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LETTER TO THE EDITOR

Venous thromboembolism risk models in hospitalized medical patients: the time for implementation, not never-ending development

To the Editor,

We read with interest the validation study by Wilkinson et al. [1], where they attempted to externally validate both the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) Venous Thromboembolism (VTE) and Bleed Risk models in their population of hospitalized medical patients within the University of Vermont Health network in the United States. The authors found modest discrimination but poor accuracy of the models in this independent population. They concluded that "new approaches are needed to assess thrombosis and bleed risk in medical inpatients."

There are several major methodological concerns in this validation study of a clinical prediction rule (CPR) and critical omissions in the authors' discussion points. First and foremost, to properly validate a specific CPR, one must choose the correct CPR and established score thresholds of that CPR for the outcome of interest. The 4-factor IMPROVE VTE risk assessment model (RAM) that was used by the authors was last assessed over a decade ago as an academic exercise where the timing of a particular variable in the model (such as age using a clear cut-off) clearly preceded VTE [2]. However, there are many well-established VTE RAMs in clinical use (such as the Khorana VTE score in cancer patients or Caprini VTE score in surgical inpatients) that include variables—especially continuous variables such as immobility or laboratory variables—where the timing of a particular variable relative to a VTE outcome is less clearly defined, thoroughly assessed, or available at initial deployment. Despite this potential limitation, the characteristics of these VTE RAMs show good predictive ability. As should be well-known to this author group, the fewer variables a CPR has, the greater the chance of poor discrimination and calibration in external validation efforts, making it more likely that the 4-factor IMPROVE VTE RAM would produce poor results. Unlike the authors' assertion in their Discussion, the established IMPROVE VTE RAM that has undergone external validation and the one that is endorsed by multiple antithrombotic guidelines is the 7-factor, not 4-factor, RAM despite uncertainty in some variables at admission deployment [3,4].

Second, the IMPROVE VTE RAM has a trinary VTE risk scheme of low (score 0-1 points), moderate (score 2-3 points), and high VTE risk (≥4 points), not a binary one as used by the authors [2]. Failure to use established score cut-off thresholds could have profound implications

in model discrimination and model sensitivity/specificity and calibration efforts. Indeed, previous extensive external validation efforts using the trinary 7-factor IMPROVE VTE RAM (plus elevated D-dimers if available to improve model discrimination) in medical inpatients (including COVID-19 patients) have shown area under the curve values of 0.70 to 0.77 with very good to excellent model calibration [5,6].

Third, the authors failed to mention in their Discussion that the 7-factor IMPROVE VTE RAM has been used prospectively in randomized controlled trials [7,8]. These clinical trials have shown that the established IMPROVE VTE RAM (± elevated D-dimers) can identify a high VTE risk medical (including COVID-19) inpatient population that significantly benefits from extended postdischarge thromboprophylaxis [8,9]. The authors' assertion that current guidelines do not recommend postdischarge thromboprophylaxis and hence not relevant to their validation efforts is simply not true: their internal data show that the majority of their VTE events (66%) occurred postdischarge and the most current 2024 International Consensus Statement VTE Guidelines recommend extended postdischarge thromboprophylaxis for patients with an IMPROVE VTE score of ≥4 points [4].

Lastly, and perhaps most importantly, the authors failed to disclose in their Discussion the results of the only large impact analysis of a VTE RAM in 10,699 medical inpatients conducted as a clustered randomized trial at the hospital level [10]. This trial demonstrated that a clinical decision support tool incorporating IMPROVE-D-Dimer VTE was able to accurately identify moderate and high VTE risk medical inpatients that significantly benefited both from appropriate inpatient as well as extended postdischarge thromboprophylaxis at study hospitals versus control hospitals, with reductions in major thromboembolism [10].

The 7-factor IMPROVE VTE RAM represents one of the most well-validated VTE RAMs in medical inpatients and is endorsed by multiple antithrombotic guidelines [3,4]. Rather than the never-ending development and validation of new VTE RAMs, as the authors suggest, which take nearly a decade, implementation of existing optimal VTE RAMs represents the next most important step in moving the field of medical inpatient thromboprophylaxis. Toward this end, our group is planning to implement the IMPROVE-D-Dimer VTE RAM into the largest health system in the United States, comprising 123 hospitals.

AUTHOR CONTRIBUTIONS

Both authors contributed equally to the framework and writing of the manuscript.

Alex C. Spyropoulos[1,2,3] 🆔 𝕏
Eduardo Ramacciotti[4,5,6]

[1]*Department of Medicine, Anticoagulation and Clinical Thrombosis Service, Northwell Health at Lenox Hill Hospital, New York, New York, USA*
[2]*The Donald and Barbara Zucker School of Medicine at Hofstra/ Northwell, Hempstead, New York, USA*
[3]*Institute of Health Systems Science, The Feinstein Institutes for Medical Research, Manhasset, New York, USA*
[4]*Science Valley Research Institute, Santo André, São Paulo, Brazil*
[5]*Hospital e Maternidade Christóvão da Gama, Grupo DASA, Santo André, São Paulo, Brazil*
[6]*Hemostasis and Thrombosis Research Laboratories, Loyola University Medical Center, Maywood, Illinois, USA*

Handling Editor: Michael Makris

Correspondence
Alex C. Spyropoulos, The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, The Institute of Health System Science, The Feinstein Institutes for Medical Research, Anticoagulation and Clinical Thrombosis Services, Northwell Health at Lenox Hill Hospital, 130 E 77th Street, New York, NY 10075, USA.
Email: aspyropoul@northwell.edu

ORCID

Alex C. Spyropoulos 🆔 https://orcid.org/0000-0002-3175-461X

X

Alex C. Spyropoulos 𝕏 @AlexSpyropoul

REFERENCES

[1] Wilkinson KS, Sparks AD, Gergi M, Repp AB, Al-Samkari H, Thomas R, et al. Validation of the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) Risk Scores for venous thromboembolism and bleeding in an independent population. *Res Pract Thromb Haemost.* 2024;8:102441. https://doi.org/10.1016/j.rpth.2024.102441

[2] Spyropoulos AC, Anderson FA, FitzGerald G, Decousus H, Pini M, Chong BH, et al. Predictive and Associative models to identify hospitalized medical patients at risk for VTE. *Chest.* 2011;140:706–14.

[3] Schünemann HJ, Cushman M, Burnett AE, Kahn SR, Beyer-Westendorf J, Spencer FA, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv.* 2018;2:3198–225.

[4] Nicolaides AN, Fareed J, Spyropoulos AC, Kakkar RHL, Antignani PL, Avgerinos E, et al. Prevention and management of venous thromboembolism. International Consensus Statement. Guidelines according to scientific evidence. *Int Angiol.* 2024;43:1–222.

[5] Goldin M, Lin SK, Kohn N, Qiu M, Cohen SL, Barish MA, et al. External validation of the IMPROVE-DD risk assessment model for venous thromboembolism among inpatients with COVID-19. *J Thromb Thrombolysis.* 2021;52:1032–5.

[6] Mahan CE, Liu Y, Turpie AG, Vu JT, Heddle N, Cook RJ, et al. External validation of a risk assessment model for venous thromboembolism in the hospitalised acutely-ill medical patient (VTE-VALOURR). *Thromb Haemost.* 2014;112:692–9.

[7] Spyropoulos AC, Ageno W, Albers GW, Elliott CG, Halperin JL, Hiatt WR, et al. Rivaroxaban for thromboprophylaxis after hospitalization for medical illness. *N Engl J Med.* 2018;379:1118–27.

[8] Ramacciotti E, Barile Agati L, Calderaro D, Aguiar VCR, Spyropoulos AC, de Oliveira CCC, et al. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. *Lancet.* 2022;399:50–9.

[9] Spyropoulos AC, Ageno W, Albers GW, Elliott CG, Halperin JL, Hiatt WR, et al. Post-discharge prophylaxis with rivaroxaban reduces fatal and major thromboembolic events in medically ill patients. *J Am Coll Cardiol.* 2020;75:3140–7.

[10] Spyropoulos AC, Goldin M, Koulas I, Solomon J, Qiu M, Ngu S, et al. Universal EHRs clinical decision support for thromboprophylaxis in medical inpatients. *JACC: Advances.* 2023;2:100597. https://doi.org/10.1016/j.jacadv.2023.100597