Analytical Concordance of Diverse Point-of-Care and Central Laboratory Troponin I Assays

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Guest: Dr. Albert Tsui is a Clinical Biochemist with Alberta Public Laboratories at the University of Alberta Hospital.

Randye Kaye: Hello, and welcome to this edition of "JALM Talk," from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye.

Cardiac troponin is the supreme biomarker for the diagnosis of acute myocardial infarction. The ability of the clinical laboratory to provide rapid and reliable troponin results is critical for patient management in the emergency room. In clinics and environments far from a laboratory, point-of-care troponin testing may be necessary for timely results and patient triage. However, questions remain about the concordance among point of care and laboratory-based methods and whether the same result cut-offs should be used for clinical decision making.

A study published in the March 2019 issue of *The Journal of Applied Laboratory Medicine* investigates the analytical concordance of three point-of-care cardiac troponin I assays against the added high sensitivity troponin I assay. This study provides insight into how lab-based methods and point-of-care methods for troponin might co-exist. The corresponding author of the study is Dr. Albert Tsui, a Clinical Biochemist with Alberta Public Laboratories at the University of Alberta Hospital. Dr. Tsui is an Assistant Professor with the University of Alberta. Welcome Dr. Tsui.

Dr. Albert Tsui: Thank you.

Randye Kaye: First question. Why consider point-of-care troponin assays and what prompted you to perform this study?

Dr. Albert Tsui: So, point-of-care troponin assays, despite that it's actually being less sensitive than a central lab troponin assay, are useful in institutions with the lab troponin result cannot provided within one hour. For example, point-of-care assay is often deployed in rural labs where its access to central labs is limited, or as a backup to the central lab instruments at our small sites.

So as many are very familiar, one of the biggest challenges of troponin testing is the lack of standardization. This means that two assays of different manufacturers can give different values, even if the same sample is measured side by side. And they also have different values for the 99th percentile cut-off. This presents a problem for us since our physicians do practice in different locations within our health region. To make this even more complicated, we have five different troponin assays in our region. So that means physicians could be dealing with potentially five different cut-offs for the same blood test, which can be very confusing.

Since our region would be using a single lab information system as well as the health information system as early as this year, we looked into the possibility to harmonize troponin testing cut-off. If the same cut-off can be used then the same standards of care would be applied across different labs that use different assays. The limitation, of course, is that we would need to conduct clinical trials to assess if the cut-offs are clinically efficacious.

Despite that many labs already switched to high-sensitivity assays, point-of-care assays in the market is still contemporary assays. It's not high sensitivity. So, when used together, it's important to understand their strengths and limitations. And one thing we always wonder is whether these different 99th percentile cut-offs set up by the manufacturers actually provide the same interpretation across assays.

What motivates us to perform the study is the lack of evidence in this regard, particularly in the field of point-of-care troponin assays using fresh whole blood, as most studies today used frozen stored serum or plasma which is often not really the sample type used clinically in point-of-care settings.

Randye Kaye: All right, thank you. Can you just briefly describe for me the correlation study approach and what was unique about how the study was performed?

Dr. Albert Tsui: The study actually compares the analytical agreement of a number of point-of-care and contemporary troponin I assays to the central lab high-sensitivity assay. So, we specifically investigate the ones we used within our region.

So, unlike many previous studies using serum or frozen samples on point-of-care testing, we simulate the actual clinical testing environment by obtaining two sample types, one lithium heparin and one EDTA. And these are fresh whole blood obtained from the coronary care units and then immediately performed point-of-care assays at the bedside.

After that, the same tubes of blood were then sent to the central laboratory for plasma analysis of troponin. The main reason to obtain samples from the CCU is that we can get more positive troponin samples than obtaining from the emergency department. Hence, this increased our efficiency for doing the correlation study. With the results, we compared the analytical concordance using each assay's manufacturer-recommended 99th percentile cut-off, and a harmonized cut-off.

This is to determine if the harmonized cut-off for the pair of point-of-care and central lab assays would provide a better analytical concordance and these comparisons are done using the sample type -- actually the same sample type. That means heparin whole blood versus heparin plasma. And likewise, EDTA whole blood versus EDTA plasma. This is to control the effects of anticoagulant on troponin values.

Randye Kaye: So, sum up for me, what were the most important findings and is there anything there that could be considered maybe controversial about the findings?

Dr. Albert Tsui: As we know, medical lab guidelines recommend that the 99th percentile cut-off of the assay should be used to rule in and rule out myocardial infarction and in a perfect world, we would expect that no matter which assay is tested on a sample, the result in assay A should give the same interpretation as in assay B when the assays' own 99th percentile cut-off is used, despite that their troponin value is very different.

And we are surprised or perhaps puzzled at first, to find that the analytical concordance between point-of-care and high-sensitivity troponin assays used in the manufacture-suggested 99th percentile cut-off can be up to 3% discrepant. What this means is that one in three could have a discordant interpretation. So that means I can have a positive troponin in one lab, but I can also get a negative troponin result if it is tested in a different lab using a different assay. So, the question is, is my troponin normal or abnormal?

Our study reinforces the fact that different troponin I assays cannot be compared due to a lack of standardization. Hence, the guideline recommends to serial monitor troponin using the same assay. In addition our findings also point to the weakness on just relying on the manufacture's derived 99th percentile cut-off for different troponin I assays. While our attempt to harmonize cut-off between those point-of-care and high-sensitivity assays will provide better analytical concordance, this could mean reducing the sensitivity of high-sensitivity assays to a non-high sensitivity assay, which really defeats the purpose of using high-sensitivity

assay in the first place. Hence, I think it is really important to locally evaluate or validate the cut-off using both clinical and analytical correlation prior to implementing these troponin assays. However, from a resource perspective, this might be challenging for small or rural labs, which would predominantly be the users of these point-of-care troponin instruments.

Randye Kaye: You've already explained some I think, but what could be some of the reasons for the biases observed among the different methods?

Dr. Albert Tsui: There are several reasons. So first, troponin I assays are not standardized because different standard materials are used to calibrate the assays among different manufacturers. Second, immunoassay is now often the method to use for troponin I and these immunoassays use two antibodies to recognize different parts of the troponin protein. However, each troponin assay probably uses slightly different antibodies against different regions thus picking up fragments that are likely different between individuals in the severity of myocardial injury. So, this would create different readings among different assays.

And in addition, not only are there biases among methods that exist, there are differences in how the 99th percentile cut-off is determined. Hence, this might explain our observational discrepant interpretation using the 99th percentile cut-off. The reason being that methods to establish this cut-off is not standardized. There are differences in the selection criteria for the reference population to derive this cut-off such as differences in age, ethnicity, inpatient versus outpatient versus healthy volunteers.

Also, the use of different sample types such EDTA versus heparin plasma also contribute to this difference. So, we think it is important to critically assess how the 99th percentile is established and determine if it's suitable to be used in your own lab.

Randye Kaye: All right, thank you. And my last question, can you sum up what are the implications of the study findings and what should other labs and health systems keep in mind for troponin testing.

Dr. Albert Tsui: So, that's a very insightful question. First, our results suggested that methods to determine a 99th percentile cut-off should be standardized across manufacturers to minimize the discordant interpretation. And often that rural labs in clinics using point-of-care assays would have to rely on manufacturers to provide this cut-off and it is important that details on how the 99th percentile cut-off is derived are

included in the package inserts. It will be optimal for manufacturing lab communities to continue to work together for the development of high-sensitivity troponin I assays particularly in the point-of-care field to minimize these differences in the future.

Second, laboratories and physicians should understand the strength and the limitations of the old troponin assay in relation to their local clinical and testing environment. So, for example, how is the 99th percentile cut-off idetermined and can it be applied to our patient population?

Third, the findings of our study can also provide information to labs when selecting which point-of-care and high-sensitivity troponin assay can co-exist, by taking into account their similarities and differences. Lastly, our findings also support the importance of evaluating and validating the old troponin I cut-off from the clinical and analytical performance perspective.

Randye Kaye: Thank you so much for joining us today, Dr. Tsui.

Dr. Albert Tsui: Thank you.

Randye Kaye: That was Dr. Albert Tsui from the Alberta Public Laboratories at the University of Alberta Hospital describing analytical concordance of diverse point of care and central laboratory troponin assays from the March 2019 issue of JALM. Thanks for tuning in to this episode of JALM Talk. See you next time, and don't forget to submit something for us to talk about!