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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 patients with pancreatic cancer. 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 TF (MP TF) level between patients who had pancreatic cancer 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 score. The HR and 95% CI of each study will be pooled for survival outcome, and the standardised mean difference (SMD) with 95% CIs 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.

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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 tissue factor measuring methods may exist.
► The findings are potentially subject to publication bias.

cause of death in the USA 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, patients with pancreatic cancer 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 patients with pancreatic cancer are prone to VTE in 1938.[4] Subsequently, the reported incidence of VTE in patients with pancreatic cancer 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

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

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 biological 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 (OS).[9 22–24] Therefore, we hypothesise 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.

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, patients with pancreatic cancer 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: (1) individually report the level of circulating MP TF of patients with VTE and without VTE; or (2) report survival endpoints (including 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 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 online supplementary file 1. 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 (HR, 95% CI) related to TF expression. In addition, methods for statistical analysis, summary statistics and items associated with a risk of bias will also be summarised.

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 V.5.3. The pooled SMD with 95% CIs 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 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 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 use 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 patients with pancreatic cancer 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 individualised diagnosis and treatment of patients with pancreatic cancer. 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.

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