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Association of tissue factor expression with prognosis and clinical features in human pancreatic cancer: a systematic review protocol

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Abstract

Introduction： Pancreatic cancer is a type of highly aggressive digestive system tumour with poor prognosis. Venous thromboembolism (VTE) is a well-known complication of pancreatic cancer. Tissue factor (TF) is an important factor which contributes to the generation of a hypercoagulable state and thrombotic disease in pancreatic cancer. Several studies showed that TF expression with different types was related to the clinicopathological features of pancreatic cancer and influenced the survival of patients with pancreatic cancer. We thus want to conduct a systematic review of the literature to clarify the association between TF expression and clinicopathological features/prognosis of pancreatic cancer patients.

Methods and analysis: Studies comparing the clinicopathological features and the prognosis between pancreatic cancer patients with high and low expression of TF in tissue, plasma and MVs levels are eligible for the review. The outcomes include survival endpoints and the relationship between TF expression and clinicopathological features, such as VTE, tumor embolus, tumour size, clinical tage, and differentiation. Primary studies of any type published in English are included. Two reviewers will search the Medline, EMBASE and Cochrane from inception to Jan 2020 and retrieve the relevant studies. The same reviewers independently select the literatures and extract the data of included studies. The quality of the each included study is assessed by the Newcastle-Ottawa Scale (NOS score). The HR and 95% CI of each study are pooled for the survival outcome, and the pooled odds ratio (OR) and 95% CI are used for other outcomes. If a meta-analysis is not appropriate,

the result will only be reported qualitatively. Subgroup and sensitivity analyses are considered to identify the source of heterogeneity. The Grades of Recommendation, Assessment, Development and Evaluation method is applied to assess the level of evidence obtained from this systematic review.

Ethics and dissemination: There is no concerning ethical issue. The result will be sought for publication.

PROSPERO registration number: CRD42019133665

Key words: pancreatic cancer; tissue factor; microvesicle; prognosis; systematic review

Strengths and limitations of this study

- This is the first systematic review addressing the significance of the TF for pancreatic cancer from different levels.
- Multiple outcomes are collected and analysed in this systematic review.
- It may be difficult to combine the results due to a small number of studies and substantial heterogeneity.

Introduction

Pancreatic cancer is a type of highly aggressive digestive system tumor with poor prognosis.[1] It is estimated that pancreatic cancer will be the second largest cancer-related cause of death in the United States by 2030.[2] Pancreatic cancer has insidious onset, rapid progression, low rate of early diagnosis and radical resection.[3] Most of the patients already have advanced or distant metastasis at the first diagnosis. Despite recent advances in surgical techniques as well as chemotherapy and radiation therapy, pancreatic cancer patients still has a dismal 5-year survival rate.[3]

Venous thromboembolism (VTE), associated with the generation of an intrinsic hypercoagulable state, is a well-known complication of malignant tumor. Spreau first discovered that pancreatic cancer patients are prone to VTE in 1938. [4]Subsequently, the incidence of VTE in pancreatic cancer patients ranges from 17% to 57% by Khorana.[5] Furthermore, several studies have found that thrombosis and diffuse intravascular coagulation are associated with poor prognosis in patients with pancreatic cancer.[6-10] However, the relationship between VTE and pancreatic cancer and the biological significance of VTE are not completely understood.

Several factors may play an important part in the generation of a hypercoagulable state and VTE in pancreatic cancer. Of prime importance is tissue factor (TF), a single chain transmembrane-receptor glycoprotein with a molecular weight of approximately 47 kDa, which initiates the extrinsic pathway of coagulation.[11] In recent years, It was reported that TF is expressed in many malignant tumours tissues, including

pancreatic cancer, leading to increased blood coagulability and a high risk of VTE.[12,13] Similarly, the plasma TF concentration increased significantly in patients with pancreatic cancer and thrombosis.[14] Pancreatic cancer cells express TF and release Tissue factor - positive(TF^+) microvesicles (MVs) (TF^+MVs)[15] and circulating TF^+MVs can be detected in patients.[16] Importantly, the levels TF+ MVs are associated with VTE in patients with pancreatic cancer.[17-19]

Emerging data suggest that the hemostatic system has a regulatory role in tumour invasion and metastasis. Therefore, the activation of the hemostatic system may not only contribute to VTE but also promote tumor invasion and metastasis. In recent studies found that TF was shown to promot angiogenesis[20], inflammatory reaction[21], tumour invasion[22] and metastasis.[23] Some evidence showed that the expression of TF in metastatic melanoma cells was significantly higher than in non-metastatic cells;[24] the expression of TF in metastatic cancer sublines was significantly higher than in parental lines.[25] Similarly, studies have found that TF expression is related to the invasion phenotype of pancreatic cancer.[26] In addition, compared with tumour cells with a higher degree of differentiation in pancreatic cancer, tumour cells with lower degree of differentiation seem to have higher TF expression and associated with decreased overall survival.[13,26-28] Therefore, there seem be a significant association between TF and pancreatic cancer, and TF may be a potential marker of disease prognosis in patients with pancreatic cancer. We plan to undertake a systematic review of the literature to summarize previous evidence regarding this topic and

clarify the prognostic significance of TF in pancreatic cancer.

Why it is important to do this review

Pancreatic carcer is one of the most aggressive malignant tumours in the clinic. The 3-year survival rate after surgical resection of primary tumours is only 17%. Therefore, identifying markers that may predict poor prognosis will benefit patients with radical or molecular targeted therapies. Some methods have been established to study the TF in pancreatic cancer. However, to date, no systematic review has been conducted to study the association between TF expression or activity and clinicopathological features/prognosis of pancreatic cancer.

Objectives

To systematically clarify the relationship between TF expression/activity and clinicopathological features in patients with pancreatic cancer and to explore the prognostic value of TF as a marker for pancreatic cancer.

Methods and analysis

Registration

This protocol was registered with PROSPERO (International Prospective Register of Systematic Reviews) (CRD42019133665)

Eligibility criteria

Participants

Patients with pancreatic cancer are eligible for the review. The diagnosis is histologically confirmed. Surgery is performed by several surgeons in accordance with the standard criteria for pancreatic cancer resection, but there are no restrictions regarding the type of surgery. The resected specimens are histologically examined according to the Union for International Cancer Control (UICC) tumour-node-metastasis (TNM) classification. Patients are excluded if they are unresectable, or have other malignancies, or receive preoperative therapy.

Exposure

The expression/activity of TF in tissue, plasma and MVs is the exposure variable of this study. The TF is detected based on the resected specimens, plasma and MVs in pancreatic cancer patients using the respective test methods. This review compares the clinicopathological features and the prognosis between pancreatic cancer patients with high and low level of TF expression or activity.

Outcomes

The study is included if it reports survival endpoints and provides the relationship between TF and clinicopathological features, such as VTE, tumor embolus, primary tumour size, clinical stage, and differentiation. The study should also provide sufficient information to estimate the hazard ratio (HR).

Studies

Any prospective or retrospective published studies which evaluate the relationship

between TF and pancreatic cancer are included. There is no limitation regarding the number of participants. Only studies published in English were included.

Information sources

We will search the Medline, Embase, and Cochrane Library from inception to Jan 2020.

Search strategy

Two reviewers search the Medline, EMBASE and Cochrane using a combination of subject terms with free-text terms. The following search words are adopted for each database: (pancreas or pancrea* or pancreas [MeSh]) and (carcinoma [MeSh] or adenocarcinoma [MeSh] or carcinoma, ductal [MeSh] or neoplasms [MeSh] or cancer* or carcin* or neoplas* or tumo* or cyst* or growth* or adenocarcin* or malig*) and (tissue factor or CD142 antigens or coagulation factor III or thromboplastin [MeSh]). Reference lists of eligible studies and relevant review articles are also hand-searched to identify any potentially eligible studies that are recorded in the databases. We will also search in Google Scholar to identify any grey literatures.

Study records

Data management

All study records are processed through EndNote X9, which can identify and remove duplicates. All extracted data are stored in a Microsoft Excel spreadsheet.

Study selection and data collection process

Two reviewers independently screen first the titles and abstracts of all retrieved articles after removing duplicates, and then the full texts of the selected articles. Disagreements are resolved by face-to-face discussion, or in case of persistent disagreement, a third researcher will be consulted. The same reviewers extract the data of included studies based on a predefined data extraction form.

Data items

The data extracted include author, publication year, country, study design, number of participants, follow-up period, baseline and clinicopathological information of patients, survival outcomes, hazard ratio (HR), and 95% confidence interval (CI) related to TF expression. In addition, methods for statistical analysis, summary statistics, and items associated with a risk of bias are also summarized.

Risk of bias in individual studies

Two researchers will independently assess the quality of the each included study using the Newcastle-Ottawa Scale (NOS score).[29] Scores of the NOS are split into three aspects: object selection, inter-group comparability, and outcome measurement. It is generally considered that an article with a score 0–5 point(s) is of low quality, and the article with a score >6 is considered high-quality.

Data synthesis

All statistical tests are calculated with RevMan 5.3. The hazard ratio (HR) and 95%

CI of each study are used to assess the relationship between the expression of TF and the prognosis. The association between TF expression and clinicopathological features is calculated using the pooled odds ratio (OR) and 95% CI. The HR and 95% CI of each study are directly extracted from the original published study. The method from Tierney et al[30] is used to extract the data or conduct a variable transformation if the studies do not directly provide HR and 95% CI. For example, some studies provide only the survival curve. The HR and 95% CI of each study are finally combined using the method of generic inverse variance in RevMan software, so the ln (HR) and SEln (HR) will be calculated in advance based on the data extracted. The level of statistical significance is set at the 5%. If a meta-analysis is not appropriate because of small number of studies or concerns regarding substantial variability, the result will only be reported qualitatively. The heterogeneity is assessed using the I^2 statistic. We will utilize the fixed effect model when the effects are assumed to be homogenous ($p>0.05$, $I^2 \leq 50\%$) and the random effect model when they are heterogeneous ($p<0.05$, $I^2 \geq 50\%$). To explore the source of heterogeneity, subgroup analysis is considered. Sensitivity analysis will also be conducted and will be focused on studies with a low risk of bias.

Meta-biases

Reporting bias will be explored graphically by a funnel plot and statistically by the Egger's test[31] if 10 or more studies are available. $P<0.05$ is considered to indicate publication bias.

Confidence in cumulative evidence

The Grades of Recommendation, Assessment, Development and Evaluation method is applied to assess the level of evidence obtained from this systematic review.[32]

Patient and Public Involvement

No patient involved.

Discussion

Studies have shown that TF is closely related to the clinicopathological features and prognosis of pancreatic cancer.[13,26,28] Nevertheless, no systematic review on the association of different types TF expression with pancreatic cancer patients have been published in English. Thus, we plan to conduct a systematic review and meta-analysis on this topic. We hope that the results of this review will provide researchers and clinicians with more convincing evidence on whether TF is a potential biomarker of thrombotic risk and prognostic factor, and thereby promote the development of individualized diagnosis and treatment of pancreatic cancer patients.

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Competing interest

None declared

Authors' contribution

HYL and HC conceived the idea and planned the entire methods to undertake it. HYL and YY wrote the manuscript of this protocol. YY, QLS, XPC and PZ designed the search strategy and planned the data extraction. DFW, PXT, BHG, XML, TZ, LX, DYX, LG and MEP made contributions in conceiving this research project. All authors revised and approved the final version of the manuscript.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359-386.

2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res*. 2014;74(11):2913-2921.

3. Chu LC, Goggins MG, Fishman EK. Diagnosis and Detection of Pancreatic Cancer. *Cancer J*. 2017;23(6):333-342.

4. Sproul EE. Carcinoma and Venous Thrombosis: The Frequency of Association of Carcinoma in the Body or Tail of the Pancreas with Multiple Venous Thrombosis. *American Journal of Cancer*. 1938;34.

5. Khorana AA, Fine RL. Pancreatic cancer and thromboembolic disease. *Lancet Oncol*. 2004;5(11):655-663.

6. Unruh D, Sagin F, Adam M, et al. Levels of Alternatively Spliced Tissue Factor in the Plasma of Patients with Pancreatic Cancer May Help Predict Aggressive Tumor Phenotype. *Ann Surg Oncol*. 2015;22 Suppl 3:S1206-1211.

7. Davila M, Robles-Carrillo L, Unruh D, et al. Microparticle association and heterogeneity of tumor-derived tissue factor in plasma: is it important for coagulation activation? *J Thromb Haemost*. 2014;12(2):186-196.

8. Bharthuar A, Khorana AA, Hutson A, et al. Circulating microparticle tissue factor, thromboembolism and survival in pancreaticobiliary cancers. *Thromb Res*. 2013;132(2):180-184.

9. Boone BA, Zenati MS, Rieser C, et al. Risk of Venous Thromboembolism for Patients with Pancreatic Ductal Adenocarcinoma Undergoing Preoperative Chemotherapy Followed by Surgical Resection. *Ann Surg Oncol*. 2019;26(5):1503-1511.

10. Mier-Hicks A, Raj M, Do RK, et al. Incidence, Management, and Implications of Visceral Thrombosis in Pancreatic Ductal Adenocarcinoma. *Clin Colorectal Cancer*. 2018;17(2):121-128.

11. Nemerson Y. Tissue factor and hemostasis. *Blood*. 1988;71(1):1-8.

12. Haas SL, Jesnowski R, Steiner M, et al. Expression of tissue factor in pancreatic adenocarcinoma is associated with activation of coagulation. *World J Gastroenterol*. 2006;12(30):4843-4849.

13. Khorana AA, Ahrendt SA, Ryan CK, et al. Tissue factor expression, angiogenesis, and thrombosis in pancreatic cancer. *Clin Cancer Res*. 2007;13(10):2870-2875.

14. Khorana AA, Francis CW, Menzies KE, et al. Plasma tissue factor may be predictive of venous thromboembolism in pancreatic cancer. *J Thromb Haemost*. 2008;6(11):1983-1985.

15. Wang JG, Geddings JE, Aleman MM, et al. Tumor-derived tissue factor activates coagulation and enhances thrombosis in a mouse xenograft model of human pancreatic cancer. *Blood*;119(23):5543-5552.

16. Tesselaar MET, ROMIJN FPHTM, LINDEN IKVD, PRINS FA, BERTINA RM, OSANTO S. Microparticle-associated tissue factor activity: a link between cancer and thrombosis? *Journal of Thrombosis & Haemostasis Jth*;5(3):520-527.

17. Thaler J, AY C, MACKMAN N, et al. Microparticle-associated tissue factor activity, venous thromboembolism and mortality in pancreatic, gastric, colorectal and brain cancer patients. *Journal of Thrombosis & Haemostasis*;10(7):0-0.

18. Zwicker JI, Liebman HA, Neuberg D, et al. Tumor-Derived Tissue Factor-Bearing Microparticles

Are Associated With Venous Thromboembolic Events in Malignancy. *Clinical Cancer Research*;15(22):6830-6840.

19. Bharthuar A, Khorana AA, Hutson A, et al. Circulating microparticle tissue factor, thromboembolism and survival in pancreaticobiliary cancers. *Thrombosis Research*;132(2):180-184.

20. Milsom CC, Yu JL, Mackman N, et al. Tissue factor regulation by epidermal growth factor receptor and epithelial-to-mesenchymal transitions: effect on tumor initiation and angiogenesis. *Cancer Res*. 2008;68(24):10068-10076.

21. Date K, Ettelaie C, Maraveyas A. Tissue factor-bearing microparticles and inflammation: a potential mechanism for the development of venous thromboembolism in cancer. *J Thromb Haemost*. 2017;15(12):2289-2299.

22. Hu C, Huang L, Gest C, et al. Opposite regulation by PI3K/Akt and MAPK/ERK pathways of tissue factor expression, cell-associated procoagulant activity and invasiveness in MDA-MB-231 cells. *J Hematol Oncol*. 2012;5:16.

23. Chanakira A, Westmark PR, Ong IM, Sheehan JP. Tissue factor-factor VIIa complex triggers protease activated receptor 2-dependent growth factor release and migration in ovarian cancer. *Gynecol Oncol*. 2017;145(1):167-175.

24. Mueller BM, Reisfeld RA, Edgington TS, Ruf W. Expression of tissue factor by melanoma cells promotes efficient hematogenous metastasis. *Proc Natl Acad Sci U S A*. 1992;89(24):11832-11836.

25. Kataoka H, Uchino H, Asada Y, et al. Analysis of tissue factor and tissue factor pathway inhibitor expression in human colorectal carcinoma cell lines and metastatic sublines to the liver. *Int J Cancer*. 1997;72(5):878-884.

26. Chen K, Li Z, Jiang P, et al. Co-expression of CD133, CD44v6 and human tissue factor is

associated with metastasis and poor prognosis in pancreatic carcinoma. *Oncol Rep*. 2014;32(2):755-763.

27. Kakkar AK, Lemoine NR, Scully MF, Tebbutt S, Williamson RCN. Tissue factor expression correlates with histological grade in human pancreatic cancer. *British Journal of Surgery*. 1995;82(8):1101-1104.

28. Nitori N, Ino Y, Nakanishi Y, et al. Prognostic significance of tissue factor in pancreatic ductal adenocarcinoma. *Clin Cancer Res*. 2005;11(7):2531-2539.

29. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European journal of epidemiology*. 2010;25(9):603-605.

30. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*. 2007;8(1):16.

31. Duval S, Tweedie R. Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56(2):455-463.

32. Iorio A, Spencer FA, Falavigna M, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. *bmj*. 2015;350:h870.

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Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Oncology, Gastroenterology and hepatology, Patient-centred medicine
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Prognostic significance of tissue factor in patients with pancreatic cancer: a systematic review protocol

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Abstract

Introduction: Pancreatic cancer is a highly aggressive digestive system tumour with poor prognosis. Venous thromboembolism (VTE) is a well-known complication of pancreatic cancer, and tissue factor (TF) contributes to the generation of a hypercoagulable state and thrombotic disease in pancreatic cancer. Several studies showed that an elevated TF level was related to the development of VTE and influenced the survival of pancreatic cancer patients. Thus, we wish to conduct a systematic review of literature to clarify the prognostic significance of TF in pancreatic cancer.

Methods and analysis: Studies comparing the circulating microparticle-associated MP TF level between pancreatic cancer patients with and without VTE will be included to evaluate the roles of TF in VTE development. Studies comparing the survival data between patients with high TF expression and low TF expression will also be included to explore the association of TF expression with patient survival. The outcomes are plasma MP TF level and survival endpoints (overall and progression-free survival), respectively. Primary studies of any type published in English will be included. Two reviewers will search Medline, EMBASE and Cochrane databases from inception to June 2020, retrieve relevant studies, and independently select the literatures and extract data from the included studies. The quality of each included study will be assessed by the Newcastle-Ottawa Scale (NOS score). The HR and 95% CI of each study will be pooled for survival outcome, and

the standardized mean difference with 95% confidence intervals will be used for continuous outcomes. If meta-analysis is inappropriate, the result will only be reported qualitatively. Subgroup and sensitivity analyses will be considered to identify sources of heterogeneity. The Grades of Recommendation, Assessment, Development and Evaluation method will be applied to assess the level of evidence of this systematic review.

Ethics and dissemination: There are no concerning ethical issues. The results will be published.

PROSPERO registration number: CRD42019133665

Key words: pancreatic cancer; tissue factor; microvesicle; prognosis; systematic review

Strengths and limitations of this study

- A detailed and completed search strategy will be used to collect potentially eligible studies.
- Sources of heterogeneity will be carefully considered, and multiple solutions will be considered.
- The included literature will be limited to studies published in English.
- Heterogeneity among the TF measuring methods may exist.
- The findings are potentially subject to publication bias.

INTRODUCTION

Pancreatic cancer is a type of highly aggressive digestive system tumour with poor prognosis.[1] It is estimated that pancreatic cancer will be the second largest cancer-related cause of death in the United States by 2030.[2] Pancreatic cancer has insidious onset, rapid progression, low rate of early diagnosis and radical resection.[3] Most of the patients already have advanced or distant metastasis at the first diagnosis. Despite recent advances in surgical techniques as well as chemotherapy and radiation therapy, pancreatic cancer patients still has a dismal 5-year survival rate.[3]

Venous thromboembolism (VTE), associated with the generation of an intrinsic hypercoagulable state, is a well-known complication of malignant tumour. Sproul first discovered that pancreatic cancer patients are prone to VTE in 1938. [4] Subsequently，the reported incidence of VTE in pancreatic cancer patients ranges from 17% to 57%.[5] Several factors and pathological mechanisms contribute to the generation of a hypercoagulable state and VTE in pancreatic cancer.[6] Of prime importance is tissue factor (TF), a single chain transmembrane-receptor glycoprotein with a molecular weight of approximately 47 kDa, which initiates the extrinsic pathway of coagulation.[7] In recent years, it was reported that TF is expressed in many malignant tumour tissues, including pancreatic cancer, leading to increased blood coagulability and a high risk of VTE.[8 9] In addition, high level of the plasma TF was detected in patients with pancreatic cancer.[10] Pancreatic cancer cells express TF and release microparticle-associated TF (MP TF) into blood.[11 12]

Several studies have found that thrombosis and diffuse intravascular coagulation are associated with poor prognosis in patients with pancreatic cancer.[13-17] Meanwhile, substantial evidence indicated that TF is of predictive value in the biologic features of tumours and the survival of patients. It was found that TF plays an important role in promoting angiogenesis,[18] inflammatory reaction,[19] tumour invasion,[20] and metastasis.[21] Compared with tumour cells with a higher degree of differentiation in pancreatic cancer, tumour cells with lower degree of differentiation seem to have higher TF expression and associated with decreased overall survival.[9 22-24] Therefore, we hypothesize that the elevated circulating TF level may contribute to the development of VTE, and TF expression in tumour tissue may be associated with poor prognosis in patients with pancreatic cancer. To test this hypothesis, we plan to undertake a systematic review of previous studies assessing the association between TF and pancreatic cancer.

METHODS AND ANALYSIS

Objective of the review

This review aims to clarify the prognostic significance of TF in pancreatic cancer. This review contains two sections. First, we will evaluate the association between circulating MP TF level and VTE. Second, we will explore the impact of TF expression on patients' survival.

Registration

This protocol was registered with PROSPERO (International Prospective Register of Systematic Reviews) (CRD42019133665)

Eligibility criteria

Participants

Patients with pancreatic cancer are eligible for the review. The diagnosis will be pathologically confirmed. There are no limitations on the stages, grades, and types of pancreatic cancer. Patients will be excluded if they have primary haematological system disease or other malignancies or receive transfusion therapy during the study course.

Exposure

To evaluate the association between circulating MP TF level and VTE, pancreatic cancer patients will be divided into two groups based on the presence or absence of VTE. The MP TF level will be compared between two groups. There are no strict restrictions on the diagnosis approach for VTE, and diagnosis by clinical assessment, imaging, and D-dimer testing are all acceptable. To explore the impact of TF expression on patients' survival, patients will be defined as groups of high TF expression or low TF expression. Survival between different TF-expression groups will be compared. The TF will be detected using immunohistochemistry analysis of the tissue specimens.

Outcomes

According to different purpose, studies are eligible if they: a) individually report the level of circulating MP TF of patients with VTE and without VTE; or b) report survival endpoints (including overall survival [OS] and progression free survival [PFS]) of patients in the groups of high TF expression and low TF expression. In addition, the level of circulating MP TF is determined by flowcytometry or activity tests. The studies reporting survival data should also provide sufficient information to estimate the hazard ratio (HR).

Studies

Any prospective or retrospective published studies which evaluate the relationship between TF and pancreatic cancer are included. There is no limitation regarding the number of participants. Only studies published in English were included.

Information sources

We will search the Medline, Embase, and Cochrane Library from inception to June 2020.

Search strategy

Two reviewers search the Medline, EMBASE and Cochrane using a combination of subject terms with free-text terms. The following search words are adopted for each database: (pancreas or pancrea* or pancreas [MeSh]) and (carcinoma [MeSh] or adenocarcinoma [MeSh] or carcinoma, ductal [MeSh] or neoplasms [MeSh] or cancer* or carcin* or neoplas* or tumo* or cyst* or growth* or adenocarcin* or

malig*) and (tissue factor or TF expression or microparticle or TF-positive MP or TF+MP or TF-bearing MP or MP-associated or MP TF or microvesicle or TF-positive MV or TF+MV or TF-bearing MV or MV-associated or MV TF or CD142 antigens or coagulation factor III or thromboplastin [MeSh]). An example of the Medline search strategy is provided in the supplementary file. Reference lists of eligible studies and relevant review articles will also be hand-searched to identify any potentially eligible studies that are recorded in the databases. We will also search Google Scholar to identify any grey literature.

Study records

Data management

All study records will be processed through EndNote X9, which can identify and remove duplicates. All extracted data will be stored in a Microsoft Excel spreadsheet.

Study selection and data collection process

Two reviewers will independently screen first the titles and abstracts of all retrieved articles after removing duplicates, and then the full texts of the selected articles. Disagreements will be resolved by face-to-face discussion, or in case of persistent disagreement, a third researcher will be consulted. The same reviewers will extract the data of included studies based on a predefined data extraction form.

Data items

The data extracted will include author, publication year, country, study design,

number of participants, follow-up period, baseline and clinicopathological information of patients, methods used to measure TF, circulating MP TF level related to VTE presence, OS and PFS (hazard ratio [HR], 95% confidence interval [CI]) related to TF expression. In addition, methods for statistical analysis, summary statistics, and items associated with a risk of bias will also be summarized.

Risk of bias in individual studies

Two researchers will independently assess the quality of the each included study using the Newcastle-Ottawa Scale (NOS score).[25] Scores of the NOS are split into three aspects: object selection, inter-group comparability, and outcome measurement. It is generally considered that an article with a score 0–5 point(s) is of low quality, and an article with a score >6 is of high quality.

Data synthesis

All statistical tests are calculated with RevMan 5.3. The pooled standardized mean difference (SMD) with 95% confidence intervals (CI) will be used to compare the circulating MP TF level in VTE group and non-VTE group because the MP TF level reported in studies may have inconsistent units. The hazard ratio (HR) and 95% CI of each study will be used to evaluate the survival difference between groups with different strength of TF expression. The case number and mean and standard deviation (SD) of MP TF level are collected from included studies. The HR and 95% CI will first be extracted from the original published study. The method from Tierney et al[26] is used to extract the data or conduct a variable transformation if the studies do

not directly provide HR and 95% CI. For example, some studies provide only the survival curve. The HR and 95% CI of each study are finally combined using the method of generic inverse variance in RevMan software; therefore, the ln (HR) and SEln (HR) will be calculated in advance based on the data extracted. The level of statistical significance is set at 5%. If a meta-analysis is not appropriate because of small number of studies or concerns regarding substantial variability, the result will only be reported qualitatively. The heterogeneity will be assessed using the I^2 statistic. We will utilize the fixed-effect model when the effects are assumed to be homogenous ($p>0.05$, $I^2 \leq 50\%$) and the random effect model when they are heterogeneous ($p<0.05$, $I^2 \geq 50\%$). To explore the source of heterogeneity, subgroup analysis will be performed according to the same regions, study design, types of tumour, and methods of measuring MP TF level. Sensitivity analysis will also be conducted and focused on studies with a low risk of bias.

Meta-biases

Reporting bias will be explored graphically by a funnel plot and statistically by the Egger's test[27] if 10 or more studies are available. $P<0.05$ is considered to indicate publication bias.

Confidence in cumulative evidence

The Grades of Recommendation, Assessment, Development and Evaluation method is applied to assess the level of evidence obtained from this systematic review.[28]

Patient and Public Involvement

No patients are involved.

Discussion

Studies have shown that TF is closely related to the VTE development and survival of patients with pancreatic cancer.[9 22 24 29] Nevertheless, no systematic review regarding the predictive value of plasma MP TF level and tissue TF expression strength on pancreatic cancer patients have been published in English. Thus, we plan to conduct a systematic review and meta-analysis on this topic. We hope that the results of this review will provide researchers and clinicians with more convincing evidence on whether TF is a potential biomarker of thrombotic risk and prognostic factor, and thereby promote the development of individualized diagnosis and treatment of pancreatic cancer patients. This article provides a detailed and complete description of the methodology of the review; however, some limitations may become apparent during the course of this review. First, only studies published in English will be included. The exclusion of non-English articles will negatively influence the representativeness of the results to a global population. Second, the inclusion criteria regarding the methods used to measure TF are not strict. Heterogeneity in the measuring methods will reduce the accuracy of results. Third, as with all systematic reviews and meta-analyses, there are potential risks of publication bias. Overall, regardless of the potential methodological deficiencies, we believe that each aspect of the review has been addressed and the protocol will help ensure study's integrity and

transparency.

Ethics and dissemination

This proposed systematic review and meta-analysis is based on published data, and no information of an individual patient will be accessed and discussed in this review. Therefore, ethical approval is not required. The results of this review will be sought for publication in a peer-reviewed journal and relevant conference proceedings. Data generated during the research will be available from the corresponding author on reasonable request.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International journal of cancer* 2015;136:E359-86. doi: 10.1002/ijc.29210

2. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer research* 2014;74:2913-21. doi: 10.1158/0008-5472.can-14-0155

3. Chu LC, Goggins MG, Fishman EK. Diagnosis and Detection of Pancreatic Cancer. *Cancer journal (Sudbury, Mass)* 2017;23:333-42. doi: 10.1097/ppo.0000000000000290

4. Sproul EE. Carcinoma and Venous Thrombosis: The Frequency of Association of Carcinoma in the Body or Tail of the Pancreas with Multiple Venous Thrombosis. *American Journal of Cancer* 1938;34

5. Khorana AA, Fine RL. Pancreatic cancer and thromboembolic disease. *The Lancet Oncology* 2004;5:655-63. doi: 10.1016/s1470-2045(04)01606-7

6. Campello E, Ilich A, Simioni P, et al. The relationship between pancreatic cancer and hypercoagulability: a comprehensive review on epidemiological and biological issues. *Br J Cancer* 2019;121:359-71. doi: 10.1038/s41416-019-0510-x

7. Nemerson Y. Tissue factor and hemostasis. *Blood* 1988;71:1-8.

8. Haas SL, Jesnowski R, Steiner M, et al. Expression of tissue factor in pancreatic

adenocarcinoma is associated with activation of coagulation. *World J Gastroenterol* 2006;12:4843-9.

9. Khorana AA, Ahrendt SA, Ryan CK, et al. Tissue factor expression, angiogenesis, and thrombosis in pancreatic cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2007;13:2870-5. doi: 10.1158/1078-0432.ccr-06-2351

10. Khorana AA, Francis CW, Menzies KE, et al. Plasma tissue factor may be predictive of venous thromboembolism in pancreatic cancer. *Journal of thrombosis and haemostasis : JTH* 2008;6:1983-5. doi: 10.1111/j.1538-7836.2008.03156.x

11. Wang JG, Geddings JE, Aleman MM, et al. Tumor-derived tissue factor activates coagulation and enhances thrombosis in a mouse xenograft model of human pancreatic cancer. *Blood*;119:5543-52.

12. Tesselaar MET, ROMIJN FPHTM, LINDEN IKVD, et al. Microparticle-associated tissue factor activity: a link between cancer and thrombosis? *Journal of Thrombosis & Haemostasis Jth*;5:520-27.

13. Unruh D, Sagin F, Adam M, et al. Levels of Alternatively Spliced Tissue Factor in the Plasma of Patients with Pancreatic Cancer May Help Predict Aggressive Tumor Phenotype. *Annals of surgical oncology* 2015;22 Suppl 3:S1206-11. doi: 10.1245/s10434-015-4592-2

14. Davila M, Robles-Carrillo L, Unruh D, et al. Microparticle association and heterogeneity of tumor-derived tissue factor in plasma: is it important for

coagulation activation? *Journal of thrombosis and haemostasis : JTH* 2014;12:186-96. doi: 10.1111/jth.12475

15. Bharthuar A, Khorana AA, Hutson A, et al. Circulating microparticle tissue factor, thromboembolism and survival in pancreaticobiliary cancers. *Thrombosis research* 2013;132:180-4. doi: 10.1016/j.thromres.2013.06.026

16. Boone BA, Zenati MS, Rieser C, et al. Risk of Venous Thromboembolism for Patients with Pancreatic Ductal Adenocarcinoma Undergoing Preoperative Chemotherapy Followed by Surgical Resection. *Annals of surgical oncology* 2019;26:1503-11. doi: 10.1245/s10434-018-07148-z

17. Mier-Hicks A, Raj M, Do RK, et al. Incidence, Management, and Implications of Visceral Thrombosis in Pancreatic Ductal Adenocarcinoma. *Clinical colorectal cancer* 2018;17:121-28. doi: 10.1016/j.clcc.2018.01.008

18. Milsom CC, Yu JL, Mackman N, et al. Tissue factor regulation by epidermal growth factor receptor and epithelial-to-mesenchymal transitions: effect on tumor initiation and angiogenesis. *Cancer research* 2008;68:10068-76. doi: 10.1158/0008-5472.can-08-2067

19. Date K, Ettelaie C, Maraveyas A. Tissue factor-bearing microparticles and inflammation: a potential mechanism for the development of venous thromboembolism in cancer. *Journal of thrombosis and haemostasis : JTH* 2017;15:2289-99. doi: 10.1111/jth.13871

20. Hu C, Huang L, Gest C, et al. Opposite regulation by PI3K/Akt and MAPK/ERK pathways of tissue factor expression, cell-associated procoagulant activity and

invasiveness in MDA-MB-231 cells. *Journal of hematology & oncology* 2012;5:16. doi: 10.1186/1756-8722-5-16

21. Chanakira A, Westmark PR, Ong IM, et al. Tissue factor-factor VIIa complex triggers protease activated receptor 2-dependent growth factor release and migration in ovarian cancer. *Gynecologic oncology* 2017;145:167-75. doi: 10.1016/j.ygyno.2017.01.022
22. Chen K, Li Z, Jiang P, et al. Co-expression of CD133, CD44v6 and human tissue factor is associated with metastasis and poor prognosis in pancreatic carcinoma. *Oncology reports* 2014;32:755-63. doi: 10.3892/or.2014.3245
23. Kakkar AK, Lemoine NR, Scully MF, et al. Tissue factor expression correlates with histological grade in human pancreatic cancer. *British Journal of Surgery* 1995;82:1101-04.
24. Nitori N, Ino Y, Nakanishi Y, et al. Prognostic significance of tissue factor in pancreatic ductal adenocarcinoma. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2005;11:2531-9. doi: 10.1158/1078-0432.ccr-04-0866
25. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European journal of epidemiology* 2010;25:603-05.
26. Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;8:16.
27. Duval S, Tweedie R. Trim and fill: a simple funnel-plot–based method of testing

and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56:455-63.

28. Iorio A, Spencer FA, Falavigna M, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. *bmj* 2015;350:h870.

29. Geddings JE, Mackman N. Tumor-derived tissue factor-positive microparticles and venous thrombosis in cancer patients. *Blood* 2013;122:1873-80. doi: 10.1182/blood-2013-04-460139

Authors' contribution

HYL and HC conceived the idea and planned the entire method of undertaking this study. HYL and YY wrote the protocol. YY, QLS, XPC and PZ designed the search strategy and planned the data extraction. DFW, PXT, BHG, XML, TZ, LX, DYX, LG and MEP made contributions in conceiving this research project. All authors revised and approved the final version of the manuscript.

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Competing interest

None declared

Word count

1782

The search strategy in Medline

#1	pancreas [MeSh]
#2	pancreas [Title/Abstract]
#3	pancrea* [Title/Abstract]
#4	#1-3 or
#5	carcinoma [MeSh]
#6	adenocarcinoma [MeSh]
#7	carcinoma, ductal [MeSh]
#8	neoplasms [MeSh]
#9	cancer* [Title/Abstract]
#10	carcin* [Title/Abstract]
#11	neoplas* [Title/Abstract]
#12	tumo* [Title/Abstract]
#13	cyst* [Title/Abstract]
#14	growth* [Title/Abstract]
#15	adenocarcin* [Title/Abstract]
#16	malig* [Title/Abstract]
#17	#5-16 or
#18	thromboplastin [MeSh]
#19	tissue factor [Title/Abstract]
#20	TF expression [Title/Abstract]
#21	TF-positive microparticle [Title/Abstract]
#22	TF-positive MP [Title/Abstract]
#23	TF+MP [Title/Abstract]
#24	TF-bearing microparticle [Title/Abstract]
#25	TF-bearing MP [Title/Abstract]
#26	microparticle-associated [Title/Abstract]
#27	MP-associated [Title/Abstract]
#28	MP TF [Title/Abstract]
#29	TF-positive microvesicle [Title/Abstract]
#30	TF-positive MV [Title/Abstract]
#31	TF+MV [Title/Abstract]
#32	TF-bearing microvesicle [Title/Abstract]
#33	TF-bearing MV [Title/Abstract]
#34	microvesicle-associated [Title/Abstract]
#35	MV-associated [Title/Abstract]
#36	MV TF [Title/Abstract]
#37	CD142 antigens [Title/Abstract]
#38	coagulation factor III [Title/Abstract]
#39	#18-38
#40	#4 and #17 and #39

PRISMA-P 2015 Checklist

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	Page 1, line 1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	Not Applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	Page 3, line 53
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	Page 1, line 3-16
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	Page 18, line 346-351
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	Not Applicable
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	Page 18-19, line 353-363
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	Page 18-19, line 353-363
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	Page 18-19, line 353-363
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	Page 5-6, line 72-105
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	Page 6, line 109-113
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	Page 7-8, line 117-145
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	Page 8, line 146-148
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Page 8-9, line 149-162
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	Page 9, line 164-166
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	Page 9, line 167-172
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	Page 9, line 167-172
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	Page 9-10, line 173-179
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	Page 7-8, line 134-141
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	Page 10, line 180-185
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	Page 10-11, line 186-208
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	Page 10-11, line 186-208
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	Page 10-11, line 186-208
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	Page 10-11, line 186-208
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	Page 11, line 209-212
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	Page 11, line 213-215