Original Article

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Coagulopathy associated with poor prognosis in intrahepatic cholangiocarcinoma patients after curative resection

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Summary **As a rare type of liver cancer, intrahepatic cholangiocarcinoma (ICC) has become an increasingly important malignancy and continues to present significant therapeutic challenges. Since coagulopathy is associated with poor prognosis in hepatocellular carcinoma (HCC), and prognostic factors of ICC after curative resection were still not clear, we aim to analyze the characteristics of ICC patients with coagulopathy and its correlation to prognosis. From January 2000 to June 2011, 541 ICC patients, after curative resection, were enrolled in our study. Survival curves were depicted by the Kaplan-Meier method and analyzed by the log-rank test. The Cox proportional hazard regression was adopted for multivariate survival analysis. Student's *t* test was performed to analyze the difference between the coagulopathy group and the normal group. The correlation between coagulation parameters and prognosis was also evaluated. The incidence rate of at least one coagulation parameter abnormality was 22.6% (122/541) while PT was the most common factor (8.87%, 48/541). The one-year survival rate of patients with coagulopathy was significantly lower than that of patients with normal coagulation ($p < 0.01$). In a univariate analysis, patients with prolonged PT was associated with shortened DFS ($p < 0.05$). Meanwhile, PT was negatively correlated with pre-albumin level. TNM stage, CA19-9, GGT, and pre-albumin level were independent prognostic factors of DFS in the multivariate analysis. In conclusion, the incidence rate of coagulopathy of ICC patients is lower than HCC patients. Prolonged PT, advanced TNM stage, low pre-albumin level, and high CA19-9 and GGT level were correlated with high recurrence rate and poor prognosis.**

Keywords: Intrahepatic cholangiocarcinoma, coagulopathy, prognosis

1. Introduction

Intrahepatic cholangiocarcinoma (ICC), a rare type of liver cancer, is different from hepatocellular carcinoma (HCC) and extrahepatic bile duct carcinoma. The incidence rate of ICC accounts for 10% of primary liver cancer, which is far below than that of HCC (*1*). Although the rate of curative resection increased significantly due to the improvement of diagnosis and treatment (*2,3*), the postoperative recurrence rate is still high and the long-term survival rate is unsatisfactory (*4-6*).

Hypercoagulability is a well-known condition in patients with cancer, but it is exceedingly rare in HCC because liver is the main organ that synthesizes proteins (*7,8*) which include fibrinogen, prothrombin, and factors V, VII, IX, X, XI, and XII, and the reduction of the clotting factors can also reflect impaired liver function (*9*). Previous research revealed that

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coagulopathy is associated with poor prognosis in HCC (*10.11*). However, prognostic factors of ICC after curative resection were still not clear. On one hand, ICC patients have little impaired liver function and better reversed liver function due to the rare combination with cirrhosis. On the other hand, ICC is a malignant tumor that may lead to hypercoagulability for many reasons.

As a result, the correlation between coagulation abnormality and prognosis in ICC patients is still unclear. This triggers our interest to follow the changing pattern of some coagulation factors in patients with ICC and to test whether there is a correlation between some hemostatic variables and the prognosis of patients.

In this study, we retrospectively analyzed 541 ICC patients in Zhongshan Hospital of Fudan University from January 2000 to June 2011, following up for 4 to 5 years. The coagulopathy and its prognosis were further investigated.

2. Materials and Methods

2.1. *Patients*

From January 2000 to December 2011, 541 ICC patients at the Liver Cancer Institute of Fudan University were enrolled in our study and retrospectively analyzed. The median age of patients was 58 years (27 to 89 years). There were 331 men (61%, 331/541) and 210 women (39%, 210/541). The median course of disease was 1 month. Median hospital stay time was 15 (5 to 94) days. All patients underwent curative surgical treatment and were diagnosed as ICC by postoperative pathology. This study was approved by the institutional review board of Zhongshan Hospital and complied with the standards of the Declaration of Helsinki and current ethical guidelines.

2.2. *Coagulation parameters and clinicopathological factors*

Coagulation parameters and clinicopathological factors that were potentially related to survival were selected in this study. Coagulation parameters include prothrombin time (PT), activated partial thromboplastin time (APTT), prothrombin time ratio (PTR), international normalized ratio (INR), and blood biochemistry parameters including gamma-glutamyl transferase (GGT), total bilirubin (TB), carbohydrate antigen 19-9 (CA19-9), albumin (ALB), and pre-albumin (PA) which were all tested according to regular methods. Tumor related characteristics were also recorded including TNM stage, tumor volume, regional lymph node metastasis, vascular invasion, and distant metastasis. Vascular invasion refers to trunk or branch vascular invasion of portal vein and/or hepatic vein. All pathological specimens were reviewed by two pathologists to confirm the histological type, differentiation, lymph node metastasis, and neural invasion. The staging of tumors was determined according to the 7th edition of the TNM classification system (*12*). Coagulation and demographic characteristics of the groups are shown in Tables 1 and 2.

2.3. *Follow-up*

All patients were followed up every 2 months till December 31, 2015 at the Outpatient Department and prospectively monitored for recurrence by a standard protocol. Overall survival (OS) refers to the period between initial diagnosis and last follow-up or death. Disease free survival (DFS) refers to the length of time after primary treatment that the patient survives without tumor recurrence.

2.4. *Statistical analysis*

OS time and DFS time were calculated by the Kaplan-Meier method and compared by the log-rank test. The Cox proportional hazard regression was performed for a multivariate survival analysis. For continuous variables, the Student's *t*-test was used to compare the differences in indexes between the normal group and the coagulopathy group. The SPSS 18.0 software was used to perform statistical analysis. Two-tailed $p < 0.05$ was considered as statistically significant.

3. Results

3.1. *Clinical characteristics of patients with coagulopathy*

Patients were divided into 2 groups according to their coagulation parameters: the normal group and the coagulopathy group (patients with at least 1 abnormal coagulation parameters). At least 1 abnormal coagulation parameters (PT, APTT, PTR, INR) counted for 22.6% (122/541), 8.87% of patients (48/541) with PT > 13 s, 4.8% of patients (26/541) with APTT < 23.5 s, 5.7% of patients (31/541) with APTT >37.5 s, 0.18% of patients (1/541) with PTR < 0.8, 2.22% of patients (12/541) with PTR > 1.2, and 3.0% of patients (16/541) with INR > 1.2 (Table 1). There were no statistically

Table 1. Coagulation characteristics of 541 ICC patients

Coagulation parameters	Cases	Percent (%)
At least 1 abnormal	122	22.60
PT > 13 s	48	8.87
APTT		
< 23.5 s	26	4.80
> 37.5 s	31	5.73
PTR		
< 0.8	13	2.40
> 1.2	13	2.40
INR > 1.2	16	3.00

PT, prothrombin time; APTT, activated partial thromboplastin time; PTR, prothrombin time ratio; INR, international normalized ratio.

Table 2. Clinical characteristics of 541 ICC patients

Clinical Characteristics	Normal group (n = 419)	Coagulopathy group (n = 122)	Chi-square value/t value	p value
Age yr, (range)	57 (27,89)	59 (28,80)	- 0.326	0.745
Gender			0.846	0.358
Male	252	79		
Female	167	43		
TNM Stage			6.658	0.247
Stage I	197	65		
Stage II	61	21		
Stage III	9	2		
Stage IVa	70	11		
Stage IVb	61	14		
Unknown	21	9		
Tumor Differentiation			4.62	0.202
I-II	2	48		
III	182	47		
IV	144	1		
HbsAg (positive)	174	53	0.135	0.714
GGT > 40 U/L	309	85	0.941	0.332
AFP > 20 ng/mL	37	17	2.639	0.104
CA199 > 37 U/mL	240	73	0.027	0.87
ALB < 40 g/L	274	84	0.461	0.497
PA < 0.25 g/L	209	74	0.139	0.709
TBIL > 17 μmol/L	101	35	1.027	0.311
Overall Survival	10 (0,112)	10 (0,106)	1.589	0.113
Disease Free Survival	8 (0,111)	8 (0,106)	1.167	0.244
Survival Rate				
1-year	48.02	34.43	8.267	0.004**
3-year	19.81	17.21	0.41	0.522
5-year	6.92	5.74	0.213	0.644

HbsAg, Hepatitis B surface antigen; GGT, gamma-glutamyl transferase; AFP, alpha fetoprotein; CA19-9, carbohydrate antigen 19-9; ALB, albumin; PA, pre-albumin; TBIL, total bilirubin; $^{**}p < 0.01$.

significant differences in age, gender, TNM stage, tumor differentiation, GGT, TB, and CA19-9 between the two groups (Table 2).

3.2. *Following-up postoperative survival status and survival analysis*

By December 31, 2015, there were 352 deaths. There was significant difference in 1- year survival rate between the normal group (48.02%) and coagulopathy group (34.43%) ($p < 0.01$). However, there were no statistically significant differences between 3- and 5-year survival rates ($p > 0.05$) (Table 2). The average OS time of the normal group was 20.72 months comparing to 17.2 months of the coagulopathy group, and the average DFS time of the normal group was 15.78 months comparing to 13.41 months of the coagulopathy group. However, both differences were not statistically significant (Table 2). Univariate analysis was used to analyze the effect of the single coagulation factor (PT, APTT, PTR, and INR) on prognosis (OS, DFS). We found that PT had an effect on DFS ($p < 0.05$) (Table 3). The multivariate analysis was used to further verify the relation between coagulation factors and DFS. The results showed that PT was an independent factor affected DFS, while APTT, PTR and INR were not (Table 4). Kaplan-Meier survival analysis showed that there was significant difference in the DFS rate between patients with prolonged PT (17.2%) and patients without it (27.7%) ($p < 0.05$) (Figure 1). However, the effect of PT on OS time had not been observed. APTT, PTR, and INR played no effect neither on OS nor DFS in univariate analysis ($p > 0.05$) (Table3).

3.3. *Correlation analysis between other prognostic factors and DFS*

We used univariate analysis in order to further analyze the correlation between DFS and other prognostic factors including the TNM stage, ALB, PA, GGT, TB, and CA19-9. We found that the TNM stage, PA, GGT, TB, and CA19-9 significantly influenced DFS ($p < 0.05$) (Table 5). The Cox proportional hazards model was used to detect potential predictors of DFS based on variables selected by univariate analysis. The results showed that TNM stage, PA, GGT, and CA19-9 were independent factors affected DFS, while ALB and TB were not (Table 4). Correlation analysis indicated that there was a negative correlation between PT and PA level (correlation coefficient: -0.088, $p < 0.05$) (Table 6). However, there was no statistically significant difference between PT and other liver function indicators (including GGT, TB) and tumor marker (CA19-9) ($p > 0.05$).

Table 3. Relation between coagulopathy and prognosis

Variable	Cases	Overall survival	*p* value	Disease free survival	*p* value
PT					
≥ 13 s	48	8 (0,91)	0.976	6.5 (0,51)	0.041*
< 13 s	493	11 (0,112)		8 (0,111)	
APTT					
23.5-37.5	484	11 (0,112)	0.215	8 (0,111)	0.762
Abnormal	57	8 (0,106)		7 (0,103)	
PTR					
0.8-1.2	515	11 (0,112)	0.611	8 (0,111)	0.322
Abnormal	13	9 (3,53)		9 (2,93)	
INR					
≥ 1	219	10 (0,112)	0.446	7 (0,112)	0.259
< 1	322	11.5 (0,112)		8.5 (0,112)	

PT, prothrombin time; APTT, activated partial thromboplastin time; PTR, prothrombin time ratio; INR, international normalized ratio; *$p < 0.05$.

Table 4. Multivariate analysis

Variable	Regression coefficients	Standard error	*p* value	Relative risk	95% CI
PT	0.436	0.192	0.023*	5.159	1.062 - 2.254
APTT	- 0.179	0.190	0.345	0.892	0.577 - 1.212
PTR	- 0.355	0.373	0.342	0.902	0.337 - 1.458
INR	- 0.060	0.114	0.601	0.273	0.753 - 1.178
TNM stage	0.193	0.036	< 0.001***	28.841	1.131 - 1.302
CA19-9	0	0	< 0.001***	19.881	1
TB	- 0.001	0.001	0.245	1.351	0.997 - 1.001
ALB	- 0.003	0.003	0.417	0.657	0.99 - 1.004
GGT	0	0	0.011*	6.395	1.0 - 1.001
PA	0.001	0.001	0.022*	5.281	1.0 - 1.002

PT, prothrombin time; APTT, activated partial thromboplastin time; PTR, prothrombin time ratio; INR, international normalized ratio; CA19-9, carbohydrate antigen 19-9; TB, total bilirubin; ALB, albumin; GGT, gamma-glutamyl transferase; PA, pre-albumin. *$p < 0.05$; ***$p < 0.001$.

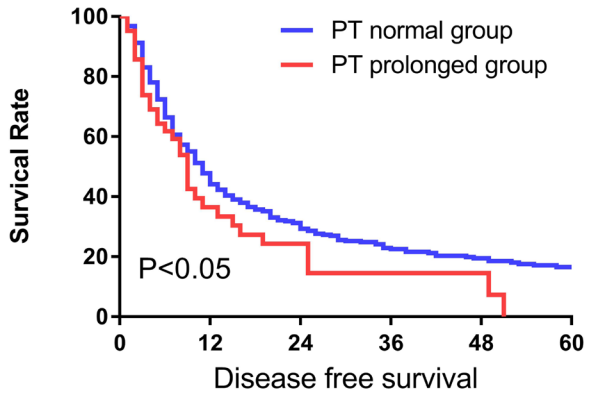

Figure 1. Disease free survival comparison between PT normal group PT prolonged group.

Table 5. Other factors' affection to disease free survival

Variables	Cases	Disease free survival	*p* value
TNM Stage			
Stage I	262	9 (0,111)	0.001**
Stage II	82	7 (0,103)	
Stage III	11	7 (2,21)	
Stage IVa	81	7 (0,81)	
Stage IVb	75	6 (0,108)	
PA			
< 0.25 g/L	283	7 (0,111)	0.012*
≥ 0.25 g/L	127	11 (0,109)	
ALB			
< 40 g/L	358	8 (0,111)	0.795
≥ 40 g/L	182	7 (0,81)	
GGT			
< 40 U/L	145	10 (0,111)	< 0.001***
≥ 40 U/L	394	7 (0,108)	
TB			
< 17 μmol/L	404	8 (0,111)	0.001**
≥ 17 μmol/L	136	7 (0,79)	
CA19-9			
< 37 U/mL	207	9 (0,106)	0.004**
≥ 37 U/mL	313	7 (0,111)	

PA, pre-albumin; ALB, albumin; GGT, gamma-glutamyl transferase; TB, total bilirubin; CA19-9, carbohydrate antigen 19-9; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

4. Discussion

PT, APTT, PTR, and INR are common parameters for the coagulation function evaluation. PT mainly represents the content and function of factor VII while APTT relates to factors VIII, IX, XI, and XII which is the most common screening test for the intrinsic pathway (*13*). In HCC patients, the global effect of liver disease with regard to hemostasis is complex because of impaired liver function, which may result in reduced plasma levels of procoagulant and anticoagulant clotting factors and reduced capacity to clear activated

Table 6. Correlation analysis

Variable	PT/CC#	*p* value	APTT/CC#	*p* value	PTR/CC#	*p* value	INR/CC#	*p* value
TNM Stage	- 0.042	0.347	- 0.022	0.626	- 0.063	0.158	- 0.051	0.249
TB	- 0.017	0.693	- 0.031	0.468	- 0.023	0.590	- 0.026	0.553
ALB	0.039	0.362	- 0.200	0.001**	- 0.019	0.658	- 0.024	0.573
GGT	- 0.014	0.738	0.002	0.969	- 0.043	0.321	- 0.083	0.055
PA	- 0.088	0.044*	0.051	0.243	- 0.092	0.034*	- 0.060	0.168
CA19-9	- 0.016	0.718	0.019	0.668	0.041	0.350	0.020	0.646

CC#: correlation coefficient; TB, total bilirubin; ALB, albumin; GGT, gamma-glutamyl transferase; PA, pre-albumin; CA19-9, carbohydrate antigen 19-9; *$p < 0.05$; **$p < 0.01$.

hemostatic proteins and protein inhibitor complexes from the circulation, so that patients can experience severe bleeding or even thrombotic complications (*14,15*). However, few researchers analyzed coagulopathy in ICC patients.

ICC is a rare primary liver cancer which has become a malignancy of increasing importance and continues to present significant biological and therapeutic challenges (*16-18*). The clinical features of ICC are diverse and often advanced at the time of diagnosis, often precluding surgical treatment. Hepatic resection is regarded as the treatment of choice, but tumor recurrence is common after curative resection (*19-22*). Different from HCC, ICC patients have little impaired liver function and with better reversed liver function because of rare combination with cirrhosis. According to our study, the incidence of at least 1 abnormal coagulopathy was 22.6% (122/541 cases). Prolonged PT counted for most (n = 48, 8.8%) and prolonged APTT counted for second (n = 31, 5.7%), which are far lower than those of HCC (*15,23*).

Long-term survival is rare in ICC due to high malignancy and poor prognosis. The first optional treatment for ICC is surgical resection. Few patients can survive over 3 years without operation (*24*). So far, the prognostic factors of post resection outcomes in ICC studies are still inconsistent and even conflicting, probably due to the relatively small number of patients studied. In a validation study with patients from Chinese and Japanese centers, TNM stage, GGT and CA19-9 were related with prognosis. Lymph node metastasis, invasion of peripheral nerves, and tumor size over 5cm are related to low DFS rate (*25*). In our study, we found that the 1-year survival rate of patients with coagulopathy was lower than that of patients with normal coagulation ($p < 0.01$). Univariate analysis showed that patients with prolonged PT had shorter DFS ($p < 0.05$). Meanwhile, prolonged PT was negatively correlated with pre-albumin level. Because PT and pre-albumin are sensitive factors of reversed liver function, we speculate that more tumor infiltration was in patients with prolonged PT, whatever more tumor burden, massive type, multiple lesions, intrahepatic micrometastases or tumor thrombus that can't be detected by current methods, that leads to a decrease in liver reverse function. It seems to be the same reason for the lower 1-year survival rate in patient with abnormal coagulopathy ($p < 0.01$). However, no significant differences were found in 3- and 5-year survival rate between patients with abnormal coagulopathy and patients with normal coagulopathy. One possible reason is that the long-term survival rate of ICC was very low, which was lower than 20% in both groups. More cases need to be analyzed due to the small difference between the two groups.

Interestingly, as a test for intrinsic pathway, APTT was not an independent factor that affected DFS. The reason may be coagulation factor VIII is synthesized mainly by the hepatic but also nonhepatic sinusoidal endothelial cells (*26*), thus the plasma concentration of VIII did not decrease with liver disease and may have even increased, as many chronic liver diseases including ICC are associated with chronic inflammation (*27*). In this study, we also found that that TNM stage, CA19-9, GGT, and pre-albumin level acted as independent factors of DFS, which indicated that higher TNM stage, lower pre-albumin level, and increased CA19-9 and GGT levels were correlated with earlier tumor recurrence and poor prognosis. In presence of prolonged PT, patients were in high-risk of recurrence and we provided them with strict postoperative supervision which is beneficial for the treatment once tumor recurred.

In conclusion, this study found that PT is an independent factor related with ICC recurrence. Higher TNM stage, lower pre-albumin level, and increased CA19-9 and GGT levels suggest earlier tumor recurrence and poor prognosis.

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