ORIGINAL ARTICLE

Prevalence of Venous Thromboembolism in Cholangiocarcinoma Patients Receiving Chemotherapy and Validation of Khorana Score

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Background: Khorana score (KS) have used to evaluate the risk of chemotherapy-associated venous thromboembolism (VTE) and provide thromboprophylaxis for high-risk patients. However, the applicability of the score to cholangiocarcinoma (CCA) patients remains unclear due to the limited inclusion of patients with CCA in the score derivation process.

Objective: The primary objective focused on the prevalence of VTE within 180 days and the KS score was externally validated in this particular cohort.

Materials and Methods: This retrospective cohort study was conducted at a tertiary care hospital in Northeastern Thailand between January 2014 and December 2021. The study collected baseline clinical characteristics and laboratory data of patients with CCA undergoing palliative chemotherapy and follow-up data to assess the endpoints.

Results: Among the 402 patients included in the cohort, 48 (11.9%) experienced VTE within 180 days. Consequently, the decision was made to assign 1 point for a primary site of cancer factor in the KS calculation. The KS was found to be significantly associated with VTE incidents, with an odds ratio (OR) of 1.63 (95% CI 1.16, 2.29, p=0.005) and an AUC of 0.616 (95% CI 0.534, 0.698). The presence of VTE and higher KS scores were both associated with a worse prognosis.

Conclusion: CCA should be considered a high-risk tumor type for chemotherapy-associated VTE. The KS has been validated as useful in predicting VTE in this particular tumor type. Additionally, VTE or higher KS were associated with shorter overall survival.

Keywords: Cholangiocarcinoma; Chemotherapy; Venous thromboembolism; Khorana score; External validation; Survival

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Cholangiocarcinoma (CCA) is a heterogeneous group of epithelial cancers that affect the biliary tree. While the occurrence of CCA is relatively low in Western nations, it exhibits a notably higher prevalence in endemic regions like China and Thailand[1]. Our hospital-based data reveals that liver cancers, including CCA and hepatocellular carcinoma, have consistently ranked as the most prevalent cancers in men over several decades. Furthermore, CCA has emerged as the second most common cancer in females, following breast cancer.

Venous thromboembolism (VTE) represents a significant complication in cancer patients. The risk of developing VTE is ranging from 4 to 7-fold higher in individuals diagnosed with cancer compared to the general population[2,3]. The risk of VTE is particularly elevated during the initial phase of cancer diagnosis[3,4]. Additionally, the use of cytotoxic chemotherapy further amplifies this risk[2,5]. Many studies are presently focused on identifying risk factors for VTE development, as well as developing risk-scoring models to identify high-risk populations[6-10]. These risk factors encompass patient-related, treatment-related, and cancer-related factors, as well as various biomarkers[11]. Moreover, several studies have indicated that the occurrence of VTE in cancer patients is associated with a worsened prognosis[12].

The Khorana score is simple and is the most endorsed method for predicting chemotherapy-associated VTE in ambulatory cancer settings. Developed by Khorana et al. in the United States, this scoring system was proposed in 2008[6]. In summary, the Khorana score is calculated by

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summing points derived from five factors, including the site of primary cancer, body mass index (BMI), hemoglobin level, white blood cell count, and platelet count. Higher scores are indicative of higher-risk groups, thus predicting an increased prevalence of VTE. Recent meta-analyses have further supported the use of the Khorana score in identifying high-risk VTE patients[13]. Many studies and guidelines utilize the Khorana score as a decision-making tool for prophylactic anticoagulation[14-16]. A Khorana score of 2 or higher typically warrants at least 6 months of thromboprophylaxis such as apixaban and rivaroxaban[17,18]. Other scoring systems may also be employed, provided they can effectively predict the high-risk population, defined as a 6-month incidence of VTE of at least 8 to 10%[15]. Despite being recommended, the Khorana score has demonstrated inadequate performance in specific types of cancers, such as lung, uterine, and hepatocellular carcinoma[19-21]. So, the applicability of the Khorana score to patients with CCA is uncertain for several reasons. Firstly, this score was developed in different populations and typically necessitate external validation. Secondly, CCA is not as prevalent in Western populations, leading to a limited number of CCA patients in Khorana's original derivation cohort.

Considering the limited number of studies documenting the prevalence of VTE in CCA and the absence of a well-validated predictive scoring system, this study aims to determine the actual prevalence of VTE in CCA patients, externally validate the Khorana score in this population and assess its impact on overall survival.

Materials and Methods

The present study is a single-center retrospective cohort study, conducted at Srinagarind Hospital, Khon Kaen University, which serves as a tertiary care and major referral center in Northeastern Thailand. The research aimed to examine patients diagnosed with CCA who underwent palliative chemotherapy between January 2014 and December 2021. Electronic medical records were searched using specific criteria, including the presence of CCA as a diagnosis code and records of chemotherapy infusions as a procedural code. Subsequently, the screened records were reviewed by investigators to verify if patients fulfilled all the inclusion criteria, which encompassed confirmation of CCA diagnosis through imaging or pathology, age of 18 years or older, received at least one infusion of palliative chemotherapy, and undergone at least one follow-up imaging to identify clinically suspected VTE or asymptomatic VTE. Patients with a history of VTE before chemotherapy, current use of anticoagulants, presence of a second primary cancer within the last 5 years, or incomplete data for calculating the Khorana score were excluded from the study.

The primary objective of this study was to ascertain the prevalence of VTE occurring within 180 days after the initiation of chemotherapy. The decision to set the follow-up period at 180 days was based on the recommended duration of thromboprophylaxis[15,17,18]. VTE was defined as imaging-confirmed deep venous thrombosis (DVT), pulmonary embolism, or other sites of VTE, excluding tumor thrombus. A secondary objective of the study was to identify independent risk factors associated with VTE, externally validate the Khorana score, and assess the impact of these factors on overall survival. The follow-up period was calculated from the date of chemotherapy initiation, while overall survival was defined from the date of chemotherapy initiation to death from any cause or until the data cutoff date. The statistical analysis was conducted using data up to 31 December 2022.

The data collection process encompassed gathering baseline clinical characteristics (such as age, gender, and BMI), comorbid conditions (such as hypertension, dyslipidemia, diabetes, peripheral artery disease, coronary artery disease, and cerebrovascular disease), cancer-related factors (including anatomy subsites and stage), treatment-related factors (specific chemotherapy regimen used), laboratory values (including complete blood counts, serum creatinine, and CA19-9 levels), follow-up outcome data (including the date, sites, and symptoms of VTE occurrence), and date of death.

The Khorana risk score calculation. However, we did some specific changes in its application. Instead of adopting the BMI cut-point at $\geq$35 kg/m^2, the present study used WHO Asian-specific criteria for obesity, a BMI cut-point of $\geq$25 kg/m^2[22]. Furthermore, the original Khorana score treated CCA as an "other tumor" and assigned 0 points for the primary site of cancer factor. However, the present study chose to follow the score derivation methodology of Khorana et al. and assigned points to CCA based on the actual prevalence of VTE in this particular cohort relative to the average Thai cancer patients (5.4%)[6,23]. Accordingly, CCA will be assigned 2, 1, and 0 points if the prevalence of VTE was more than 16.2% (very high risk), 5.4 to 16.2% (high risk), and 5.4% or below (low risk), respectively.

The present study received ethical approval from the Khon Kaen University Ethics Committee for Human Research (HE651427).

Statistical analysis

The sample size was calculated to estimate single proportions based on a study conducted on Thai cancer patients. We assumed an prevalence of VTE in CCA to be 8.4%[24] with a margin of error of 3%. Consequently, the minimum required sample size was determined to be 328 patients.

A comparison of baseline characteristics between the

VTE and non-VTE groups was performed using Fisher's exact test for proportions. A univariable logistic regression analysis was conducted to ascertain the risk factors associated with VTE. Factors that exhibited statistical significance ($p<0.05$) or clinical relevance were included in the multivariable logistic regression analysis. To validate the Khorana score, we tested its correlation with VTE using univariable logistic regression. The results were presented in terms of odds ratios, predicted probabilities, and 95% confidence intervals. The discriminative ability of the Khorana score was demonstrated using the area under the receiver operating characteristic (ROC) curve. To assess the agreement between predicted and observed probabilities, we used a calibration plot and performed the Hosmer-Lemeshow Goodness-of-Fit test. For evaluating overall survival, we used the Kaplan-Meier survival curve. The hazard ratio for death was estimated using Cox regression analysis, and differences between groups were evaluated using the Log-rank test. The data analysis was carried out using STATA version 18.

Results

Between January 2014 and December 2021, a total of 503 patients fulfilled the inclusion criteria, out of which 101 patients were subsequently excluded. The rationales for exclusion were as follows: incomplete or missing data (n=30), VTE occurrence before chemotherapy (n=36), anticoagulant use (n=10), and concurrent diagnosis of a second primary cancer (n=25). Consequently, the final cohort consisted of 402 patients.

VTE prevalence and risk factors

The median follow-up time for VTE in this study was 180 days (interquartile range: 151, 180). Among the 402 patients included in the study, 48 patients (11.9%) experienced VTE within 180 days after receiving chemotherapy, and this group was referred to as the "VTE group." The median time to VTE occurrence in the VTE group was 67 days (95% CI 42, 91). The remaining 354 patients (88.1%) did not experience any VTE events during the follow-up period and were referred to as the "non-VTE group." The types of VTE observed were distributed as follows: 26 patients (54.2%) had DVT in the extremities, 15 patients (31.3%) had intra-abdominal DVT, 11 patients (22.9%) had a pulmonary embolism, and 4 patients (8.33%) experienced VTE at multiple sites. Among these VTE cases, 22 (46.8%) were symptomatic, while 25 cases (53.2%) were asymptomatic.

Based on the observed VTE prevalence of 11.9% in this particular cohort, we classified CCA as a high-risk primary site of cancer and assigned 1 point for the Khorana score calculation in this study. A comparison between the VTE group and the non-VTE group was conducted to assess baseline clinical characteristics and laboratory data, as presented in Table 1. Notably, multiple cardiovascular diseases, elevated white blood cell counts, Khorana score, and Khorana risk group showed statistically significant differences between the two groups according to univariable analysis. Nevertheless, the present study revealed that BMI, hemoglobin level, and platelet count, which are components of the Khorana score, did not exhibit significant associations with VTE. A complete list of variables collected in the study, and their univariable analysis of risk factors for VTE.

A multivariable logistic regression analysis was performed, considering factors such as BMI $\geq$25 kg/m^2, multiple cardiovascular diseases, hemoglobin levels <10 g/dL, white blood cell counts >11,000 mm^3, and platelet counts $\geq$350,000 mm^3. The results indicated that multiple cardiovascular diseases and increased white blood cell counts were independent risk factors for VTE, with adjusted OR of 2.30 (95% CI 1.09, 4.87, p=0.029) and 2.54 (95% CI 1.25, 5.19, p=0.010), respectively as shown in Table 2.

External validation of Khorana score

According to the univariable logistic regression analysis, the Khorana score exhibited a statistically significant correlation with the prevalence of VTE. The unadjusted odds ratio was found to be 1.63 (95% CI 1.16, 2.29, p=0.005). The predicted probability of VTE based on the Khorana score was estimated and shown in Table 3. Particularly, it was observed that a Khorana score of 2 corresponded to a predicted probability of VTE to 12.9% (95% CI 9.5, 16.4).

The area under the ROC curve was calculated to be 0.616 (95% CI 0.534, 0.698), indicating a fair discriminative ability of the Khorana score within this specific cohort. Moreover, the calibration plot revealed a good alignment between the predicted and observed probabilities. The Hosmer-Lemeshow Goodness-of-Fit test further supported this alignment by indicating no significant difference between the predicted and observed probabilities (p=0.512) (Figure 1).

Overall survival

In this study, the median follow-up time for overall survival was 9.8 months (interquartile range: 6.3 to 15.1 months). A comparison between patients in the VTE group and the non-VTE group revealed that those in the VTE group experienced significantly poorer overall survival. The hazard ratio for death in the VTE group was 1.79 (95% CI 1.32, 2.44, p=0.0002). The median overall survival time for patients in the VTE group was 6.5 months (95% CI, 5.2 to 7.9 months), whereas it was 10.5 months (95% CI, 9.5 to 11.4 months) in the non-VTE group, as shown in Figure 2.

Table 1. Baseline characteristics of patients categorized by presence of VTE within 180 days

Variables	Total, n=402	VTE, n=48		Non-VTE, n = 354		p-value
		n	%	n	%	
Age ≥65 years	402	21	43.6	114	32.2	0.142
Female gender	402	18	37.5	119	33.6	0.628
Body mass index ≥25 kg/m^2	402	9	18.8	44	12.4	0.254
Multiple cardiovascular diseases[a]	402	12	25.0	43	12.2	0.023
Hemoglobin <10 g/dL	402	10	20.8	48	13.6	0.190
White blood cells >11,000 mm^3	402	15	31.3	53	15.0	0.008
Platelet ≥350,000 mm^3	402	14	29.2	84	23.7	0.473
Chronic kidney disease G3	391[b]	19	39.6	93	27.1	0.088
Elevated CA19-9 (>37 U/mL)	278[c]	26	70.3	157	65.2	0.582
Chemotherapy regimen						
Gemcitabine/platinum	163	19	39.6	144	40.7	1.000
5-FU/platinum	223	27	56.3	196	55.4	
Other	16	2	4.2	14	4.0	
Khorana score						0.024
1	198	16	33.3	182	51.4	
2	143	18	37.5	125	35.3	
3	50	12	25.0	38	10.7	
4	10	2	4.2	8	2.3	
5	1	0	0.0	1	0.3	
Khorana risk group						0.009
Low-risk (score 0)	0	0	0.0	0	0.0	
Intermediate risk (score 1 to 2)	341	34	70.8	307	86.7	
High risk (score ≥3)	61	14	29.2	47	13.3	

[a] Multiple cardiovascular diseases defined as at least 2 of a personal history of peripheral artery disease, ischemic stroke, coronary artery disease, hypertension, hyperlipidemia, diabetes (excluding obesity); [b] Missing value 11 (2.7%), [c] Missing value 124 (30.8%)

VTE=venous thromboembolism

Table 2. Multivariable analysis of risk factors of VTE within 180 days

Risk factors	Adjusted odd ratio	95% confidence interval	p-value
Body mass index ≥25 kg/m^2	1.63	0.71, 3.73	0.249
Multiple cardiovascular diseases	2.30	1.09, 4.87	0.029
Hemoglobin <10 g/dL	1.41	0.64, 3.13	0.395
White blood cells >11,000 mm^3	2.54	1.25, 5.19	0.010
Platelet ≥350,000 mm^3	1.09	0.53, 2.26	0.806

Table 3. Predicted probability of VTE within 180 days

Khorana score	Predicted probability of VTE, %	95% confidence interval
0	5.3	1.7, 9.0
1	8.4	5.0, 11.4
2	12.9	9.5, 16.4
3	19.5	12.1, 26.9
4	28.4	12.7, 43.8
5	39.1	13.2, 64.9

Moreover, the study explored and demonstrated a correlation between higher Khorana scores and lower overall survival. Specifically, the median overall survival times for patients with Khorana scores of 1, 2, 3, and 4 were 11.7 months (95% CI 10.1 to 12.6 months), 9.2 months (95% CI 8.1 to 10.5 months), 7.7 months (95% CI 6.4 to 9.2 months), and 7.6 months (95% CI 1.3 to 8.6 months), respectively, as shown in Figure 3.

Discussion

The prevalence of VTE in CCA patients undergoing chemotherapy is high. Our findings reveal that 11.9% of patients experienced VTE events within 180 days of initiating chemotherapy. This observed prevalence is twice as high as the average prevalence among Thai cancer patients receiving chemotherapy (5.4%)[23]. However, the

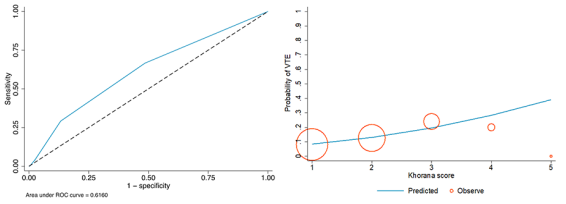

Figure 1. A receiver operating characteristic (ROC) curve and calibration plot of Khorana score on the presence of VTE within 180 days.

Left: The ROC curve illustrates the discriminative ability of the Khorana score.

Right: The calibration plot presents the predicted probability by the blue line, while the observed probability is represented by the red line. The size of the circles corresponds to the number of patients falling into each score category.

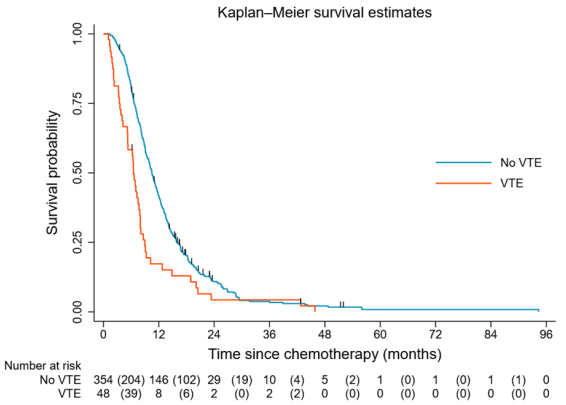

Figure 2. Overall survival according to the occurrence of VTE within 180 days.

The blue line illustrates the survival probability of patients who did not experience venous thromboembolism (VTE), while the red line illustrates the survival probability of patients who suffered from VTE.

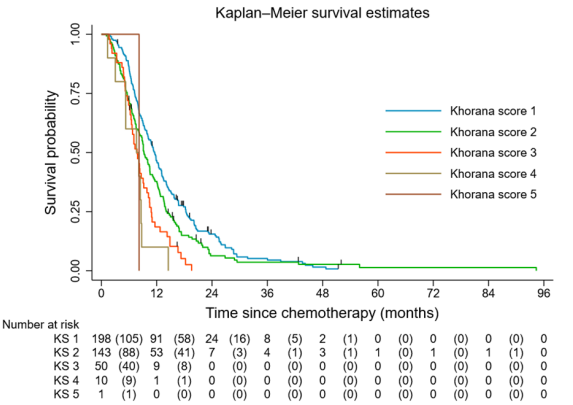

Figure 3. Overall survival according to Khorana score.

Each line represents the Kaplan-Meier survival probability of patients within their respective Khorana score categories. The blue line is for a KS of 1, the green line is for a KS of 2, the red line is for a KS of 3, the brown line is for a KS of 4, and the dark red line is for a KS of 5.

prevalence is lower than that observed in the VTE study conducted in Korean (14.7%, 32.8%) and German (29.3%), and the United States CCA patients (22%)[25-28]. It should be noted that these particular studies were characterized by smaller sample sizes, mixed stages, and the collection of total prevalence data rather than limited to a specific 6-month period after chemotherapy. The most frequent sites of VTE in our study were DVT in the extremities (54.2%), followed by intra-abdominal thrombosis (31.3%), and pulmonary embolism (22.9%). Nearly half of the VTE cases (46.8%) were symptomatic, underscoring the significance of predicting, preventing, detecting, and treating VTE in CCA patients.

Our study identified certain independent risk factors for VTE in CCA. Specifically, an elevated baseline white blood cell count exceeding 11,000 mm^3 (OR = 2.54, p=0.010) and the presence of multiple cardiovascular diseases (OR = 2.30, p=0.029) were associated with a higher risk of VTE in this cohort. It is worth noting that cardiovascular risk factors have been reported as predictive risk factors for VTE in cancer patients and are incorporated into the calculation of the COMPASS-CAT score[7]. In our study, the definition of multiple cardiovascular diseases was modified from the COMPASS-CAT score, with obesity excluded as it is already accounted for in the Khorana score calculation. However, other factors present in the Khorana score, including BMI, hemoglobin level, and platelet count, did not demonstrate a significant association with the occurrence of VTE in our cohort.

Before implementing the Khorana score in our clinical practice, we performed external validation on our patient population, following the methodology described by Khorana et al[6]. Considering that the actual prevalence of VTE in CCA patients exceeded but did not surpass three times that of the average Thai cancer patients, we assigned 1 point to the primary site of cancer factor for CCA, and we recommend adopting this approach in real-life practice[23]. Additionally, the authors suggest using BMI cutoffs of ≥25 kg/m^2 instead of 35, as this aligns with other Khorana score validation studies in Asian populations[12,22,29]. It is noteworthy that no patients in our study had a BMI of 35 kg/m^2 or higher. With these 2 modifications, our study demonstrated a significant correlation between the Khorana score and VTE prevalence (OR=1.63, p=0.005). The Khorana score exhibited fair discriminative ability, with an area under the ROC curve of 0.616, consistent with other validation studies[12,24]. The calibration plot and statistical test illustrated a strong correlation between observed and predicted probabilities.

According to our study, patients with a Khorana score of 2 have a predicted probability of 12.9% of experiencing VTE within 180 days (95% CI 9.5 to 16.4%), which is slightly higher than that reported in other studies[30]. This

cut-point of 2 and the associated predicted probability align with previous research and guidelines, justifying its use as a decision point for administering thromboprophylaxis[15,17,18]. In simplified terms, patients diagnosed with CCA who has at least 1 additional point on the Khorana score are considered to be at sufficiently high risk for thromboprophylaxis. Both the presence of VTE and higher Khorana scores were found to have predictive value for survival. CCA patients who developed VTE had shorter survival times, and a higher Khorana score was also associated with reduced overall survival[12,25,27,28].

The present study possesses several strengths, including being the largest investigation focusing on the prevalence of VTE in CCA and validating the Khorana score. The study highlights the high prevalence of VTE, emphasizes the importance of thromboprophylaxis, and verifies the applicability of the Khorana score in this specific population. However, it is essential to acknowledge certain limitations in this study. The retrospective nature of this study may have some missing data and biases. Moreover, the prevalence of VTE might be underestimated due to the absence of a pre-planned specific protocol for detecting asymptomatic VTE. Additionally, patients with early-stage or adjuvant disease were not included in the study, leaving the utility of the Khorana score in these settings undefined.

Conclusion

The prevalence of VTE within 180 days of CCA patients receiving palliative chemotherapy is high. The Khorana score has been validated and proven applicable in this context. We suggest classifying CCA as a high-risk tumor type and assigning 1 point for the primary site of cancer. VTE or higher Khorana scores were associated with shorter overall survival.

What is already known on this topic?

The prevalence of chemotherapy-associated VTE varies among cancer types, with it being most common study in Western populations. Studies have shown that Khorana scoring is useful for predicting chemotherapy-associated VTE.

What this study adds?

This is the largest study focused on CCA patients. We report the real-world prevalence of chemotherapy-associated VTE in our common cancer and demonstrate that the Khorana score is also useful in our population.

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Potential conflicts of interest

The authors declare no conflict of interest.

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