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Letter to the Editor

Between-day versus within-day imprecision using the Abbott high-sensitivity cardiac troponin I assay at concentrations around 5 ng/l

To the Editor

Laboratory practice recommendations endorse measurement of quality control (QC) material for high-sensitivity cardiac troponin (hs-cTn) assays at least once per day in the normal range (i.e., at a concentration above the limit of detection (LoD) and below the lowest sex-specific 99th percentile concentration) [1]. Ideally, this normal QC concentration should be targeted to concentrations that have been proposed to be used for early rule-out/in of myocardial infarction. For Abbott's hs-cTnI assay, proposed cutoffs for early decision-making have ranged from below the commonly used LoD of 1.9 ng/l to around 5 ng/l [2–4]. Our laboratory program since 2014 has manufactured a low QC material near this concentration to monitor imprecision (at least once per day) and for reagent lot evaluation [5,6]. We have observed that repeat testing on the same patient lithium heparin plasma samples may reclassify approximately 10% of patients when using the European Society of Cardiology (ESC) 0/1 h algorithm [7]. This raises the question whether more frequent QC testing in the normal range is required to properly capture the variation present? To this end, we calculated the imprecision over 400 measurements using our QC material that we measure at least once daily (i.e., between-day imprecision) and compared this imprecision to an EDTA plasma pool that had 400 measurements performed over 2 days (i.e., within-day imprecision) (analyses performed with Analyse-it and Medcalc statistical software).

At our hospital site, we have been using the same QC lot material to monitor the hs-cTnI assay in the normal range since September 17, 2017, on an Abbott ARCHITECT i2000 analyzer. The overall mean and standard deviation (SD) from September 17, 2017 to November 8, 2018 was 5.0 ng/l and 0.7 ng/l (n = 539). The last 400 results were obtained from January 7, 2018 to November 8, 2018 and during this time we had only 1 QC failure (2-2S rule with consecutive hs-cTnI results of 3.2 ng/l and 3.4 ng/l), which occurred after yearly preventative maintenance by the field service engineer and was corrected by a recalibration. Over these 400 measurements which were performed via 4 different reagent lots and 2 different calibrator lots, the mean was 4.9 ng/l and SD was 0.6 ng/l with only one result at minus 3SD (i.e., 3.1 ng/l). Of note, these data were not normally distributed with the median (interquartile range) being 4.8 ng/l (4.4–5.4) (Shapiro-Wilk test, Fig. 1).

To assess within-day imprecision 60 EDTA plasma samples with a range of hs-cTnI concentrations from 4 ng/l to 9 ng/l were pooled together, mixed, centrifuged (10 min at 2300g) with an aliquot tested (n = 10) which yielded a concentration of 5.9 ng/l for the pool. EDTA plasma was chosen as the sample type to mitigate any storage effects on the measurements, which have been observed when using lithium heparin plasma with the Abbott hs-cTnI assay [8]. The pool was then aliquotted to make 4 sets of 5 tubes of the EDTA pool which were then stored at -80 °C. The first set (i.e., 5 tubes) was tested at approximately 13:30 on November 6, 2018, the second set at approximately 01:30 on November 7, 2018 (i.e., 12 h later), the third set at approximately 18:30 on November 7, 2018, and the fourth set at approximately 18:30 on November 8, 2018. Once the tubes were removed from the freezer, they were thawed at room temperature, mixed by hand inversion, centrifuged 10 min at 2300g with 20 hs-cTnI tests programmed for each tube to yield 100 tests all from the same 500-test reagent pack, with the results generated within approximately 1 h of loading the samples. Over the 400 measurements, the mean was 5.7 µg/l and SD was 0.3 ng/l, with the median (IQR) being 5.7 ng/l (5.5–5.9) as data not normally distributed (Sharpiro-Wilk Test, Fig. 1). Of note, the first 200 results measured approximately 12 h apart were normally distributed with a mean of 5.8 ng/l and SD of 0.3 ng/l (p = .27) however, the next 200 results measured approximately 24 h apart were not normally distributed with a mean (SD) = 5.7 ng/l (0.3) and median (IQR) = 5.7 ng/l (5.5–5.9) (p = .022). The maximum concentration for the QC and EDTA pool was 6.5 ng/l; however, the lowest concentration was 5.1 ng/l for the EDTA pool that was measured over 2 days as compared to 3.1 ng/l for the QC material that was measured over 305 days (Fig. 2). During the EDTA pool testing period of 2 days the QC material was measured 6 times with a range of results of 5.4 to 6.1 ng/l.

These data confirm that within-day precision is superior to between-day precision for hs-cTnI which is important as serial measurements over 1–3 h with small absolute deltas are often used to make a decision using hs-cTn assays. However, differences of ± 1 ng/l can be observed when reporting results as whole numbers as recommended for patient reporting [1]. Specifically, only 54% of the results would be reported as 5 ng/l for the between-day QC measurements (QC mean as whole number = 5 ng/l) and 83% of the results would be reported as 6 ng/l for the within-day EDTA pool (Pool mean as whole number = 6 ng/l). Using whole numbers with rounding, the range of results for the between-day QC would be 3 ng/l to 7 ng/l and for the within-day would be 5 ng/l to 7 ng/l. Thus, additional metrics besides only one low hs-cTn concentration cutoff may be necessary to prevent misclassification using a low cutoff in the normal range. It is likely had we been using a concentration closer to the LoD, this problem would have been more significant [9].

Conflict of interest

Dr. Kavsak has received grants/reagents/consultant/advisor/honoraria from Abbott Laboratories, Abbott Point of Care, Abbott Diagnostics Division Canada, Beckman Coulter, Ortho Clinical Diagnostics, Randox Laboratories, Roche Diagnostics and Siemens Healthcare Diagnostics. McMaster University has filed patents with Dr. Kavsak listed as an inventor in the acute cardiovascular biomarker field. Dr. Jaffe has consulted for the majority of the diagnostic companies who have manufactured troponin assays.

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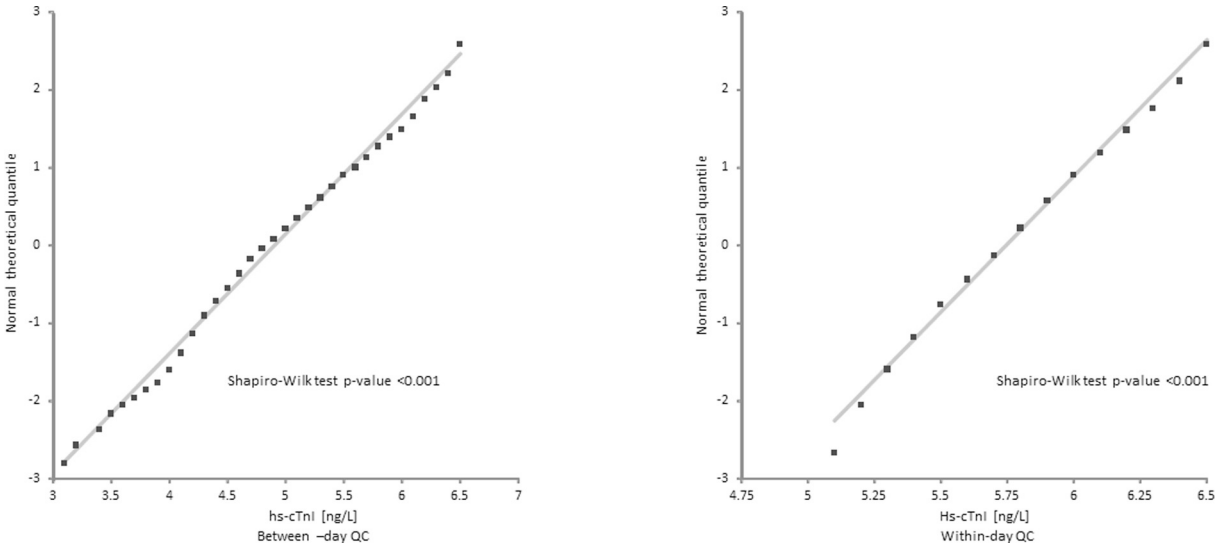

Fig. 1. Q-Q plots of the Between-day QC (n = 400 over 305 days) and Within-day QC (n = 400 over 2 days).

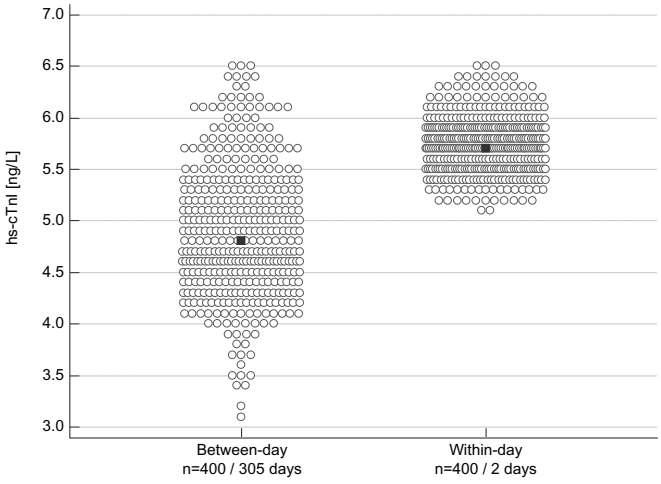

Fig. 2. Distribution of 400 hs-cTnI results for QC measured at least daily over 305 days versus 400 hs-cTnI results measured over 2 days (the black square represents the median concentrations for each material).

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