6-1-2020

Age-Adjusted D-dimer Cutoffs: A Warning From the Laboratory

Marian A. Rollins-Raval
Department of Pathology, University of New Mexico, Albuquerque, NM

Richard A. Marlar
Department of Pathology, University of New Mexico, Albuquerque, NM

Andrew J. Goodwin
Department of Pathology and Laboratory Medicine, University of Vermont Larner College of Medicine, Burlington, VT

Recommended Citation

Rollins-Raval MA, Marlar RA, Goodwin AJ. Age-Adjusted D-dimer Cutoffs: A Warning From the Laboratory. Ann Emerg Med. 2020 Jun;75(6):783-784. doi: 10.1016/j.annemergmed.2020.02.004. PMID: 32471582.

Table. Risk of venous thromboembolism, pulmonary embolism, and deep venous thrombosis for sequential 3-month periods after carbon monoxide poisoning after exclusion of all patients who died during the 2-year follow-up period (n=21,234).

	Hazard Ratio*	95% CI*
Venous thromboembolism†		
CO poisoning	3.12	1.17–5.49
ICU admission	4.69	1.002–21.90
Pulmonary embolism†		
CO poisoning	8.31	2.12–23.69
ICU admission	4.19	0.29–59.49
Deep venous thrombosis†		
CO poisoning	1.62	0.81–3.23
ICU admission	9.91	1.17–83.80

CI, Confidence interval; *CO*, carbon monoxide.
*Hazard ratios and 95% CIs of outcomes for sequential 3-month periods after carbon monoxide poisoning were calculated by stratified Cox regression with adjustment for ICU admission. Each patient with CO poisoning was matched with his or her own control in the crossover period 1 year later.
†Definition of venous thromboembolism: an inpatient or outpatient with a diagnosis of pulmonary embolism (*International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10]* code I26) or deep venous thrombosis (*ICD-10* code I80.x)

21,234 patients were analyzed after exclusion of all patients who died during the follow-up period of 2 years. Stratified Cox proportional hazard regression was performed because matching data were used. The time-varying coefficients of carbon monoxide poisoning on the risk of venous thromboembolism are shown in the Figure. At all risks of venous thromboembolism, pulmonary embolism, and deep venous thrombosis, the coefficients were highest immediately after carbon monoxide poisoning and gradually decreased to zero at approximately 90 days afterward. We further reduced the follow-up period to 90 days to determine the hazard ratios of the risk periods and conducted further analyses after adjusting for ICU admission as a covariate (Table). After this, although slightly lower than in the previous study, the risk of venous thromboembolism and pulmonary embolism increased by 3.1 and 8.3 times, respectively. The hazard ratio for deep venous thrombosis was 1.62, but it was not significantly increased (95% confidence interval 0.91 to 3.23).

Different study designs and statistical methods have their advantages and disadvantages. To overcome this issue, we conducted various subgroup and sensitivity analyses in our previous study to confirm the results from various perspectives. Although carbon monoxide poisoning might not have a causal relationship with venous thromboembolism, we were able to identify the association. In addition, the risk of venous thromboembolism after carbon monoxide poisoning was increased even after adjusting for risk factors such as ICU admission and hospitalization. Therefore, we suggest that monitoring for venous thromboembolism is needed for patients with carbon monoxide poisoning. Further study on the association of venous thromboembolism in patients with carbon monoxide poisoning may help clinicians better understand it.

Yongil Cho, MD, PhD
Hyunggoo Kang, MD, PhD
Jaehoon Oh, MD, PhD
Tae Ho Lim, MD, PhD
Byuk Sung Ko, MD, PhD
Department of Emergency Medicine
College of Medicine
Hanyang University
Seoul, Republic of Korea

https://doi.org/10.1016/j.annemergmed.2020.01.031

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). This study used the National Health Insurance Service database (NHIS-2018-1-195). This work was supported by a National Research Foundation of Korea grant funded by the government of Korea (Ministry of Science, ICT and Future Planning) (No. 201800000001207). This research was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) and funded by the Korean government (MSIT)(NRF-2019M3E5D1A01066060).

The interpretations and conclusions reported here do not represent those of the National Health Insurance Service.

1. Xu Y, Li WZ. Is carbon monoxide poisoning a risk factor or a bystander of deep vein thrombosis? *Ann Emerg Med*. 2020;75:781-782.
2. Cho Y, Kang H, Oh J, et al. Risk of venous thromboembolism after carbon monoxide poisoning: a nationwide population-based study. *Ann Emerg Med*. 2019; https://doi.org/10.1016/j.annemergmed.2019.08.454.
3. Zhang Z, Reinikainen J, Adeleke KA, et al. Time-varying covariates and coefficients in Cox regression models. *Ann Transl Med*. 2018;6:121-130.

Age-Adjusted D-dimer Cutoffs: A Warning From the Laboratory

To the Editor:

D-dimer assays have been Food and Drug Administration (FDA)–approved or cleared for results below a manufacturer-defined cutoff in conjunction with

low or intermediate pretest clinical probability to rule out venous thromboembolism.[1] Given apparent overall increase of D-dimer level with age, clinical guidelines have recommended application of an age-adjusted D-dimer–level cutoff to exclude suspected pulmonary embolus specifically in patients with low or intermediate pretest clinical probability.[2,3] Despite additional studies and literature availble, these guidelines themselves rest solely on the Age-Adjusted D-Dimer Cutoff Levels to Rule Out Pulmonary Embolism: The ADJUST-PE Study,[4] applying an age-adjusted D-dimer–level cutoff defined as age×10 in patients aged 50 years or older to elderly patients presenting to the emergency department with low or intermediate pretest clinical probability of pulmonary embolus. Theoretically, by using this strategy to exclude pulmonary embolus in more patients, health systems could reduce cost and improve diagnostic efficiency without sacrificing sensitivity for identifying patients at risk for pulmonary embolus.

Numerous D-dimer assays (≈30) with various sensitivities and specificities are used worldwide, with no international standard available for harmonization. Expression of results is not standardized and uses different magnitudes (ie, nanograms per milliliter or milligrams per liter) and different nonequivalent units, including fibrinogen equivalent units (FEU) and D-dimer units (DDU) (DDU at 1 ng/mL are ≈FEU at 2 ng/mL). Guidelines from the Clinical and Laboratory Standards Institute for adequate evaluation of quantitative D-dimer to exclude venous thromboembolism in clinical studies are strict, with only a handful of assays meeting this criterion for age-adjusted D-dimer–level cutoff in suspected pulmonary embolus.[5] Currently, no manufacturer has obtained FDA approval or clearance for use of age-adjusted D-dimer–level cutoffs. Assuming that all currently commercially available assays will correctly perform with the provided age-adjusted D-dimer–level cutoff is misguided, and, as recommended previously, these parameters (with harmonization of standards and appropriate units added) should be clarified in research studies, trials, and clinical guidelines.[3,5]

Many laboratories now use FDA-approved or -cleared D-dimer assays as an "aid in diagnosis" or for "exclusion" in venous thromboembolism evaluation. However, adding *any* postanalytic modification of assay, including manipulations of units or magnitude, or adding comment text not approved by the FDA, changes this FDA-approved or -cleared assay into a laboratory-developed test. Laboratory regulations require that a laboratory-developed test be fully validated by the specific laboratory before it is implemented into patient care, a challenging undertaking for most institutions; this is especially true for age-adjusted D-dimer–level cutoffs in patients older than 75 years, a largely uncharacterized population. In the absence of a validated laboratory-developed test at their institution, laboratories should refrain from broadly accepting the postanalytic modification of the age-adjusted D-dimer–level cutoff. Pathologists should work with clinical colleagues to explain the limitations of the age-adjusted D-dimer–level cutoffs and highlight the importance of properly validating a specific D-dimer assay before calculating an age-adjusted D-dimer–level cutoff.

Marian A. Rollins-Raval, MD, MPH
Richard A. Marlar, PhD
Department of Pathology
University of New Mexico
Albuquerque, NM

Andrew J. Goodwin, MD
Department of Pathology and Laboratory Medicine
University of Vermont Larner College of Medicine
Burlington, VT

https://doi.org/10.1016/j.annemergmed.2020.02.004

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

1. Riley RS, Gilbert AR, Dalton JB, et al. Widely used types and clinical applications of D-dimer assay. *Lab Med*. 2016;47:90-102.
2. Raja AS, Greenberg JO, Qaseem A, et al. Evaluation of patients with suspected acute pulmonary embolism: best practice advice from the Clinical Guidelines Committee of the American College of Physicians. *Ann Intern Med*. 2015;163:701-711.
3. Lim W, Le Gal G, Bates SM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. *Blood Adv*. 2018;2:3226-3256.
4. Righini M, Van Es J, Den Exter PL, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. *JAMA*. 2014;311:1117-1124.
5. Goodwin AJ, Higgins RA, Moser KA, et al. Issues surrounding age-adjusted D-dimer cutoffs that practicing physicians need to know when evaluating patients with suspected pulmonary embolism. *Ann Intern Med*. 2017;166:361-363.

A Brief Review of Lung Ultrasonography in COVID-19: Is It Useful?

To the Editor:

The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-Cov2), is known to cause mild to severe lower respiratory disease (coronavirus disease 2019