Prognostic Factors of Hilar Cholangiocarcinoma Patients After Surgical Resection

Gangshan Liu
Shengjing Hospital of China Medical University
Shuodong Wu
Shengjing Hospital of China Medical University
Jiannan Zhao
Shengjing Hospital of China Medical University
Xuecheng Li
Shengjing Hospital of China Medical University
Ying Fan (m18940258876@163.com)
Shengjing Hospital of China Medical University https://orcid.org/0000-0002-2925-507X

Research

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Abstract

Background

Hilar cholangiocarcinoma (HC) is one of the most common malignancies in China with poor prognosis and its incidence rate is increasing. Surgical resection is the most possible curative treatment option. However, comprehensive knowledge of prognostic markers is less or not accurate. So, the aim of this study was to analyze the prognostic factors in the surgical resection of HC patients.

Methods

A retrospective analysis of 85 cases of HC patients attending our hospital between January 2014 and December 2018 were included in the study. The patients diagnosed as HC and treated with radical surgery were included.Excluded the patients undergoing non-radical surgery, with tumors in other organs, with perioperative death,with death not caused by this disease and with lost follow-up.The clinical data were collected from the Hospital Information System.The patients was follow-up history at July 2019.The end point was that the patient died of recurrence of HC. Cox proportional hazards model analysis was performed to identify indexes of prognosis. All indicators were analyzed by univariate and multivariate analysis.

Results

The significantly related prognostic factors are imaging staging,blood loss during surgery, lymphatic metastasis, tumor size, Tumor Node Metastasis(TNM) stage, surgical margin and level of carbohydrate antigen 19–9(CA19-9) in blood. Among them, TNM stage, surgical margin and level of CA19-9 in blood are independent prognostic factors.

Conclusions

Good prognosis in HC patients is indicated by early stages of TNM staging, no resection margin invaded and low level of CA19-9.

Background

Hilar cholangiocarcinoma (HC), firstly described by Klatskin, is a malignant tumor originated from bile duct epithelium with poor prognosis [1]. It is accounting for more than 60% of bile duct carcinoma, but only 2% of human malignant tumors [2]. It is also one of the most common cancers in China and its incidence rate is increasing [3]. Surgical resection is considered to be the most possible curative approach to offer patients opportunity for long-term survival [4]. However, although some patients undergo surgical resection, the recurrence rate in those patients is very high [5, 6]. There is a multitude of risk factors

related to HC patients, such as aging, gender, primary sclerosing cholangitis, choledochocyst, bile duct stones, cholangitis, parasitic infection, inflammatory bowel disease and liver cirrhosis [7]. Also, researches show that tumor differentiation, tumor staging,resection margin and lymph node metastasis are independent prognostic factors [8]. But there were not enough prognostic studies about height, weight, Body Mass Index(BMI), American Society of Anesthesiologists(ASA) grade, serum total bilirubin(TBIL), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartic aminotransferase (AST), albumin(ALB), CA19-9,operative time, biliary plastic or intraoperative blood loss. In addition, there is no accurate conclusion about the follow factors: removal of the caudate lobe, tumor size and intraoperative blood transfusion, et al [9, 10]. All of the aforementioned indices can thus maybe important indicators for further decision-making after surgery. Therefore, the aim of this study is to investigating the 22 prognostic factors of HC after surgical resection. By the way, we are aim to provide the data in resent five years of our hospital.

Methods

Patients

We retrospectively collected the clinical data of HC patients who underwent surgical treatment in Shengjing hospital of China Medical University between 2014 and 2018.The clinical data were collected from the Hospital Information System.The patients diagnosed as HC and treated with radical surgery were included.Excluded the patients undergoing non-radical surgery, with tumors in other organs, with perioperative death,with death not caused by this disease and with lost follow-up.The patients was follow-up at July 2019.The end point was that the patient died of recurrence of HC.A total of 120 consecutive patients diagnosed with HC and underwent surgery. Of the 120 patients, 85 had follow-up results available and were enrolled in this study.

Statistical analyses

All statistical analyses were performed using the SPSS statistical software package (SPSS Standard version 20.0). A $P < 0.05$ in a two-sided analysis was considered to be statistically significant. Cox single-factor analysis was used to include the correlated prognostic factors. Then according to the included factors, Cox proportional hazard model for multivariable regression analysis was used to determine the independent prognostic factors and present the Comprehensive test of model coefficients at the end.

Results

The 85 enrolled patients included 56 men and 29 women (average 63 years old) with age of onset of HC ranging between 45 and 84 years. The clinical pathological characteristics of the 85 patients are summarized in Table 1. Men were comparatively more predisposed to HC than females. There were 16 patients in ASA grade Ⅱ and 69 in grade Ⅲ. Ranges of operative time and estimated blood loss were 80 to 668 minutes and 50 to 2500 ml, respectively. For most of the people, many relevant biochemical

examinations such as AST,ALT,ALP,TBIL and CA19-9 are higher than normal range.50 patients needed blood transfusion in 85patients. About 21 patients have Caudate lobe resection and the range of the tumor size was 0.5cm to 6cm.The mean diameter of the tumor was 2.676 cm as measured in the pathological report.Classified according to TMN stage, there were 23in stage I, 31 in stage II, 26 in stage III, and 5 in stage Ⅳ.

Patients were followed up in January 15, 2019. We determined the relationship between observed indexes and postoperative prognosis using Cox single-factor regression analysis (Table 2). Seven indexes were significantly correlated (P<0.05):imaging staging, CA19-9, blood loss during surgery, lymphatic metastasis, TNM staging, tumor size and resection margin(Table 2).

All seven indexes were used in Cox model regression analysis. With a=0.05,we were able to import three independent factors related to HC postoperative prognosis because all variables passed the Cox multivariable analysis (Table 3).And the comprehensive test of the model coefficients can be seen in Table 4.

The risk of death increased by 1.794 times as TNM staging increases a level. The risk of death on patients with negative resection margins was 0.266 times that of patients with positive resection margins. Patients who had high CA19-9 in blood had a risk of death 2.602 times that of those who had normal CA 19-9, and the patients who had high CA19-9 more than 1000 u/ml had a risk of death 2.602 times that of those who had high CA19-9 but less than 1000u/ml.

Discussion

Survival of patients with HC is relatively poor. Surgery remains the only line of treatment offering the possibility of cure. But most HC patients are at an advanced, unresectable stage when diagnosed. The resectability rate of HC is different from 20to 80% according previous studies.Even in those who can receive radical resection, there is high risk of relapse.The actual 5-year survival after radical resection of HC varieswidely from 14 to 48%[11–17]. We thus performed a single-factor analysis with the subsequent multi-factor analysis to determine the prognostic factors in the surgical resection of HC patients.

As summarized in Table 2, our analysis revealed 7 indexes that could affect prognosis in HC patients. Our study gets the result that height, weight, BMI, ASA grade, serum total bilirubin, ALP, ALT, AST, ALB, operative time, biliary plastic or resect Caudate lobelt or not are not associated with the prognosis. It also has been previously shown that early stages of TNM staging was a significant good prognosis factor[18] and we get the same result. It is difficult to investigate the true effect of surgical resection and disease

prognosis in the clinical because most cases are in advanced stage when diagnosed and do not receive surgical resection.So more people are needed to devote themselves to this field.

CA19-9 has been suggested as a prognostic marker for HC patients undergoing tumor resection[19] in 2014. But Sven H [20] suggested that carcinoembryonic antigen(CEA) but not CA19-9 was an independent prognostic factor in patients undergoing resection of cholangiocarcinoma in 2017. However,we got the conclusion that CA19-9 was an independent prognostic factor of HC patient after surgical in this study.So the prognostic values of CA19-9 in the clinical setting of surgical resection have remained inconclusive. We hold the opinion that serum levels of CA19-9 are also elevated in patients with non-malignant biliary diseases such as primary sclerosing cholangitis or biliary obstruction due to choledocholithiasis[21, 22].Therefore, further related articles are urgently needed.

Many reports indicate that a positive resection margin strongly affects prognosis. Hirano et al. [23] reported that the survival rates among patients with histologically positive margins were significantly inferior to the corresponding rates observed in patients with negative margins. The present study also revealed that proximal margin positivity (hazard ratio [HR], 2.688; $p = 0.007$) was independent survival prognostic factor[24]. We also got the result that positive margins was an independent prognostic factor. However, several authors have suggested that patients whose positive margins contain carcinoma could survive beyond 5 years. Volkan Öter et.al [25] reported that the survival of patients with tumor positive margins was not found to be worse than those with tumor negative margins. Further large volume prospective studies are required to identify the impact of positive proximal margins on the survival rate.

As we performed single-factor analysis, the statistical tests on imaging staging, lymphatic metastasis, tumor size have statistical -interpretation. But when doing multi-factor analysis, they do not have difference in statistical tests, which indicates they maybe not independent prognostic factors. But Hai-Jie Hu et.al [26] got the conclusion that Bismuth classification type III/IV was independent factors of overall survival in the subgroup of patients who developed early recurrence.Yunfeng Gao[27] reported that Patients with greater numbers of negative lymph nodes had an increased cancer-specifific survival rate compared to patients with fewer negative lymph nodes. In the study of Felice Giuliante[28],the ratio of positive to negative lymph nodes was the only independent prognostic factor for overall survival but was influenced by the total number of retrieved lymph nodes.In this respect, thorough lymph nodes dissection may be important, and should be prospectively evaluated and studied in the future.

The limitations of this study mainly include the following: Only one follow-up was conducted, so it is only suitable for COX analysis, not for survival analysis. It is planned that in the future that further follow-up would be conducted for the survival of such patients until death or loss of follow-up. Some major indicators cannot be studied due to incomplete data, such as CEA, CA125 and postoperative complications.

Conclusions

In conclusion, our data seem to indicate that early stages of TNM staging, no resection margin invaded and low level of CA19-9 are good prognostic factors of HC. Though imaging staging,blood loss during surgery, lymphatic metastasis and tumor size are not independent factors in this study,they are significantly related to prognosis($p < 0.05$) of HC.Patients with risk factors should be monitored closely after curative surgery.There are also many factors that were not studied in this article.Thus it is imperative to conduct further research to gain understanding and provide reference value for comprehensive treatment strategies for HC.

Abbreviations

HC
Hilar cholangiocarcinoma
CA19-9
carbohydrate antigen19–9
ALP
alkaline phosphatase
ALT
alanine aminotransferase
AST
aspartic aminotransferase
ALB
albumin
CEA
arcinoembryonic antigen
TBIL
total serum bilirubin
BMI
Body Mass Index
ASA
American society of anesthesiologists
TNM
Tumor Node Metastasis

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Institutional Review Board of Shengjing hospital of China Medical University. Informed consent was obtained for all patients' data.

Consent for publication

Written informed consent was obtained from all the patient for publication of this article.

Availability of data and materials

The data sets used and analyse during the study are available from the corresponding author and first author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Gangshan Liu,Ying Fan ,Jiannan Zhao,Xuecheng Li have been involved in the data collection of the patient. Gangshan Liu and Ying Fan have been involved in the Study designing and date analysis.All authors read and approved the final manuscript.

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Tables

Table 1. Clinicopathological characteristics of the enrolled 85 patients.

Program	Group	Patients	Percentage
Gender	Male	56	65.9
	Female	29	34.1
Age	<64 years	44	51.8
	64 years	41	48.2
ASA grade		0	0
		69	81.2
		16	18.8
		0	0
Height	<167cm	38	44.7
	167cm	47	55.3
Weight	<60kg	23	41.2
	60kg	62	58.8
BMI	Low	6	7.1
	Normal	52	61.2
	High	27	32.7
TBIL umol/L	3.4-20.5	5	5.9
	>20.5	80	94.1
ALP U/L	40-150	4	4.7
	>150	81	95.3
ALT U/L	0-40	8	9.4
	>40	77	90.6
AST U/L	5-34	8	9.4
	>34	77	90.6
ALB(g/L)	35-53	65	76.5
	<35	20	23.5
CA19-9(U/ml)	0-37	10	11.8
	38-1000	64	75.3
	>1000	11	12.9
Imaging staging	NA	2	2.3
	Type I	13	15.3
	Type II	29	34.1
	Type IIIa	8	9.4
	Type IIIb	10	11.8
	Type IV	23	27.1
Caudate lobe	Yes	21	24.7
	No	64	75.3
Surgical time	<300min	38	44.7
	300min	47	55.3
Biliary plastic	Yes	25	29.4
	No	60	70.6

Table1. Continued

Intraoperative blood loss	<500ml	63	74.1
	500ml	22	25.9
Blood transfusion	Yes	50	58.8
	No	35	41.2
Tumor size	<3cm	49	57.6
	3cm	36	42.4
Lymphatic metastasis	Yes	20	23.5
	No	65	76.5
Resection margin	Positive	16	18.8
	Negtive	69	81.2
TNM staging	0	0	0
	I	23	27.1
	II	31	36.5
	III	26	30.6
		5	5.8

Table2. Cox single factor analysis for cholangiocarcinoma clinical data and treatment characteristics.

Factor	b	SE(b)	Wald	df	p value	Hazard Ratio (HR)	95% CI for HR
Gender	-0.075	0.315	0.057	1	0.811	0.928	0.500-1.719
Age	-0.055	0.296	0.034	1	0.854	0.947	0.531-1.690
Height	-0.089	0.298	0.089	1	0.766	0.915	0.510-1.641
Weight	0.302	0.372	0.658	1	0.417	1.353	0.652-2.806
BMI	-0.145	0.257	0.315	1	0.574	0.865	0.523-1.433
ALT	-0.012	0.527	0.001	1	0.982	0.988	0.352-2.774
AST	-0.250	0.528	0.225	1	0.635	0.779	0.277-2.190
ALB	0.114	0.359	0.102	1	0.750	1.121	0.555-2.265
Excise caudate lobe or not	-0.077	0.347	0.049	1	0.825	0.926	0.469-1.829
Operation time	0.034	0.297	0.013	1	0.910	1.034	0.577-1.853
Bile duct plastic or not	-0.338	0.303	1.245	1	0.264	0.713	0.394-1.291
Blood transfusion	0.149	0.301	0.247	1	0.619	1.161	0.644-2.093
CA199	1.058	0.324	10.686	1	0.001	2.880	1.5275.429
Lymphatic metastasis	-0.835	0.312	7.159	1	0.007	0.434	0.235-0.800
ASA grade	0.465	0.364	1.629	1	0.202	1.592	0.780-3.250
TBIL	0.601	0.321	3.511	1	0.061	1.823	0.973-3.418
ALP	-0.581	0.602	0.933	1	0.334	.559	0.172-1.819
Imaging staging	0.236	0.099	5.686	1	0.017	1.266	1.043-1.537
Intraoperative blood loss	0.876	0.330	7.054	1	0.008	2.401	1.258-4.583
Tumor size	1.096	0.302	13.121	1	0.000	2.991	1.653-5.411
TNM staging	0.691	0.186	13.796	1	0.000	1.997	1.386-2.876
Resection margin	-1.825	0.366	24.848	1	0.000	0.161	0.0790-0.330

Table 3. Multivariable regression analysis of HC using Cox proportional hazard model.

Factor	b	SE(b)	Wald	df	P value	Hazard Ratio (HR)	95% CI for HR
CA19-9	0.956	0.347	7.605	1	0.006	2.602	1.319-5.135
TNM staging	0.584	0.180	10.555	1	0.001	1.794	1.261-2.552
Resection margin	-1.487	0.373	15.917	1	0.000	0.226	0.109-0.469

Table 4.Comprehensive test of model coefficients [d]

steps	-2ln(L)	Overall (score)			Change from the previous step		
		Wald	df	Sig.	Wald	df	Sig.
1[a]	306.574	16.637	1	0.000	7.642	1	0.006
2[b]	294.145	27.760	2	0.000	12.430	1	0.000
3[c]	289.190	32.065	3	0.000	4.955	1	0.026

a:Input variables resection margin in step1,

b:Input variables TNM staging in step2,

c:Input variables CA19-9 in step3,

d: Test method :step forward (likelihood ratio).