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Original Article

Clinical Significance of Venous Thromboembolism in Patients with Advanced Cholangiocarcinoma

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Background/Aims: Patients with active cancer frequently develop venous thromboembolism (VTE). However, there is little data about VTE in patients with advanced cholangiocarcinoma (CCA). Therefore, we investigated the clinical significance of VTE in patients with advanced CCA.

Methods: We analyzed the data of a total of 332 unresectable CCA patients diagnosed between 2010 and 2020 in this retrospective study. We investigated the incidence and risk factors for VTE, and its effect on survival in patients with advanced CCA.

Results: During a median follow-up of 11.6 months, 118 patients (35.5%) developed VTE. The cumulative incidence of VTE was 22.4% (95% confidence interval [CI], 0.18 to 0.27) at 3 months and 32.8% (95% CI, 0.27 to 0.38) at 12 months. Major vessel invasion was an independent risk factor for VTE (hazard ratio, 2.88; 95% CI, 1.92 to 4.31; p<0.001). Patients who developed VTE during follow-up had shorter overall survival than patients who did not (11.50 months vs 15.83 months, p=0.005). In multivariable analysis, VTE (hazard ratio, 1.58; 95% CI, 1.23 to 2.02; p<0.001) was associated with poor overall survival.

Conclusions: Major vessel invasion is related to the occurrence of VTE in advanced CCA. The development of VTE significantly decreases the overall survival and is an important unfavorable prognostic factor for survival. **(Gut Liver 2024;18:165-173)**

Key Words: Venous thromboembolism; Cholangiocarcinoma; Prognostic factor; Advanced stage

INTRODUCTION

Venous thromboembolism (VTE) occurs in 15% to 20% of all cancer patients.[1] VTE is clinically one of the most important causes of morbidity and mortality in cancer patients.[2-5] Several large epidemiologic studies have reported the highest risk of VTE in intraabdominal tumors such as ovarian, gastric, and pancreatic cancers.[3,6] However, few studies have been conducted on VTE in cholangiocarcinoma (CCA).

CCA is a relatively rare disease, accounting for about 3% of all gastrointestinal tumors.[7,8] The incidence of CCA has been reported to be higher in Asians.[9] CCA is a malignant disease originating from the epithelium of the bile duct, and is classified into intrahepatic, perihilar, and extrahepatic, depending upon the location. Most of these cancers are highly lethal because they are diagnosed at an advanced stage.[10,11] The clinical significance of CCA has increased with the growth of disease burdens in recent years.[12,13]

Some previous studies have investigated VTE occurrence in CCA patients. These studies have limitations in that they do not represent the characteristics of the entire patient group because they only targeted patients who had undergone surgery.[14-16] One study including all subtypes of CCA reported that the incidence of VTE in CCA is approximately 14.7%. However, this study had limitations because of the small number of VTE patients, and patients with advanced CCA were only analyzed by subgroup analysis. There was little data analyzing the occurrence of VTE in CCA patients at an advanced stage. Nevertheless,

the occurrence of VTE in advanced stages of CCA is clinically important, because the risk of VTE in cancer patients is higher in advanced stages than in early stages.[5,17,18] Accordingly, there is an increased need for studies of VTE in advanced CCA patients.

Therefore, the purpose of this study is to investigate the clinical significance of VTE in patients with advanced CCA.

MATERIALS AND METHODS

1. Study design and patients

This retrospective study investigated patients newly diagnosed with CCA at a single tertiary center (Seoul National University Hospital, Seoul, Korea) between 2010 and 2020, using an electronic medical records database (Fig. 1). The diagnosis of CCA was confirmed using pathological records, and we considered all subtypes of CCA, including intrahepatic, hilar, and extrahepatic, except for gallbladder cancer. Among them, we included patients with advanced CCA, defined as those who had been diagnosed with unresectable CCA or recurred after operation.[19] We analyzed those patients who had had adequate follow-up for at least 1 month. We excluded patients according to the following exclusion criteria: VTE associated with causes other than CCA, a diagnosis without pathologic confirmation, and patients with insufficient data.

We defined VTE as all venous thromboembolisms, including splanchnic venous thrombosis, deep vein thrombosis, or pulmonary thromboembolism.[18] Trained experts confirmed the diagnosis of VTE based on radiologic studies such as Doppler sonography and/or computed tomography.

The Institutional Review Board of the Seoul National University Hospital approved this retrospective study (IRB number: H-2009-146-1159), and informed consent was waived.

2. Data collection and definition

Patient characteristics were retrospectively collected, including age, sex, body mass index, location of tumor, clinical stage including major vessel invasions and distant metastases, laboratory findings (carcinoembryonic antigen, carbohydrate antigen 19-9), and treatment modalities such as chemotherapy and surgery. Patients with CCA were managed according to National Comprehensive Cancer Network guideline during the follow-up period. In cases of cancer recurrence after operation, the recurrence date was defined as the date of diagnosis. This is because this study was conducted on unresectable CCA patients who had received anticancer treatment or supportive care. Anticancer treatment included palliative chemotherapy and radiotherapy, and patients who received palliative chemotherapy were defined as those whose disease status had been evaluated at least once after initiation of chemotherapy. Major vessel invasion was defined as cancer invasion of the hepatic artery, portal vein, and its branches and variant hepatic vessels.[20] The Khorana score was calculated as previously used in patients with cancer.[21] Progression-free survival (PFS) is defined as the time from diagnosis to cancer progression during first-line chemotherapy. Overall survival (OS) was defined from the date of diagnosis to the date of death in months, or the date of the last follow-up.

3. Study outcome measures

The primary outcome of this study was the incidence and risk factors for VTE in patients with advanced CCA. The secondary outcomes were defined as the prognostic factors for CCA and the effect of VTE on PFS and OS.

4. Statistical analysis

To compare the basic characteristics, we used the Student t-test and chi-square test for continuous and dichotomous variables, respectively. If any subgroups had fewer than four subjects, the Fisher exact test was used instead of a chi-square test. Cumulative incidence of VTE, PFS, and OS were calculated using the Kaplan-Meier method. A log-rank test was used to compare survival between groups in univariable analysis. Survival data was gathered from the national database of the Ministry of Public Administration. The body mass index of two patients was missing and their Khorana score could not be obtained. Missing data were replaced with the median because the number is very small.

In multivariable analysis, a Cox proportional hazard model was used to analyze the risk factors for VTE development and survival. Variables with $p<0.05$ in univariable analysis were included in a multivariable analysis. A three-state unidirectional illness-death model was used to analyze death without VTE and factors related to VTE development or death.[18,22] Moreover, to study the effect of VTE onset time on mortality, we extended the multistate model to include VTE onset time.[18] The multistate model was designed to analyze three different states (Supplementary Fig. 1). State 1 is a state of being alive without VTE at the time of diagnosis. In state 2, the patient who developed VTE is alive or in a transient state. State 3 is an absorbing state in cases of death. This model has three potential transitions, depending on these states. Patients diagnosed with CCA may develop VTE (transition 1) or die (transition 2) after diagnosis. In addition, living patients with CCA who

develop VTE might die (transition 3). p<0.05 indicated statistical significance. Statistical calculations were performed with R environment ver. 4.1.0 (The R Foundation for Statistical Computing, Vienna, Austria) using the *mstate* library.

RESULTS

1. Baseline characteristics of the study population

Of the 534 patients newly diagnosed as having CCA with at least a 4-week follow-up, 193 had resectable CCA. Patients with advanced CCA included 97 patients with postoperative relapse and 341 with unresectable CCA. Among them, we excluded 106 patients according to the exclusion criteria, and we analyzed a total of 332 patients (Fig. 1). As a result, 118 patients (35.5%) were diagnosed with VTE. The median follow-up period was 11.6 months (range, 1 to 82 months). Table 1 shows the comparison of baseline characteristics in the advanced CCA patients according to VTE. Intrahepatic CCA was the most common (66.3%). Patients having recurrence after operation (36.7% vs 15.4%, p<0.001) or who had received anticancer treatment (84.1% vs 70.3%, p=0.005) had significantly less VTE.

Major vessel invasion was also significantly higher in the patient group with VTE (34.4% vs 63.2%, p<0.001). Baseline carbohydrate antigen 19-9 was significantly higher in patients with VTE (1,929 U/mL vs 7,462 U/mL, p=0.022). There was no significant difference between two groups in other variables.

2. Primary study outcomes

Of the 118 VTE patients, 45 of them (38.5%) had VTE at the time of CCA diagnosis. Visceral venous thrombosis was the most common with 97 patients (82.9%), pulmonary thromboembolism with 27 patients (23.1%), and deep vein thrombosis with 14 patients (12.0%). Among visceral venous thrombosis cases, portal vein thrombosis was the most common type of VTE, accounting for 74 patients (Table 2). Only 13.6% (16/118) of patients with VTE had cholangitis prior to diagnosis of VTE.

The cumulative incidence rates of VTE were 22.4% (95% confidence interval [CI], 0.18 to 0.27) at 3 months and 32.8% (95% CI, 0.27 to 0.38) at 12 months (Fig. 2).

In the univariable analysis, hilar location, major vessel invasion and anticancer treatment recurrences after operation were factors that significantly affected the incidence of VTE. In multivariable analysis, major vessel invasion (hazard ratio [HR], 2.88; 95% CI, 1.92 to 4.31; p<0.001), was an independent risk factor for the onset of VTE. Hilar location (HR, 0.18; 95% CI, 0.06 to 0.52; p=0.002), anti-

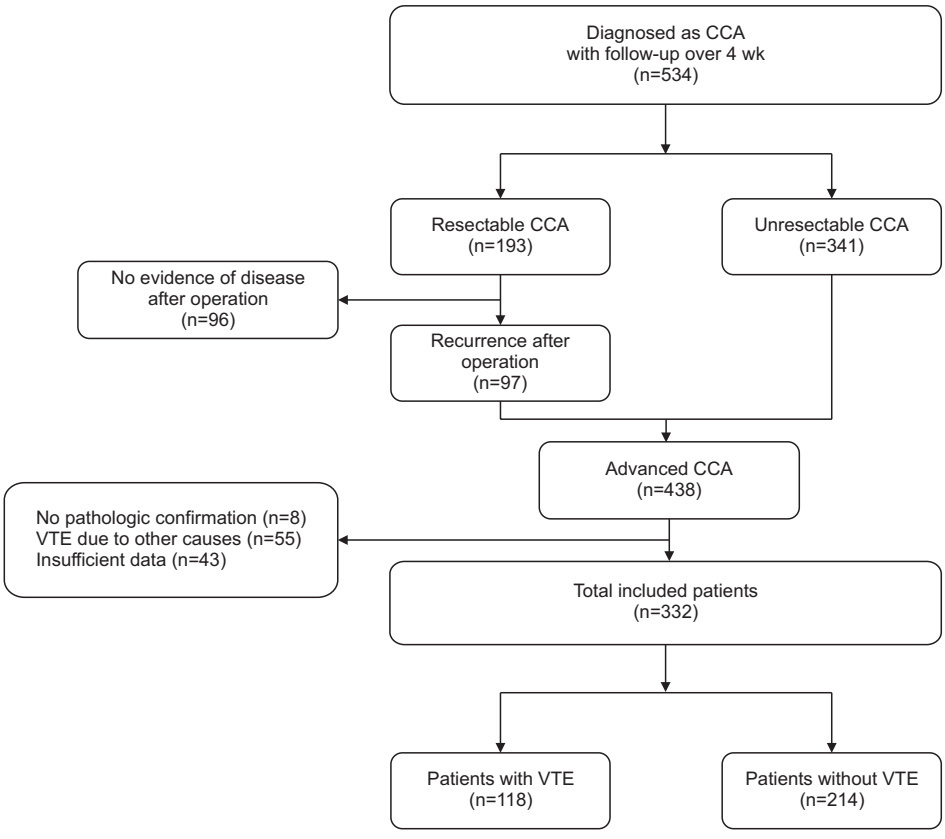

Fig. 1. Study flowchart. CCA, cholangiocarcinoma; VTE, venous thromboembolism.

Table 1. Baseline Characteristics of Patients According to the Presence of VTE

Characteristic	All patients (n=332)	Patients without VTE (n=214)	Patients with VTE (n=118)	p-value
Mean age, yr	63.9	63.7	64.0	0.808
Male sex	212 (63.9)	131 (60.9)	81 (69.2)	0.219
Mean body mass index, kg/m^2	23.5	23.5	23.3	0.768
Tumor location				0.008
Hilar	107 (32.2)	81 (37.7)	26 (22.2)	
Intrahepatic	220 (66.3)	132 (61.4)	88 (75.2)	
Extrahepatic	5 (1.5)	1 (0.5)	4 (3.4)	
Clinical stage				
Major vessel	148 (44.6)	74 (34.4)	74 (63.2)	<0.001
Distant metastasis	252 (75.9)	166 (77.2)	86 (73.5)	0.411
Recurrence after operation	97 (29.2)	79 (36.7)	18 (15.4)	<0.001
Anticancer treatment	263 (79.2)	180 (84.1)	83 (70.3)	0.005
Laboratory findings, mean				
CEA, ng/mL	60.4	70.6	42.5	0.616
CA19-9, U/mL	3,914	1,929	7,462	0.022
Khorana score				
Low	243 (73.2)	160 (74.4)	83 (70.9)	0.520
Intermediate	84 (25.3)	52 (24.2)	32 (27.4)	0.635
High	3 (0.9)	1 (0.5)	2 (1.7)	0.594

Data are presented as number (%) unless otherwise indicated.
VTE, venous thromboembolism; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Table 2. Anatomical Distribution of Venous Thromboembolism

Site	No. (%)
Initial venous thromboembolism	45 (38.5)
DVT&PTE	39 (33.3)
DVT	14
PTE	27
Visceral venous thrombosis	97 (82.9)
Portal vein	74
Superior mesenteric vein	8
Hepatic vein	13
Inferior vena cava	12
Others	3

DVT, deep vein thrombosis; PTE, pulmonary thromboembolism.

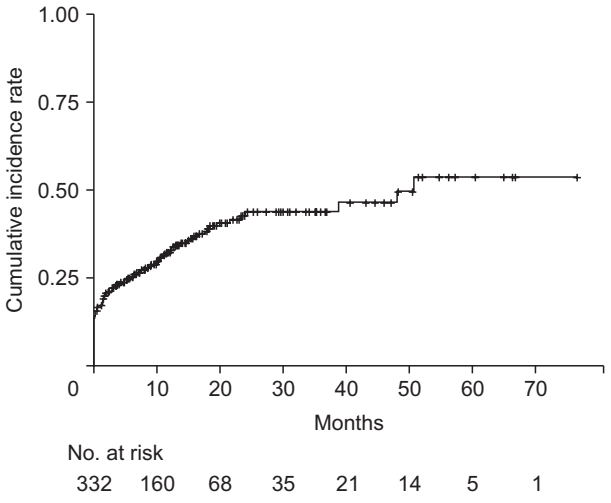

Fig. 2. Cumulative incidence of venous thromboembolism.

cancer treatment (HR, 0.42; 95% CI, 0.28 to 0.63; p<0.001), and recurrence after operation (HR, 0.57; 95% CI, 0.33 to 0.96; p=0.036) showed significant protective effect on the development of VTE (Table 3).

3. Secondary study outcomes

The overall median PFS in the VTE group was 8.56 months (95% CI, 6.47 to 13.87), and in the non-VTE group, 9.67 months (95% CI, 8.80 to 12.77). This is not statistically significant (p=0.122) (Fig. 3). In the univariable analysis, distant metastases affected PFS. The multivariable Cox regression analysis showed distant metastases (HR, 2.61; 95% CI, 1.60 to 4.30; p<0.001) was the only independent risk factor for reduced PFS (Table 4).

The median OS was 11.50 months (95% CI, 10.00 to 14.63) and 15.83 months (95% CI, 14.17 to 19.40) in the VTE and non-VTE groups, respectively. The VTE group showed a significantly shorter OS (p=0.005) (Fig. 3). In univariable analysis, major vessel invasion, anticancer treatment, recurrences after operation, and VTE were factors that affected the OS. As a result of multivariable analysis in Cox regression analysis, distant metastases (HR, 1.47; 95% CI, 1.11 to 1.95; p=0.007) and VTE (HR, 1.58; 95% CI, 1.23 to 2.02; p<0.001) are risk factors for a shorter OS. On the other hand, anticancer treatment (HR, 0.32; 95% CI, 0.24 to 0.43; p<0.001) had a favorable effect on OS (Table 5). And patients with recurrence after operation showed relatively better prognosis than those who were

Table 3. Risk Factors for the Development of Venous Thromboembolism until the Date of Last Follow-up or Death after a Diagnosis of Cholangiocarcinoma

Factor	Univariable		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age >60 yr	1.00 (0.70–1.50)	0.931		
Male sex	1.30 (0.85–1.90)	0.242		
Location				
Extrahepatic	Reference		Reference	
Hilar	0.23 (0.08–0.67)	0.007	0.18 (0.06–0.52)	0.002
Intrahepatic	0.47 (0.17–1.28)	0.138	0.41 (0.15–1.14)	0.086
Major vessel invasion	2.90 (2.00–4.20)	<0.001	2.88 (1.92–4.31)	<0.001
Distant metastasis	0.97 (0.64–1.40)	0.864		
Anticancer treatment	0.38 (0.25–0.57)	<0.001	0.42 (0.28–0.63)	<0.001
Recurrence after operation	0.32 (0.19–0.53)	<0.001	0.57 (0.33–0.96)	0.036

HR, hazard ratio; CI, confidence interval.

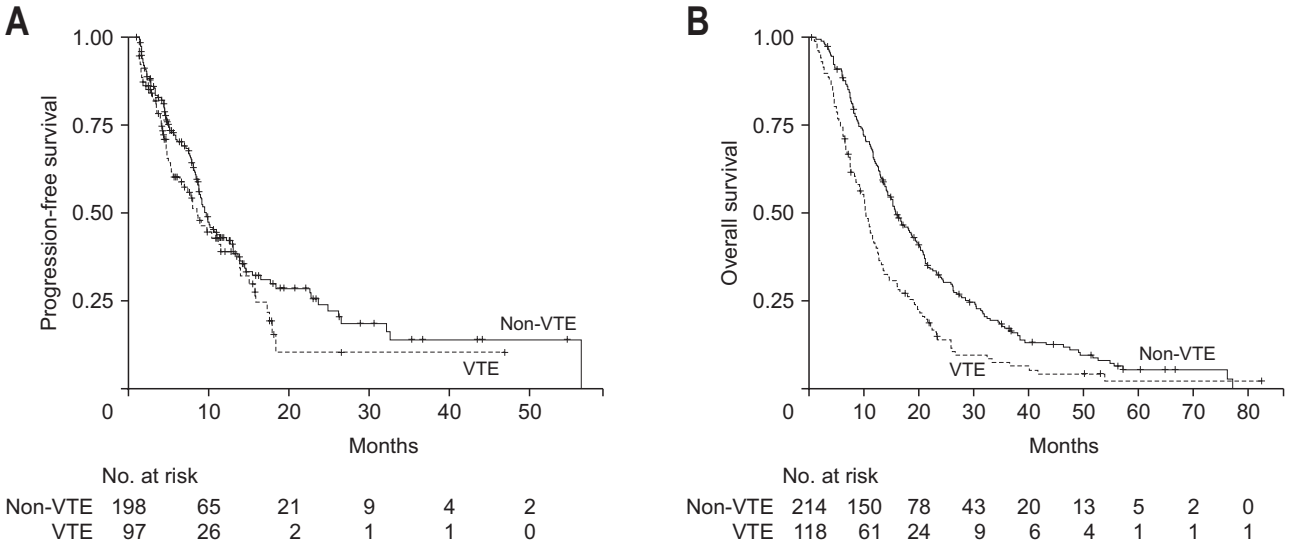

Fig. 3. Comparison of (A) progression-free survival and (B) overall survival between the venous thromboembolism (VTE) group and the non-VTE group.

Table 4. Prognostic Factors Influencing Progression-Free Survival

Factor	Univariable		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age >60 yr	0.75 (0.54–1.00)	0.079		
Male sex	0.91 (0.66–1.30)	0.589		
Location				
Extrahepatic	Reference			
Hilar	0.42 (0.17–1.00)	0.057		
Intrahepatic	0.49 (0.20–1.20)	0.121		
Major vessel invasion	0.73 (0.51–1.00)	0.073	0.94 (0.65–1.40)	0.741
Distant metastasis	2.60 (1.60–4.10)	<0.001	2.61 (1.60–4.30)	<0.001
Recurrence after operation	0.86 (0.61–1.20)	0.390		
Venous thromboembolism	1.20 (0.80–1.70)	0.437	1.30 (0.89–1.90)	0.180

HR, hazard ratio; CI, confidence interval.

initially diagnosed with unresectable CCA (HR, 0.68; 95% CI, 0.51 to 0.97; p=0.009) (Table 5).

Fig. 4 is the result of analysis using a three-state unidirectional illness-death model to confirm the effect of VTE on OS. We did not include patients who have VTE at diagnosis of CCA when analyzing the multistate model (Supplementary Fig. 1). As a result, patients diagnosed with CCA rapidly transitioned to death after developing VTE. Of the 276 patients diagnosed with CCA without VTE, 183 (66.3%) died (transition 1) and 56 (91.8%) of the 62 patients who developed VTE died (transition 2) (odds ratio, 14.07; 95% CI, 0.11 to 0.26; p=0.002).

We also performed a subgroup analysis of patients with VTE to analyze the effects of anticoagulation, and 31.4% (37/118) of VTE patients received anticoagulation. Patients who received anticoagulation had a significantly better OS (p=0.010) (Supplementary Fig. 2), but anticoagulation was not a statistically significant prognostic factor in multivariable analysis (HR, 0.81; 95% CI, 0.52 to 1.26; p=0.349) (Supplementary Table 1).

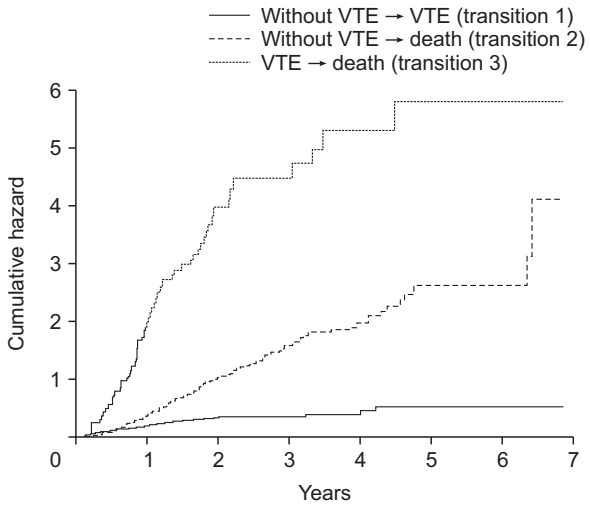

Fig. 4. Multistate model of state occupation probabilities during the entire follow-up period showing clinical course in patients with advanced cholangiocarcinoma at risk of venous thromboembolism (VTE) and death.

DISCUSSION

The clinical significance of VTE in advanced CCA is not understood well. This study shows that VTE is more likely to occur in patients with major vessel invasion. On the other hand, patients with hilar CCA or who had received anticancer treatment had lower incidence of VTE. Portal vein thrombosis was the most common type of VTE. There was no difference in PFS between the two groups, but OS was significantly shorter in the VTE group. Distant metastases and VTE were independent risk factors for worsening OS. In addition, CCA patients without VTE rapidly transitioned to death when VTE developed.

In this study, VTE occurred more frequently than in previous studies.[23] This may be because this study was conducted in patients who were diagnosed with higher stages of CCA, including 75.9% having distant metastases, than in the other study.[23] The occurrence of VTE according to the location of CCA had a similar tendency to that of a previous study.[23] VTE occurred more frequently in intrahepatic CCA. This may be due to direct invasion of intrahepatic CCA into the portal venous system.[14]

Cancer treatments such as chemotherapy are known to increase the risk of VTE.[24] However, in this study, the non-VTE group received more anticancer treatments. This may be because the target patient group was different. Seventy-five percent of patients in this study with advanced CCA received chemotherapy, which is much higher than a previous study (19%), which included a broad stage of CCA

Table 5. Prognostic Factors Influencing Overall Survival

Factor	Univariate		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age >60 yr	0.98 (0.77–1.30)	0.883		
Male sex	0.91 (0.72–1.20)	0.433		
Location				
Extrahepatic	Reference			
Hilar	0.42 (0.17–1.00)	0.057		
Intrahepatic	0.49 (0.20–1.20)	0.121		
Major vessel invasion	1.40 (1.10–1.80)	0.003	1.26 (0.97–1.65)	0.086
Distant metastasis	1.30 (0.97–1.70)	0.085	1.47 (1.11–1.95)	0.007
Anticancer treatment	0.30 (0.23–0.40)	<0.001	0.32 (0.24–0.43)	<0.001
Recurrence after operation	0.58 (0.45–0.76)	<0.001	0.68 (0.51–0.97)	0.009
Venous thromboembolism	1.60 (1.30–2.10)	<0.001	1.58 (1.23–2.02)	<0.001

HR, hazard ratio; CI, confidence interval.

patients.[23] In addition, since the period after recurrence was analyzed in patients who had undergone surgery, there was no VTE related to operation.

Distant metastases and VTE are significant independent risk factors in reducing OS. These results are consistent with previous studies. Jeon *et al.*[23] analyzed patients with resectable and advanced CCA and reported VTE occurred in 14.7% and that an advanced stage and VTE significantly reduced survival rates. Lu *et al.*[14] reported that the development of portal vein tumor thrombus significantly reduced the survival rate in patients with intrahepatic CCA who had undergone surgery. Some studies have reported that VTE reduced survival rate in other cancers as well. Frere *et al.*[18] studied pancreatic cancer patients, and the patients with VTE had significantly shorter OS. Lee *et al.*[17] reported that VTE occurred more frequently in advanced cases and worsened the survival rate in gastric cancer patients.

It is unclear how VTE affects cancer's poor prognosis. Patients with VTE may have more biologically aggressive cancer.[5] Certain cancers are actively involved in the development of hypercoagulable state through procoagulants such as tissue factor, and this clinical hypercoagulable status is a surrogate for adverse tumor biology.[25] Some studies report that overexpression and increased levels of tissue factor are associated with a poor prognosis in pancreatic and ovarian cancer.[26,27] In addition, a recent study investigated cancer-associated thrombosis in pancreatic cancer at the molecular level and reported that vascular cell adhesion molecule-1 was also associated with hypercoagulable state and tumor progression.[28] Based on these results, active tumor biology causes a more hypercoagulable state, which leads to increased VTE and mortality. Further studies are needed to confirm this hypothesis.

We found that VTE had no significant effect on PFS. Because the definition of PFS was based on first-line chemotherapy, the relation between CCA and VTE occurring after disease progression could be less. The number of patients was too small to perform subgroup analysis by specific cycle of chemotherapy. Further large-scale studies on the relationship between VTE occurrences and cancer progression according to a specific cycle of chemotherapy are needed in the future.

Prophylactic anticoagulation and treatment are recommended for VTE in cancer patients.[29] However, anticoagulation for VTE in cancer patients is often difficult to perform in many patients because of the high risk of bleeding and recurrence of VTE.[24] In this study, anticoagulation was associated with a prolonged OS, but it was not significant in multivariable analysis. Since this is a retrospective study and the number of patients analyzed in subgroup analysis is insufficient, it is difficult to explain the relationship between anticoagulation and survival rate. Further studies on anticoagulation for VTE in advanced CCA patients will be needed in the future.

This study has several limitations. First, since it is a retrospective study, there may be unexpected bias. Since CCA is a rare disease, we focused on including more patients in analysis. We also performed multivariable analysis to adjust for confounding factors. Second, it is a single-center study. Our institution is one of the largest tertiary referral centers in South Korea, and the severity of patients tended to be relatively high. It might affect a higher rate of VTE compared to other studies. Therefore, validation through a multicenter study is needed in the future. Third, both tumor thrombus and bland thrombosis are included in VTE. However, it is difficult to differentiate between tumor thrombus and bland thrombus based on imaging findings. A subgroup analysis was considered for the VTE subtype, but it was not performed because the number of patients was not sufficient for the analysis. Fourth, the causes of death in patients with VTE have not been investigated. The national database from the Ministry of Public Administration does not provide causes of death. Therefore, we used a multistate statistical model to describe the relationship between VTE and mortality.

This study has several strengths. To the best of our knowledge, this study is the largest study based on real world data investigating VTE in advanced CCA. And this is the first study to show the impact of newly developed VTE on the OS in advanced CCA using a validated multistate statistical model. Thus, it is meaningful despite its retrospective nature.

In conclusion, major vessel invasion is a risk factor for the occurrence of VTE in patients with advanced CCA. Distant metastases and VTE are prognostic factors for reducing OS, and the risk of death rapidly increases following the onset of VTE. Therefore, the occurrence of VTE might have the potential to be a predictor of clinical course. It is necessary to verify these results through a prospective cohort study in the future.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: J.S.K., S.H.L. Data acquisition: M.W.L., N.P., J.H.C. Data analysis and interpretation: J.S.K., W.H.P. Drafting of the manuscript: J.S.K. Critical revision of the manuscript for important intellectual content: J.H.C., I.R.C., J.K.R., Y.T.K. Statistical analysis: J.S.K., W.H.P. Obtained funding: S.H.L. Administrative, technical, or material support; study supervision: S.H.L. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl220477.

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