PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk and timing of venous thromboembolism in gastrointestinal cancer patients: A nationwide Danish cohort study
AUTHORS	Tønnesen, Jacob; Pallisgaard, Jannik; Rasmussen, Peter; Ruwald, Martin; Lamberts, Morten; Nouhravesh, Nina; Strange, Jarl; Gislason, Gunnar; Hansen, Morten Lock

VERSION 1 – REVIEW

REVIEWER	Horvath-Puho, Erzsebet Aarhus Universitetshospital
REVIEW RETURNED	12-May-2022

GENERAL COMMENTS	The manuscript by Jacob Tønnesen et al. reports the results of a retrospective cohort study of patients with first-time gastrointestinal cancer diagnosis using Danish registry data (n = 87,069, study period: 2008-2018). The study has multiple aims: 1) to assess the 1-year VTE risk in gastrointestinal cancers; 2) to investigate potential clinical risk factors; 3) to assess overall mortality and 30-days mortality after VTE in patients with GI cancer; and 4) to describe oral anticoagulant therapy during follow-up. A few major questions arise regarding the research questions and methods when reviewing the manuscript. Major concerns: - The study raises many important research questions related to thrombogenicity of GI cancer patients. However, each objective (VTE incidence, risk factor analyses, mortality after VTE, assessment of anticoagulation therapy) would require a more detailed analytic plan and modelling, and probably also different study designs. In the absence of those steps, it is hard to justify the conclusions by the results. - For example, a multivariable prediction model would be needed to assess risk factors of VTE in patients with GI cancer (including data on cancer stage, cancer treatment, comorbidities, VTE history, age, sex, etc.). - As described in Table 2 and as the authors mention in the Discussion section, death is a strong competing event for all analyzed outcome events (according to Table 2, mortality varies between 21% and 70% in different GI cancer types). This might bias the results if not properly handled. - p-values estimated from logistic regression models are presented and conclusion on risk factors are based on those estimates. In accordance with current reporting guidelines for observational studies and thinking in modern epidemiology, it is not recommended to rely on significance testing when interpreting the results and making further decisions. Please see Von Elm, Erik, et al. "The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting

	observational studies." PLoS medicine 4.10 (2007): e296 and Wasserstein, R. L. and N. A. Lazar (2016). "The ASA's Statement on p-Values: Context, Process, and Purpose." American Statistician 70(2): 129-131. I would suggest calculating and reporting 95% confidence intervals instead of p-values (for both cumulative incidences and odds ratios). - The manuscript would benefit from a more detailed description of the performed statistical analyses (who were included in the risk analyses, which factors were included in the regression model, how was death treated in the different analyses). - The authors concluded that thrombogenicity differed by GI cancer type. There are additional papers describing the VTE incidence in GI cancer. For example, a Danish paper published in 2021 has reported the 1-year incidence of VTE in most of the presented cancer types (Mulder, Blood. 2021 Apr 8;137(14):1959-1969.) - According to the authors, the VTE risk decreases among those with age over 80 years. This conclusion seems to be based on p-values and it seems to be affected by the competing risk of death. Minor comments: - METHODS: o Page 5, Line 8: Were only patients born in Denmark included in the study? If not, needs to be added: “assigned a unique civil registration number (CPR) at birth or upon immigration”. o Page 5, Line 32: It is not clear who was the study population. “Study population includes first-time cancer diagnoses”, however prior cancer is mentioned under “Comorbidities and medications”. o Page 5, Line 44: According to methods, the primary outcome was first incident VTE event. Were cancer patients with prior VTE excluded from the “risk of VTE” analyses? o Authors might consider estimating separately the risk pf pulmonary embolism and deep venous thrombosis after GI cancer. - RESULTS o Page 7, line 29: do all the patients have complete follow-up? What about mortality, emigration? o Page 8, Table 1: at which time point were comorbidities and medications measured? o Page 8, Line 10: it is unclear what do the authors mean by “Figure 2 shows that the incidence of VTE was highest in the initial period after index GI cancer diagnosis”. o Page 8, Line 11: it is important to present (in text or figure) the confidence intervals of the cumulative VTE incidence estimates (and overall and in subgroup analyses). In addition, a cumulative mortality curve of patients with GI cancer would help the understanding of the results. - TABLES and SUPPLEMENT o Page 21, Line 41: Cancer type - and age-stratified analyses need to be added to the STROKBE checklist. o Page 25: Figure 3 is very informative, and the manuscript should focus on these results.

REVIEWER	Ando, Katsuyoshi Asahikawa Medical University
REVIEW RETURNED	16-May-2022

GENERAL COMMENTS	Thank you for giving me the opportunity of reviewing your manuscript. This paper is a retrospective, nation-wide observational cohort which demonstrate high incidence of venous thromboembolism (VTE) in gastrointestinal cancer (especially in pancreatic and gallbladder cancer), the timing and risk factors of developing VTE and a high one-year mortality and 30 days mortality after VTE. Additionally, the frequency of induction of oral anticoagulants (OAC) have been demonstrated to differ among types of gastrointestinal cancer. This study is suggested to be valuable because of high quality real-world data using nation-wide registries. However, several issues are concerned. Major Revision 1. In the conclusion section of abstract, the authors concluded that there was a high 1-year and '30 days after post VTE mortality'. However, no description regarding 'the 30 days post VTE mortality' was referred in the results section of abstract. The conclusion in abstract should be induced based on the description in the results of the abstract. 2. In this cohort, the staging and treatment of the cancer were not included in the baseline characteristics. It is presumed that the proportion of the patients with advanced stage (distant metastasis), treated with chemotherapy and surgery and with indwelling of central venous catheter (CVC) is differ depending on the types of gastrointestinal cancer. The advanced stage, chemotherapy, surgery and CVC are generally regarded as the high-risk group of cancer-VTE. Additionally, the proportion of early stage in colorectal cancer is more likely to be relatively higher in comparison to that in the pancreatic and gallbladder cancer. Therefore, the incidence of VTE in colorectal cancer might be underestimated. 3. In the Table 2, the authors should explain what the percentage of mortality in 1-year incidence and 30-days mortality after VTE is calculated to. 4. The data of the mortality shown in this study have not fully demonstrated whether VTE with gastrointestinal cancer affect the prognosis or not. One-year mortality in patients with or without VTE in gastrointestinal cancer is recommended to be examined. 5. In this study, the proportion of OAC treatment initiation within 30 days after VTE differed among types of gastrointestinal cancer (11.9 % in pancreatic cancer and 44.0% in colorectal cancer). Generally, the risk of major gastrointestinal bleeding originating from tumor was suggested to be higher in cancer in gastrointestinal tract (esophagus, stomach, small intestine and colorectum) than that in liver, gallbladder and pancreas. How do the authors consider this discrepancy?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

The manuscript by Jacob Tønnesen et al. reports the results of a retrospective cohort study of patients with first-time gastrointestinal cancer diagnosis using Danish registry data (n = 87,069, study period: 2008-2018). The study has multiple aims: 1) to assess the 1-year VTE risk in gastrointestinal cancers; 2) to investigate potential clinical risk factors; 3) to assess overall

mortality and 30-days mortality after VTE in patients with GI cancer; and 4) to describe oral anticoagulant therapy during follow-up. A few major questions arise regarding the research questions and methods when reviewing the manuscript.
Major concerns:

- **The study raises many important research questions related to thrombogenicity of GI cancer patients. However, each objective (VTE incidence, risk factor analyses, mortality after VTE, assessment of anticoagulation therapy) would require a more detailed analytic plan and modelling, and probably also different study designs. In the absence of those steps, it is hard to justify the conclusions by the results.**

- **For example, a multivariable prediction model would be needed to assess risk factors of VTE in patients with GI cancer (including data on cancer stage, cancer treatment, comorbidities, VTE history, age, sex, etc.).**

Authors response: We would like to thank the reviewer for the time invested in reviewing our manuscript and the qualified comments and considerations.

After reviewing our study, we completely agree that the study design needed changing, and the aim of the study needed to be refocused. Therefore, we decided to solely focus on the 1-year VTE risk in gastrointestinal cancers, the timing thereof, to investigate potential clinical risk factors impacting the 1-year VTE risk, and the mortality.

Further, we have decided to exclude logistic regression analyses from the revised manuscript. Instead, we have implemented a multivariate Cox Proportionel-Hazards model to evaluate the risk factors contributing to the 1-year risk of VTE. In the analyses we have included important clinical risk factors and we believe that the analyses are very robust. Though, our registries do not contain valid information on cancer staging and treatment – this information has been added to our limitation section.

The analysis plan now reads:

Statistical analysis
Descriptive tables and charts were employed to describe the study population (first hospital contact due to GI-cancer) and categorical variables summarized with counts and percentages.
The timing of the VTE incidence was estimated using the Aalen-Johansen estimator, taking the competing risk of death and emigration into account, and depicted graphically. Further, the cumulative incidence was investigated at certain time-points and reported.
The 1-year incidence of VTE was estimated and stratified by GI cancer groups and age groups using the Aalen-Johansen estimator and presented graphically and by counts and percentages with corresponding 95% confidence intervals (95% CI).
Risk factors for the primary outcome were examined using multivariate survival analysis by Cox Proportional-Hazards models, presented as hazard ratios (HR) with corresponding 95% confidence

intervals (95% CI). The risk factors included in the analysis were sex, age, a history of VTE, heart failure, peripheral vascular disease, COPD, CKD, diabetes, and hypertension. Mortality was high in this patient category but use of the Cox model enabled censoring. Further, patients that emigrated were censored. Assumptions for proportionality and linearity were tested and verified.
The incident 1-year mortality was investigated and presented as counts and percentages. The impact of a VTE event on mortality was examined using Cox Proportional-Hazards models, using the exposure group as time dependent covariates. The models allowed patient-switching regarding exposure groups. The Cox model was multivariate and adjusted for sex, age, a history of VTE, heart failure, peripheral vascular disease, COPD, CKD, diabetes, and hypertension.

- **As described in Table 2 and as the authors mention in the Discussion section, death is a strong competing event for all analyzed outcome events (according to Table 2, mortality varies between 21% and 70% in different GI cancer types). This might bias the results if not properly handled.**

Authors response: We absolutely acknowledge the reviewers point and agree that mortality is a strong competing event the analyses. In the revised manuscript we therefore have changed our analysis to Cox modelling, enabling censoring of death. Further, when depicting our cumulative incidence we use the Aalen Johansen estimator, taking death as competing risk into account.

- **p-values estimated from logistic regression models are presented and conclusion on risk factors are based on those estimates. In accordance with current reporting guidelines for observational studies and thinking in modern epidemiology, it is not recommended to rely on significance testing when interpreting the results and making further decisions. Please see Von Elm, Erik, et al. "The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies." PLoS medicine 4.10 (2007): e296 and Wasserstein, R. L. and N. A. Lazar (2016). "The ASA's Statement on p-Values: Context, Process, and Purpose." American Statistician 70(2): 129-131. I would suggest calculating and reporting 95% confidence intervals instead of p-values (for both cumulative incidences and odds ratios).**

Authors response: Thank you for pointing this important issue out. We absolutely agree with the reviewer on this matter. In the revised manuscript 95% confidence intervals have been applied instead of p-values both for cumulative incidences (%) and hazard ratios (HR).

- **The manuscript would benefit from a more detailed description of the performed statistical analyses (who were included in the risk analyses, which factors were included in the regression model, how was death treated in the different analyses).**

Authors response: Thank you for the comment. We have elaborated on the statistical analyses performed and the level of detail in the variable definitions has generally been improved in the revised manuscript.

The analysis plan now reads:

Statistical analysis

Descriptive tables and charts were employed to describe the study population (first hospital contact due to GI-cancer) and categorical variables summarized with counts and percentages.

The timing of the VTE incidence was estimated using the Aalen-Johansen estimator, taking the competing risk of death and emigration into account, and depicted graphically. Further, the cumulative incidence was investigated at certain time-points and reported.

The 1-year incidence of VTE was estimated and stratified by GI cancer groups and age groups using the Aalen-Johansen estimator and presented graphically and by counts and percentages with corresponding 95% confidence intervals (95% CI).

Risk factors for the primary outcome were examined using multivariate survival analysis by Cox Proportional-Hazards models, presented as hazard ratios (HR) with corresponding 95% confidence intervals (95% CI). The risk factors included in the analysis were sex, age, a history of VTE, heart failure, peripheral vascular disease, COPD, CKD, diabetes, and hypertension. Mortality was high in this patient category but use of the Cox model enabled censoring. Further, patients that emigrated were censored. Assumptions for proportionality and linearity were tested and verified.

The incident 1-year mortality was investigated and presented as counts and percentages. The impact of a VTE event on mortality was examined using Cox Proportional-Hazards models, using the exposure group as time dependent covariates. The models allowed patient-switching regarding exposure groups. The Cox model was multivariate and adjusted for sex, age, a history of VTE, heart failure, peripheral vascular disease, COPD, CKD, diabetes, and hypertension.

- **The authors concluded that thrombogenicity differed by GI cancer type. There are additional papers describing the VTE incidence in GI cancer. For example, a Danish paper published in 2021 has reported the 1-year incidence of VTE in most of the presented cancer types (Mulder, Blood. 2021 Apr 8;137(14):1959-1969.)**

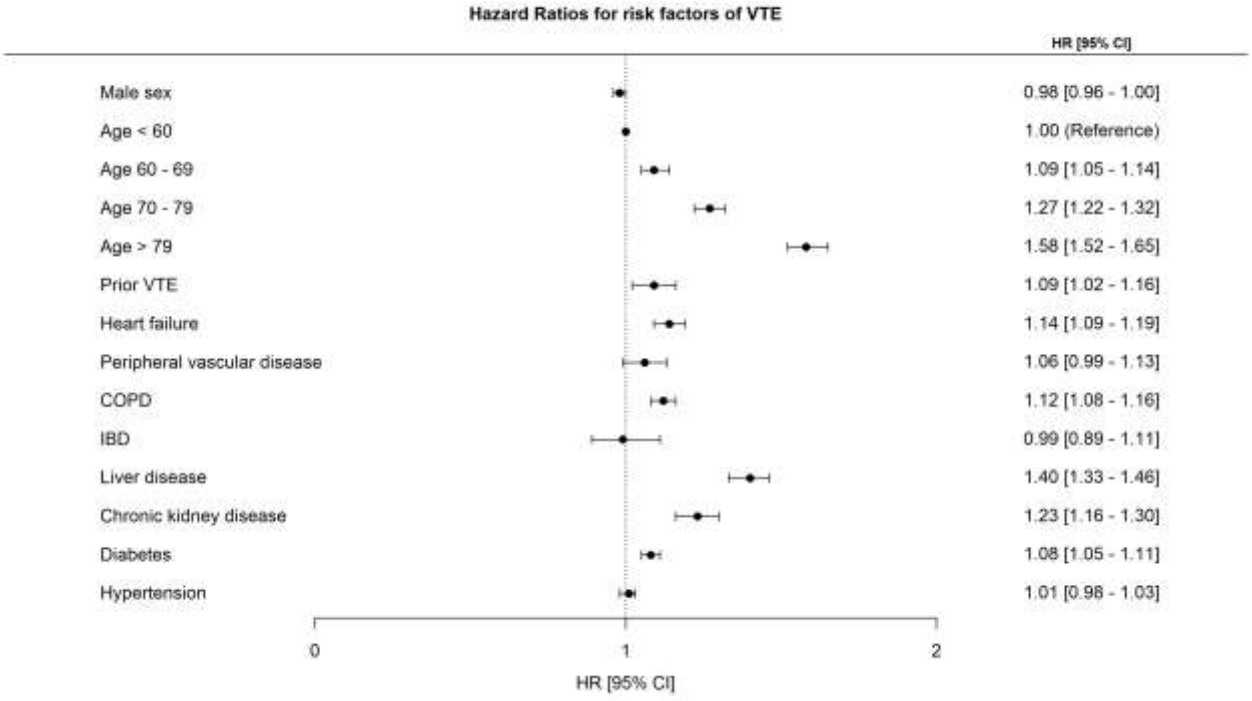
Authors response: Thank you for pointing this out to us. From a clinical point of view, we believe that

our study is important and justified due to our focus on GI cancers only. Further, we also examine the timing of VTE after a GI cancer diagnosis demonstrating a high risk in the initial period thereafter. Further, our focus on comorbidities as risk factors potentially enables better patient care when faced with newly diagnosed GI cancer patients.

- **According to the authors, the VTE risk decreases among those with age over 80 years. This conclusion seems to be based on p-values and it seems to be affected by the competing risk of death.**

Authors response: We naturally agree with the reviewer, and we have removed this section in the revised manuscript. Further, we have included age as a stratified variable in the Cox proportional hazard model and now correctly find that the HR increase in older patients.

The results on page 22 now reads:



Minor comments:

- **METHODS:**

o Page 5, Line 8: Were only patients born in Denmark included in the study? If not, needs to be added: "assigned a unique civil registration number (CPR) at birth or upon immigration".

Authors response: *Thank you for pointing this out. "upon immigration" has been added in the revised manuscript.*

The line 3-4, page 4 now reads:
This study was a retrospective, observational, cohort study. In Denmark, every citizen is assigned a unique civil registration number (CPR) at birth or upon immigration[6].

- **Page 5, Line 32: It is not clear who was the study population. "Study population includes first-time cancer diagnoses", however prior cancer is mentioned under "Comorbidities and medications".**

Authors response: Thank you for the comment. *We have specified that the study population included first-time GI cancer diagnosis and clarified that non-GI cancers were included as comorbidities.*

The line 31-33, page 4 now reads:
Relevant comorbidities; prior VTE, chronic obstructive pulmonary disease, chronic kidney disease, heart failure, ischemic heart disease, atrial fibrillation, and prior non-GI cancer were identified five years prior to first GI cancer date using The Danish National Patient Registry.

- **Page 5, Line 44: According to methods, the primary outcome was first incident VTE event. Were cancer patients with prior VTE excluded from the "risk of VTE" analyses?**

Authors response: *The patients with prior VTE were not excluded from the risk of VTE analysis. From a clinical point of view, we wanted the population to be representative of a realistic GI cancer population.*

- **Authors might consider estimating separately the risk pf pulmonary embolism and deep venous thrombosis after GI cancer.**

Authors response: *Thank you for this very important input. In our group this has been debated vigorously due to the difference in severity in attaining a deep venous thrombosis (DVT) or a pulmonary embolism. We decided though, to keep the diagnosis as an entity as we feel it is one disease. Further, attaining a DVT, as you know, increase the risk of a pulmonary embolism. Lastly, we feel it is debatable whether it is possible to get a pulmonary embolism without a preceding DVT.*

- RESULTS

- **Page 7, line 29: do all the patients have complete follow-up? What about mortality, emigration?**

Authors response: Thank for you for the comment. Data on follow-up has been *clarified in the Methods section.*

The line 20-21, page 5 now reads:
Mortality was high in this patient category but use of the Cox model enabled censoring. Further, patients that emigrated were censored.

- **Page 8, Table 1: at which time point were comorbidities and medications measured?**

Authors response: Time points for measured comorbidities and medication were 5 years and 6 months, respectively. For further clarification we have added to the comorbidities and medications section in the revised manuscript.

The line 31-3, page 4-5 now reads:
Relevant comorbidities; prior VTE, chronic obstructive pulmonary disease, chronic kidney disease, heart failure, ischemic heart disease, atrial fibrillation, and prior non-GI cancer were identified five years prior to first GI cancer date using The Danish National Patient Registry. Relevant medications included oral steroids, antipsychotics and OAC treatment and were identified 180 days prior to first GI cancer date using The Danish National Prescription Register.

- **Page 8, Line 10: it is unclear what do the authors mean by "Figure 2 shows that the incidence of VTE was highest in the initial period after index GI cancer diagnosis".**

Authors response: Thank you for pointing this unclear statement out. Additional time-marks in our cumulative mortality incidence has been provided in table 2. Additional information has been added to the results segment

The lines 18-20 page 7 now reads:

Table 2 emphasize that most VTE events happen in the initial 120 days; the cumulative incidence of VTE after 120 days compared to 365 days varied from 54 % in esophageal cancer patients to 74 % in pancreatic cancer patients.

- **Page 8, Line 11: it is important to present (in text or figure) the confidence intervals of the cumulative VTE incidence estimates (and overall and in subgroup analyses). In addition, a cumulative mortality curve of patients with GI cancer would help the understanding of the results.**

Authors response: Thank you for this important input. We have added confidence intervals to cumulative VTE incidence estimates as suggested. Further, we have added an additional mortality analysis to underline the impact of a VTE event on mortality.

- TABLES and SUPPLEMENT

- **Page 21, Line 41: Cancer type - and age-stratified analyses need to be added to the**

STROKBE checklist.

Authors response: Thanks for pointing this out. In our revised manuscript Cox proportional hazard analyses demonstrated an association between age strata and VTE risk. No interaction was found between GI cancer type and age strata. Therefore, we excluded figure 4 and supplementary figures S1-S7 from the revised manuscript. In the manuscript, HR for different age strata is illustrated in the forest plot, Figure 4.

- **Page 25: Figure 3 is very informative, and the manuscript should focus on these results.**

Authors response: Thank you for this statement. After the changes we have made, we now feel there is more focus on the VTE risk in different GI cancer types. Though, we believe from a clinician perspective that timing of VTE after GI cancer diagnosis is also very important and that risk estimation at time of diagnosis is very important.

Reviewer: 2

Dr. Katsuyoshi Ando, Asahikawa Medical University

Comments to the Author:

Thank you for giving me the opportunity of reviewing your manuscript. This paper is a retrospective, nation-wide observational cohort which demonstrate high incidence of venous thromboembolism (VTE) in gastrointestinal cancer (especially in pancreatic and gallbladder cancer), the timing and risk factors of developing VTE and a high one-year mortality and 30 days mortality after VTE. Additionally, the frequency of induction of oral anticoagulants (OAC) have been demonstrated to differ among types of gastrointestinal cancer. This study is suggested to be valuable because of high quality real-world data using nation-wide registries. However, several issues are concerned.

Major Revision

1. In the conclusion section of abstract, the authors concluded that there was a high 1-year and '30 days after post VTE mortality'. However, no description regarding 'the 30 days post VTE mortality' was referred in the results section of abstract. The conclusion in abstract should be induced based on the description in the results of the abstract.

We would like to express our appreciation and thank the reviewer for the time invested in reviewing our manuscript and the qualified comments.

Thank you for pointing this out, and we completely agree.

The abstract now reads:

ABSTRACT

Aims: Cancer is a well-known risk factor of venous thromboembolism (VTE). Some cancers are believed to be more thrombogenic than others such as pancreatic and gastric cancers. The purpose of this study was to investigate the characteristics of patients with incident gastrointestinal (GI) cancers and their associated 1-year risk and timing of venous thromboembolic events (VTE) and the 1-year mortality.

Methods: This study was a retrospective cohort study. Through Danish nationwide registries, all patients with first-time gastrointestinal cancer (GI cancer) diagnosis from 2008 until 2018 were identified. Incident VTE events were identified within a 1-year follow-up after GI cancer diagnosis using the Aalen Johansen estimator. The Cox proportional-hazards model was applied to investigate risk factors for VTE events and the impact of VTE on mortality.

Results: A total of 87,069 patients were included of which 5.8% patients were diagnosed with liver cancer, 12.0% with pancreatic cancer, 6.9% with gastric cancer, 1.9% with small intestinal cancer, 61.8% with colorectal cancer, 7.3% with esophageal cancer, and 3% with gallbladder cancer. The cancer groups were relatively similar regarding comorbidities and relevant medicine usage. Most VTE events happened close to onset of the cancer diagnosis with declining events by time. The 1-year cumulative incidence of VTE differed according to cancer type with pancreatic cancer being most thrombogenic (7.8%), and colorectal and liver cancer being the least (3.6%). Prior VTE HR (95%CI) 1.09 (1.02 to 1.16), heart failure 1.14 (1.09 to 1.19), chronic obstructive pulmonary disease (COPD) 1.12 (1.08 to 1.16), liver disease 1.40 (1.33 to 1.46), chronic kidney disease (CKD) 1.23 (1.16 to 1.30), and diabetes (DM) 1.08 (1.05 to 1.11) increased the VTE risk. Overall, the GI cancer patients had high 1-year mortality of 33.3% with pancreatic cancer patients having the highest mortality (70.3%).

Conclusion: We found that most VTE events happen close to onset of the GI cancer diagnosis and thrombogenicity differs by type of GI cancer, ranging from 7.8% in pancreatic cancer patients to 3.6% in colorectal and liver cancer patients. Prior VTE, heart failure, COPD, liver disease, CKD, and DM were associated with increased risk of VTE.

2. In this cohort, the staging and treatment of the cancer were not included in the baseline characteristics. It is presumed that the proportion of the patients with advanced stage (distant metastasis), treated with chemotherapy and surgery and with indwelling of central venous catheter (CVC) is differ depending on the types of gastrointestinal cancer. The advanced stage, chemotherapy, surgery and CVC are generally regarded as the high-risk group of cancer-VTE. Additionally, the proportion of early stage in colorectal cancer is more likely to be relatively higher in comparison to that in the pancreatic and gallbladder cancer. Therefore, the incidence of VTE in colorectal cancer might be underestimated.

Authors response: Thank you for this insightful comment. Unfortunately, our data do not contain valid information on staging and treatment of the cancers. We are aware that this is a limitation and has been added to our limitations-section. We agree that the incidence of VTE might be underestimated in colorectal cancers, but we still feel our results are valid from a clinician's point of view.

3. **In the Table 2, the authors should explain what the percentage of mortality in 1-year incidence and 30-days mortality after VTE is calculated to.**

Authors response: Thank you for pointing this out. This information has been added to the manuscript.

The lines 23-27 page 5 now reads:

The incident 1-year mortality was investigated compared to index date and presented as counts and percentages. The impact of a VTE event on mortality was examined using Cox Proportional-Hazards models, using the exposure group as time dependent covariates. The models allowed patient-switching regarding exposure groups. The Cox model was multivariate and adjusted for sex, age, a history of VTE, heart failure, peripheral vascular disease, COPD, CKD, diabetes, and hypertension.

4. **The data of the mortality shown in this study have not fully demonstrated whether VTE with gastrointestinal cancer affect the prognosis or not. One-year mortality in patients with or without VTE in gastrointestinal cancer is recommended to be examined.**

Authors response: Thank you for this important issue. We have changed our analysis regarding the mortality and the impact of a VTE event as seen in the pasted text in your question 3.

5. **In this study, the proportion of OAC treatment initiation within 30 days after VTE differed among types of gastrointestinal cancer (11.9 % in pancreatic cancer and 44.0% in colorectal cancer). Generally, the risk of major gastrointestinal bleeding originating from tumor was suggested to be higher in cancer in gastrointestinal tract (esophagus, stomach, small intestine and colorectum) than that in liver, gallbladder and pancreas. How do the authors consider this discrepancy?**

Authors response: Thank you for this comment. After revising our manuscript, we decided not to focus on OAC treatment to keep focus on VTE incidence and mortality.

VERSION 2 – REVIEW

REVIEWER	Horvath-Puho, Erzsebet Aarhus Universitetshospital
REVIEW RETURNED	02-Nov-2022

GENERAL COMMENTS	Thank you for giving me the opportunity of reviewing the revised manuscript on “Incidence and timing of venous thromboembolism in gastrointestinal cancer patients: A nationwide Danish cohort study” by Jacob Tønnesen et al. The revised introduction presents the updated focus of the study, namely assessing the 1-year VTE risk in gastrointestinal cancers and investigating potential risk factors which might impact the 1-year VTE risk. To achieve these goals, the authors implemented competing risk analyses using the Aalen-Johansen estimator for risk assessment and Cox proportional hazards regression models to analyze the risk factors. If the main research question relates to prediction, the assessment of the risk factors may benefit from an additional analysis which estimates the subdistribution hazard ratios using e.g. Fine and Gray models (as recommended by Austin et al.: Practical recommendations for reporting Fine-Gray model analyses for competing risk data Statistics in Medicine. 2017;36:4391–4400.).

	Through the manuscript, the term “multivariate survival analysis” needs to be replaced by “multivariable survival analysis” (ref: Hidalgo B, Goodman M. Multivariate or multivariable regression? Am J Public Health. 2013 Jan;103(1):39-40.). Regarding the new regression analyses, the authors state that assumptions for proportionality and linearity were tested and verified. Please add information on which method was used for testing the proportionality assumption. The response letter confirms that patients with prior VTE were not excluded from the analyses. In this case, is it correct to call the analyzed outcome an incident event or would be “risk of VTE” a better description? (e.g. in Title: “Incidence and timing of venous thromboembolism”, Statistical analysis: “1-year incidence of VTE”). The authors added a forest plot (Figure 4) which nicely summarizes the results of Cox proportional-hazards regression. The Results section mentions the effect of prior comorbidities, however the results on age- and sex-variables are not discussed in the manuscript.

REVIEWER	Ando, Katsuyoshi Asahikawa Medical University
REVIEW RETURNED	23-Oct-2022

GENERAL COMMENTS	Thank you for giving me the opportunity of reviewing your revised manuscript. The authors appropriately responded to the reviwers' concerns and thoughtful discussion. Additionally, in accordance with the editor and reviewers' suggestion, the revised manuscript is adequately corrected by focusing on the incidence of VTE as outcome of the study and adding the statistical analysis. Further detailed study regarding mortality and oral anti-coagulation medicine for VTE is hoped to be performed in the future.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Dr. Katsuyoshi Ando, Asahikawa Medical University

Comments to the Author:

Thank you for giving me the opportunity of reviewing your revised manuscript. The authors appropriately responded to the reviwers' concerns and thoughtful discussion. Additionally, in accordance with the editor and reviewers' suggestion, the revised manuscript is adequately corrected by focusing on the incidence of VTE as outcome of the study and adding the statistical analysis. Further detailed study regarding mortality and oral anti-coagulation medicine for VTE is hoped to be performed in the future.

Authors response:

Dear Dr. Katsuyoshi Ando. Thank you very much for your previous comments – they very much improved the manuscript.

Reviewer: 1

Dr. Erzsebet Horvath-Puho, Aarhus Universitetshospital

Comments to the Author:
Thank you for giving me the opportunity of reviewing the revised manuscript on “Incidence and timing of venous thromboembolism in gastrointestinal cancer patients: A nationwide Danish cohort study” by Jacob Tønnesen et al.
The revised introduction presents the updated focus of the study, namely assessing the 1-year VTE risk in gastrointestinal cancers and investigating potential risk factors which might impact the 1-year VTE risk. To achieve these goals, the authors implemented competing risk analyses using the Aalen-Johansen estimator for risk assessment and Cox proportional hazards regression models to analyze the risk factors. If the main research question relates to prediction, the assessment of the risk factors may benefit from an additional analysis which estimates the subdistribution hazard ratios using e.g. Fine and Gray models (as recommended by Austin et al.: Practical recommendations for reporting Fine-Gray model analyses for competing risk data Statistics in Medicine. 2017;36:4391–4400.).
Through the manuscript, the term “multivariate survival analysis” needs to be replaced by “multivariable survival analysis” (ref: Hidalgo B, Goodman M. Multivariate or multivariable regression? Am J Public Health. 2013 Jan;103(1):39-40.).

Authors response:
Dear Dr. Erzsebet Horvath-Puho thank you very much for these corrections and the previous corrections. The manuscript is now much better.

Multivariate has been replaced by multivariable throughout the manuscript. Changes are highlighted in yellow.

Regarding the new regression analyses, the authors state that assumptions for proportionality and linearity were tested and verified. Please add information on which method was used for testing the proportionality assumption.

Authors response:
Thank you for pointing this out. The following has been added to the manuscript:
Assumptions for proportionality were tested and verified with graphical test by visual inspection of log-minus-log plots.

The response letter confirms that patients with prior VTE were not excluded from the analyses. In this case, is it correct to call the analyzed outcome an incident event or would be “risk of VTE” a better description? (e.g. in Title: “Incidence and timing of venous thromboembolism”, Statistical analysis: “1-year incidence of VTE”).

Authors response:
Thank you for this correction. Incidence has been changes to risk in the manuscript, including the title.

The authors added a forest plot (Figure 4) which nicely summarizes the results of Cox proportional-hazards regression. The Results section mentions the effect of prior comorbidities, however the results on age- and sex-variables are not discussed in the manuscript.

Authors response:

Thank you for noticing this. Information on age and sex has been added to the manuscript:

Of significant patient characteristics and comorbidities and their Hazard ratios HR (95%CI), age over 79 years 1.58 (1.52 to 1.65), a history of previous VTE 1.09 (1.02 to 1.16), heart failure 1.14 (1.09 to 1.19), COPD 1.12 (1.08 to 1.16), liver disease 1.40 (1.33 to 1.46), CKD 1.23 (1.16 to 1.30), and DM 1.08 (1.05 to 1.11) were associated with an increased risk of a VTE event (Figure 4). Male sex decreased the risk of an event 0.98 (0.96 to 1.00).