Risks and impacts of thromboembolism in patients with pancreatic cancer

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ABSTRACT

Introduction: Patients with pancreatic cancer have a high risk of thromboembolism (TE), which may increase mortality. Most relevant studies have been conducted in Western populations. We investigated risk factors for TE in a predominantly Chinese population of patients with pancreatic cancer, along with effects of TE on overall survival.

Methods: This retrospective cohort study included patients diagnosed with exocrine pancreatic cancer in Prince of Wales Hospital in Hong Kong between 2010 and 2015. Data regarding patient demographics, World Health Organization performance status, stage, treatment, TE-related information, and time of death (if applicable) were retrieved from electronic medical records. Univariate and multivariable logistic regression analyses were performed to identify risk factors for TE. Survival analyses were performed using Kaplan-Meier analysis and Cox proportional hazards regression.

Results: In total, 365 patients were included in the study. The overall incidence of TE (14.8%) was lower than in Western populations. In univariate logistic regression analysis, stage IV disease and non-head pancreatic cancer were significantly associated with TE (both P=0.01). Multivariable logistic regression analysis showed that stage IV disease was a significant risk factor (odds ratio=1.08, 95% confidence interval [CI]=1.00-1.17; P=0.046). Median overall survival did not significantly differ between patients with and without TE (4.88 months vs 7.80 months, hazard ratio=1.08, 95% CI=0.80-1.49; P=0.58) and between patients with TE who received anticoagulation treatment or not (5.63 months vs 4.77 months, hazard ratio=0.72, 95% CI=0.40-1.29; P=0.27).

Conclusion: The incidence of TE was low in our Chinese cohort. Stage IV disease increased the risk of TE. Overall survival was not affected by TE or its treatment.

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New knowledge added by this study

- The incidence of thromboembolic events in patients with pancreatic cancer was lower in our Chinese cohort than in previous studies involving Western populations.
- Stage IV disease was associated with a greater risk of thromboembolism.
- In patients with pancreatic cancer, overall survival was not affected by thromboembolism or its treatment.

Implications for clinical practice or policy

- Differences in the incidence and treatment outcomes of thromboembolism between Western and Chinese populations of patients with pancreatic cancer are highlighted.
- Low-molecular-weight heparin and direct oral anticoagulants are valid options for the treatment of thromboembolism in patients with pancreatic cancer. Treatment decisions should include patient preference, bleeding risk, patient renal function, and life expectancy.
- Patients with poor general condition (eg, World Health Organization performance status score of 3 to 4) or life expectancy <3 months should not receive anticoagulation treatment for thromboembolism.

血栓栓塞在胰臟癌患者的風險及影響

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引言：胰臟癌患者患有血栓栓塞的風險較高，嚴重者可因此而死亡。不過，大部分文獻記載都是以西方人為研究對象。我們在本研究探討血栓栓塞在患有胰臟癌的華人中的風險及對整體存活期的影響。

方法：這項回顧性研究納入從2010年至2015年期間於香港威爾斯親王醫院確診外分泌腺胰臟癌症的患者。從醫院電子病歷中收集的數據包括患者的人口統計學數據、世界衛生組織日常體能狀態、癌症分期、治療方案、血栓栓塞相關資料及死亡時間（如適用）等。研究採用了單變量及多變量邏輯迴歸分析預測引致血栓栓塞的因素，並使用了Kaplan-Meier法計算存活數據及Cox比例風險迴歸模型分析存活期風險因素。

結果：本研究共納入365名患者。血栓栓塞的整體發生率為14.8%，較西方人口的發生率為低。在單變量邏輯迴歸分析中，第四期癌症及非胰臟頭部的癌症與血栓栓塞顯著相關（兩者均為P=0.01）。在多變量邏輯迴歸分析中，第四期癌症是重要的風險因素（勝算比=1.08，95%置信區間=1.00-1.17；P=0.046）。有血栓栓塞與沒有血栓栓塞的患者的中位整體存活期並沒有明顯不同（4.88月vs 7.80月，風險比=1.08，95%置信區間=0.80-1.49；P=0.58）。在血栓栓塞患者中，使用抗凝血藥與否未有對中位整體存活期帶來明顯改變（5.63月vs 4.77月，風險比=0.72，95%置信區間=0.40-1.29；P=0.27）。

結論：在本研究中，華人的血栓栓塞發生率較低。第四期胰臟癌患者有較高風險患上血栓栓塞。血栓栓塞及其治療並沒有改變胰臟癌患者的整體存活期。

Introduction

The association between malignancy and thromboembolism (TE) was first described more than 100 years ago as 'migratory thrombophlebitis', commonly found in patients with visceral cancer.[1] Indeed, TE is a common complication in patients with cancer and the second most common cause of death among such patients.[2]

Although the association between TE and pancreatic cancer is well established, its effects on overall survival remain unclear. The results of studies conducted in Western countries generally support the notion that TE is associated with worse overall survival.[3,4] For example, a recent large retrospective study in France demonstrated a statistically significant decrease in overall survival of 2.9 months among patients with TE, compared with patients who did not exhibit TE.[3] In contrast, studies involving Asian populations tend to show similar overall survival in patients with and without TE.[5-7] Furthermore, among the published retrospective studies concerning the incidence of TE in Asian patients with pancreatic cancer, very few data have focused on the impact of TE in Chinese patients with pancreatic cancer.

In this study, we aimed to investigate the incidence of TE among patients with pancreatic cancer in our centre, where >99% of patients are Chinese; explore risk factors associated with the development of TE; and assess the prognostic impact of TE.

Methods

Design

This retrospective study included patients with a histological diagnosis of exocrine pancreatic cancer who were treated at the Department of Clinical Oncology of Prince of Wales Hospital in Hong Kong between 2010 and 2015; eligible patients were identified by a review of electronic medical records. If histological findings were unavailable because of the clinician's decision to omit biopsy evaluation, patients were identified using clinical diagnoses based on radiological findings and substantial elevation of the level of serum marker carbohydrate antigen 19-9 (CA 19-9) (ie, >500 IU/mL). Patients were excluded if they had an atypical clinical presentation (eg, normal CA 19-9 level) or histological findings of non-exocrine pancreatic malignancies, such as neuroendocrine tumour or metastatic disease.

Study procedures

The following data were extracted from each patient's electronic and physical medical records: (1) demographics (sex and age); (2) World Health Organization (WHO) performance status score (0: able to perform normal activities without restriction; 1: ambulatory and able to perform light work with limitations on strenuous activities; 2: ambulatory [>50% of waking hours] and capable of self-care but unable to perform any work activities; 3: symptomatic and in a chair or bed for >50% of the day but not bedridden; 4: completely disabled [bedridden] and unable to perform any self-care); (3) disease stage (according to the seventh edition of the American Joint Committee on Cancer tumour-node-metastasis staging system); (4) site of disease (head, neck, body, or tail); (5) CA 19-9 level at diagnosis; and (6) initial treatment (surgery, chemoradiotherapy, chemotherapy, or supportive care). Any occurrences of TE (venous, arterial, or both) were recorded from the time of diagnosis until death or last follow-up; the site of thrombosis (lung, lower limb, multiple, or other) and type of anticoagulation treatment were also recorded. After data entry, all patient data were verified by two authors (LL Chan and KY Lam) under the supervision of the corresponding author (SL Chan). Each patient's survival status was last updated on 31 October 2019.

Statistical analyses

Patient factors (eg, age, sex, WHO performance

status, and initial treatment), tumour-related factors (eg, histological diagnosis status, CA 19-9 level at diagnosis, stage, and site) and TE-related factors (eg, type and site) were summarised as numbers and percentages for categorical variables, and as medians and interquartile ranges for continuous variables. The Wilcoxon rank-sum test and Chi squared test were used to identify variables associated with the development of TE. Variables that displayed statistical significance in univariate analysis were included in multivariable analysis. Age and sex were included in multivariable analysis as adjustment variables because they are known risk factors for the development of TE in patients with cancer, as well as standard clinical variables commonly included in such analyses.[8-10] Kaplan-Meier survival analysis and Cox proportional hazards regression analysis were performed to evaluate the relationship between overall survival and TE. P values <0.05 were considered statistically significant. All analyses were performed with R version 3.5.1.[11]

Results

Study population

In total, 365 patients (217 [59.5%] men and 148 [40.5%] women; median age, 65 years [interquartile range=57-72]) were included in the study; baseline characteristics are summarised in Table 1. Of these patients, 268 (73.4%) had WHO performance status score of 0 to 1, whereas 97 (26.6%) scored 2 to 4. Furthermore, 219 patients (60.0%) had a histologically confirmed diagnosis; the remaining 146 patients (40.0%) were diagnosed by radiological and serological modalities. In terms of tumour staging, 171 patients (46.8%) had stage I to III disease; 194 patients (53.2%) had stage IV disease. The tumour location was at the pancreatic head in 203 patients (55.6%) and other sites (neck, body, or tail) in 162 patients (44.4%). Initial treatment was surgery in 78 patients (21.4%), chemotherapy or chemoradiotherapy in 153 patients (41.9%), and supportive care in 134 patients (36.7%). Additional details are provided in Table 1.

TABLE 1. Patient demographic data*

	All patients (n=365)	Patients without TE (n=311)	Patients with TE (n=54)	P value
Age at diagnosis, y	65 (57-72)	65 (57-72)	64.5 (59-73)	0.56
Sex				0.17
Male	217 (59.5%)	190 (61.1%)	27 (50.0%)	
Female	148 (40.5%)	121 (38.9%)	27 (50.0%)	
WHO performance status score				0.70
0-1	268 (73.4%)	230 (74.0%)	38 (70.4%)	
2-4	97 (26.6%)	81 (26.0%)	16 (29.6%)	
Diagnostic criteria				0.79
Histological	219 (60.0%)	188 (60.5%)	31 (57.4%)	
Radiological	146 (40.0%)	123 (39.5%)	23 (42.6%)	
Stage (AJCC 7th edition)				0.01
I-III	171 (46.8%)	155 (49.8%)	16 (29.6%)	
IV	194 (53.2%)	156 (50.2%)	38 (70.4%)	
Tumour site				0.01
Head	203 (55.6%)	182 (58.5%)	21 (38.9%)	
Other sites (body/neck/tail)	162 (44.4%)	129 (41.5%)	33 (61.1%)	
Initial treatment				0.10
CT or CRT	153 (41.9%)	125 (40.2%)	28 (51.9%)	
Surgery	78 (21.4%)	72 (23.2%)	6 (11.1%)	
Supportive care	134 (36.7%)	114 (36.7%)	20 (37.0%)	
Elevated CA 19-9 level at diagnosis				0.34
Yes	175 (47.9%)	148 (47.6%)	27 (50.0%)	
No	45 (12.3%)	41 (13.2%)	4 (7.4%)	

Abbreviations: AJCC = American Joint Committee on Cancer; CA 19-9 = carbohydrate antigen 19-9; CRT = chemoradiotherapy; CT = chemotherapy; TE = thromboembolism; WHO = World Health Organization

* Data are shown as median (interquartile range) or No. (%), unless otherwise specified

Risk of thromboembolism

Among the 54 patients (14.8%) who developed TE, 32 (59.3%) had venous TE, 18 (33.3%) had arterial TE, and four (7.4%) had both. Lower limbs were the most common sites of thrombosis, with 55.6% of all thromboembolic events. Furthermore, three patients (5.6%) had pulmonary embolism. These findings are summarised in Table 2.

Predictors and prognosis of thromboembolism

In univariate analysis, non-head pancreatic cancer (P=0.01) and stage IV disease (P=0.01) were significantly associated with TE. Other factors such as age at diagnosis, sex, WHO performance status, elevated CA 19-9 level at diagnosis, and initial treatment were not significantly associated with TE (Table 1). Multivariable analysis showed that stage IV disease was a significant risk factor (odds ratio=1.08, 95% confidence interval [CI]=1.00-1.17; P=0.046) [Table 3]. Median overall survival times in patients with and without TE were 4.88 months and 7.80 months, respectively (Fig 1); the difference between groups was not statistically significant (hazard ratio =1.08, 95% CI=0.80-1.49; P=0.58). Among patients with TE, median overall survival was not affected by anticoagulation treatment (no anticoagulation=4.77 months vs anticoagulation=5.63 months, hazard ratio=0.72, 95% CI=0.40-1.29; P=0.27) [Fig 2].

Discussion

In the present study, approximately 15% of patients with pancreatic cancer developed TE. Lower limbs were the most frequent sites of TE, and venous TE

TABLE 2. Distribution of thromboembolic events (n=54)

	No. (%)
Type of thromboembolism	
Venous	32 (59.3%)
Arterial	18 (33.3%)
Venous and arterial	4 (7.4%)
Site of thromboembolism	
Lower limb	30 (55.6%)
Lung	3 (5.6%)
Multiple	4 (7.4%)
Others	17 (31.4%)

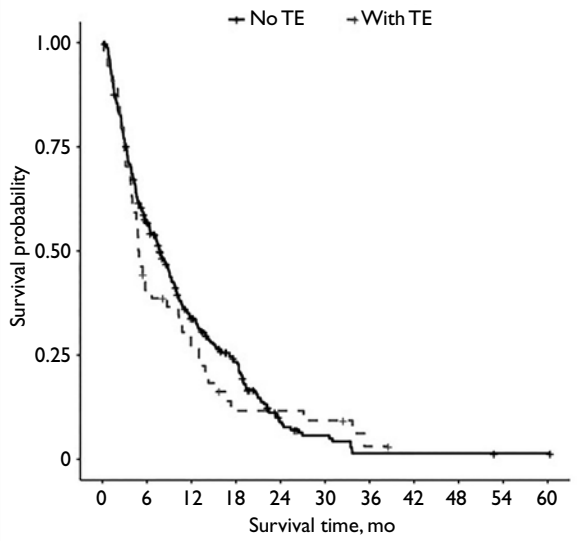
TABLE 3. Multivariable analysis of risk factors for thromboembolism

Variable	Odds ratio	95% Confidence interval	P value
Age	1.00	1.00-1.01	0.351
Male sex	0.95	0.88-1.02	0.146
Stage IV disease	1.08	1.00-1.17	0.046
Non-head pancreatic cancer	1.08	0.99-1.16	0.068

TABLE 4. Recent studies of thromboembolism incidence in patients with pancreatic cancer

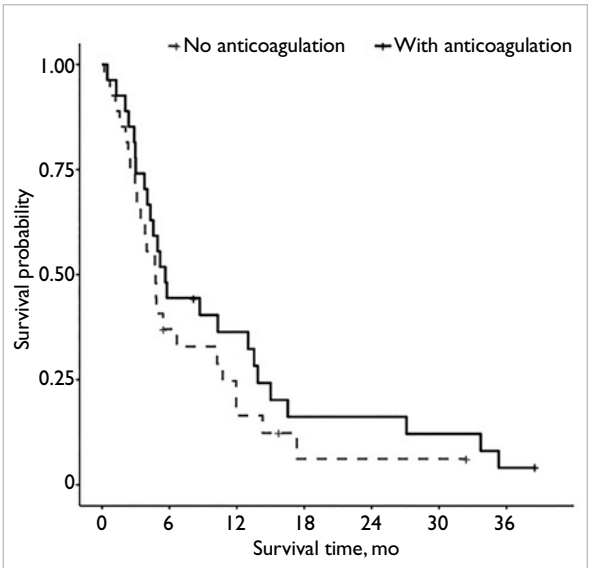
Study	Country/ region	No. of patients	Study period	Proportion of patients with metastatic disease	Proportion of patients receiving systemic treatment, No. (%)	Incidence of TE, No. (%)	Proportion of patients with TE receiving anticoagulation, No. (%)	Types of TE	Association with mOS (TE vs non-TE)
Suzuki et al, 2021[5]	Japan	432	2010-2019	Resectable: 35% BR/LA: 12% Metastatic: 53%	251 (58.1%)	31 (7.2%)	17 (54.8%)	PE: 7% DVT: 26% Visceral: 42%	No (249 vs 249 days)
Frere et al, 2020[3]	France	731	2014-2018	Resectable: 29% BR/LA: 44% Metastatic: 27%	432 (59.1%)	152 (20.8%)	N/A	PE: 17% DVT: 26% Visceral: 30%	Yes (9.1 vs 14.6 months)
Chen et al, 2018[6]	Taiwan	838	2010-2016	Resectable: 0% LA: 21.8% Metastatic: 78.2%	792 (94.5%)	67 (8.0%)	N/A	PE: 21% DVT: 62% Visceral: 0%	No (6.5 vs 7.8 months)
Yoon et al, 2017[7]	Korea	505	2006-2012	Resectable: 0% LA: 45.7% Metastatic: 49.9%	332 (65.7%)	94 (18.6%)	44 of 56 venous TE (78.6%)	PE: 20% DVT: 40% Visceral: 40%	No (9.0 vs 8.2 months)
Kruger et al, 2017[4]	Germany	172	2002-2017	Resectable: 0% LA: 20.3% Metastatic: 79.7%	172 (100%)	71 (41.3%)	N/A	PE: 10% Venous: 22% Visceral: 58%	Yes -
Ouaissi et al, 2015[14]	France	162	2004-2012	Resectable: 46% LA: 8% Metastatic 46%	119 (73.5%)	28 (17.3%)	N/A	PE: 46% Venous 39% Visceral: 0%	Yes (12 vs 18 months)

Abbreviations: BR = borderline resectable; DVT = deep vein thrombosis; LA = locally advanced; mOS = median overall survival; N/A = not applicable; PE = pulmonary embolism; TE = thromboembolism



	Median overall survival, mo	Hazard ratio (95% confidence interval)
No TE	7.80	1.08 (0.80-1.49)
With TE	4.88	

FIG 1. Kaplan-Meier survival curves for patients with and without events of thromboembolism (TE) [P=0.58]



	Median overall survival, mo	Hazard ratio (95% confidence interval)
No anticoagulation	4.77	0.72 (0.40-1.29)
With anticoagulation	5.63	

FIG 2. Kaplan-Meier survival curves for patients with thromboembolic events who did and did not receive anticoagulation treatment (P=0.27)

was the most common type. In univariate analysis, both the site (non-head) and stage (IV) of disease were significantly associated with TE; multivariable analysis revealed that stage IV disease was a significant risk factor for TE.

There is considerable evidence of an association between pancreatic cancer and TE. In the first case series describing the relationship between TE and cancer, the incidence of TE was 60% in patients with pancreatic cancer, whereas it was 15% to 30% among patients with other malignancies.[12] Several pathological processes have been implicated in this association.[13] First, pancreatic cancer is characterised by high expression levels of tissue factor, which triggers the extrinsic coagulation pathway leading to thrombin formation. Second, the release of tumour-associated microvesicles promotes hypercoagulability and activates platelet aggregation. Third, the establishment of neutrophil extracellular traps secondary to neutrophil activation generates a matrix for platelet and tumour-associated microvesicle adhesion, resulting in blood clot formation.

Thromboembolism incidence of around 15% in our cohort is similar to that reported in other studies of Asian populations[5-7] but lower than that in most Western populations (Table 4).[3,4,14] The figures ranged from 20% to 40% in Western populations and 8% to 18% in Asian populations. Consistent with the findings in other studies of Asian populations, we observed no difference in overall survival between patients with and without TE. However, the literature suggests that, in Western populations, overall survival is affected by TE (Table 4).

Taken together, these findings support the hypothesis that TE incidences and outcomes are influenced by genetic and environmental differences between Western and Asian populations. For example, genetic variants in the clotting cascade (eg, factor V Leiden and thrombin gene G20210A) reportedly increase the risk of TE.[15] These variants are much more prevalent in Western populations than in Asian populations.[16] The resulting relative hypercoagulability may be one of the main reasons for the higher background incidence of TE in Western populations than in Asian populations.[17] Another factor that may contribute to the difference in TE incidence between the two populations is obesity, an established risk factor for TE that is more common in Western populations.[18]

With respect to TE and pancreatic cancer prognosis, survival appears to be inherently longer in Western populations than in Asian populations (Table 4). Considering the aggressive nature of pancreatic cancer, it is possible that patients with shorter survival (eg, patients in Asian populations)

do not live long enough to benefit from treatment of TE, whereas patients with longer survival (eg, patients in Western populations) experience a survival benefit from treatment of TE. Indeed, in a recent systematic review regarding the treatment outcomes of FOLFIRINOX and gemcitabine plus nab-paclitaxel in patients with pancreatic cancer, Lee et al[19] showed that, compared with Asian populations, Western populations experienced a greater survival benefit from FOLFIRINOX (ie, standard treatment for metastatic pancreatic cancer) but a smaller survival benefit from gemcitabine plus nab-paclitaxel (which was not available to our patients during the present study). Therefore, a reasonable assumption is that anticoagulation can prolong survival in Western populations among patients treated with FOLFIRINOX. Further studies are needed to determine whether any subgroup of Asian patients with pancreatic cancer can benefit from the treatment of TE.

In univariate analysis, both non-head pancreatic cancer and metastatic disease were associated with the development of TE. However, in multivariable analysis, the association with non-head pancreatic cancer disappeared; metastatic disease was the sole risk factor for TE. This is not surprising—non-head pancreatic cancer is often detected at a late stage because clinical symptoms (eg, biliary obstruction) do not occur until the tumour becomes quite large. Therefore, the association of TE with non-head pancreatic cancer is mainly related to the advanced stage of disease. This finding is also consistent with the results of previous studies in which non-head pancreatic cancer was frequently detected at a later stage of disease.[3,20]

In the present study, we found that metastatic disease was a risk factor for TE, which is consistent with the results of previous studies.[20-23] The underlying pathophysiological mechanisms involve multiple factors. For example, an advanced stage of disease is often associated with a higher tumour burden and bulky metastases, which can compress blood vessels and inhibit blood flow. Higher tumour burden can also affect WHO performance status, resulting in decreased mobility and bedridden status.

During the present study, most of our patients received low-molecular-weight heparin (LMWH) as treatment for cancer-associated TE, based on the results of the 2003 CLOT (Comparison of Low-molecular-weight heparin versus Oral anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer) trial in which LMWH demonstrated superior efficacy in preventing recurrent TE compared with coumarins (eg, warfarin) while maintaining a similar risk of bleeding.[24] Recent studies have shown that direct oral anticoagulants (DOACs) such as edoxaban[25] and apixaban[26] are non-inferior to LMWH as secondary prophylaxis for TE with similar safety profiles. Accordingly, both LMWH and DOACs are valid options for the treatment of TE in patients with pancreatic cancer. This approach is consistent with the latest National Comprehensive Cancer Network 2021 guidelines.[27] Although LMWH and DOACs demonstrate similar efficacy in preventing recurrent TE, other factors to consider in drug selection include baseline renal function, patient preference, ease of administration, risk of bleeding (eg, by tumour infiltration into the upper gastrointestinal tract), and availability of antidotes that can reverse anticoagulation.

Considering the overall poor prognosis of pancreatic cancer and the lack of an overall survival benefit associated with anticoagulation treatment of TE, factors such as quality of life should be considered when deciding whether to initiate or discontinue anticoagulation treatment. It is important to have clear discussions with patients regarding the risks and benefits of anticoagulation, particularly during the management of aggressive malignancies such as pancreatic cancer, where the life expectancy is often only months or weeks. Anticoagulation treatment, such as LMWH, may cause subcutaneous injection–related discomfort and carries an increased risk of bleeding, but the therapeutic effects of anticoagulation may relieve symptoms of TE (eg, calf swelling and dyspnoea). In a retrospective study of 128 patients with cancer-associated venous TE, Napolitano et al[28] analysed the effects of anticoagulation on quality of life using the EORTC-C30 questionnaire; they found that long-term LMWH was not associated with worse quality of life. However, patients approaching the end of life often prefer to minimise their medication intake.[29] In our clinic, we tend not to administer anticoagulation treatment if a patient's life expectancy is <3 months or whose WHO status score is 3 to 4. This approach is consistent with the patient populations in recent clinical trials comparing the efficacies of DOACs and LMWH in the treatment of cancer-associated TE; patients with poor WHO performance status and short life expectancy were excluded from those trials.[25,26]

Limitations

This study had a few limitations. First, its retrospective nature may have permitted bias related to missing data and the possibility of asymptomatic TE. However, TE tends to be symptomatic in patients with cancer; thus, it is unlikely that events were missed. Additionally, analyses of symptomatic TE are more relevant to real-world clinical practice. Second, the overall survival time of patients in the present study was worse than the survival times reported in randomised clinical trials of patients with metastatic pancreatic cancer.[30,31] This discrepancy

may have occurred because our study cohort was representative of real-world patients who more frequently have reduced liver function and worse WHO performance status. It may also be related to the absence of more effective chemotherapy (eg, nab-paclitaxel) during the study period.

Conclusion

In conclusion, this study demonstrated that the incidence of TE was around 15% in Chinese patients with pancreatic cancer. Notably, the presence of TE was not associated with worse overall survival, and metastatic disease increased the risk of TE.

Author contributions

Concept or design: LL Chan, KY Lam, SL Chan.
Acquisition of data: All authors.
Analysis or interpretation of data: LL Chan, DCM Lam, KY Lam, SL Chan.
Drafting of the manuscript: LL Chan, SL Chan.
Critical revision of the manuscript for important intellectual content: All authors.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Ethics approval

This study protocol was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (Ref No.: 2016.730). Informed patient consent was waived by the Committee due to the retrospective nature of the research.

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