



The incidence of venous thromboembolism is not low in Korean patients with advanced pancreatic cancer

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Background

Pancreatic cancer is among the most common malignancies associated with venous thromboembolism (VTE). Asian patients are known to have a lower incidence of VTE compared to Caucasian patients. However, few studies have investigated the incidence of VTE in Asian patients with pancreatic cancer.

Methods

This retrospective review of medical records was performed on 505 patients with histopathologically proven advanced stage pancreatic cancer, from January 2006 to December 2012, at Soonchunhyang University Hospitals.

Results

Ninety-four patients (18.6%) had at least one pulmonary embolism (PE), deep vein thrombosis (DVT), or splanchnic vein thrombosis (SVT); 38 patients had isolated SVT; and 56 patients (11.1%) had at least one classic VTE (PE and/or DVT of lower extremities). Patients with more advanced stages of pancreatic cancer (distant metastatic stage, recurrence) or who had received chemotherapy had a higher incidence of classic VTE. Patients who were simultaneously diagnosed with pancreatic cancer and classic VTE had a poorer prognosis than patients with subsequent VTEs. There was a significant difference in overall survival (OS) between the presence and absence of a concurrent classic VTE diagnosis (median: OS, 2.1 mo vs. 10.7 mo; $P < 0.001$). Even when VTE included SVT, the result was similar ($P < 0.001$).

Conclusion

In Korean patients with advanced pancreatic cancer, the incidence of VTEs is comparable to that of Caucasian patients. We also found that pancreatic cancer patients with concurrent VTEs had a poor prognosis compared to patients who developed VTEs later.

Key Words Korean, Advanced pancreatic cancer, Venous thromboembolism

INTRODUCTION

VTE is a well-recognized complication of malignant diseases. Patients with cancer have a four to six-fold higher risk for VTE compared to those without cancer [1]. Pancreatic cancer, in particular, is among the most common malignancies that co-presents with VTE [2]. In a cohort study of 202 patients with pancreatic cancer, the incidence of VTE was 108.3 per 1,000 patient-years (10.8%), resulting

in a 58.6-fold increase in relative risk compared to an age- and gender-adjusted general population [3]. The causes of high VTE risk in pancreatic cancer are divided into endogenous and exogenous factors. An endogenous factor is the activation of platelets and the release of several procoagulant factors by pancreatic cancer cells, including tissue factor and thrombin, which can cause a hypercoagulable state. Exogenous factors are those that are associated with treatment modalities, which include chemotherapy, targeted therapy, and surgery [4]. The reported clinical VTE incidence

in pancreatic cancer varies widely from 5% to 29% [2, 3, 5, 6]. Various patient-, treatment-, and pancreatic cancer-related factors contribute to VTE [7]. Several studies have reported that the incidence of VTE is low in Asians, and according to some studies that compared ethnicities, the incidence of VTE among Asian-Americans and Asian-Pacific Islanders is 2.5 to four-fold lower than that among Caucasians [8-10]. In 2008, a Korean group reported that the incidence of VTE in Korean patients with advanced pancreatic cancer was 5.3% (4 of 75 patients), which is lower than that observed in other ethnic groups [5]. However, there have not been enough studies on patients with pancreatic cancer with VTE in Korea. Therefore, we conducted a retrospective study to primarily determine the incidence of VTE and concomitantly identify the significance of VTE in patients with advanced pancreatic cancer.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of 505 patients with histopathologically-proven pancreatic cancer, from January 2006 to December 2012, at Soonchunhyang University Hospitals. We investigated 505 patients with advanced pancreatic cancer, with respect to age, gender, co-

morbidities, performance status, clinical staging at diagnosis, tumor location, administration of chemotherapy, chemotherapy regimen, and survival periods. In our study, VTE was defined as PE, DVT, and SVT. Classic VTE was defined as PE and DVT of the lower extremities. DVT of the upper extremities, which is mainly central venous catheter-related, was not included in this study. VTE had been detected through computed tomography (CT) (chest CT, pulmonary angiographic CT, or abdomen and pelvis CT) or low extremity ultrasonography. Advanced pancreatic cancer included locally advanced, unresectable pancreatic cancer and metastatic disease. We also reviewed the medical records of the 56 patients with pancreatic cancer who were diagnosed with classic VTE. Subsequently, we found more information on the diagnosis of classic VTE, such as the cancer stage, cancer status, type of VTE treatment, treatment-related complications, and treatment failure, of patients who had classic VTE. Maintenance therapy for classic VTE is administered for a finite period beyond the initial period. In our study, concurrent VTE is defined as those diagnosed before or up to one month after a pancreatic cancer diagnosis. Our study protocol was approved by the Institutional Review Board of Soonchunhyang University Hospitals. All statistical analyses used procedures available in the SPSS 18.0 software (SPSS, Chicago, Illinois, USA). The confounding factors, all of which

Table 1. Clinical characteristics of patients with pancreatic cancer.

	Classic VTE, N	N (%)	Crude		Adjust ^{b)}	
			OR	P	OR	P
Gender						
Female	25	211 (41.8)	1.0			
Male	31	294 (58.2)	1.176	0.589		
Age		65.1(32-88) ^{c)}				
ECOG PS						
2-4	3	32 (6.3)	1.0			
0-	53	473 (93.7)	1.179	0.805		
Comorbidities						
Diabetes mellitus	20	195 (38.6)	0.908	0.760		
Hypertension	21	191 (37.8)	1.037	0.908		
Location of tumor						
Head	29	259 (51.3)	1.0			
Body	8	72 (14.3)	0.879	0.769		
Tail	13	122 (24.1)	0.705	0.353		
Not specified/other	6	52 (10.3)	0.981	0.969		
Cancer stage						
Locally advanced stage	16	231 (45.7)	1.0		1.0	
Distant metastatic stage	34	252 (49.9)	2.254	0.015 ^{a)}	2.079	0.022 ^{a)}
Recurrence	6	22 (4.4)	5.092	0.003 ^{a)}	5.014	0.003 ^{a)}
Palliative chemotherapy						
No	12	177 (34.3)	1.0			
Yes	44	332 (65.7)	2.191	0.030 ^{a)}	2.031	0.039 ^{a)}
Gemcitabine containing regimens	43	308 (61.0)				
5-FU containing regimens	14	105 (20.8)				
Total	56 (11.1%)	505 (100)				

^{a)} $P < 0.05$, ^{b)}Adjust for cancer stage, palliative chemotherapy, ^{c)}median age (range).

Abbreviations: ECOG, Eastern Cooperative Oncology Group; OR, odds ratio; PS, Performance status; VTE, venous thromboembolism.

may influence the risk of VTE, were analyzed with logistic regression analyses. Odds ratios (ORs) were calculated with 95% confidence intervals (CIs). Variables with P -values < 0.05 were considered to be statistically significant. The survival curves were constructed via the Kaplan-Meier method. Differences in survival between groups were determined using the log-rank test.

RESULTS

Patient characteristics

A total of 505 patients with the pathologic diagnosis of advanced stage of pancreatic adenocarcinoma were evaluated at Soonchunhyang University Hospitals, between January 2006 and December 2012. Of these patients, 58.2% were male (N=294) and 41.8% were female (N=211). The mean age of the study population at the time of diagnosis was 65.1 (range, 32–88) years. The tumors were located in the head (259 patients, 51.3%), body (72 patients, 14.3%), tail (122 patients, 24.1%), and other/non-specified sites (52 patients, 10.3%). Twenty-two patients who were initially diagnosed with localized pancreatic cancer experienced cancer recurrence during and after treatment. Three hundred and thirty-two patients (65.7%) received palliative chemotherapy, and the remaining patients (N=177, 34.3%) did not receive chemotherapy (Table 1).

Incidence of thromboembolic events

Of the 505 patients with pancreatic cancer, 94 (18.6%) had at least one documented VTE, 38 had isolated SVT without symptoms, 19 had only PE, 18 had only DVT, and 19 had both PE and DVT. Of the 19 patients who developed PE, 11 (57.9%) were asymptomatic prior to the chest CT that resulted in the incidental discovery of PE. The lack of symptoms was confirmed based on a medical records review. The remaining eight patients had symptoms suggestive of PE, including dyspnea, chest pain, and hypotension. Conversely, most patients with DVTs (N=17) had symptoms that included edema, pain, and color change. Only one patient had asymptomatic DVT (Table 2). The median time

Table 2. Incidence of thromboembolic events.

Event	N	Asymptomatic	Symptomatic
PE	19	11	8
DVT	18	1	17
PE and DVT	19	7	12
Classic VTE (PE or DVT)	56	19	37
SVT (with PE or DVT)	9	2	7
Isolated SVT	38	38	0
VTE (PE or DVT or SVT)	94	57	37

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; SVT, splanchnic vein thrombosis; VTE, venous thromboembolism.

from the pancreatic cancer diagnosis to VTE occurrence was 3.9 (range, 0–38.4) months.

Characteristics of patients with classic VTEs

Among 56 patients, 31 males and 25 females were identified. The tumors were located in the head (29 patients), body (8 patients), tail (13 patients), and other/non-specified sites (6 patients). Sixteen (6.9%) of the 231 patients who were diagnosed with pancreatic cancer at a locally advanced stage had classic VTEs. Thirty-four (13.5%) of the 252 patients with distant-metastatic stage pancreatic cancer had classic VTEs. Six (27.2%) of the 22 patients who experienced a recurrence during or after treatment had classic VTE. Forty-four (13.3%) of the 332 patients who received palliative chemotherapy had classic VTE (Table 1). The confounding factors (gender, ECOG performance status, diabetes, hypertension, stage, chemotherapy), all of which may influence the risk of classic VTE, were analyzed with logistic regression analyses. Patients with more advanced stages of pancreatic cancer (distant metastatic stage: OR, 2.079; 95% CI, 1.112–3.887; $P=0.022$, recurrence: OR, 5.014; 95% CI, 1.711–14.698; $P=0.003$) or who received chemotherapy (OR, 2.031; 95% CI, 1.036–3.981; $P=0.039$) had a significantly higher incidence of classic VTEs (Table 1).

At the time of classic VTE diagnosis, four patients (7.1%) had locally-advanced disease and 52 (92.9%) had distant metastatic disease. Eleven patients had stable disease and 32 had progressive disease. Thirteen patients were diagnosed with pancreatic cancer and VTE within a month, 12 had distant metastatic disease, and one had locally-advanced

Table 3. Clinical characteristics of patients with classic VTE (PE, DVT).

	N of patients with VTE (N=56)
Cancer stage at VTE diagnosis	
Locally advanced	4 (7.1%)
Distant metastatic	52 (92.9%)
Disease status at VTE diagnosis	
Stable disease	11 (19.6%)
Progressive disease	32 (57.1%)
At diagnosis	13 (23.2%)
Initial therapy for VTE	
None	7 (12.5%)
UFH	2 (3.6%)
LMWH	42 (75.0%)
Thrombolytic therapy	3 (5.4%)
IVC filter	1 (1.8%)
Aspirin	1 (1.8%)
Maintenance therapy for VTE	
None	14 (25.0%)
Warfarin	29 (51.9%)
UFH or LMWH	11 (21.5%)
Aspirin	2 (3.6%)

Abbreviations: DVT, deep vein thrombosis; IVC, inferior vena cava; LMWH, low molecular weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin; VTE, venous thromboembolism.

disease. Forty-two patients were given low-molecular-weight heparin for initial VTE treatment; 29 were given warfarin for maintenance VTE treatment; and three of the patients who received VTE treatment experienced gastrointestinal bleeding when they used aspirin (1 patient), low molecular weight heparin (1 patient), and warfarin (1 patient). Two patients with DVT experienced a new PE during anticoagulant therapy with warfarin (Table 3).

Survival analysis

There were 439 (86.9%) deaths at the end of the study period. The median overall survival (OS) time was 8.4 (95% CI, 7.6–9.2) months. Survival time was assessed according to classic VTE development and compared with that of patients without classic VTEs. For the group without classic VTEs, the median OS was 8.2 (95% CI, 7.4–9.1) months, and for the classic VTE group, the median OS was 9.0 (95% CI, 7.5–10.5) months. There was no significant difference

in OS between the presence and absence of a classic VTE diagnosis ($P=0.475$). Even if VTE included SVT, there was no significant difference in OS between whether VTE was diagnosed or not ($P=0.237$) (Fig. 1). There was no significant difference in the OS of patients with VTEs between the isolated SVT group ($N=38$) and the classic VTE group ($N=56$) ($P=0.879$). There was no significant difference in the OS of patients with classic VTEs between whether the patients had symptoms or not ($P=0.365$). Patients with concurrent VTEs had worse OS than those with classic VTEs [median, 2.1 (95% CI, 1.0–3.2) mo vs. 10.7 (95% CI, 8.9–12.5) mo; $P<0.001$] and those with VTEs that included SVTs [median, 3.4 (95% CI, 0.7–6.1) mo vs. median 10.0 (95% CI, 8.2–11.7) mo; $P<0.001$] after the diagnosis of pancreatic cancer (Fig. 2).

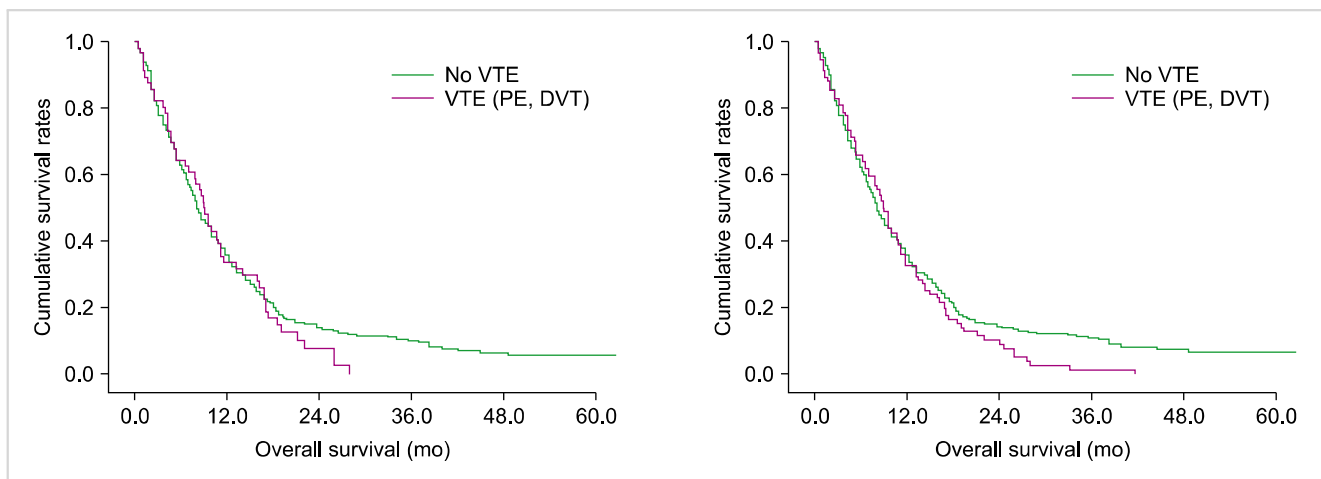


Fig. 1. Kaplan-Meier survival analysis for patients with pancreatic cancer with or without classic VTE ($P=0.475$). Kaplan-Meier survival analysis for patients with pancreatic cancer patients with or without VTE ($P=0.237$).

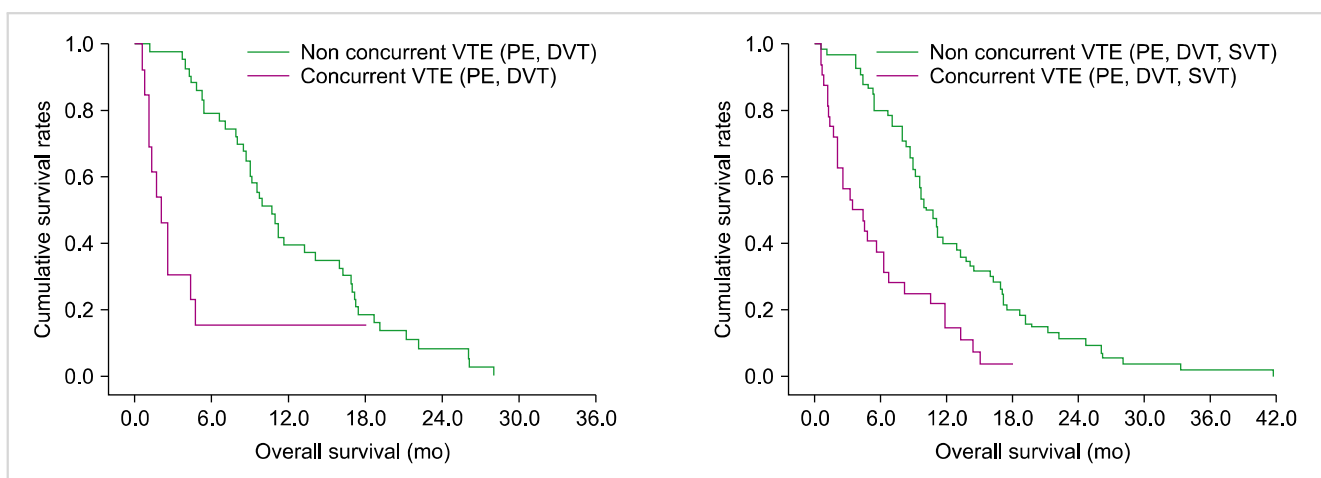


Fig. 2. Kaplan-Meier survival analysis for patients with pancreatic cancer with or without concurrent classic VTE ($P<0.001$). Kaplan-Meier survival analysis for patients with pancreatic cancer with or without concurrent VTE ($P<0.001$).

DISCUSSION

In our study, classic VTEs were radiologically detected in 56 (11.1%) of 505 patients with advanced pancreatic cancer. In general, VTEs were determined to be either PE or DVT; however, VTEs included SVTs, which broadly involve the portal, splenic, mesenteric, or hepatic veins. If SVT is to be considered as a type of VTE, 94 patients (18.6%) had at least one VTE.

Although it is widely known that Asian patients have a lower incidence of VTEs than western patients, our study shows that the incidence of VTEs in Korean patients with advanced-stage pancreatic cancer is not low. An explanation of ethnic disparities in the incidence of VTE could include both genetic and environmental factors. Asians have a low prevalence of the thrombophilic trait known as the Factor V Leiden mutation and may have lower mean levels of fibrinogen, factor VIIc, and factor VIIIc. Another thrombophilic genetic variant, thrombin gene G20210A, is associated with increased plasma prothrombin and may also be less prevalent in Asians. Homocysteinemia, a partially genetically-determined promoter of VTE, is not less prevalent in Asians [11]. Lifestyle is another possible cause of the ethnic disparity. Steffen *et al.* [12] reported that a diet that includes abundant vegetables, fish, and little meat was associated with a lower risk of VTE. Different dietary habits between Eastern and Western countries may contribute to the differences in VTE incidences. However, little has been known about the role of lifestyle in the development of VTE until recently.

In a study on VTE in patients with gastric cancer in Korea, the 2-year cumulative incidences of all VTE events were 0.5%, 3.5%, and 24.4% in stage I, II-IV(M0), and IV(M1), respectively [13]. The incidence of VTE in patients with stage IV(M1) gastric cancer was not lower than observed in western patients [14, 15]. The authors suggested that the protective effect of ethnicity on VTE development in Asian patients with distant metastases disappears as the gastric cancer tumor activity increases. Our study included 52 patients with distant metastases and four with locally-advanced stages. In the study of Chew *et al.* [14], the 2-year cumulative incidences of VTE in patients with pancreatic cancer with localized, regional, and remote stages were 3.2%, 3.0%, and 5.4%, respectively. Our results suggest the possibility that the incidence of VTE in Korean patients with advanced-stage pancreatic cancer is comparable to that of Caucasian populations.

It has generally been suspected that VTE may be a high risk factor that results in earlier death in patients with cancer [14, 16, 17]. However, in our study, there was no significant difference in the OS of patients with pancreatic cancer between whether VTE was diagnosed or not ($P=0.475$). There were many patients (252 patients, 49.1%) with distant metastases, and 127 patients did not receive any treatment for pancreatic cancer. Our results suggest, because the patients in our study had advanced disease stages, that there was no significant difference in OS between whether VTE was

diagnosed or not.

When the patients were simultaneously diagnosed with pancreatic cancer and VTE, they had a poor prognosis compared to those who did not have a simultaneous diagnosis. Epstein *et al.* documented that early thromboembolic events [hazard ratio (HR), 2.1; 95% CI, 1.7-2.5; $P<0.01$ vs. late or no thrombosis] correlated with shorter survivals, where early thromboses were defined as those diagnosed before, or up to 1.5 months after, a pancreatic cancer diagnosis [7]. In the study of Mandalà *et al.* [6], among 227 patients with unresectable pancreatic cancer, 59 (26.0%) developed a VTE. A synchronous VTE occurred in 28 (12.3%) patients, a VTE during chemotherapy was observed in 15 (6.6%) patients, and 16 (7.0%) patients experienced both events. The presence of a synchronous VTE was associated with a higher probability of not responding to treatment (OR, 2.98; 95% CI, 1.42-6.27; $P=0.004$). The authors suggested that patients with VTEs may have more biologically aggressive cancer. Further studies are required to determine the reason that concurrent VTEs are strongly related to poor prognoses.

Patients who received palliative chemotherapy had a higher incidence of VTEs. Recently, there has been an increased use of targeted agents for the treatment of pancreatic cancer. We should pay closer attention to the occurrence of VTEs in patients with pancreatic cancer who received chemotherapy.

In general, for patients with incidentally-detected SVTs, there is no specific treatment guideline [18]. In our study, there was no significant difference in the OS of patients with VTEs between the isolated SVT group ($N=38$) and the classic VTE group ($N=56$) ($P=0.879$). We suggest that when patients are simultaneously diagnosed with pancreatic cancer and SVT, we should pay attention to SVT. Future studies should investigate the management of patients with SVT and cancer.

There are some limitations to our study. First, as our study was a retrospective review, the occurrence of VTE may have been underestimated. Second, we analyzed only patients who had been treated in Soonchunhyang University Hospitals; therefore, selection bias may be present. Third, many of the patients with VTE did not undergo further evaluations regarding risk factors other than cancer, which may have contributed to the development of VTE in these patients.

In conclusion, although it is widely known that Asian patients have a lower incidence of VTE than Caucasian patients, our study shows that the incidence of VTE is considerable in Korean patients with pancreatic cancer, especially in those with advanced stage cancer. We also found that patients with pancreatic cancer with concurrent VTE had poor prognoses compared to patients who developed VTE later.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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