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August 1, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: WJG 10704 Manuscript August 1 2014 submit.doc). Please note that the manuscript includes both a clean version of the manuscript followed by a version that includes tracked changes.

Title: Colectomy is a Risk Factor for Venous Thromboembolism in Ulcerative Colitis

Author: Gilaad G Kaplan, Allen Lim, Cynthia H. Seow, Gordon W Moran, Subrata Ghosh, Yvette Leung, Jennifer Debruyn, Geoffrey C Nguyen, James Hubbard, and Remo Panaccione.

Name of Journal: *World Journal of Gastroenterology*
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The manuscript has been improved according to the suggestions of the editors and reviewers.

Following this letter is a point-by-point response to the reviewer comments. In Summary, we have made the following changes:

1. We have included disease duration in Table 1.
2. We have revised the limitation of the discussion to acknowledge that we were not able to assess the number of flares since diagnosis and disease severity using a validated disease activity index.
3. Extra-intestinal manifestations of UC were added to Table 1.
4. We have revised the method to explain the rationale for the stepwise selection approach for our multivariate regression analysis and revised Table 3 to explicitly state the variables tested in the model.
5. We have revised the second paragraph of the discussion to address reviewer concerns regarding the clinical presentation of VTE, imaging studies used to assess VTE, and the diagnosis of incidental VTE.
6. We have revised the limitation section of our discussion to acknowledge that we were not able to assess oral contraceptive pills.
7. The proportion of UC patients who underwent an elective colectomy for dysplasia or colorectal cancer was added to Table 1.
8. The “Comments” section has been added to the manuscript.

Thank you again for considering to publish our manuscript in the *World Journal of Gastroenterology.*

Sincerely,

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RESPOSNE TO REVIEWER COMMENTS

REVIEWER #1

This is an excellent original contribution analyzing cohort of 1020 hospitalised UC patients towards risk of VTE. The Authors determined that patients who underwent elective or emergent colectomy had 4-5-fold increased risk of VTE when compared to UC patients treated non-surgically. Comments: 1. It would be worth to include the following clinical variables in Table 1 and in multivariate logistic regression analysis: A) duration of UC since initial diagnosis, B) numbers of UC flares since initial diagnosis, C) clinical disease severity at the time of hospitalization using validated clinical index, D) presence or absence of any extraintestinal manifestations of UC E) history of any prior surgery for UC.

Response: Thank you for your kind assessment of the manuscript. We appreciate your recommendation to include the following clinical variables in Table 1 and multivariate regression model: disease duration; number of flares since the initial diagnosis; clinical disease severity using a validated clinical index; extra-intestinal manifestations; history of prior surgery for UC. We have included disease duration in Table 1. Disease duration was then evaluated in the multivariate regression model as a continuous variable to assess its independent effects on VTE. Using the stepwise selection approach with 0.1 as the entry and exit p-value, disease duration was not found to be a significant variable and thus, it was not kept in the final model.

Unfortunately, due to the retrospective nature of the study we were not able to include all the clinically relevant variables that was likely associated with UC outcomes. Our data extraction was reliant on the accuracy of recording clinical information in the medical chart. The number of flares that occurred between diagnosis and hospital admission was not recorded consistently in the medical charts and thus, we were not able to include in our analysis. Similarly, we were not able to calculate disease severity using a validated clinical index (e.g. Mayo Score or Seo Index). When we reviewed the hospital charts, we realized that the clinical information recorded in the chart was not sufficient to retrospectively assign a score using a disease severity index. In response, we evaluated ‘proxy’ markers of disease severity (e.g. diarrhea and blood in the stool); however, we acknowledge that this approach is inferior to a validated disease index. We have revised the limitation of the discussion to acknowledge that we were not able to assess the number of flares since diagnosis and disease severity using a validated disease activity index.

Extra-intestinal manifestations for IBD were included in our assessment of comorbidities. The comoribidities that we assessed include a combination of extra-intestinal manifestations (e.g. primary sclerosing cholangitis) and conditions that are associated with IBD (e.g. coronary artery disease). Additionally, this list of comorbidities have been previously validated to be associated with UC patients undergoing colectomy (reference – PMID: 22943760). As per your recommendation we have also added to Table 1 to the following extra-intestinal manifestations: primary sclerosing cholangitis, ankylosing spondylitis, sacroileitis, episcleritis, uveitis, and iritis.

For ulcerative colitis patients who underwent colectomy the hospital admission that included their primary colectomy was recorded as the index hospital admission (i.e. no other surgery UC was

performed prior to the index date).

Reviewer Comment:
2. What kind of heparin was used for VTE prophylaxis: Low Molecular Weight Heparin or Unfractionated Heparin? 3. My understanding is that the variables from Table 1 were included in the logistic regression analysis. This information should be clearly stated in the manuscript.

Response: The majority of patients used unfractionated heparin of VTE prophylaxis as this was the standard recommended clinical practice during the time period evaluated. However, patients who used alternative pharmacological VTE prophylaxis therapy (e.g. low molecular weight heparin) were recorded as having undergone VTE prophylaxis. We have clarified this in the methods/discussion.
Our primary exposure, "disease course" (i.e. medically responsive to in-hospital management, emergent colectomy, and elective colectomy), VTE prophylaxis, and age were *a priori* forced into the regression model. The rest of the variables (those listed in Table 1) were subsequently evaluated for independent effects on VTE development using the stepwise selection approach with 0.1 as the entry and exit p-value. This approach allowed us to adjust our model for significant variables (e.g. in-hospital complications) associated with VTE, while optimizing the efficiency of the model - i.e. avoiding overfitting the model with multiple variables in a setting where the sample size of our outcome (i.e. VTE) was 48. We have revised the method to explain the rationale for the stepwise selection approach for our multivariate regression analysis and revised Table 3 to explicitly state the variables tested in the model.

REVIEWER#2
How was the presence of VTE determined? Were there clinical signs or symptoms of VTE that prompted evaluation? How many in each group were incidental VTE? Since sicker patients with UC are more likely to have imaging including abdominal CT for their disease might not this have lead to a higher rate of VTE (i.e. detection bias) compared to those with less severe symptoms where imaging may have been less likely? This is alluded to in the discussion session with regard to post-operative VTE but needs to be accounted for in all groups.

Response: The presence of VTE was determined using standard clinical evaluation that depended on the site of VTE and the clinical presentation. The investigations that were used based on clinical presentation included chest X-ray, D-Dimer, Doppler ultrasound of the extremities, V/Q scan, CT PE protocol, and angiography. Additionally, some cases of VTE were incidentally identified in the abdomen following investigations (U/S with Doppler flow and CT) of the abdomen that were ordered for another reason (e.g. assess an intra-abdominal complication). Incidental cases were primarily identified in postoperative patients following colectomy (11 cases among elective and 10 cases among emergent colectomy). One incidental intra-abdominal VTE was identified in the medically responsive group. Because some cases were identified incidentally, we acknowledge that we may have missed some cases of VTE that were asymptomatic. However, we believe that the proportion of clinically relevant VTE that we missed was low. First, a recent study of inpatient and outpatient

UC patients who were actively flaring, but were asymptomatic for a DVT, were screened for DVT in their extremities using ultrasound. In this study no cases of DVT were identified during screening with ultrasound (reference – PMID: 23429463). Second, we evaluate every case for readmission to hospital for a VTE within 6 months of the discharge from hospital admission. Thus, we were able to capture clinically meaningful cases of VTE that were missed in hospital (or developed post-discharge). Please note that readmission to hospital for VTE post-discharge was assessed in all groups of patients.

We have revised the second paragraph of the discussion to address the concerns you have raised.

Was prior oral contraceptive use considered for women?
Response: Unfortunately, oral contraceptive use was not consistently recorded in the medical charts and thus, we were not able to assess this variable. We have included this limitation in our discussion.

It is important to understand why elective colectomies were done. How many were patients with quiescent disease have colectomy for dysplasia compared to those with active disease who had failed medical therapy (i.e. biologics)? The risk of VTE would be very different in these groups. It appears that 1/2of the elective group did have symptoms of active disease in Table 1.

Response: Thank you for raising this important point. We have assessed the proportion of UC patients who underwent an elective colectomy for dysplasia or colorectal cancer. This variable has been added to Table 1. Among UC patients undergoing an elective colectomy 17% were for dysplasia or cancer whereas the rest (83%) were for medically refractory disease. Dysplasia/cancer was not the indication for colectomy for UC patients undergoing an emergent colectomy.

REVIEWER #3:
This is an excellent paper. Minor revision is needed. What kind of imaging studies did the authors perform in diagnosing VTE? Please describe.
Response: As per our response to Reviewer #2: The presence of VTE was determined using standard clinical evaluation that depended on the site of VTE and the clinical presentation. The investigations that were used based on clinical presentation included chest X-ray, D-Dimer, Doppler ultrasound of the extremities, V/Q scan, CT PE protocol, and angiography. Additionally, some cases of VTE were incidentally identified in the abdomen following investigations (U/S with Doppler flow and CT) of the abdomen that were ordered for another reason (e.g. assess an intra-abdominal complication).

We have revised the manuscript to include this information. Please see the second paragraph of the discussion.