

Major Bleeding After Catheter-Directed Thrombolysis for Acute Pulmonary Embolism: Derivation and Transferability of the F-HARP Risk Assessment Model

Benedetta Madaro¹, Nikolaos Tsaftaridis^{1,2}, Aline Fürbringer-Schwarz^{1,2}, Riccardo M. Fumagalli¹, Filippo Catalani^{1,3}, Leonie Rimann¹, Efthymios Avgerinos⁴, Behnood Bikdeli⁵, Alessandra Bura-Riviere⁶, Rabi A. Chaer⁴, Rolf P. Engelberger⁷, Ioannis T. Farmakis^{3,8}, Assaf Graif⁹, Leticia Guirado¹⁰, Wissam A. Jaber¹¹, Friederike Klein¹², Frederikus A. Klok^{3,13}, Stavros V. Konstantinides^{3,14}, Josef Kroupa¹⁵, Nils Kucher^{1,2}, R. Peter Lokken¹⁶, Manuel M. Monreal¹⁷, Slobodan Obradovic¹⁸, Evren Ozcinar¹⁹, Joseph S. Rossi²⁰, Zoltán Ruzsa²¹, Ignacio M. Seropian²², Mohsen Sharifi^{23,24}, Alex C. Spyropoulos^{25,26}, Lauren Stewart²⁷, Simon Wolf¹, Stefano Barco^{1,3}

1. Department of Vascular Medicine, University Hospital Zurich (USZ), Zurich, Switzerland
2. University of Zurich (UZH), Faculty of Medicine, Zurich, Switzerland
3. Center for Thrombosis and Hemostasis (CTH), University Medical Center Mainz, Mainz, Germany
4. Division of Vascular Surgery, University of Pittsburgh Medical Center, Pittsburgh, USA
5. Division of Cardiovascular Medicine, Heart and Vascular Institute, Mass General Brigham, Thrombosis Research Group, Brigham and Women's Hospital, Harvard Medical School, Boston 02115, Massachusetts, USA
6. Vascular Medicine Department, Toulouse University Hospital, Toulouse, France
7. Angiology, HFR Fribourg-Spital Cantonal, Fribourg, Switzerland
8. Department of Medicine I, LMU University Hospital, Munich, Germany
9. Department of Vascular and Interventional Radiology, Christiana Care Health System, Newark, Delaware, USA
10. Department of Internal Medicine, Hospital Universitario Virgen de Arrixaca, Murcia, Spain
11. Division of Cardiology, Emory University School of Medicine, Atlanta, Georgia, USA
12. Department of Internal Medicine I, Division of Cardiology, University Hospital Jena, Jena, Germany

13. Division of Thrombosis and Hemostasis, Department of Medicine, Leiden University Medical Center, Leiden, the Netherlands
14. Department of Cardiology, Democritus University of Thrace, Alexandroupolis, Greece
15. Department of Cardiology, Third Faculty of Medicine, Charles University, University Hospital Královské Vinohrady, Prague, Czech Republic
16. Department of Radiology and Biomedical Imaging, University of California San Francisco, USA
17. Faculty of Health Sciences, Universidad Católica San Antonio de Murcia, Spain, CIBER Enfermedades Respiratorias, Madrid, Spain
18. Clinic of Cardiology, School of Medicine, University of Defense, Belgrade, Serbia
19. Department of Cardiovascular Surgery, Heart Center, Cebeci Hospitals, Ankara University School of Medicine, Ankara, Turkey
20. University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA
21. Semmelweis University of Budapest, Heart and Vascular Center, Budapest, Hungary
22. Servicio de Hemodinamia y Cardiología Intervencionista, Instituto de Medicina Cardiovascular, Hospital Italiano, Buenos Aires, Argentina
23. Arizona Cardiovascular Consultants & Vein Clinic, Mesa, AZ, USA
24. A.T. Still University, Mesa, AZ, USA
25. Anticoagulation and Clinical Thrombosis Services, Department of Medicine, Northwell, New Hyde Park, NY, USA; Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA
26. Institute of Health System Science, Feinstein Institutes for Medical Research, Manhasset, NY, USA
27. Indiana University School of Medicine, Department of Emergency Medicine, Indianapolis, IN, USA

Abstract

Background: Catheter-directed thrombolysis is an established reperfusion strategy for intermediate- or high-risk acute pulmonary embolism. No validated model exists to predict early major bleeding in this population.

Objectives: To derive a baseline-only risk assessment model for major bleeding after catheter directed thrombolysis, and to assess its transferability in an independent cohort.

Patients/Methods: We pooled patient-level data from 16 cohort studies and randomized trials of catheter-directed thrombolysis for acute pulmonary embolism. The most stable baseline predictors of major bleeding were identified by adaptive LASSO across 1000 bootstrap iterations. Candidate models including 2 to 6 of these predictors were compared on optimism corrected discrimination and calibration. The selected model was applied to an independent cohort from the RIETE registry.

Results: Of 1246 patients with outcome data and without contraindications to thrombolysis, 75 (6.0%) experienced major bleeding, including 10 intracranial hemorrhages. On internal validation, the F-HARP model (Female sex, Hypertension, Age, high-Risk Pulmonary embolism) showed an optimism-corrected area under the receiver operating characteristic curve (AUROC) of 0.695 (95%CI: 0.639-0.755). In the independent cohort (N=566), patients classified as high risk had higher odds of major bleeding within 30 days than the remainder (11.2% vs. 3.8%; OR 3.18, 95%CI: 1.44-7.05). AUROC was 0.638 (95%CI: 0.519-0.742) and calibration slope 0.630 (95%CI: 0.153-1.107).

Conclusions: The F-HARP model uses four readily available baseline predictors to identify a subgroup at meaningfully higher odds of major bleeding after catheter-directed thrombolysis. A powered external validation is required prior to its use for precise risk quantification.

Figure. External cohort cumulative incidence of major bleeding within 30 days, stratified by F-HARP predicted risk category

