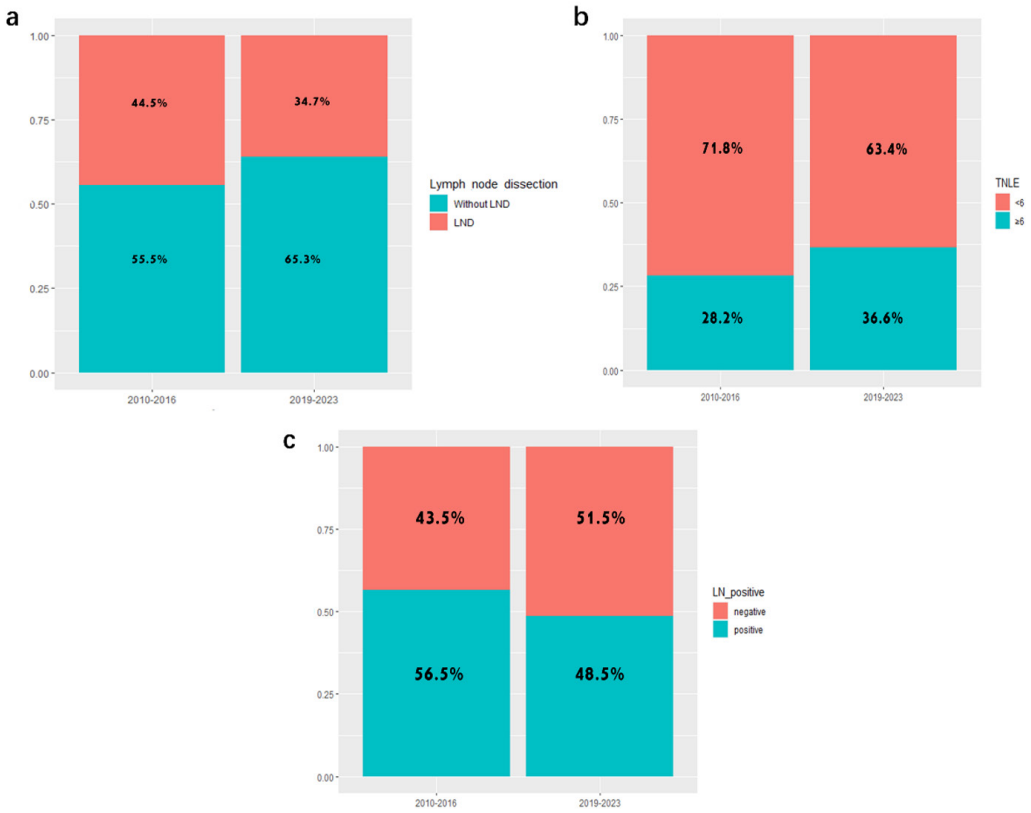

Figure 2. (a): Proportion of lymph node dissection. (b): Proportion of adequate lymph node dissection. (c): Proportion of positive lymph nodes.

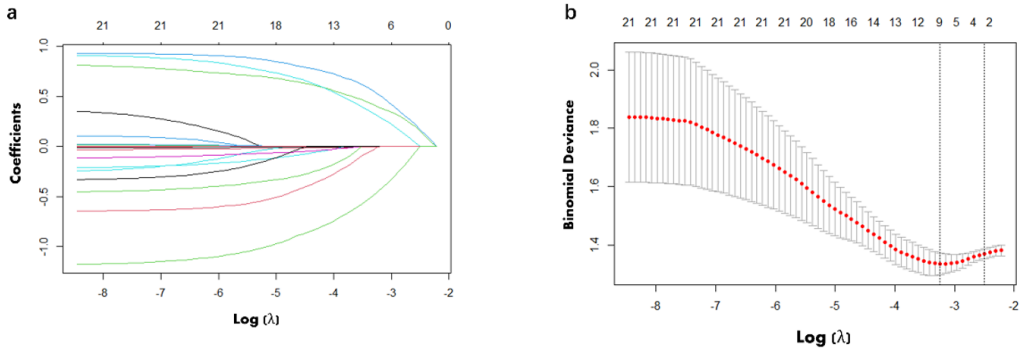

Figure 3. (a): Plots of the LASSO regression coefficients for various penalty parameters. (b): Cross validation plot of penalty terms.

Table 2. Stepwise regression outcomes

Variables									AIC*
age	PLT	TB	AFP	CEA	CA19-9	Tumor number	PST#	Tumor differentiation	221.03
-age									220.13
-age	-PLT								219.19
-age	-PLT		-AFP						218.91
-age	-PLT		-AFP				-PST		218.57

*AIC: Akaike information criterion; #PST: primary site of the tumor.

has attracted considerable attention in previous studies (*18*). Nevertheless, recent studies have provided limited findings regarding the correlation between MVI and LN metastasis. Stepwise regression of these variables was subsequently performed. Table 2 shows that a lower Akaike information criterion (AIC) corresponds to a superior model fit. Statistically speaking, the best model should include five predictors: TB, CEA, CA19-9, tumor number, and tumor differentiation. The primary site of the tumor (PST) itself has little influence on model fit, but prior studies have indicated that there is a potential link between this variable and LN metastasis (*11,17*), so the decision was to include it. Moreover, an extremely high level of TB was considered a relative contraindication for hepatectomy and there was no evidence to suggest that TB was associated with LN metastasis. As a result, it was excluded from the final model. Ultimately, the features utilized in modeling were: *CEA*, *CA19-9*, *tumor number*, *tumor differentiation*, and *PST*.

3.3. Outcomes of logistic regression

Initially, multivariate logistic regression was performed, and the results are shown in Table 3. When CA19-9 was no lower than 200 U/mL, the likelihood of LN metastasis increased significantly (HR:2.36; 95% CI: 1.17-4.84; $p = 0.017$), and this is also the case when the tumor is poorly differentiated (HR:2.56; 95% CI: 1.18-5.88; $p = 0.020$). Moreover, patients positive for CEA (HR: 2.02; 95% CI: 0.97-4.33; $p = 0.064$) or with multiple tumors (HR:1.87; 95% CI: 0.93-3.64; $p = 0.062$) tended to have LN metastasis, but the difference was not significant.

Table 3. Outcomes of logistic regression

Predictors	Hazard ratio	95% CI	*P*-value
CEA			
positive	2.02	0.97-4.33	0.064
negative	Ref.	Ref.	Ref.
CA19-9			
≥200 U/mL	2.36	1.17-4.84	0.017&
<200 U/mL	Ref.	Ref.	Ref.
Tumor number			
multiple	1.87	0.97-3.64	0.062
solitary	Ref.	Ref.	Ref.
Tumor differentiation			
poor	2.56	1.18-5.88	0.020&
moderate/well-differentiated	Ref.	Ref.	Ref.
PST#			
left	0.68	0.34-1.33	0.262
right	Ref.	Ref.	Ref.

#PST: primary site of the tumor. &significant difference.

3.4. Development and validation of three models

Out of three machine-learning models, RF had the best discrimination with the training set (AUC: 0.780; 95% CI: 0.710–0.849), followed by the LR (AUC: 0.703; 95% CI: 0.629–0.786) and SVM (AUC: 0.705; 95% CI: 0.626–0.784) (Supplemental Figure S1a, S1c, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=226,* and 4a). Figure 5 shows the importance of each variable according to the RF algorithm. The top three factors were CA19-9, CEA, and tumor differentiation. In other words, removing them would greatly affect the accuracy and heterogeneity of this model. In the validation cohort, the SVM (AUC: 0.754; 95% CI: 0.661-0.847) slightly outperformed LR (AUC:

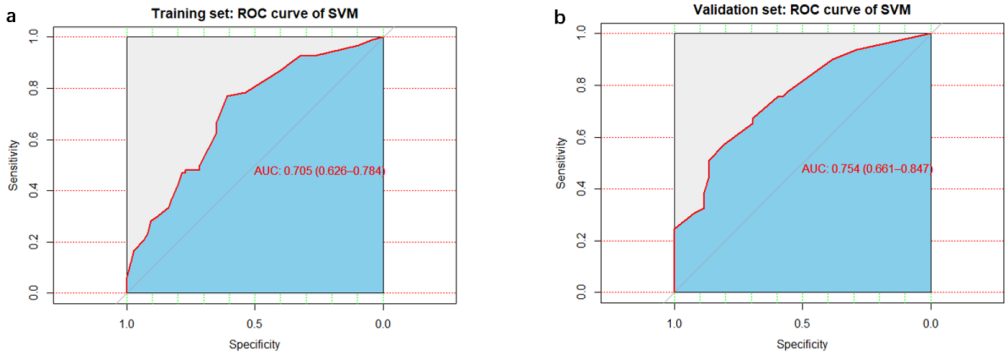

Figure 4. (a): ROC curve from the training set for the SVM. (b): ROC curve from the validation set for the SVM.

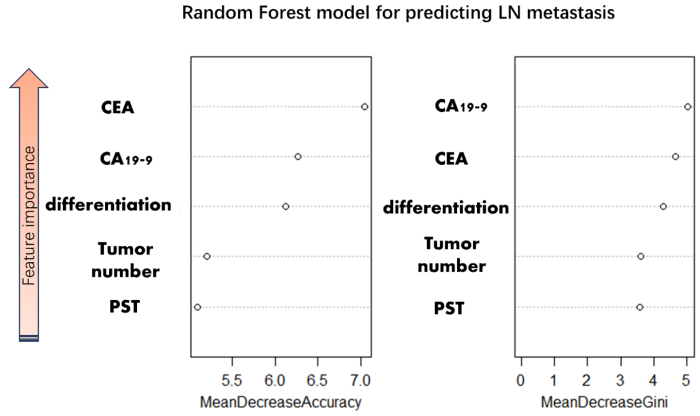

Figure 5. Feature importance in an RF model.

0.736; 95% CI: 0.640-0.833), while the RF (AUC: 0.693; 95% CI: 0.588-0.798) clearly lagged behind the other models (Supplemental Figure S1b, S1d, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=226,* and 4b). Moreover, a comprehensive assessment of the three models was performed. With the validation set, the RF model had an accuracy of 0.67 (95% CI: 0.57-0.76), with a precision (positive predictive value) of 0.86, a recall (sensitivity) of 0.39, a F1 score of 0.54, a specificity of 0.94, and a negative predictive value of 0.62. The LR model had an accuracy of 0.63 (95% CI: 0.53-0.73), a precision (positive predictive value) of 0.73, a recall (sensitivity) of 0.39, a F1 score of 0.51, a specificity of 0.86, and a negative predictive value of 0.60. The SVM model had an accuracy of 0.70 (95% CI: 0.59-0.78), a precision (positive predictive value) of 0.76, a recall (sensitivity) of 0.53, a F1 score of 0.62, a specificity of 0.84, and a negative predictive value of 0.66 (Table 4). The AUC for the RF model plummeted with the validation set, potentially indicating overfitting of the training set. In turn, the performance of the LR and SVM with the validation set was similar to that with the training set. Moreover, the SVM had the lowest misclassification rate with the validation set, followed by the RF and LR. Additionally, the SVM model had the highest F1 score (a combined measure of precision and recall), in contrast to that of the RF or LR model. After comprehensive consideration, the SVM model was chosen for the final model. To enhance the accessibility of the model, a user-friendly calculator was developed and made accessible on a website (*mieureka.shinyapps.io/Supporting_Vector_Machine_for_ICC_lymph_node_metastasis*). This calculator helps clinicians to predict the likelihood of LN metastases in individuals who did not undergo LND or who underwent an insufficient LN examination.

Table 4. Metrics of three models

Metrics	Model		
	Support Vector Machine	Logistic Regression	Random Forest
Accuracy	0.70	0.63	0.67
Specificity	0.84	0.86	0.94
Sensitivity	0.53	0.39	0.39
PPV[#]	0.76	0.73	0.86
NPV[&]	0.66	0.60	0.62
F1-score	0.62	0.51	0.54

[#]PPV: positive predictive value. [&]NPV: negative predictive value.

3.5. Survival analysis

Survival analysis was performed among patients

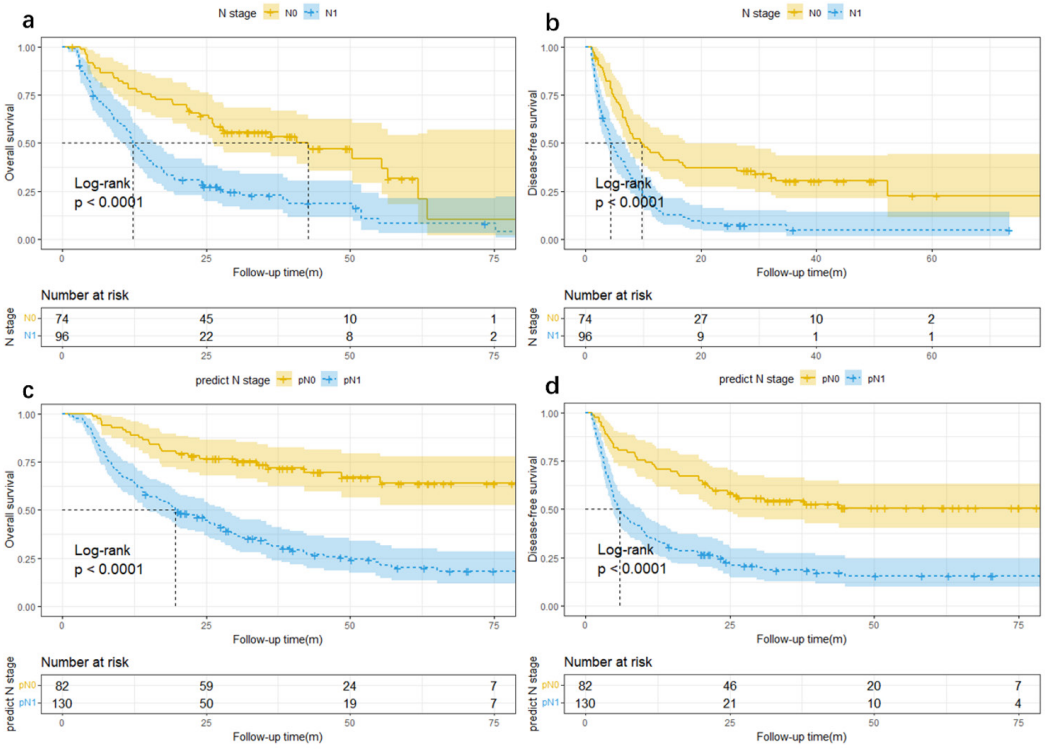

Figure 6. (a): OS curve for different N stages. (b): DFS curve for different N stages. (c): OS curve for different predicted N stages. (d): DFS curve for different predicted N stages.

undergoing LND with a different LN status and patients not undergoing LND with a different predicted LN status. The median follow-up was 17.9 months for OS and 6.5 months for DFS for individuals who underwent LND. The median OS was 12.2 months for the N1 group and 40.7 months for the N0 group, while the median DFS was 4.3 months for the N1 group and 9.5 months for the N0 group. A log-rank test indicated a significant difference ($p < 0.001$ for both), as shown in Figure 6a, 6b. Each patient who did not undergo LND was subsequently classified by the SVM into a predicted N1 group or a predicted N0 group. With a median follow-up of 25.9 months, the median OS for the pN1 group was 19.7 months. The median OS for the pN0 group was not determined at the conclusion of the follow-up (Figure 6c). The median DFS for the pN1 group was 5.7 months, with a median follow-up of 11.5 months. The median DFS for the pN0 group was not determined at the conclusion of the follow-up (Figure 6d).

4. Discussion

Presented here is the rate of LND and adequate LN examination (≥ 6) performed at our facility. Additionally, a bar plot was used to depict the rate at which LNs tested positive. LASSO and stepwise regression were performed to screen variables, eliminate multicollinearity, and streamline the final model. Three machine-learning models (LR, SVM, and RF) were subsequently established and validated with two cohorts from different time periods (2010-2016 and 2019-2023). The SVM algorithm had superior performance with both the training and validation sets, so it was therefore selected to assess the LN status in patients not undergoing LND. The Kaplan-Meier curve indicated a significant correlation between positive LNs and a poorer OS and DFS, and this trend remained in the prediction cohort, further corroborating the reliability of the current results.

LN metastasis has been confirmed to be a prognostic indicator of ICC in two large-sample studies (*6,19*). In specific terms, Zhang *et al.* found that there was a direct correlation between the number of LN metastases and the OS rate, *i.e.*, OS decreased as the number of LN metastases increased (*6*). Studies have also modified the 8th edition of the AJCC (American Joint Committee on Cancer) staging system and redefined the N stage (*20,21*). Moreover, several studies have contended that ICC with positive LNs tends to benefit from adjuvant therapy (*22,23*). A study has even reported that ICC with positive LNs can be treated with chemotherapy alone instead of surgery, without compromising prognosis (*24*). Given these findings, lymphadenectomy needs to be performed in order to acquire pathological verification of the status of LNs. Nevertheless, a substantial body of research opposes the routine performance of lymphadenectomy because it fails to confer a prognostic benefit, prolongs operating time, and increases the risks of postoperative complications (*7*) (*25-27*). Both the 8th AJCC guideline and Chinese consensus suggest routine

lymphadenectomy in patients with ICC, and the number of nodes dissected should be no less than 6. However, the rate of LND at our facility used to be less than 50% and has declined in recent years (Figure 2a). Conversely, the rate of sufficient LND has risen to nearly 40% (Figure 2b). At our facility, a mere 12.5% of patients underwent sufficient LN sampling for accurate nodal staging, which is well below the international benchmark (*28*). Hence, a system needs to be promptly developed to serve as a reference for patients with a lack of nodal staging or inadequate nodal staging.

Our model can aid in clinical decision-making both intraoperatively and postoperatively. Patients identified as having a high risk of LN metastasis should undergo LND during surgery, and the number dissected nodes and extent of LND should be ensured. For patients who underwent surgery without LND, our web-based calculator can assess the risk of LN metastasis, offering a reference for adjuvant therapy. Since a previous study has claimed that there is no statistical difference in LN metastasis between small ICC and large ICC when using a tumor size of 3 cm as the threshold (*29*), we believe that this model is applicable to surgical patients without distant metastasis. However, a point worth noting is that this model may not apply to patients with locally advanced unresectable tumors or distant metastases, as they often do not undergo LN biopsy and the risk or pattern of LN metastasis in this population has yet to be fully determined.

A point that warrants mention is that the sample sizes for the training and validation cohorts were constrained due to the low prevalence of ICC. The limited sample size may compromise the generalizability of our model, thereby hindering its application to real-world scenarios. Smaller samples might lead to potential overfitting, resulting in the model exhibiting significantly superior performance with the training set compared to the validation set. This situation also arose in the current study, where the RF model demonstrated the potential for overfitting. Moreover, having a small sample increases the likelihood of outliers, which increases the variance of logistic regression predictors and diminishes the accuracy of model predictions. We have adopted a series of strategies to address these issues. First, to ensure predictive capability, we used regularization techniques (LASSO) and stepwise regression to restrict the number of features incorporated in the model as much as possible. Second, we opted for the SVM over the RF as the final model, as a simple model is less prone to the danger of overfitting. Finally, there can be intrinsic deficiencies in developing and validating a model with the same cohort, as a group of patients may possess some unpredictable characteristics that hinder generalizability to a new dataset. Hence, we selected two cohorts from different timeframes for modeling and validation to enhance the scientific rigor of this study.

To date, a series of studies have constructed models to predict LN metastasis but with a limited sample size. Owing to the relative low incidence of ICC, most training sets consist of approximately 100 cases(*13,30,31*). This may increase the influence of outliers in logistic regression, perhaps resulting in an increase in the mean square error (MSE). Moreover, a rule of thumb for logistic or Cox regression is that 10 or 20 events per predictor (EPV) are generally considered robust and reliable (*32*), suggesting that the aforementioned studies should have 3 to 5 variables or even fewer. Machine learning is suited to solving small-sample models because it screens variables and is less impacted by outliers. In 2022, an RF algorithm was introduced to predict LN metastasis, and the machine-learning model markedly outperformed logistic regression (*12*). Surprisingly, an RF model was not constructed or validated in a cohort of patients not undergoing LND. Thus, we validated our model with a group of 212 patients not undergoing LND, and we incorporated the model in an online calculator to enhance its credibility and user-friendliness.

To the extent know, the current work describes the first online calculator based on machine learning to evaluate LN metastasis. The training set, validation, set and non-LND dataset have relatively substantial sample sizes. Nevertheless, there are several limitations worth mentioning. First, at least six LNs needed to be examined in the patients in this study in order to reduce the risk of underestimation. However, this is impossible to achieve in the real world since the rate of adequate LND is relatively low, which may be because dissection offers no prognostic benefit but potentially prolongs operating time and can results in complications (*33*). This should be considered in the design of prospective trials. Additionally, there are some discrepancies in the demographics of training and test data that might potentially compromise the sensitivity or specificity of the model when applied to the validation set. Finally, whether pN1 patients are more likely to benefit from adjuvant therapy compared to the pN0 group is still unclear, and this should be the focus of a subsequent study.

5. Conclusion

To summarize, a model to predict LN metastasis based on a SVM was developed and verified in different time cohorts for patients with ICC. The predicted outcome indicated a survival difference in patients not undergoing LND, suggesting that it is applicable to patients not undergoing LND or patients with inadequate LND. A RF model indicated that CEA, CA19-9, and tumor differentiation represented the top three crucial features, warranting particular attention. In order to enhance the accuracy and reliability of the model, multicenter studies should be conducted with large cohorts and sufficient LN sampling.

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