Manuscript ID: 45521

Title: **Effectiveness of Venous Thromboembolism Prophylaxis in Patients with Liver Disease**

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Editor	
Reviewer 1	
Reviewer comments	Response
1. Cirrhosis was previously considered to be a hypo coagulable state and prophylaxis for VTE was felt to be unnecessary or even potentially harmful due to presumed risk of bleeding. This notion has however changed and there is a significant body of literature proving that cirrhotics are at risk for VTE especially PVT and that the risks of chemoprophylaxis may be outweighed by its benefits. Multiple retrospective studies have tried to answer this question however given the variations in size, methodology and populations included in these studies, firm conclusions cannot be arrived at. What this field really needs is standardized, well designed Randomized Controlled trials. Additionally, reports suggest that chemoprophylaxis may slow disease progression and fibrosis in cirrhotics and improve long term outcomes therefore this field is highly relevant.	We thank the reviewer for this comment.
2. Authors present a retrospective study to assess if there is a net clinical benefit of chemoprophylaxis in cirrhotic patients. Being retrospective in nature, the study is prone to certain biases. The authors perform propensity score matching between patients who did or did not receive VTE prophylaxis in order to arrive at a reliable conclusion. VTE and major bleeding were primary (and secondary) end points. Authors observed that chemoprophylaxis did not reduce risk of VTE in cirrhotic patients. Interestingly they observed that the risk of major bleeding was lower in those receiving chemoprophylaxis.	We thank the reviewer for this comment. While we agree that retrospective studies are prone to certain biases (most notably selection bias), we feel that we accounted for these biases in the best manner available to us in a study of this type by performing both propensity score matching and multivariable analysis.
3. When talking about major bleeds, the authors list “critical sites”. There is no mention of GI bleeds. What percentage of patients with bleeding had a GI bleed? What percent of these bleeds were considered to meet criteria for major bleed?	When defining major bleeding events, we used the definition recommended by the *International Society on thrombosis and Haemostasis* for clinical evaluations of antihemostatic agents (reference 14 in our manuscript). This definition does not include bleeding into the gastrointestinal tract. Given that smaller amounts of bleeding into the GI tract are not likely to cause lasting harm, and that larger bleeds would be included in our

	major bleeding definition based on a drop in hemoglobin of 2g/dL or more or the transfusion of 2 or more units of packed red blood cells, we did not feel that adding GI bleeding to the major bleeding definition was necessary. Because of this, rate of GI bleeding specifically was not captured in this study. We felt that development of a venous thromboembolism carried similar clinical consequences to a major bleeding event as we have defined it, so we chose to use these two pieces for our composite primary outcome in an attempt to determine net clinical benefit or harm of providing chemoprophylaxis in this population.
4. The decision to start someone on DVT prophylaxis is usually made by the admitting physician and patients with higher perceived risk of bleeding are usually not given prophylaxis. This can significantly skew the results during retrospective analysis.	We thank the reviewer for this comment. We agree that retrospective studies have the potential for selection bias, and have done our best to minimize this by propensity score matching our populations and by performing multivariable analysis on our primary outcome, as well as on major bleeding events alone. After propensity score matching, major factors that could indicate a higher propensity to bleed (MELD, liver disease etiology, INR, aPTT, platelet count, albumin concentration, etc.) were well balanced between the groups (see absolute standardized differences in Table 6). However, we agree that not all bias can be taken into account with a retrospective study, no matter how well designed and seemingly balanced statistically. Unfortunately, the only remedy for this is to conduct a large-scale, randomized, controlled trial, which is out of the scope of this dataset and our resources at this time.
5. Cirrhosis is a complex state with a fragile balance between the new levels of anticoagulants and procoagulants. While the study compares INR, PT and APTT they have been shown to poor predictor of VTE in cirrhotic patients. Data on genetic coagulation abnormalities for patients with VTE is not available in this study.	We than the reviewer for this comment. We agree that standard measures of coagulation fall short in determining coagulopathy in a cirrhotic patient. We did not include patients with genetic coagulation abnormalities in the study, as all patients with factor V Leiden, anti-phospholipid syndrome, prothrombin G20210A, protein C or S deficiency, prothrombin mutation, or anti-thrombin deficiency were excluded (manuscript page 7). I have included all of the specific thrombophilias that were excluded to further clarify this in the revised manuscript.
6. Please provide breakdown by definitions used to define incident VTE. Additionally, provide the percentages of Portal vs non-portal VTE	We did not collect this data initially as we felt that a VTE in any location carried negative clinical consequences. As this study is closed with the study site IRB, this data cannot be gathered at this time. If it is considered necessary for publication by the editor, the authors would need to re-submit to the IRB to gather this data.
7. Patients presenting with Variceal Hemorrhage were not excluded from the study. Did anyone with variceal hemorrhage receive chemoprophylaxis?	We did not gather the source of bleeding as long as it met our criteria for major bleeding. Similar to the comment about site of VTE, we would not be able to gather this data without an additional IRB

	submission.
8. It is ok to use ICD code for identification of patients with possible cirrhosis. However specific criteria should during medical record review to confirm a diagnosis of cirrhosis. What criteria did the authors use?	The authors did not confirm diagnosis of cirrhosis for multiple reasons. First, the authors felt it would be necessary to include a large patient population given the small difference in rates of VTE and major bleeding noted in previous studies of VTE prophylaxis (1806 patients ultimately included). Because of this, it was not feasible to review imaging or biopsy results for every patient to confirm cirrhosis. However, we feel that the rate of miscoding would likely be low, and that it would likely be evenly distributed between groups. Secondly, as the study site is a major referral center, many patients had a diagnosis of cirrhosis made at other institutions for whom we do not have access to historical records. We did not feel it was appropriate to exclude these patients. Many other retrospective trials have used ICD codes to define a population, and we feel ours is no different (though this is a noted limitation of our study and other studies that use this methodology).
9. Rate of incident VTE and risk of major bleeding are primary and secondary endpoints.	We thank the reviewer for this comment. We included both incident VTE and major bleeding in the composite outcome as we were attempting to define the net clinical benefit or harm experienced by cirrhotic patients when exposed to VTE chemoprophylaxis. However, we were also interested in the effect of chemoprophylaxis on the individual components of the primary outcome, and thus, chose to include them as secondary outcomes.
10. Core tip needs to be revised.	We have revised the Core Tip.
11. What are the novel findings in this study?	While not necessarily novel findings, our study does confirm the findings of several smaller retrospective studies on this topic/population. We also feel that our study does the best job of the currently available retrospective studies of minimizing bias by propensity score matching the groups and performing multivariable analysis. In addition, we found no increase in major bleeding in patients provided chemoprophylaxis (a concern that has previously caused hesitation in some clinicians to provide chemoprophylaxis). These findings are outlined in the discussion section of the manuscript, and will be further outlined in the research summary.
Reviewer 2	
Reviewer comments	Response
1. The core tip should not enumerate authors but should state the central idea and result of the study.	We have revised the Core Tip.
2. Do you see a reasonable explanation why the group with no prophylaxis had an increase in	The authors have no definitive explanation for this finding. While there is some thought that lessening activation of the coagulation cascade

bleeding events?	may prevent hepatic decompensations (Villa E et al. *Gastroenterology.* 2012;143:1253–1260), it is unclear whether providing prophylactic anticoagulation for such a short period during a hospital stay could prevent additional portal hypertension and possibly reduce events like variceal bleeding. Given that speculation on this would be only conjecture at this point, we have chosen to make no conclusion or hypothesis about why patients receiving chemoprophylaxis experienced such a significantly lower rate of bleeding. It is possible that biases for which we could not account explain this result, though we feel that the groups were very well balanced and that any remaining imbalance would likely have been minimized by multivariable analysis.
3. Did you take into account the localization of VTE in the decision of anticoagulation and especially type of anticoagulation?	This study evaluated only prophylactic anticoagulation, and thus, the anticoagulation was provided prior to the development of a VTE.
4. Why did you exclude new oral anticoagulants? They are suitable for patients with liver disease (for example chronic hepatitis) without cirrhosis.	This study specifically focused on VTE prophylaxis, and the novel oral anticoagulants had not been studied extensively for this indication at the time we initiated the study. In addition, betrixaban is not on the hospital formulary at the study site, so NOAC use for traditional VTE prophylaxis (i.e. primary VTE prevention, not following a course of therapeutic anticoagulation in a patient at high risk for recurrence) is exceedingly rare at the study site.
5. The schematic of exclusion/ inclusion criteria should be more extensive.	We thank the reviewer for this comment. The inclusion/exclusion schematic provides the reason for exclusion of every excluded patient, and characteristics of included patients are provided in Table 1. The authors are unsure how this could be made more extensive.
6. I think your work should be completed by a prospective clinical trial assessing indications for prophylactic anticoagulation based on biologic parameters (coagulation times, serum levels proteins C and S), in order to establish a clear recommendation on anticoagulation.	The authors agree that a prospective, randomized clinical trial would be best to answer this question definitively. However, we feel that our study does significantly add to the literature given the effort we undertook to minimize biases inherent to retrospective literature (the only literature type currently available to answer this question), and the large sample size that was included relative to the previous literature.