PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prognostic significance of tissue factor in patients with pancreatic cancer: a systematic review protocol
AUTHORS	Li, Haiyuan; Yu, Yang; Shi, Qianling; Chen, Xueping; Zheng, Peng; Wang, Dengfeng; Tao, Pengxian; Gu, Baohong; Li, Xuemei; Zhang, Tao; Xiang, Lin; Xi, Dayong; Gao, Lei; Maswikiti Ewetse, Paul; Chen, Hao

VERSION 1 – REVIEW

REVIEWER	Dr. M. C. Hasselluhn Department of Gastroenterology and Gastrointestinal Oncology, University Medical Center Goettingen, Germany
REVIEW RETURNED	03-Mar-2020

GENERAL COMMENTS	The study protocol of Li et al. focusses on the impact of tissue factor (TF) expression/activity on the clinicopathological features of resected pancreatic cancer patients. This study is of great interest to assess risks of hypercoagulation associated with pancreatic cancer and identify the potential of TF as a prognostic factor in pancreatic cancer patients in a systematic meta-analysis. To improve the study protocol, the following points are suggested: - Limitation: Only a small fraction of patients are eligible for pancreatic cancer resection, thus limiting the number of included individuals. - Data items: In case of inconsistencies of TF expression/activity measurement in the evaluated studies, please include the corresponding method. - Language: Please carefully check for American vs. British spelling in your manuscript. Some passages are highlighted in the uploaded document for your convenience. - It remains unclear whether “different types of TF expression” refers to the different sites (tumor vs. plasma vs. microvesicles) or other proteins of the tissue factor pathway or the expression strength itself. Please elaborate.

REVIEWER	Nigel Mackman University of North Carolina at Chapel Hill
REVIEW RETURNED	17-Mar-2020

GENERAL COMMENTS	The manuscript describes a plan to review papers on tissue factor expression and pancreatic cancer. I see no value publishing this manuscript.

REVIEWER	Paolo Simioni Department of Medicine, University of Padova, Padova, Italy
REVIEW RETURNED	22-Mar-2020

GENERAL COMMENTS	BMJ open-2020-037431 Association of tissue factor expression with prognosis and clinical features in human pancreatic cancer: a systematic review protocol The protocol by Haiyuan Li et el. deals with a systematic review on the association of TF expression and prognosis in pancreatic cancer. The protocol is well written, complete and the idea behind the study is very interesting. However, it is difficult to review studies dealing with TF expression because of the heterogeneity of methods used to measure TF. These are major observations. - It is not clear what did Authors mean in their aim as "clinicopathological features" (see title, abstract, introduction and objectives). As the variable is so heterogeneous (TF expression), the endpoint associated should be clearly identified (VTE, mortality, recurrence) since beginning. The numerous outcomes considered may increase heterogeneity. - TF positive MV are measured by flowcytometry (CD142) or by functional tests (MV activity). Several studies in pancreatic cancer used TF-MV activity. It seems that in the search strategy TF Mv activity is completely missing. - Exposure. Type of MV considered (number – activity) should be clarified - Possible limitations or challenges should be addressed - Bibliography seems not updated. A very recent published review on hypercoagulability and pancreatic cancer is missing (BJC 2019, Campello E. et al. The relationship between pancreatic cancer and hypercoagulability: a comprehensive review on epidemiological and biological issues). - Finally, the topic is probably more suitable for an oncology or hematology / haemostasis journal.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

The study protocol of Li et al. focusses on the impact of tissue factor (TF) expression/activity on the clinicopathological features of resected pancreatic cancer patients. This study is of great interest to assess risks of hypercoagulation associated with pancreatic cancer and identify the potential of TF as a prognostic factor in pancreatic cancer patients in a systematic meta-analysis. To improve the study protocol, the following points are suggested:

Response: thank you for your valuable suggestions and comments. Our paper has been improved greatly by following these comments. Explanation of each revision was presented below.

- Limitation: Only a small fraction of patients are eligible for pancreatic cancer resection, thus limiting the number of included individuals.

Response: thank you for highlighting this limitation of our study. We total agree with you. In the current protocol, we have extended the inclusion criterion of patients--we cancel the limitation of surgery resection and patient will be included as long as they are diagnosed as pancreatic cancer by

pathological examination. At the same time, the exclusion criterion was also slightly revised for this section. Please see the texts marked in the manuscript.

- Data items: In case of inconsistencies of TF expression/activity measurement in the evaluated studies, please include the corresponding method.

Response: thank you for your suggestions. We have provided the specific methods for TF expression or activity measurement in the corresponding section. Please see the section of 'exposure' and 'outcomes'.

- Language: Please carefully check for American vs. British spelling in your manuscript. Some passages are highlighted in the uploaded document for your convenience.

Response: thank you a lot for your careful checking of the language of our manuscript. Now we have re-checked our spelling carefully and the full-texts have received a specialized language editing service by a native editor (the language certificate has been submitted as a supplementary material). Any spelling mistakes, discordance of expression and grammar issues have been corrected.

- It remains unclear whether "different types of TF expression" refers to the different sites (tumor vs. plasma vs. microvesicles) or other proteins of the tissue factor pathway or the expression strength itself. Please elaborate.

Response: we are sorry that our poor expression confused you. With regard to 'different types of TF expression', we originally want to express TF detected from different sites (i.e., tissue, plasma, and microvesicles). We think the previous protocol is not good enough in the study design. Based on the comments from you and other reviewers, we revised somewhere inappropriate in the study design. In the revised version, this review will contain two purposes. First, we will compare the circulating microparticle-associated TF level between pancreatic cancer patients with and without VTE to evaluate the roles of TF on VTE development. Second, we will compare the survival time between patients with different TF expression strength (high and low expression in tumor tissue) to explore the impact of TF expression on patients' survival. Getting these two sections together, we want to clarify the prognostic significance of TF in pancreatic cacner. Of course, corresponding sections related to the previous 'different types of TF expression' are revised accordingly.

Reviewer 2:

The manuscript describes a plan to review papers on tissue factor expression and pancreatic cancer. I see no value publishing this manuscript.

Response: we are sorry that we can't agree with you completely. Our study aims to clarify the association between TF and pancreatic cancer and to explore the prognostic significance of TF in pancreatic cancer patients. This study is a question-based research, and the findings of the study will be helpful for clinical practice. As a part of the project regarding the role of coagulation in cancer, this work obtained supports from several grants, which indicates its considerable research value.

Reviewer 3:

The protocol by Haiyuan Li et el. deals with a systematic review on the association of TF expression and prognosis in pancreatic cancer. The protocol is well written, complete and the idea behind the study is very interesting. However, it is difficult to review studies dealing with TF expression because of the heterogeneity of methods used to measure TF. These are major observations.

Response: thank you for your valuable suggestions and comments. We agree with you that the heterogeneity of methods of measuring TF is a major barrier for this review. In order to improve consistency, we revised the study design to some extent. At present, two questions will be individually solved based on different methods used to measure TF. First, we will compare the plasma circulating microparticle-associated TF (measured by flowcytometry or activity tests) between pancreatic cancer patients with and without VTE to evaluate the roles of TF on VTE development. Second, we will compare the survival time between patients with different TF expression strength (high and low expression in tumor tissue; measuring by immunohistochemistry analysis) to explore the impact of TF expression on patients' survival. In addition, we also provide a more detailed explanations regarding how to process heterogeneity during data analysis. Please see the texts marked red.

- It is not clear what did Authors mean in their aim as "clinicopathological features" (see title, abstract, introduction and objectives). As the variable is so heterogeneous (TF expression), the endpoint associated should be clearly identified (VTE, mortality, recurrence) since beginning. The numerous outcomes considered may increase heterogeneity.

Response: thank you for your valuable suggestions. We total agree with you that numerous outcomes will increase the heterogeneity during data analysis. Thus, we remove the outcomes regarding 'clinicopathological features', and define a more specific outcome for each comparison. In the current protocol, there are two major outcomes, i.e., the MP TF level and the survival time. Explanation for the outcomes can be seen in the section of 'outcomes'.

- TF positive MV are measured by flowcytometry (CD142) or by functional tests (MV activity). Several studies in pancreatic cancer used TF-MV activity. It seems that in the search strategy TF Mv activity is completely missing.

Response: thank you for your comments. It is true that TF MV activity is an important word for searching targeted literatures and its missing will have a great impact on retrieval accuracy and comprehensiveness. Thus, we have supplemented it in the current search strategy, and provide a precise and detailed search strategy of MEDLINE database as an example. Please see the corresponding section marked red of the manuscript and the supplementary file.

- Exposure. Type of MV considered (number – activity) should be clarified

Response: we are sorry that the previous protocol had not clearly illustrate this point. At present, we have elaborated the methods of measuring MV in the section of 'outcomes'--both of flowcytometry and activity tests will be considered. By the way, SMD with 95% CI will be used to pool data from flowcytometry and activity tests, and to test heterogeneity, subgroup analysis based on the same measuring method will be performed.

- Possible limitations or challenges should be addressed

Response: we have supplemented the limitations about this research in the revised manuscript. Please see the texts marked red in the section of 'Discussion'.

- Bibliography seems not updated. A very recent published review on hypercoagulability and pancreatic cancer is missing (BJC 2019, Campello E. et al. The relationship between pancreatic cancer and hypercoagulability: a comprehensive review on epidemiological and biological issues).

Response: thank you for reminding of this reference. Now, we have updated our bibliography and added this reference in our manuscript.

- Finally, the topic is probably more suitable for an oncology or hematology / haemostasis journal.

Response: it is true that the topic of our manuscript is suitable for an oncology or hematology journal, but we think BMJ open is also a suitable journal to publish this paper. As a famous comprehensive journal, BMJ open has a wide readership in medical fields, including oncology and hematology, thus can deep the impact of our paper too. Anyway, thank you for your kind suggestions.

Again, we would like to thank the reviewers for their careful reading of our manuscript and thank all editors' warm work. We have revised the manuscript carefully and believe that the new version is much better than the old one. We hope this meets the requirements for a publication.

VERSION 2 – REVIEW

REVIEWER	Marie C. Hasselluhn University Medical Center Goettingen, Germany
REVIEW RETURNED	20-May-2020

GENERAL COMMENTS	The study protocol of Li et al. has been considerably improved concerning the limitations, methods, and overall clarity. I'd like to thank the authors for their thorough work and recommend this study protocol for publication.

REVIEWER	Paolo Simioni University of Padova, Italy
REVIEW RETURNED	30-May-2020

GENERAL COMMENTS	Authors addressed all the issues raised. I reccommend pubblication.