Re: 86206, Observational Study
Risk assessment of venous thromboembolism in inflammatory bowel disease by inherited risk in a population-based incident cohort

Andrzej S Tarnawski, DSc, MD, PhD
Editor-in-Chief
World Journal of Gastroenterology

Dear Dr. Tarnawski,

Thank you for reviewing our above referenced manuscript. We appreciate the conditional acceptance and the questions and comments from the reviewers. As a result, we hope our manuscript is now suitable for publication.

Our point-by-point responses to the comments and suggestions are detailed below. In addition, we updated our analysis based on the latest phenotype information released on 10/07/2022 by the UK Biobank (the previous analysis was based on the release date on 01/05/2022). All major findings remain the same.

Regarding the language quality of the manuscript, we wanted to note that the first author who drafted the manuscript is a native English speaker. Additionally, many of the co-authors are native English speakers. If the reviewers or editorial staff have specific comments regarding the language quality of the manuscript, we are fully committed to addressing them.

Sincerely,

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Point-by-point responses to the comments and suggestions are detailed below:

Reviewer: 1

The authors Rifkin and colleagues have generated rather interesting and novel data emphasising the relative importance of polygenic genetic risk assessment for thromboembolic events in IBD. The study has been very well-written and the data presented in a concise fashion. While the premise of the study is similar to Takeo Naito et al (also quoted as reference 24)'s earlier publication in Gastroenterology 2020, this current study utilises genotyping scoring data from a much larger cohort of thromboembolic cases and validates its scoring model in a very large IBD cohort (8300 patients) extracted from a biobank. Secondly, the authors were able to demonstrate polygenic risk scoring was superior to monogenic risk screening (F5/F2) in risk stratifying the cohort, with a distinct risk difference between the top and bottom deciles of PGS. It is well established that there are limitations in F5 and F2 monogenic mutation risk screening alone : the authors have alluded to this as well, and demonstrated this clearly in their data.

Our response: Thank you for reading our manuscript, your excellent summary, and positive comments.

The authors have mentioned the effects of ancestry and ethnicity briefly in their discussion - it could be discussed in greater detail by the authors that F5/F2 mutations are exceedingly rare in certain populations eg Asian and African populations, and this begets the question whether their polygenic risk screening model would be even more discerning over monogenic (F5/F2)screening in other non-Caucasian populations.

Our response: Your suggestion to elaborate on the difference of *F5*/*F2* mutations between European and non-European populations is excellent. Accordingly, we expanded our discussion to emphasize how PGS could offer advantages over monogenic screening in these non-Caucasian populations **(Page 11)**.

I agree with the authors' statement in their discussion that "additional data for non-European IBD patients is urgently needed" in this regard. As this study was derived from data extraction off a biobank, it is perfectly understandable that major clinical and disease-specific variables (eg disease activity scores, medication use , biologic use,) would not be available for co-analysis. Yet, it has been quite well known IBD disease activity and perhaps medication use eg steroids , have major roles in modulating thromboembolic risk, and it is not clear if these polygenic risk models would be able to better enhance risk-stratification for VTE in these already high-risk patients. While the authors have acknowledged these limitations in their discussion, I would suggest the authors propose a clinical risk-stratification strategy utilising

their proposed PGS scoring. As the authors pointed out, at least compared to cancer patients, IBD patients have a protracted risk of thromboembolic events long after hospital discharge. How do the authors propose using their PGS scoring to risk stratify which patients may require extended-duration thromboembolic prophylaxis for instance ?

Our response: Thank you for this important comment and we appreciate your suggestion to propose a clinical risk-stratification strategy based on our polygenic risk scoring. In fact, we have initiated a study of IBD patients diagnosed and treated at NorthShore University HealthSystem to 1) understand how other major clinical and disease-specific variables are related to the VTE complication, 2) effect of IBD treatment and thromboembolic prophylaxis on VTE rate, and 3) long-term follow-up for VTE after IBD diagnosis. The last aim is feasible for our large community-based healthcare system where most patients are continuously cared in our system. We have added a new paragraph to discuss clinical utility of PGS for personalized thromboprophylaxis in the revised manuscript **(Page 11)**.

In addition, there are already clinical risk scores available for VTE risk - could the authors briefly propose how their PGS scoring could complement these clinical scores ? For instance , if a patient is already deemed high risk for a VTE based on clinical factors, would the PGS scoring influence perhaps choice of drug (steroids vs steroid-sparing agent , type/choice/duration of thromboembolic prophylaxis?)

Our response: Thanks for the thoughtful suggestion. As responded above, we now have an ongoing study at NorthShore University HealthSystem to assess how PGS complements clinical scores for making treatment decisions for IBD and VTE. One unique question is whether bleeding events are more common among IBD patients who have low PGS and are on thromboembolic prophylaxis. These results will be summarized in our upcoming paper.

Reviewer: 2

In a population-based study of genetic risk stratification for VTE by F5/F2 and non-F2F5PGS in a large number of IBD patients, the finding that PGSnonF5/F2 is particularly useful is of interest. 1. The results showed that VTE was similar to that in cancer-bearing patients and developed over time. Previous reports have identified disease activity, hospitalization, and surgery as risk factors for the development of VTE. Please discuss whether the results are consistent with previous reports.

Our response: Thank you for reviewing our manuscript and for your positive comments. Your question on known risk factors of VTE such as disease activity, hospitalization, and surgery is excellent. As acknowledged in our discussion, this is a major limitation of our study. These detailed clinical variables are difficult to obtain in the UKB, a population-based biobank. However, we have initiated a study of IBD patients diagnosed and treated at NorthShore University HealthSystem, a large community-based healthcare system where most patients are continuously cared for in our system. Please see our response above to Reviewer #1 who had a similar recommendation.

2. In Figure 1, the legends of Figs 1.c and d do not seem listed. Please fill in the contents of Fig1a-d in

Our response: Thank you for pointing out this mistake. We have added the figure legends for Fig 1c and Fig 1d.

3. The top 10 quantile of PGSnonF5/F2 was more useful as a risk assessment method than F5/F2. Is it possible to develop a kit for clinical testing in the future?

Our response: Your suggestion to explore the potential development of a clinical testing kit for $PGS_{non F5/F2}$ is excellent. While such an application is supported by the current data and feasible; it necessitates rigorous validation and robust testing before clinical implementation. As such, we are 1) further assessing the clinical validity of the PGS in our large biobank with ~30,000 patients consented for genetic studies, 2) working with a CLIA-certified genetic testing laboratory to assess analytical validity of this PGS, and 3) working with champion physicians in gastroenterology and vascular medicine to develop a clinical workflow for interpretation and personalized care. We will follow the approach described in a recent Nature Medicine paper (Ho L, et al., Development of a clinical polygenic risk score assay and reporting workflow. Nat Med. 2022 May;28(5):1006-1013). The clinical-grade PGS test is expected to be available for patients at NorthShore in the last quarter of this year.

4. Discuss prophylaxis in genetically high-risk cases of VTE.

Our response: This is a great point and is also commented by Reviewer #1. We added a new paragraph in the discussion to hypothesize genetic-based personalized thromboprophylaxis strategy **(Page 11)**.