Letters to the Editor

We would welcome collaboration to achieve this end.

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References


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Assessment of the 99th or 97.5th Percentile for Cardiac Troponin I in a Healthy Pediatric Cohort

To the Editor:

Recent publications on high-sensitivity cardiac troponin in Clinical Chemistry have detailed how to derive an appropriate 99th percentile cutoff (1), highlighted its impact on health outcomes (2), and even questioned the 99th percentile in the diagnosis of acute coronary syndrome (3). Much attention has focused on the selection of a “healthy population,” with differences in high-sensitivity cardiac troponin T (hs-cTnT)1 and hs-cTnI concentrations being evident between sexes in the adult population (1). Accordingly, it is plausible that biological differences in high-sensitivity cardiac troponin concentrations between ethnic groups may also be apparent. This issue has recently been addressed via the study by Gaggin and colleagues, who found no significant difference in hs-cTnT concentrations in a US population (i.e., 98.8% with concentrations <14.0 ng/L) vs a Vietnamese population (98.1% with concentrations <14.0 ng/L) (4). Unfortunately, it is not clear why the derived 99th percentile in the Vietnamese population (19.0 ng/L) was higher than in the US population (15.1 ng/L). The authors noted that there were 3 additional Vietnamese participants with concentrations above the 99th percentile, yet it is unclear why common statistical techniques were used to remove potential outliers. Although there are publications emphasizing additional laboratory and imaging tests required to define a healthy population (1, 3), there have been no recommendations made regarding what statistical tests to use for the detection of potential outliers when deriving reference intervals with high-sensitivity cardiac troponin assays. To address this point and further explore potential sex and age effects on high-sensitivity cardiac troponin concentrations, we measured hs-cTnI in a group of healthy children in the Canadian Laboratory Initiative in Pediatric Reference Intervals (CALIPER) population (5).

For this study, to avoid potential inclusion of unhealthy individuals when deriving population percentiles, no samples from hospital outpatients were analyzed. Specifically, serum samples from healthy community children (n = 315) between 1 and 18 years of age comprised the healthy cohort (5). There was equal representation of children age 1–9 years (n = 157) and 10 to <19 years (n = 158) and both sexes within these age groups (<10 years, 79 females/78 males; ≥10 years, 76 females/82 males). The serum samples were analyzed with the Abbott hs-cTnI assay [see (2) for analytical performance]. Visual examination of the data revealed 2 outliers (251 and 313

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Nonstandard abbreviations: hs-cTnI, high-sensitivity cardiac troponin I; CALIPER, Canadian Laboratory Initiative in Pediatric Reference Intervals.
ng/L) or 0.6% of the results from the healthy cohort, which most likely were analytical errors, consistent with a reported outlier rate (0.59%) for this hs-cTnI assay (6).

The remaining 313 results did not show a gaussian distribution, and transformations via Box and Cox, square root, or logarithmic transformations did not normalize the data and consequently neither the Tukey nor Dixon Q methods were used to detect further potential outliers (Medcalc statistical software version 13.1.2 used for analyses). However, another method for detecting potential outliers is one proposed by Reed et al. (7), which when applied to our data set did identify 1 potential outlier at 97 ng/L (Fig. 1). After removal of this result, further partitioning between females and males was not indicated when we applied the Harris–Boyd method.

To further explore what effect a potential outlier may have on the derivation of the recommended 99th percentile (1) or 97.5th percentile (suggested as an alternative) (3), the nonparametric percentile method (CLSI C28-A3) was used for both the no-outlier-removed/group A (n = 313) and the outlier-removed/group-B (n = 312). For group A, the 99th percentile was 33.6 ng/L (90% CI, 16–97 ng/L) and the 97.5th percentile was 15.2 ng/L (90% CI, 7–31 ng/L). For group B, the 99th percentile was 30.9 ng/L (90% CI, 15–41 ng/L) and the 97.5th percentile was 11.7 ng/L (90% CI, 7–30 ng/L). The CIs around these reference interval end points are simply too wide to allow any useful conclusions in relation to the effects of outlier removal.

Despite the IFCC Task Force recommendations for a minimum of 300 healthy individuals to establish a 99th percentile for cardiac troponin (1), a larger number is necessary to prevent inappropriate removal of data as outliers. In fact, this statement also applies for the determination of the 97.5th percentile for hs-cTnI in our data set and is supported by Miller et al. who “recommend that a sample size of approximately 400 be used for adequate protection against extreme values when one is estimating the 97.5 percentile value with a 90% confidence interval” (8).

Specific to this study, there does not appear to be an age or sex difference in hs-cTnI concentrations, so a common reference interval may be employed. However, there are some important limitations to our study that should be considered. First and foremost, the present analysis does not include imaging and the use of other surrogate biomarkers to confirm a cardiovascular healthy pediatric population. Second, in adolescence (≥13 years) there are differences between males and females in common enzymes (i.e., alkaline phosphatase) (5) and in left ventricular mass, so a larger number of samples in this age group is required to more thoroughly assess hs-cTnI with respect to sex and age. This leads to the third important limitation, sample size. Despite exceeding the IFCC-recommended sample size to determine the 99th percentile for cardiac troponin (i.e., >300 healthy individuals), it is evident that a larger sample size
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is needed to derive more robust estimates for both the 99th and 97.5th percentiles. We hope that the IFCC task force will revisit the requirements for both the number of healthy individuals needed to determine the 99th percentile and which statistical tests may be used to assess potential outliers. In the meantime, the present data represent the first attempt to characterize hs-CtNl in healthy children from ages 1 through 18 years and should be of importance to the pediatric community at large.

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References


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Improved Performance of Point-of-Care and Over-the-Counter Qualitative Human Chorionic Gonadotropin Measurement Devices

To the Editor:

Several studies have demonstrated the susceptibility of qualitative human chorionic gonadotropin (hCG)1 measurement devices to false-negative results caused by high concentrations of hCG β core fragment (hCGβ cf) (1–3). Although the prevalence of these false negative results is unknown, it is clear that increased urine hCGβ cf concentrations can be observed during normal pregnancy. The use of such devices poses a risk to patients if treatment is inappropriately administered to pregnant women (4).

In a recent study (3), we evaluated the susceptibility of 11 point-of-care (POC) hCG devices to false-negative results due to hCGβ cf. We reported that 9 of the devices were affected by hCGβ cf. One of the 2 most affected devices was the Elite Plus by Cen-Med.

As a follow-up to that study, we tested 5 over-the-counter (OTC) devices (AccuSure 2 min Pregnancy Test, Lot# 3295937233, exp. 03/2016; Clearblue Plus Pregnancy Test, Lot# 3196937231, exp. 09/2015; EPT, Lot# 57477, exp. 10/2015; Equate Early Result Pregnancy Test, Lot# 65841, exp. 03/2016; First Response Early Result Lot# BU3183PA, exp. 06/2015). Intact hCG was obtained from Scripps Laboratories (C0714, lot 2436602, 11584 IU/vial). hCGβ cf was purified as described previously (3). hCG-negative urine was obtained from the BJH Chemistry Laboratory. Institutional review

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1 Nonstandard abbreviations: hCG, human chorionic gonadotropin; hCGβ cf, hCG β core fragment; POC, point-of-care; OTC, over-the-counter.