Letters to the Editor

A physician to make more rational treatment decisions.

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References


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Standardizing the D-dimer Assay: Proposing the D-dimer International Managed Ratio

To the Editor:

The D-dimer assay currently lacks standardization, since each manufacturer uses a different cutoff to define an abnormal value. The existence of at least 6 commonly used assays—all with differing units and cutoffs—leads to confusion among practitioners. For instance, at our hospital, the point-of-care laboratory uses an assay with an abnormal cutoff of 230 ng/mL, but the central laboratory uses a D-dimer assay with a cutoff of 400 ng/mL. A second emergency department staffed by the same physicians uses a cutoff of 0.5 mg/L. Further, some laboratories report fibrinogen-equivalent units instead of D-dimers, resulting in a value approximately twice that of the D-dimer.

Recent literature has demonstrated that the “standard” threshold of 500 ng/mL may be adjusted depending on patient-specific factors, enhancing the D-dimer’s diagnostic specificity in evaluation of suspected venous thromboembolism in older or pregnant patients (1, 2). Variable cutoffs hamper the implementation of these adjustments, confusing practitioners when local assays do not correspond to internationally published values. In our experience, this frustrates practitioners and increases their motivation to skip D-dimer testing and proceed directly to pulmonary vascular imaging, or worse, commit frank medical error by failing to recognize a positive test result (3).

We sent an open Research Electronic Data Capture (REDCap) survey to clinicians in the US to determine physician opinions surrounding the use, adjustment, and normalization of D-dimer testing. The survey used a visual analog scale (VAS) and multiple-choice questions designed to assess the magnitude of the problem and the desire for a solution. Clinicians additionally could submit their electronic signature on a petition to the FDA, requesting that the FDA take steps to normalize the D-dimer threshold.

Statistical analysis was performed using SPSS (IBM Corp., Armonk NY). Descriptive statistics are presented for appropriate variables. Median responses are reported with interquartile ranges (IQRs) for non-normal data. A total of 1006 physicians responded, representing approximately 3.1% of all emergency

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Nonstandard abbreviations: REDCap, Research Electronic Data Capture; VAS, visual analog scale; IQR, interquartile range; INR, international normalized ratio.
physicians in the US (personal communication, J. Jones, American Board of Emergency Medicine, December 2014).

The majority of respondents (n = 880, 89%) reported not knowing which D-dimer assay their hospital used. Of the 11% of physicians who did know, Vidas assay (BioMerieux) represented 33% of the responses, HemosIL (Instrumentation Laboratory) 24%, and Liatest (Stago) 19%. No assay represented a majority.

When asked if varying cutoffs for D-dimer assays were a problem, the median response was 73/100 on VAS (IQR 58% to 88%). When asked if the assays should be standardized to a normalized ratio, similar to the international normalized ratio (INR) for prothrombin, the median response was 85/100 (IQR 68% to 97%) (Fig. 1).

A minority of physicians reported adjusting their D-dimer results to published values, such as pregnancy trimester or age (n = 236, 24%). One third of respondents did not know how to adjust their D-dimer results because their cutoff was different from published values (n = 332, 33%). Approximately one-quarter would not adjust these numbers themselves (n = 249, 25%). Many respondents were not aware that they could adjust the D-dimer (n = 186, 19%). The majority of physicians reported using a D-dimer at least weekly (n = 535, 53%), with an additional third of respondents reporting daily use (n = 331, 33%).

The majority of participants stated that 1.0 would be the preferred value for a normalized ratio (n = 597, 60%). A large minority preferred 500 (n = 387, 39%), with several write-in values of 100, 300, and 1000 representing <1% of the responses.

These data document strong clinician opinions that D-dimer variability represents a patient safety concern. Approximately 90% of clinicians are unfamiliar with the test their own hospitals use, which we believe is a major issue. Regarding recent literature on threshold adjustment, the most common response to the question “would you adjust a D-dimer cutoff” was “I would, but don’t know how my hospital’s assay compares to national guidelines.” The majority of respondents strongly supported the creation of a normalized ratio for the existing D-dimer assay.

The burden on industry to normalize all D-dimer results may be costly, requiring each manufacturer to perform standard curve testing using a validated external standard. However, we believe our data show that the effort is worth the gain, since such standardization would reduce confusion and permit wider use of threshold adjustment to the benefit of patients. One option is to normalize the D-dimer value in a fashion analogous to the INR for the prothrombin time. Ideally, this ratio would be truly “managed” and adjusted for patient factors. Given the

Fig. 1. Frequency of answers to the following question: “The INR was created to standardize the prothrombin time. How strongly do you believe that a similar standardization should be performed with the D-dimer?”

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60% preference by respondents, we propose a standard reference value of 1.0, and the nomenclature D-dimer international managed ratio.

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