

Dear Editors,

I thank you for inviting me to contribute free of charge to the special issue on Pancreatic Cancer of the *World Journal of Gastroenterology*.

Please find here enclosed the revised version of my manuscript entitled "The Burden of Venous Thromboembolism in Patients with Pancreatic Cancer" (Manuscript NO.: 63107, Minireviews) and detailed responses to the reviewers. I do thank you and the reviewers for all insightful comments on the paper, as these comments led me to improve the original manuscript.

I have now addressed all concerns accordingly in this revised version of the manuscript.

Detailed responses are given below. The original figure 1 is now provided separately as well as the tables, the signed Conflict-of-Interest Disclosure Form and the Copyright License Agreement.

I hope that the present revised version will now be acceptable for publication in *World Journal of Gastroenterology*. Indeed, I strongly believe that *World Journal of Gastroenterology* will provide the best platform for successful dissemination of this data that I hope will help clinicians and Pancreatic Cancer patients to make informed decisions for the treatment and prophylaxis of VTE.

With my best and sincere regards,

Dr Corinne Frere, corresponding author.

A. Answer to the Editors:

In addition to addressing the concerns of the reviewers the editors request to provide the signed Conflict-of-Interest Disclosure Form, the Copyright License Agreement and the original figure document in PowerPoint format.

We thank the editors for their comments.

The signed Conflict-of-Interest Disclosure Form, the Copyright License Agreement and the original figure 1 in PowerPoint format have been now enclosed in the revision.

B. Answer to Reviewer 1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: This is an excellent review about the burden of venous thromboembolism in pancreatic cancer based on their previous review [Cancers (Basel). 2020 Mar 6;12(3):618. DOI: 10.3390/cancers12030618]. Several points are worth discussing.

How to identify and diagnose the venous thromboembolism early in clinical practice?

We thank reviewer 1 for his comment and we share his concern. Systematic screening of VTE is not recommended in daily clinical practice. However, all PC patients should receive verbal and written information on the risk factors for VTE, as well as on the signs and symptoms of VTE to promote self-diagnosis and reporting of VTE symptoms.

This point is now addressed in the revised version of the manuscript as follows: “Systematic screening of VTE is not recommended in daily clinical practice. However, all PC patients should receive verbal and written information on the risk factors for VTE, as well as on the signs and symptoms of VTE to promote self-diagnosis and reporting of VTE symptoms.”

For patients requiring surgery, is there a screening method before surgery? And how to balance the risk of bleeding and embolism during the perioperative period?

We thank reviewer 1 for his comments. This point is now addressed in the revised version of the manuscript as follows: “The Caprini score is the most widely used tool to assess the risk of VTE in patients undergoing surgery. It has been validated in several types of cancers^[42]. However, this model was unable to identify patients at highest risk for VTE in a retrospective cohort of 426 PC patients undergoing preoperative treatment followed by surgical resection^[43] (...) Extended thromboprophylaxis for 4 weeks postoperatively has been shown to decrease the rate of VTE by approximately 50% in patients undergoing major abdominal surgery and is recommended by all current CPGs. (...) The risks of VTE should be balanced by the competing risk of bleeding. Numerous factors such as advanced or metastatic disease, older age, anemia, thrombocytopenia, renal impairment, liver dysfunction, and concomitant anticancer therapies may potentiate the overall bleeding risk and should be taken into account. The careful evaluation of each individual profile is warranted for overcoming management challenges.”

C. Answer to Reviewer 2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This is a review with clear concepts and I think very usefulness.

We thank reviewer 2 for his constructive evaluation of this work.

D. Answer to Reviewer 3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: I have read with interest the review by Frere C. on the weight of venous thromboembolism in pancreatic cancer patients. The review is sound and data are quite updated. However, in order to add a bit of originality to otherwise already afforded material, I would encourage to add the following items with a small comment:

- Caprini score has been validated in several types of cancers undergoing cancer surgery that might benefit from aggressive preventive strategies, and in its 2013 updated version has exhibited a higher prediction ability (Cronin M, Clin Appl Thromb Hemost 2019).

We thank reviewer 3 for his comment. The CAPRINI score is now discussed in the revised version of the manuscript as follows:

“Major abdominal surgery is also an important risk factor for VTE in PC patients. In an early observational study of 1915 patients with exocrine pancreatic cancer, 127 out of 383 (33.1%) patients requiring pancreatic surgery developed postsurgical VTE^[22]. Similarly, 31 out of 209 (14.8%) patients requiring pancreatic surgery developed postsurgical VTE in a large retrospective study of 1,115 conducted in East Asian population^[27]. (...) The Caprini score is the most widely RAM to assess the risk of VTE in patients undergoing surgery. It has been validated in several types of cancers^[42]. However, this model was unable to identify patients at highest risk for VTE in a retrospective cohort of 426 PC patients undergoing preoperative treatment followed by surgical resection^[43.]”

- TicOnco score (Muñoz Martín AJ, Br J Cancer 2018) evidencing that patients suffering from pancreatic cancer experienced VTE at a significantly higher frequency (40%) than patients with other type of cancers. The setting of pancreatic cancer has a major impact on the accuracy of the TicOnco score, that, however, has not been externally validated.

We thank reviewer 3 for his comment. The Tic-OnCo score is now discussed in the revised version of the manuscript as follows:

“Incorporation of genomic data into RAMs represents an important step forward to improve VTE risk prediction. The clinical-genetic Thrombo inCode-Oncology (TiC-Onco) score was developed in a prospective cohort of 391 ambulatory patients with various cancers initiating systemic chemotherapy, including 72 (18.5%) patients with PC^[48]. Seventy-one out of 391 (18%) patients developed VTE within 6 months. The prespecified variable selection process selected both clinical variables (tumor site, family history of VTE, BMI \geq 25 kg/m²) and genetic variables (germline polymorphisms in the *F5*, *F13* and *SERPINA10* genes) for inclusion in the score. In the derivation cohort, the TiC-Onco score performed better than the Khorana score in predicting VTE at 6 months (AUC 0.73 versus 0.58, sensitivity 49 versus 22%, specificity 81 versus 82%, positive predictive value 37 versus 22%, and negative predictive value 88 versus 82%)^[48]. Importantly, patients suffering from PC had higher rates of VTE (40%) than patients with other type of cancers (18%), suggesting that PC has a major impact on the accuracy of the TiC-Onco score. However, this model has not yet been externally validated in a cohort of PC patients.”

- CATS/MICA score (Pabinger I, Lancet Haematol 2018) that utilizes only two variables: type of cancer and a continuous scale of D-dimer levels of the latter for different types of cancers (8% pancreatic cancer). It could represent both an advantage and a drawback.

We thank reviewer 3 for his comment. The CATS/MICA score is now discussed in the revised version of the manuscript as follows:

“The CATS/MICA score was developed in the prospective Vienna Cancer and Thrombosis Study (CATS) cohort of 1,423 ambulatory patients with various cancers undergoing chemotherapy, including 118 (8%) patients with PC^[49]. During a median follow-up of 6 months, 80 out of 1,423 patients (6%) developed VTE. The prespecified variable selection process selected 2 variables for inclusion in the score, namely: tumour-site risk category (very high *versus* high and high *versus* low or intermediate) and continuous D-dimer levels. The C-index of the model was 0.66 (95% CI 0.63–0.67) compared to 0.61 (95% CI 0.51-0.70) for the Khorana score^[49]. The score was then validated in the prospective Multinational Cohort Study to Identify Cancer Patients at High Risk of Venous Thromboembolism (MICA) cohort (n=832), including 116 (14%) patients with PC^[49]. Using this RAM, all PC patients are classified at intermediate or high risk of VTE. Of note, the CATS/MICA score has not yet been externally validated in a cohort of PC patients.”

- The role of Artificial Intelligence using Machine Learning approaches for VTE risk prediction (e.g. Ferroni P, Dis. Markers 2017; Fresard ME, J Biomed Health Inform. 2020) could also be commented upon.

We thank reviewer 3 for his relevant comment. Machine learning (ML) methods are now discussed in the revised version of the manuscript as follows:

“Finally, machine learning (ML) methods are increasingly used for the development of prediction models. Two recent studies conducted in various cancer patients^[50] or in ovarian cancer patients^[51] have demonstrated that such models could improve the prediction of VTE compared to conventional methods. Whether complex models based on ML-driven approaches will allow us to significantly refine VTE risk prediction in PC patients in the near future deserves further studies.”

Finally, I would suggest not to overindulge in self citation of the BACAP-VTE study, if not otherwise strictly required, but to simply cite it among the other references. Overall, I find the review well written.

We thank reviewer 3 for his comments. Some sentences referring to the BACAP-VTE study have been deleted.

E. Answer to Reviewer 4:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: It is a very interesting review, very well written, with actualized data. I agree is an unrecognized complication in pancreatic cancer, and in others too and there is no much published on this subject. English is not native but is good.

We thank reviewer 4 for his constructive evaluation of this work.

F. Answer to Reviewer 5:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The article describes in detail and references are comprehensive. It is of great guiding value for the treatment of such patients. The language description is appropriate.

We thank reviewer 5 for his constructive evaluation of this work.

G. Answer to Reviewer 6:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This is an excellent review article which highlights the major risk of VTE in PC patients. This is an important and under recognised issue. The manuscript is very well set out, clearly identifying the problem and the providing guidance. This article summarises the data around VTE and is necessary to help PC patients to better outcomes.

We thank reviewer 6 for his constructive evaluation of this work.