THE CORRELATION OF SERUM TROPONIN LEVELS WITH AGE AND GENDER IN HEALTHY INDIVIDUALS

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ABSTRACT

Background and Objectives: Cardiac Troponin (cTn) values play a pivotal role in the diagnosis of ischemic heart disease (IHD). The advent of high sensitivity assays of both cTnI and cTnT have revolutionized the way IHD is diagnosed and managed. These high sensitivity assays have also highlighted some hitherto unknown features of cTns. It is being suggested that healthy individuals have different values depending on their gender and age. This study was planned to study these differences in a healthy population.

Methods: A total of 700 apparently healthy individuals, 350 males and 350 females were included in the study. Their ages were also noted. Their cTnI values were recorded and analyzed to find the effect of age and gender on their cTnI levels. cTn I hs was detected on immunoassay analyser Siemens Atellica® Solution IM 1300 Analyzer, USA. The cut off for normal was taken at 45.2 pg/ml as per the company's manual.

Results: Males had mean=9.39+8.6 cTnI values and females had mean=6.57+5.66.There was a statistically significant difference in cTnI levels between males and females (p-value < 0.0001) with male subjects showing higher levels. Increasing age had a positive correlation with cTnI levels in both genders but it was not statistically significant (correlation coefficient, r, 0.178 for males and 0.246 for females).

Conclusion: The reference ranges for cTn values should be separately defined for males and females. Increasing age may have an influence on the diagnostic performance of cTns.These factors should be taken into consideration so that decision for each patient is individualized instead of assuming that the binary threshold criteria is set in stone.

Keywords: Cardiac troponin, ischemic heart disease, reference range, age, gender

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Ischemic heart disease (IHD) continues to pose an ever-increasing threat to our population. Once considered a disease of affluence, mainly affecting males, it has now become a disease involving all social classes and both genders. The prevalence of IHD in our population was reported to be 17% in adults over 30 years of age.[1] Similar figures were reported earlier too.[2] This is much higher than a developed country like USA where this figure is 7% only.[3] This is not surprising because our population is reported to have a high prevalence of its risk factors.

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Starting with diabetes, which is an established risk factor for IHD, according to latest data, Pakistan has the highest prevalence of diabetes in the world, i.e., 30.8%. This figure has been rising at an alarming rate through the years.[4-6] In addition, numerous large-scale studies in our local population have revealed an astounding prevalence of hypertension; it being 18% in people over 15 years of age and 33% in people over 45 years of age.[1,7,8]

It is paradoxical that a poor country like Pakistan, where a big segment of the population is undernourished, also faces a high percentage of obesity. According to a study 25% of our adult population is obese. This is much higher than the overall world obesity prevalence of 16% as reported by World Health Organization (WHO).[9-11] And finally, let's consider smoking which is another risk factor for IHD. The percentage of smokers in Pakistan is 20.20% vs 22.98% for the world.[12]

In this setting, it may be expected that our population would be afflicted with a high prevalence of IHD.

The accurate diagnosis of IHD is of paramount importance as timely institution of therapy is vital. The mainstay of this diagnosis are the levels of cardiac troponin I (cTnI) I or cardiac troponin T (cTnT). The traditional cTnI and cTnT assays have recently been replaced with "high sensitivity" ones. The cutoff values for these high sensitivity cardiac troponins (hs-cTn) are defined differently than conventional cTn values.[13]

Since the levels of cTn are going to determine the management of a suspected case of myocardial infarction, the cutoff levels need to be clearly defined. The current upper limits of hs-cTns are 45 ng/l for cTnI (Siemens ATELLICA high-sensitivity TnI) and 14 ng/l for cTnT (Roche cobas e601, e602, E170/ TnT Gen 5 STAT) respectively. These values have been defined keeping in view the overall 99th percentile.

By convention, these values are accepted to be the same for both genders. Several recent studies have pointed out that there may be gender specific differences in these values.[14-16] there are a number of analytes which have different values in men and women, hemoglobin for example[17]. Recently differences have been reported in CKMB and NT-pro BNP too. The former has been attributed to the larger muscle mass in males, while the latter may be due to the different influence of male and female sex hormones on the production of natriuretic peptides from the myocardium.

In-depth studies have also reported that the serum level of cTn might vary with age as well. The levels seem to rise with age.[18]

In this paradigm, this study was conducted to determine any gender- and age-based differences in cTn levels in our population. Accurate determination of these values could help clinicians in avoiding both overdiagnosis and underdiagnosis of myocardial damage.

METHODS

Ethical approval from the institutional Ethical Review Committee was obtained vide letter number RPTGME-Research 300-A.

Apparently healthy individuals from various areas of Lahore presenting to Punjab institute of cardiology as attendants of patients, were included in the study. The sample size was 700 which constituted 350 males and 350 females. Subjects of all age groups were included. Non purposive, consecutive sampling technique was used. It was an observational, cross-sectional study. The study took four months to be completed.

The ages, genders and cTn I hs values of the subjects were noted. cTn I hs was detected on immunoassay analyzer Siemens Atellica® Solution IM 1300 Analyzer, USA. The cut off for normal was taken at 45.2 pg/ml as per the company's manual.

Data were entered in Microsoft Excel version 2409. Correlation coefficient between age and cTnI levels was calculated separately for males and females and value of r was assigned. The serum levels of males and females were compared using t-test and p-value was calculated. p-value of 0.05 or less was taken as significant.

RESULTS

A total of 700 patients were included in the study. This included 350 males and 350 females. The age range for males was 14-73 years, while for females it was 20-85 years.

The cTn I levels for males ranged from 2.5 to 44.59 ng/lit while for females it ranged from 2.5 to 26.2 ng/lit (Table 1)

On comparison of cTn I levels between males and females the difference was found to be extremely significant with a p-value < 0.0001. (Figure 1)

Table 1: *Gender Distribution of Subjects*

Gender	Mean	Median	Standard deviation	P value
Males	9.39	4.215	8.6	≤ 0.0001*
Females	6.57	2.94	5.66	

**calculated using t-test*

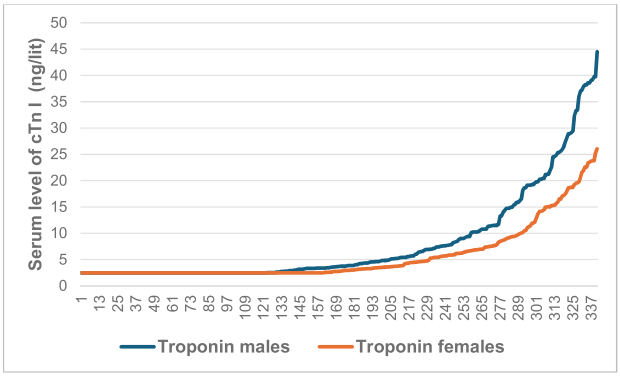

Figure 1: *Graph showing comparison of cTnI levels (ng/lit) in males and females.*

As regards the correlation of cTn I levels with age, the cTn levels showed a positive correlation with advancing age in both males or females, but this correlation was weak for both genders and did not reach statistical significance. The correlation coefficient (r) was 0.178 for males and 0.246 for females (Figure 2,3).

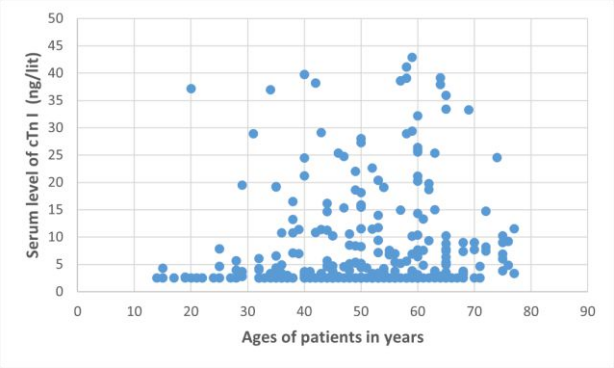

Figure 2: *Graph showing weak positive correlation (0.178) between age (years) and troponin levels (ng/lit) in males*

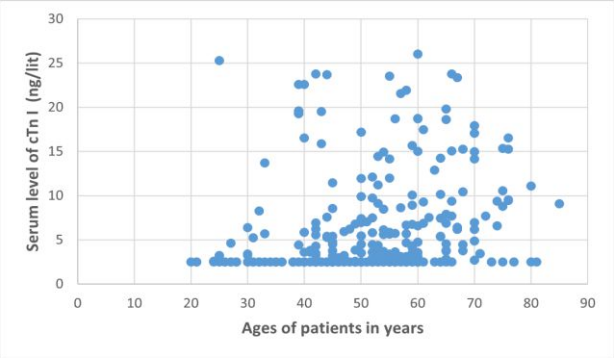

Figure 3: *Graph showing weak positive correlation (0.246) between age (years) and troponin levels (ng/lit) in females*

DISCUSSION

IHD continues to be the leading cause of death in humans. It was responsible for roughly one in every five deaths in the year 2022.[19] The immense disease burden makes it an active area of research. This coupled with the fact that a lot of these deaths were avoidable makes it even more imperative that every etiological aspect of disease is thoroughly studied.

Most patients suffering from IHD present with complaints of chest pain. But as is well known chest pain can stem from multiple causes.[20] Hence, a clearcut ruling in or ruling out of IHD is the first challenge faced by clinicians. As discussed above, cTn levels are going to be the mainstay of diagnosis which would guide further management strategies.[21] This necessitates that the cutoff values between normal and diseased individuals are clearly defined. This was the aim of this study.

The study included 700 patients, 350 each of males and females. The sample size calculated with 95% confidence interval came out to be a total of 385 but given the importance of the issue, calculations were redone with 99% confidence interval.[22]

The age range for males was 14-73 years, while for females it was 20-85 years. The study was carried out without age limit cutoffs to study the effect of age on cTn levels. There was a positive correlation of advancing age in both genders (correlation coefficient 0.178 for males and 0.246 for females) though it did not reach statistical significance. Previous studies have also reported this rising trend with some showing a significant rise in cTn levels with age. This could be due to variation in population or because of the large sample size of the study. The study included almost 20,000 patients.[23]

Another review reported similar results with rising baseline levels of cTn with advancing age. It reported a marked rise in cTn levels with advancing age and recommended that these levels be redefined in people of advanced ages. One difference was that this review included only studies on cTnT hs while our study was done with cTnI hs.[18]

Difference in levels of cTns between both genders have been reported in multiple previous studies.[18,24,25] This was supported by a p-value of <0.0001 in our study where the baseline values of cTnI were clearly higher for males than females. The finding is not new. It was reported as far back as 2003 but since today's high sensitivity assays had not yet emerged the differences were small and ignored. The increasing sensitivity of emerging assays has highlighted these differences.[14]

Hence, there is mounting evidence to suggest that the upper limits of normal should be separately defined for males and females. Age of the patient should also be taken into consideration though its significance is not yet established.[26]

The study does not have detailed demographic data of the population. Consideration of other intercurrent diseases like diabetes and hypertension could have provided further information.

CONCLUSION

The reference ranges for cTn values should be separately defined for males and females. Increasing age also has an influence on the diagnostic performance of cTns, the test shows reduced specificity and reduced positive predictive value in older patients. These factors should be taken into consideration so that decision for each patient is individualized instead of assuming that the binary threshold criteria is set in stone.

Ethical Approval:

The ethical Approval was obtained vide letter no. RTPGME-Research-300-A.

Conflict of Interest: *None*

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