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Genetic risk stratification of inflammatory bowel disease-associated venous thromboembolism (IBD-VTE): an Asian perspective

Huang JG. Genetic risk stratification of IBD-VTE

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Abstract

The utilisation of polygenic scoring models may enhance the clinician's ability to risk stratify an IBD patient's individual risk for venous thromboembolism and guide the appropriate usage of VTE thromboprophylaxis, yet there is a need to validate such models in ethnically diverse populations.

Key Words: thromboembolism; inflammatory bowel disease; genetic screening; venous thromboembolism; thromboprophylaxis

Core Tip: Polygenic scoring models may determine an IBD patient's actual risk for venous thromboembolism (VTE) with greater accuracy than monogenic screening alone. This may be due to the cumulative effect of multiple pro-thrombotic genetic loci having a greater influence on thrombotic risk, rather than specific genetic mutations. There needs to be cross-validation of such scoring models in ethnically diverse populations as there is significant heterogeneity in the prevalence of genes implicated in

thrombophilia. A composite score combining clinical and polygenic risk factors would further enhance the accuracy in determining one's VTE risk.

<u>TO THE EDITOR</u>

I read with interest a cohort study recently published by Rifkin and colleagues[1] on the utility of genetic scoring models in the risk stratification for venous thromboembolism(VTE) in IBD patients. The premise of the study is similar to an earlier publication by Naito *et al*, in which the latter demonstrates the added value of polygenic genotyping to monogenic sequencing alone in determining VTE risk in a fairly large cohort of 792 IBD patients.[2]

This current study, however, utilises genotyping scoring data from a much larger cohort of VTE cases and validates its scoring model in a large IBD cohort (n = 8300) extracted from a biobank. The authors had intentionally analysed a modified polygenic scoring model(PGS) that excluded the genetic contributions of the two mutations (F5 : Factor V Leiden , F2: G20210A prothrombin gene mutation). Hence, they were able to demonstrate the clear superiority of polygenic risk scoring to monogenic risk screening in discriminating actual risk of VTE. Patients at the lowest decile of PGS had a far lower incidence of VTE (1.58%) than non-mutation carriers (4.31%). Interestingly, there was only a modest increment in discriminatory ability once the monogenic mutations of F5/F2 were re-added back into the PGS model.

The data suggests that an individual's genetic risk for VTE may be influenced to a greater extent by the cumulative effects of multiple pro-thrombotic genetic loci , rather than specific mutations alone. A multitude of clinical factors, such as ethnicity, comorbidities, IBD extent and activity, hypoproteinemic state, physical immobility, steroid use *etc.*, further add to the complexity in determining one's VTE risk in IBD. I agree with the authors' statement that additional data for non-European IBD patients is urgently needed, as previous publications do show commonly screened genetic

mutations such as F5/F2 have a far smaller contributory role to VTE risk in other ethnic populations *e.g.* Asians and Africans[3-6]. This may also have implications in the standard diagnostic workup for thrombophilia in the non-European patient– it is possible a polygenic screening strategy may be more informative than monogenic testing. The authors also acknowledge that they did not analyse for other common mutations in SERPINC1(anti-thrombin III protein) , PROC(protein C) and PROS1(protein S) given the relative rarity of such mutations. I would like to highlight that these mutations are relatively common in the Asian population compared to F5/F2 mutations, with a recent meta-analysis by Xi-Jie *et al* demonstrating the prevalence of protein C, protein S and antithrombin III deficiency at 7.1%, 8.3% and 3.8% respectively in East Asian patients with VTE.[7] This reiterates the need to validate the PGS model in other ethnic populations, as well as its performance against regionally prevalent thrombophilia mutations.

Precision medicine and personalised therapy remain as lofty targets at least in the current realm of IBD care, but the utilisation of a personalised, regionally validated risk scoring model would provide IBD clinicians invaluable guidance and confidence in the initiation of pharmacological thromboprophylaxis. Current adherence rates to thromboprophylaxis in hospitalised IBD patients remain low in spite of existing guidelines and the potential morbidity from IBD-associated VTE.[8] A composite score combining clinical and polygenic risk factors for VTE can identify the IBD patient at highest risk, justifying the continued use of thromboprophylaxis beyond hospitalisation for instance.[9] An objective assessment of VTE risk would also personalise therapeutic decisions pertaining to IBD control itself, with a greater impetus to consciously utilise steroid-sparing strategies in high-risk patients.[10]

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