Research Article

Lodds was a Better Predictor for Lymph Node Status and was a Dependent Poor Prognostic Factor for Distal Extra Hepatic Cholangiocarcinoma after Radical Surgical Resection

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Abstract

Background: Whether log of odds between the number of positive lymph node and the number of negative lymph node (LODDS) predictlymphnode status and oncological outcomes for distal extra hepatic Cholangiocarcinoma (dECA) patients after curative resection remains rarely studied.

Methods: 743 patients from SEER database between 2004 and 2014 who received curative pancreato-duodenectomy (PD) were analyzed. We conducted receiver operating characteristic (ROC) curve and univariate (Log-Rank) and multivariate (Cox regression) analysis to identify the diagnostic and prognostic roles of LODDS.

Results: LODDS was the effective variable with the area under the ROC curve (AUC) for prediction of 3-year survival (AUC = 0.593) to predict the survival, we determined the optimum cut-off value of LODDS and LODDS<-0.94.

In multivariate analysis, LODDS (hazard ratio (HR)=0.738, 95% CI 0.574-0.949, P=0.018) was independent prognostic factor for OS.

Conclusion: LODDS was proved a good indicator predict for lymph node and survivals a nondependent indictor for OS in dECA after radical surgical resection.

Keywords: Lodds; Overall survival; Disease free survival; distal extrahepatic carcinoma; Pancreato-Duodenectomy

Abbreviations

LODDS: Log of Odds Between Plns and Nlns (Negative Lymph Node); OS: Overall Survival; Deca: Distal Extrahepatic Carcinoma; PD: Pancreato-Duodenectomy

Introduction

Distal extra hepatic carcinoma (d ECA) account for up to 20% of Cholangiocarcinoma (CC), which was a separate entities considering the differences in the frequency, pathobiology and management comparing with carcinoma originated from the intrahepatic and peripheral bile duct epithelium [1-3]. CC is the commonest primary biliary and liver tumor worldwide secondary to hepatocellular carcinoma (HCC) [4]. The incidence of d ECA varied among different countries, are about 6.69 per 100000 (men) and 2.98 per 100000 (women) in Japan, as compared with 0.42 per 100000 (men) and 0.36 per 100000 (women) in England and Wales, and 0.87 per 100000 (men) 0.80 per 1000000 (women) in Australia [5-7]. Though its incidence and mobility decreased in some countries [8], its prognosis remains dismal with a poor 1/5-year survival rate of only 28-37% and 6-11% [4], and a median overall survival of 4-8 months [5].

Until recently, pancreato-duodenectomy (PD) were the only curative surgery for d ECA [1] while the radical surgery for intrahepatic and perihilar bile duct carcinoma is consist of liver resection [9]. Chemotherapy for CC had poor results and studies remains small and disparate [1]. However, the 5-year survival rates following resection of distal extra hepatic CC can only reach at 27-37% [1].

Lymph node metastases are well-established independent predictors of survival following surgery [10-12]. Lymph nodal metastasis was found in 20–60 percent of the d ECA patients [9,13,14], which was reported with the higher recurrence and dismal outcomes [9,15-19]. The up to date American Joint Committee on Cancer (AJCC) TNM classification system for distal Cholangiocarcinoma [20], the lymph node classification defined it as N0 (negative lymph node), N1 (≥1 lymph node metastasis) and N2 (≥4lymph node metastasis) based on the numbers of LN metastasis compared with the 7th edition simply categorize as presence and absence of lymph node metastasis. However, growing evidence emphases the importance of the negative lymph node and total resected lymph node (TLNs) in addition to the positive lymph node emerging as potential system stratifying the LN involvement to better predict the long-term outcome for many gastrointestinal tumors, including pancreatic, gastric, as well as biliary cancer [21-26]. The ratio of PLNs(positive lymph node) to TLNs and log of odds between PLNs and NLNs (negative lymph node) (LODDS) have emerged as potential alternative predictive

Table 1: Demographic and Clinicopathological characteristics of patients with distal Extrahepatic holangiocarcinoma between 2004 and 2014 in SEER database.

Demographic or Characteristics	All subjects (N=743)	Training Cohort (N=495)	Validation Cohort (N=248)	P value
Age at diagnosis (year)				
x<40	8 (1.08)	6 (1.21)	2 (0.81)	
40≤x<60	156 (20.99)	95 (19.19)	61 (24.60)	
60≤x<70	253 (34.05)	164 (22.07)	89 (35.89)	0.159
x≥70	326 (43.88)	230 (46.46)	96 (38.71)	
Sex Male Female	474 (63.8) 269 (36.2)	313 (63.23) 182 (36.77)	161(64.92) 87 (35.08)	0.652
Race				
White	553 (74.43)	356 (71.92)	197 (79.44)	
Black	55 (7.40)	33 (6.67)	22 (8.87)	0.004
Others	135 (18.17)	106 (21.41)	29 (11.69)	
Grade				
High	280 (37.69)	192 (38.79)	88 (35.48)	
Medium	361 (48.59)	229 (46.26)	132 (53.23)	0.1777
Low	93 (12.52)	66 (13.33)	27 (10.89)	
Undifferentiated	9 (1.21)	8 (1.62)	1 (0.40)	
Stage				
0	3 (0.40)	3 (0.6)	0 (0.00)	
I	161 (21.67)	106 (21.41)	55 (22.18)	
II	514 (69.18)	340 (68.69)	174 (70.16)	0.705
III	29 (3.90)	21 (4.24)	8(3.23)	
IV	36 (4.85)	25 (9.29)	11 (4.44)	
LODDS*				
mean(range)	-1.461 (-2.903 -0.000)	-1.470 (-2.903 -0.000)	-1.442 (-2.881-0.000)	0.302
RLNs*				
mean (range)	14.070 (1-63)	14.00 (1-63)	14.19 (1-41)	0.174
PLNs*				
mean (range)	1.53 (0-23)	1.56 (0-23)	1.48 (0-13)	0.823
PLR				
mean (range)	0.14 (0.122 to 0.155)	0.14 (0.115- 0.156)	0.14 (0.1154 to 0.1722)	0.673
LNR*				
mean (range)	12.53 (0-56)	12.44 (0-56)	12.71 (0-40)	0.743

*LODDS: log ((the number of PLNs +0.05)/ (the number of negative nodes +0.05)); RLNs: the number of lymph node examined; PLNs: the number of positive lymph node; LNR: positive lymph node ratio; PLR: the number of PLN/RLNs.

indicator for outcomes and showed superiority to UICC/AJCC lymph node status-based assessment in many types of cancers [19,27-30]. The ratio of PLNs (positive lymph node) to TLNs was studied in ovarian cancer and found to be superior to both PLN and RLN number in predicting survival after surgery for both intrahepatic and perihilar Cholangiocarcinoma as well as other cancers [21,31-35]. However, the LNR showed some limitations in patients with all-PLNs and without PLNs, regardless of TLN [36]. Furthermore, LODDS is defined as log ((the number of PLNs +0.05)/ (the number of negative nodes +0.05)), as an alternative LN staging method with prognostic value [23,37], has been validated in predicting survival for pancreatic cancer, breast cancer, lung cancer, cervical cancer and intrahepatic CC [18,19,27-30].

No data are available on the prognostic performance of LODDS in patients undergoing curative surgery for d ECA and its comparison with other LN staging methods. The aim of this study was to evaluate and compare the prognostic value of the AJCC p N stage, PLN, PLR, and LODDS in patients with d ECA who underwent surgery with curative intent to identify the best LN staging method.

Materials and Methods

Patients

Participants and criteria: We identified dECA cases from the SEER program of the National Cancer Institute (http://seer.cancer.gov/). Inclusion criterion is that all patients who underwent surgery and are pathologically diagnosed with distal extra hepatic

Table 2: Univariate Analysis and multivariate analysis in the training cohort.

Variables	Univariate Analysis			Multivariate Analysis	
	Median survival time (95%CI)	P value		HR (95% CI)	P value
Age at diagnosis		0.046*			
x<40	29.0 (10.748-47.252)				
40≤x<60	27.0 (19.420-34.580)				
60≤x<70	22.0 (16.750-27.250)				
x≥70	19.0 (16.942-21.058)				
Sex		0.533			
Male	21 (17.846-24.154)				
Female	20 (15.808-24.192)				
Race		0.629			
White	20.0 (16.881-23.119)				
Black	42 (-)				
Others	21 (15.041-26.959)				
Grade		0.051			
High	35 (18.172-51.828)			reference	
Medium	20 (16.693-23.307)			0.191 (0.083-0.435)	<0.001
Low	21 (16.527-25.473)			0.252 (0.117-0.542)	<0.001
Undifferentiated	8 (0-19.087)			0.274 (0.127-0.590)	0.001
Stage 0	--	0.043*			
I	29.0 (15.716-42.284)				
II	20.0 (17.019-22.981)				
III	24.0 (11.371-36.629)				
IV	14.0 (9.300-18.700)				
RLN <5 ≥5	18.0 (14.530-21.470) 23.0 (20.203-25.797)	0.005*			
NLN <5 ≥5	17.0 (12.205-21.795) 24.0 (20.599-27.401)	<0.001		Reference 1.645 (1.270-2.132)	<0.001
PLN <1 ≥1	25.0 (20.485-29.515) 19.0 (17.129-20.871)	0.040*			
PLR <0.05 ≥0.05	25 (20.272-29.728) 19 (16.573-21.427)	0.006*			
LODDS <-0.94 ≥-0.94	24.0 (20.213-27.787) 18.0 (15.409-20.591)	0.001*		Reference 0.738 (0.574-0.949)	0.018
LODDS <-2.0043 ≥-2.0043	29.0 (19.803-38.197) 19 (17.155-20.845)	<0.001			

Cholangiocarcinoma cancer from the SEER database from 2004 to 2014. Exclusion criteria are as follows: unknown age of diagnosis; uncertain race; unknown marriage status; not determined grade; unknown stage; unspecified neoplasms; unknown tumor size; unknown or incomplete lymph node status. Finally, 743 distal extra hepatic Cholangiocarcinoma cancer patients were included in this study. These patients are divided into two groups 2:1 consecutive (training cohort N=495; validation cohort, N=248).

Clinical Data Collection

The total lymph node count (TLN) was defined as the total number of lymph nodes examined histological in each patient. After counting the number of involved lymph nodes, the lymph node ratio (PLR) was calculated as the ratio of the number of involved nodes to the TLN. The LODDS was calculated by log [(PLN + 0.5)/(TLN-PLN+ 0.5)]

Variables and statistics

The categorical variables are shown as whole numbers and proportions, and the continuous variables presented as the means (M) and standard deviation (SD) as appropriate. p values of <0.05 (Two-sided) was defined as with statistical significance. IBM SPSS 22.0 and R 3.4.2 version statistical software were used. To compare continuous variables that followed Gaussian distributions, t tests were

used; the K-Independent-Samples Test (Kruskal Wall is H (K) test) was used for those variables did not follow Gaussian distributions. To compare proportional variables, a Two Independent-Samples Test (Mann-Whitney U test) was used; The confounders were measured accurately using univariate Cox regression through an enter variable selection procedure. The regression models were based on Akaike's information criterion. We used univariate (Kaplan-Meier method and compared using log-rank test) and multivariate (Cox regressions) to evaluate the prognostic value and Survival curves.

Two approaches were used to evaluate and compare the predictive power of the different LN staging methods: one based on the survival ROC and the other based on the calculation of the receiver operating characteristic (ROC) curve at a given time point [33,38]. The performance of the nomogram was measured by concordance index (C-index) and it is comparing nomogram-predicted survival probability with observed Kaplan survival probability. The larger the C-index, the more accurate was the prognostic prediction.

Results

The diagnostic power of LODDS for 3-year survival in dECA patients

In the training cohort from SEER, 743 distal extra hepatic Cholangiocarcinoma cancer patients were included in this study. These patients are divided into two groups 2:1 consecutive (training cohort N=495; validation cohort, N=248). In order to facilitate the application of LODDS in clinical practice, we dichotomized LODDS into high LODDS and low LODDS based on the optimal cutoff from ROC analysis. In our training cohort, the optimal cutoff is -0.94. We further validated the predicting performance of binary LODDS in an independent external dataset.

Cut-Off values for LODDS, PLR, PLN, NLN, TLN were, <-0.94, <0.05, <1,<5 , <5respectively.

Demographics and clinical characteristics of the743 patients from SEER

The demographic and clinicopathological characteristics of patients in the training and validation cohorts are listed in Table 1.

Survival analysis

The results of the univariate and multivariate analysis are listed in Table 2. Univariate analyses demonstrated that grade, stage, PLN, NLN, TLN and LODDS were associated with OS. Multivariate analysis demonstrated that age, stage, RLN, PLN, PLR, NLN and LODDS were independent risk factors for OS in Table 2.

LODDS (hazard ratio (HR) = 0.738, 95% CI 0.574-0.949, P=0.018) was independent prognostic factor for OS. Kaplan–Meier survival curves calculated median times to death after surgery being 18 months and 24 months in high- and low-LODDS groups, respectively.

Prognostic Nomogram for OS

The prognostic nomogram that integrated all significant independent factors for OS in the training cohort is shown. The C-index for OS prediction was 0.565 (95% CI, 0.612 to 0.538) in the training cohort and 0.640 (95% CI, 0.696 to 0584) in the validation cohort. The calibration plot for the probability of survival at 3 or 5-year after surgery showed an optimal agreement between the prediction by

nomogram and actual observation in the training cohort and in the validation cohort, respectively.

Discussion

The present study suggests that grade, NLN, LODDS are independent prognostic factors of OS in cervical cancer after surgery. The nomogram is created based on these prognostic factors and was used to predict the 3-year and 5-year OS after surgery in the d ECA. However, it did not show well predictive value as a nomogram. More detailed study are needed.

Extra hepatic Cholangiocarcinoma (EC) is s a rare biliary duct cancer type Cholangiocarcinoma. Analyses of SEER data ((SEER Program; http://seer.cancer.gov/)) from 1973 to 2012 showed that incidence of extra hepatic Cholangiocarcinoma has remained stable (APC, 0.14% [annual percentage change (APC), 2.3%] [39]. Despite the stable trend worldwide over the past few decades and recent developments in surgical techniques, its prognosis remains dismal even after curative surgery [40]. The reported 5-year survival rates after radical surgery are in the range of 16% to 52% for patients with distal extra hepatic Cholangiocarcinoma [41]. PD is considered standard parts of curative resections in distal Cholangiocarcinoma [12,42-45].

It is widely accepted that an increasing TLN enhances the accuracy of nodal staging for the number of PLNs is significant depending on the number of retrieved LNs. The AJCC has endorsed a '12-node minimum' for distal Cholangiocarcinoma to prevent inadequate staging. In present study, the minimum number of TLNs to be retrieved was determined by ROC curve based on the 3-year survival, >5 Lymph node was determined, while other study calculated it should be 9 [13]. And the AJCC has endorsed a '12-node minimum' for distal Cholangiocarcinoma. Until now, the TLNs numbers were still controversial, however, the rationale for this number was not provided. Several authors [46-48] have proposed a minimum TLN of 11 for distal Cholangiocarcinoma. Assay and co-workers [49] reported that the TLN in patients after pancreaticoduodenectomy increased from 6 to 14 when a specific sampling technique was applied. According to US Surveillance, Epidemiology, and End Results [48] data, them edian TLN was only 5 in patients with Cholangiocarcinoma. What's more, several authors have thus proposed other methods of LN staging in patients with pancreatobiliary malignancy. The PLR and LOODS are mathematical tools less influenced by the extension of LN dissection and are able to increase the LN staging reliability in different cancers, such as gastric cancer, colorectal cancer, and intrahepatic Cholangiocarcinoma [21-26].

The current study is the first to evaluate and compare the specific prognostic ability of the number of PLNs, PLR, and LODDS in patients with d ECA including SEER clinical data. Moreover, the extensive statistical analysis, which involved 2 different approaches (random survival ROC and ROC curve analysis), demonstrated that the number of PLN, PLR, and LOODS had good prognostic ability. To our knowledge, PLNs have been reported as a prognostic factor for cervical cancer. However, it, as part of TLN, do not fully reflect the state of disease in all situations [50]. Therefore, it is important to take simultaneously PLNs and the number of negative lymph nodes

consideration for predicting the prognosis of cervical cancer. LODDS is an intuitive indicator that is reflective of both PLNs and the number of negative lymph nodes and it has been used to predict the prognosis of survival in other cancers. From out study, it is found that LODDS is an independent prognostic factor of d ECA and we take -0.94 as the optimal cutoff point for the LODDS based on ROC curve analysis from the training cohort. What's more, LODDS perform as the unique prominent prognostic indicator of OS ford ECA cases after curative surgery. These data confirm the results obtained using LODDS in other gastrointestinal and hepatopancreatic biliary malignancies.

In current study, some limitations should be acknowledged. Firstly, it was a retrospective including SEER data. Second, we did not include the lymph nodes tationinth is stud avoiding sacrificing the statistical power in present small sample size of current patients, besides previous study showed the position of the lymph node did not affect the survival. Thirdly, other potential confounding factors cannot be excluded, such as postoperative adjuvant therapy. Concerning until now the influences of chemotherapy and other adjuvant therapy on survival of d ECA have not been defined, it was not obligatory to include these factors.

Conclusion

In conclusion, LODDS was proved to better predict for lymph node and survival as an independent indictor for OS in d ECA after radical surgical resection. Moreover, adequate LN dissection is mandatory for curative surgery of d ECA, as well as to achieve accurate staging of the disease and the proper selection of adjuvant treatment.

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