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Title: Characterisation and risk assessment of venous thromboembolism in gastrointestinal cancers

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Reviewer code: 00613748 and 00003940

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File – Peer review response

Dear Sir/Madam,

Many thanks for the helpful comments from peer review. We were delighted overall with the comments of the reviewers and were pleased that both reviewers felt that the paper was 'Good' or 'Very good', that it should be for 'Priority publishing' and that only minor revision was required. The points made by the reviewers were also very useful and we have addressed the points made within the manuscript and our specific answers to the points raised are included below.

Reviewer number 00003940

We thank the reviewer for their thoughts and recommendations on our manuscript. 2 points were highlighted that have been addressed as follows:

- 1) The diagnosis of VTE that is dependent on scrutinising the electronic records. This is partly resolved when the CT scan report is scrutinised and finds asymptomatic cases but the fact that there were cases that were only identified by CT scan makes me concerned that the diagnosis of VTE is imprecise which results in a poor relationship between VTE and survival.

This is an important point which must be considered when interpreting data presented in this manuscript and we thank the reviewer for raising it. In order to answer this point the following sentence has been added to the discussion in the manuscript (Page 17 Paragraph 3):

- Another limitation of the approach to retrospective data collection undertaken in this study and other studies of this type is that we cannot guarantee that all thrombotic events were identified and the actual number may be underestimated. However, the approach to evaluation of both the clinical records and imaging assessments will mitigate this effect. However, the clinical heterogeneity between symptomatic and incidental VTE may impact on the relationship between VTE and survival. Future studies may require the use of an analytical strategy to account for this variation.

- 2) VTE may indicate a process where plasminogen activators are released into the circulation and the data presented may dispute this.

The following paragraph has been included in the introduction to discuss these mechanisms (Page 6 Paragraph 2):

- In addition to the classical Virchow's triad of venous stasis, thrombophilia and endothelial injury, increased incidence of VTE in cancer patients has been linked to platelet activation, direct factor X activation, decreased hepatic anticoagulant synthesis, reduced hepatic clearance of coagulation factors, and the development of antiphospholipid antibodies

Reviewer number 00613748

We thank the reviewer for taking the time to review our paper and provide some detailed thoughts for us to consider. The points raised are separated below and the additions to the manuscript are included:

- 1) This study illustrates the fact that moving from a general to a particular application of a predictive score may be tricky. The original Khorana score was developed in a large cohort of cancer patients, and was not intended to be used in a particular site-restricted cancer population. This data suggests that whereas in CANCER patients in general, the score might perform reasonably well, when applied to a specific site this might not be the case and thus, validation studies in SITE SPECIFIC cancer groups is needed.

To address this point, the following sentences have been added to the discussion acknowledging the difficulty in interpreting the data (Page 19 Paragraph 1).

- This study also highlights the difficulty of taking a score made for general application and using it in a particular patient group. The Khorana score was not developed to be applied to specific cancer sites but rather cancer patients as a whole. The fact that the Khorana score did not perform as well in colorectal cancer patients specifically suggests that further validation studies in site-specific cancer groups may be needed.

- 2) VTE found incidentally on CT scan raises the possibility of survival bias in this and other similar studies. In addition, few if any studies have used an analytical strategy accounting for competing risks.

In response to this, the following paragraph has been added to the discussion (Page 17 Paragraph 3):

- Another limitation of the approach to retrospective data collection undertaken in this study and other studies of this type is that we cannot guarantee that all thrombotic events were identified and the actual number may be underestimated. However, the approach to evaluation of both the clinical records and imaging assessments will mitigate this effect. However, the clinical heterogeneity between symptomatic and incidental VTE may impact on the relationship between VTE and survival. Future studies may require the use of an analytical strategy to account for this variation.

3) Please better describe in the methodology the nested case-control study described in the results.

The following changes have been made to address this issue:

The following sentences have been included in the methods (Page 10 Paragraph 3):

- To evaluate for the impact of VTE on patient survival, a control cohort matched for primary site, stage of disease and performance status was identified in whom no VTE was diagnosed in the patient lifetime.

The following has been added to the methods section (Page 11 Paragraph 1).

- Clinical records were also reviewed to identify additional risk factors for VTE in this cohort in order to establish whether the Khorana score could be modified or used alongside the Khorana score to more accurately identify high risk patients.

Some paragraphs have also been re-ordered in the methods section to present the data in a more appropriate way (Page 10 Paragraph 3 and Page 11 Paragraph 1).

4) Agreement with the limitations of the Khorana score regarding the short follow-up time.

We thank the reviewer for their comment and are pleased that they agree with the limitations of the Khorana score that we have described in the manuscript.

- 5) The inclusion of upper limb and splanchnic thromboses were not included in the original score which may be accounted for by running a sensitivity analysis excluding such events. Whereas splanchnic thromboses were relatively rare, upper thromboses are very frequently associated to the presence of indwelling catheters, rather than to the tumour biology or other factors.

This is a very important point and one that we have considered when completing the data analysis. The reviewer rightly points out that patients with upper limb thromboses were not included in the original Khorana score, and this is a limitation on the applicability of the results of the study to the Khorana score. The following paragraph has therefore been added to the discussion to highlight this (Page 19 Paragraph 2):

- Upper limb thromboses have been included in our results, something which differs from the original Khorana study. Although upper limb thromboses are strongly associated with indwelling catheters in general, the pro-thrombotic nature of cancer patients may be expected to make these events more frequent in this cohort of patients. Including these patients in the data analysis has allowed us to obtain a complete picture of the clinical burden of VTE in relation to cancer. Overall, the indwelling catheter-associated thromboses represent a small proportion of the overall events in this cohort. However, looking into the incidence of indwelling-catheter associated thromboses in colorectal cancer patients as compared to the general population would present an interesting future study.

In addition, as the longer follow up in this study was not used in the development of the Khorana score, the following sentence has been added to the results and discussion section (page 12, paragraph 2):

- Consistent with previous approaches a limitation of this approach is an inherent underestimation of the association between VTE and reduced survival.

Page 17 paragraph 2:

- As VTE may occur after cancer diagnosis, patients with shorter survival are less likely to develop a VTE. This represents an inherent bias underestimating the association between VTE and worse prognosis.

We thank the reviewers for their comments which we feel have overall improved this manuscript.

Many thanks for your consideration

Dr Eamon Al-Hadithi

On behalf of the submitting authors