

Re: Discrepancies between two D-dimer assays and impact on clinical decisions; a retrospective analysis of samples tested in community- and hospital-based laboratories in Auckland

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The recent publication by Adriaansen et al. 2024¹ aimed to compare two D-dimer assays in a real-world setting by evaluating systematic bias and heterophilic interference and assessing their potential impact on patient management. The study concluded that INNOVANCE® D-Dimer assay (INNOVANCE assay) yielded higher values and was more susceptible to interference from heterophile antibodies compared to the STA®-Liatest® D-Di Plus assay (Liatest assay). Adriaansen et al. also noted concern about clinician mistrust due to discordant results between laboratories.

While this publication reports on the experience and practice of a community laboratory and hospital, we aim to raise methodological concerns with the study that challenge several of the authors' conclusions, including: 1) the systemic bias of the study, 2) missing data addressing the heterophilic interference of the D-dimer assay, and 3) missing clinical outcomes, especially in patients with discordant results.

With respect to systemic bias, it should be noted that only patients who initially tested positive with the INNOVANCE assay were referred to the hospital, where a second blood draw was performed for retesting using the Liatest assay; the reverse, however, was not evaluated. Blood draws at different times (up to 24 hours in the Adriaansen et al. study) and sites could lead to a significant bias in results because of D-dimer's half-life of 8 hours,² the effects of pre-analytical variables on D-dimer testing² and different clinical presentation of the patient from first to second blood draw (i.e., clinical pretest probability [PTP]).

Selective exclusion of samples from the study also has the potential to bias the comparison. Of

the 818 samples collected for the study, 86 samples (10.5% of all samples collected) were excluded as they were above Liatest's analytical measuring interval (AMI) of 4,000µg/L fibrinogen equivalent units (FEU). This same criterion, however, was not applied for samples above the INNOVANCE AMI of 4,400µg/L FEU. An additional 44 samples (6% of all samples collected) were excluded because they demonstrated highly discordant results. For a symmetrical method comparison, sample pairs spanning the AMI for both assays should be used.

Another limitation of the manuscript is the authors' assumption regarding the cause of the highly discordant results. In the study, 44 samples gave results more than threefold higher with the INNOVANCE assay than with Liatest. After excluding high Liatest results, the authors concluded that the INNOVANCE assay likely suffered from heterophilic interference. The conclusion that the INNOVANCE assay is affected by heterophilic interference appears to be speculative, as there was no direct investigation (e.g., dilutional linearity, pretreatment with heterophilic blocking tube) or empirical data presented in the study to confirm this hypothesis. Heterophilic antibodies are known to cause interference in some immunoassays, but conclusively attributing assay performance issues to this interference without appropriate supporting evidence is premature.

To draw robust conclusions regarding suitability of D-dimer assays for clinical use, it is essential to consider the patient's PTP (i.e., Wells score or other relevant measures) and the clinical outcome. This is particularly important when assessing the 193 discordant sample pairs. However, the authors do not provide details on the number of patients who underwent additional investigation (such as

imaging) or on the final clinical determination, which complicates the ability to make definitive conclusions about assay performance. Additionally, an evaluation of a potential dependency between the patient's condition, D-dimer results and the timing of blood draw could be helpful. Laboratory test results other than D-dimer could also help in better understanding the observed discrepancies between the D-dimer assays, especially considering two-thirds of the study were carried out during the COVID-19 pandemic. For instance, elevated C-reactive protein (CRP) can indicate an inflammatory response, which could result in elevated D-dimer levels.^{3,4} Furthermore, the patient's renal status could also play a role, as D-dimer is mainly cleared by the kidneys.²

Adriaansen et al. highlight the lack of standardisation across D-dimer assays. The heterogeneity of the D-dimer antigen, the heterogeneous designs of different D-dimer assays⁵ and the lack of standardisation⁶ leads to known inherent variability between D-dimer assays. While we agree that a lack of standardisation may prevent the ability

to interchangeably use D-dimer results from different assays, it is important to remember that D-dimer is not used in isolation but is interpreted along with clinical history and presentation (e.g., clinical PTP) and other diagnostic testing which, as noted above, are parameters not provided in the study.

Due to the study design, biased exclusion of samples and the lack of clinical correlation, the ability to draw conclusions about the clinical performance of the two D-dimer assays used in this study is limited. It is certainly premature to conclude that one assay is more prone to heterophilic antibody interference in the absence of any supporting data. The findings presented by Adriaansen et al. should also be considered in context of other studies that have found comparable results between both the INNOVANCE and Liatest assay (i.e., negative predictive value, sensitivity and specificity or correlation),⁷⁻¹⁰ as well as proficiency data that have shown that the INNOVANCE and Liatest generate comparable results.⁶

COMPETING INTERESTS

CD and JM are employees of Siemens Healthineers.

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