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ORIGINAL ARTICLE

Nomograms for Physiologically Normal QT Interval in Healthy Children

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ABSTRACT

Objective: QT interval is an independent risk factor towards sudden deaths. QT interval mathematical correction formulae lead to under or over diagnosis as these were not designed for high heart rates found in children. This study was aimed at developing nomograms for calculating physiologically normal range of QT interval in children.

Study Design: It was community based cross sectional observational study.

Place and Duration of Study: The study was conducted at The Children's Hospital, Lahore, Pakistan from July 2020 to Feb 2021.

Material and Methods: A 12-lead screening electrocardiogram was recorded on children invited from local urban community. ECGs manually assessed for conduction time. Mean with 2SD assessed. Regression tests applied and outliers removed. Quantile charts plotted with multiple trendlines.

Results: A total of 1256 children had screening ECG done with M:F;1.2:1 and mean age was 47.3 $\pm$ 35.1 months. Mean heart rate was 110 $\pm$ 24 beats per min. Mean QT interval was 317 $\pm$ 41 msec. Centiles were curtailed to 5, 10, 25, 50, 75, 90 and 95th centile for relevant nomograms. Cubic regression fitted the model best. Males showed wider area of dispersion and slightly higher centile values in young children.

Conclusion: Assessing QT interval using 5th and 95th centiles on nomogram can better identify prolonged or short QT interval efficiently. Hence, over and under diagnosis of prolonged or short QT interval can be avoided, preventing unnecessary anxiety and burden of tests for further evaluation on one hand, and readily identifying outliers with actual risk on the other hand among children.

Key Words: *Child, Electrocardiogram, Infant, Heart conduction system, Long QT interval.*

INTRODUCTION

QT interval is defined as the time duration between start of QRS complex till the end of T wave during cardiac cycle. This interval is the electrical depiction of ventricular depolarization followed by repolarization as the electrical impulse crosses AV node. Prolonged QT interval has significant clinical implications in terms of propensity to develop torsade de Pointes with a potential risk of sudden death. QT interval,

measured through electrocardiogram (ECG) is well studied in adult population and comprises a major diagnostic component in labeling Long QT Syndrome using Schwartz or Keating criteria.[1-3] Corrected QT interval used in these criteria mainly aims to nullify the effects of higher heart rate resulting in shortening of QT interval. The same principle has been attempted to replication in the pediatric population.[4,5] There are limited data on actual normal QT interval in children specially infants and young children.

Infants and young children tend to have higher heart rates. The most commonly utilized Bazett's formula is designed for correcting heart rate between 60-100 beats per min. The usual heart rate in young children is generally above this threshold.[6] Various other formulae have been advocated with variable success including Fridericia, Framingham and Hodges along with independent attempts to find a representable exponential constant for RR interval adjustment.[7-10] Applying the same formulae on younger children in various cohorts has resulted in under-diagnosis or over-diagnosis due to overcorrection and under-correction at various heart rates respectively in children.[4,11,12]

On the one hand, it may leave out certain children from diagnosis but more importantly and frequently leads to over-diagnosing children with "possible" Long QT syndrome rather than evaluating further for other underlying pathologies. There are a couple of nomograms for upper limits of QT interval calculated from adult population data and higher heart rates are only theoretically extrapolated.[13] There are no actual physical data supporting these extrapolations. Thus, children are subjected to undue physical restriction, limiting medication options in certain indications as well as giving an unnecessary mental stress to children and their parents. On the other end of spectrum, these formulae and nomograms cannot help in identifying recently highlighted "Short QT syndrome" due to lack of standardization for lower limits. As a result, no unified guideline exists.[14,15]

In this study, we aimed to find normal QT interval at various heart rates and their variability with age and gender to provide a guiding threshold of physiological normality at upper and lower centiles rather than empirically labeling children with short or long QT syndrome.[16]

MATERIAL AND METHODS

The study was conducted at The Children's Hospital and Institute of Child Health, Lahore, Pakistan from July 2020 to Feb 2021 after obtaining consent from the parents. Ethical Review Board (ERB) approval was taken vide reference number 2021-451-CHICH. To include a more general healthy population, parents (randomly selected households) from various localities of the city were invited to bring their children for routine checkup and screening ECG as part of the study. Invitations were repeated in localities with response rate less than 85% in an attempt to include a truly randomized population. Considering a general population distribution, with confidence interval 95% and margin of error 3%, sample size was estimated to be 1068 children. Considering at least 85% response rate, ECG was planned to be performed on nearly 1200 children. A formal history and a general physical examination were undertaken to rule out any acute or chronic ailment. Children on any medication or having any pathological signs or symptoms were excluded from the study. All healthy children up to 10yr of age were enrolled in the study. A 12-lead digital ECG was recorded in all children without any sedation around noon (1100-1300hrs).[17] All ECGs were evaluated manually by two consultant pediatric cardiologists (AUQ, SNH) blinded to each other's assessment. Lead II was taken as a reference lead. Lead V5 was used if Lead II not clear (0.8% cases).[18] QT interval was measured using tangent method, drawing a tangent along the steepest slope of the T wave and point of intersection with iso-electric line was labeled as end of T wave. QT interval was measured from start of QRS complex till the end of T wave as labeled earlier.[5,19,20] Average of QT intervals from three consecutive sinus beats was recorded. R-R interval was taken as the average of same three consecutive sinus beat QRS complexes. Age, gender, heart rate and QT interval were recorded for each ECG. The data were entered in SPSS v. 17 and analyzed using its statistical software. Graphs were plotted through Microsoft Excel 2016. Mean with standard deviation was calculated for normally distributed data. Median with range was calculated when test of normality failed to provide optimal result using Kolmogorov-Smirnov or Shapiro-Wilk test.

Frequencies were calculated for nominal data. Pearson and Spearman correlation were calculated for quantitative and qualitative data respectively. Chi square test was used to find statistically significant difference between variables considering $p<0.05$ as significant. Linear and log-linear regression tests were applied and outliers were removed (n=3). Quantile charts (1^{st}, 3^{rd}, 5^{th}, 10th, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th}, 97^{th} and 99^{th}) were plotted with linear, logarithmic and polynomial trendlines and R^2 value for each documented to find best fit model.[9]

RESULTS

A total of 1256 children had screening ECG done. Out of these, 11 children were excluded due to vibrations on ECG recording making delineation of iso-electric line and/or T wave morphology difficult. Further 36 children were excluded due to presence of right bundle branch block and 4 children due to presence of pre-excitation delta waves to limit confounding factors. Finally, 1205 children were included in the study with M:F;1.2:1 similar to national demographics (p=0.28). Mean age was 47.3 + 35.1 months (Median age 48 months, (range 1-120 months) with acceptable normal distribution (skewness 0.17, kurtosis -1.4) and no significant difference between either sex (Male mean age 48.3 + 35.5 months, median 48 Mo (1-120 Mo), Female mean 46.1 + 34.6 months, median 42.5 Mo (1-120 Mo), p=0.27). Twenty eight percent children were below 1yr, 32% between 1 and 5 yrs and 40% 5 to 10 yrs old. Mean heart rate was 110 + 24 beats per min (bpm), median 109 bpm, range 42-192 bpm with normal distribution (skewness 0.3, kurtosis 0.2). There was no significant difference between males (mean 110 + 25 bpm, median 107, range 42-188 bpm) and female children (mean 110 + 23 bpm, median 110, range 55-192bpm), p = 0.9. Mean QT interval was 317 + 41 msec (Median 320msec, range 180-460 msec) with normal distribution (skewness 0.4, kurtosis 0.6, 3 outlier cases omitted). There was no significant difference between male (mean 318 + 42msec, median 320msec, range 192-460 msec) and female children (mean 316 + 40 msec, median 320 msec, range 180-460 msec), p=0.48. QT interval distribution was plotted for various age groups (fig 1). Heart rate had a significant negative correlation with age as expected (Pearson correlation -0.48, $p<0.001$). There was also significant negative correlation between heart rate and QT interval (Pearson Correlation -0.748, $p<0.001$). The correlation was similar in both genders (Male -0.747, Female -0.751, $p<0.001$). Logarithmic regression analysis showed a moderate model fit ($R^2=0.56$, $p<0.001$) (fig 2). Regression analysis showed a rapid fall in physiological heart rate in first 9months of life (fig 3). QT nomogram showed good model fit R^2 value across all centiles (fig 4).QT interval showed a similar regression curve at various ages (fig 2).

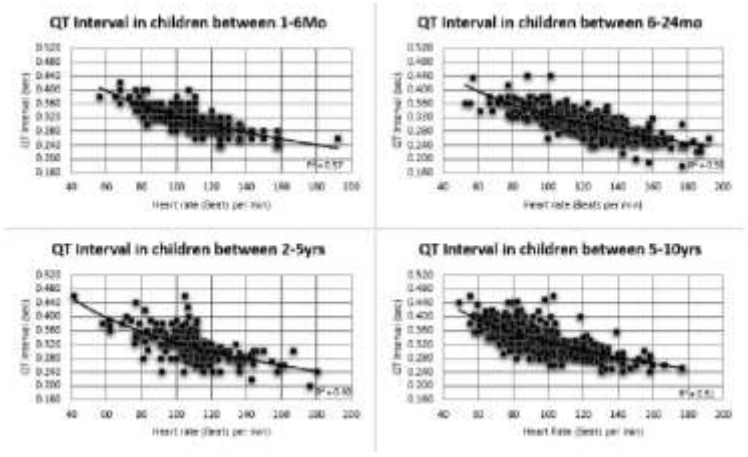


Fig1: QT interval distribution in various age groups in children (n=1205)

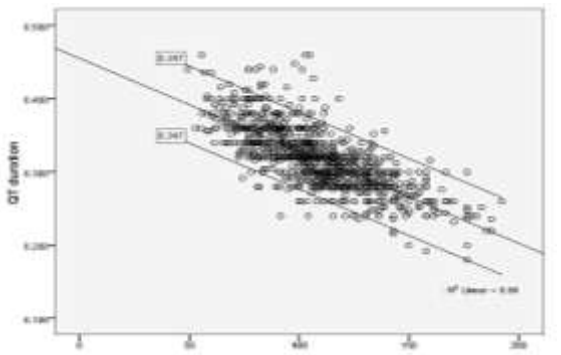


Fig 2: Regression analysis showing shorter QT interval with increasing heart rate (n=1205).

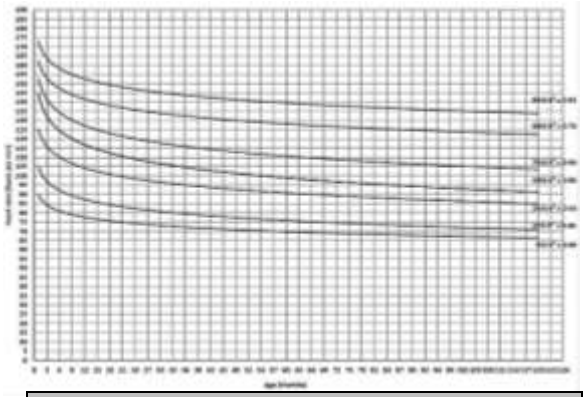


Fig 3: Variation in heart rate with age (n=1205)

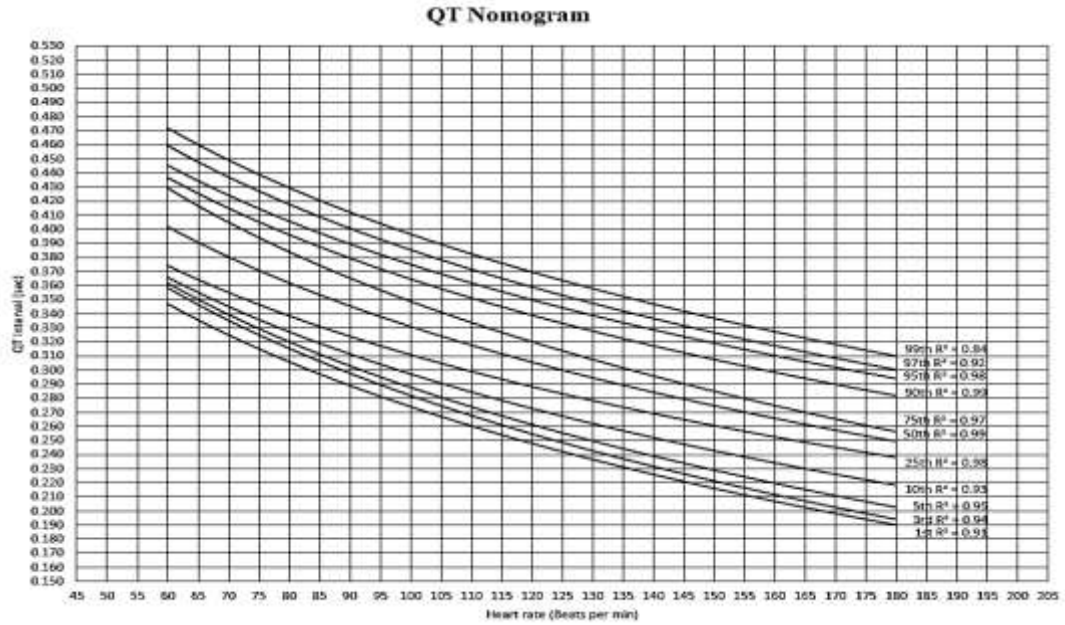
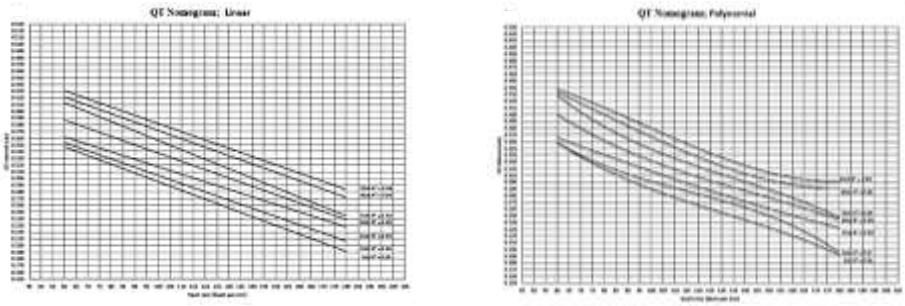
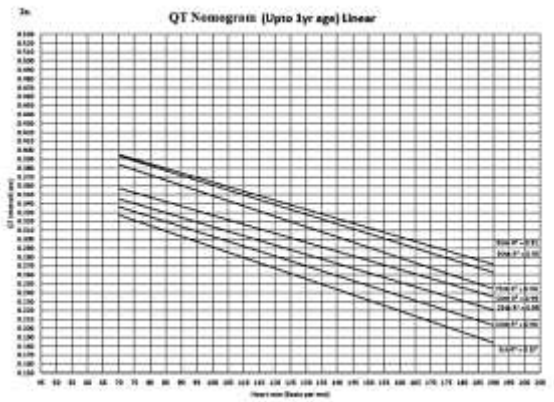
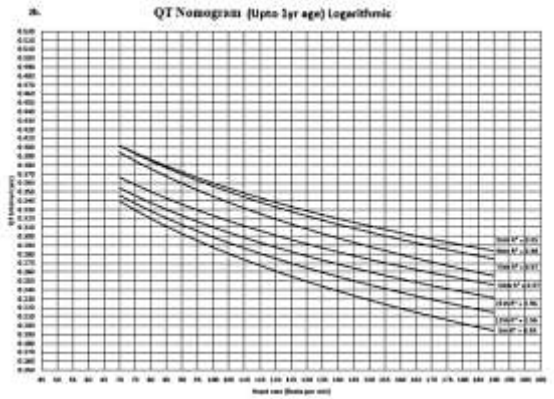


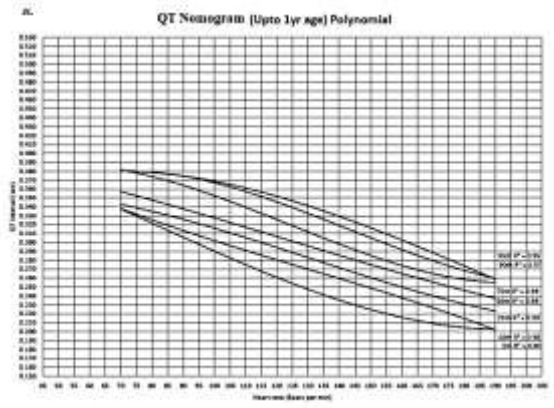
Fig 4: QT Nomogram for QT interval in indexed pediatric population (n=1205).



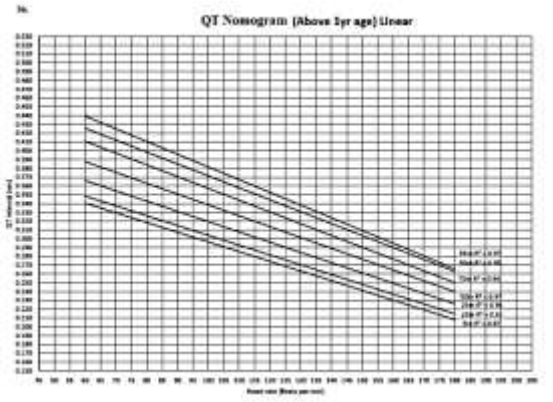
Graph 1: QT Nomogram for QT interval in linear and polynomial distribution (n=1205)

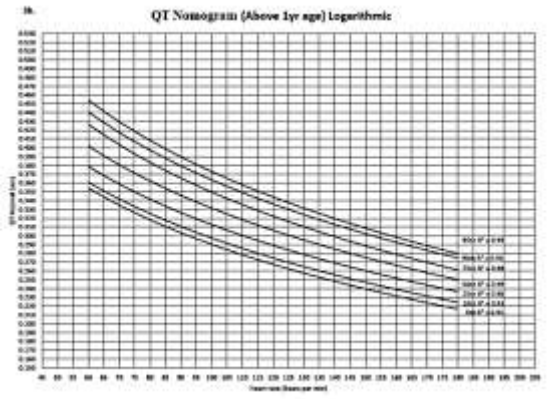


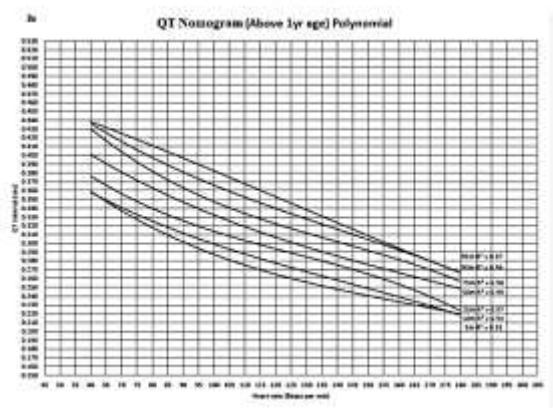




Graph 2: QT interval nomogram for children less than 1yr age in linear (a), loglinear (b) and polynomial (c) distribution (n=338/1205).







Graph 3: QT interval nomogram for children aged 1yr and above in linear (a), loglinear (b) and polynomial (c) distribution (n=867/1205).

Considering 2 standard deviations almost equating to 95 centiles, the graphs were curtailed to 5, 10, 25, 50, 75, 90 and 95th centile for developing a clinically relevant nomogram following removal of outliers (n=3). The nomogram was compared using linear, logarithmic and polynomial regression and evaluated with R^2 value giving the most representable nomogram

curve for various centile (graph 1). Linear curve produced R^2 0.95 and 0.96 for extreme (5^{th} and 95^{th}) centiles. Logarithmic and polynomial curve presented values 0.95, 0.98 and 0.96, 0.99 respectively. Polynomial curve (3^{rd} order-cubic expression) was best fit with acceptable dispersion at either value extremes with wider variance in polynomial curve. As the physiological heart rate drastically decreased during first year of life, population was divided into two subgroups. Nomograms were constructed for children up to 1 yr of age (graph 2 a,b,c) and children older than 1 yr (graph 3 a,b,c), using same sequence of calculations. In both instances, polynomial (3^{rd} order, cubic) regression line was found to be most useful and robust mode of documenting upper as well as lower limits of physiological QT interval. The groups were further divided by gender using cubic regression trendline for above mentioned centiles. There was no statistical difference between male and female children up to 10 yr age for QT interval at various heart rates, though males had a wider area of dispersion and slightly higher centile values (graph 4 a-f).

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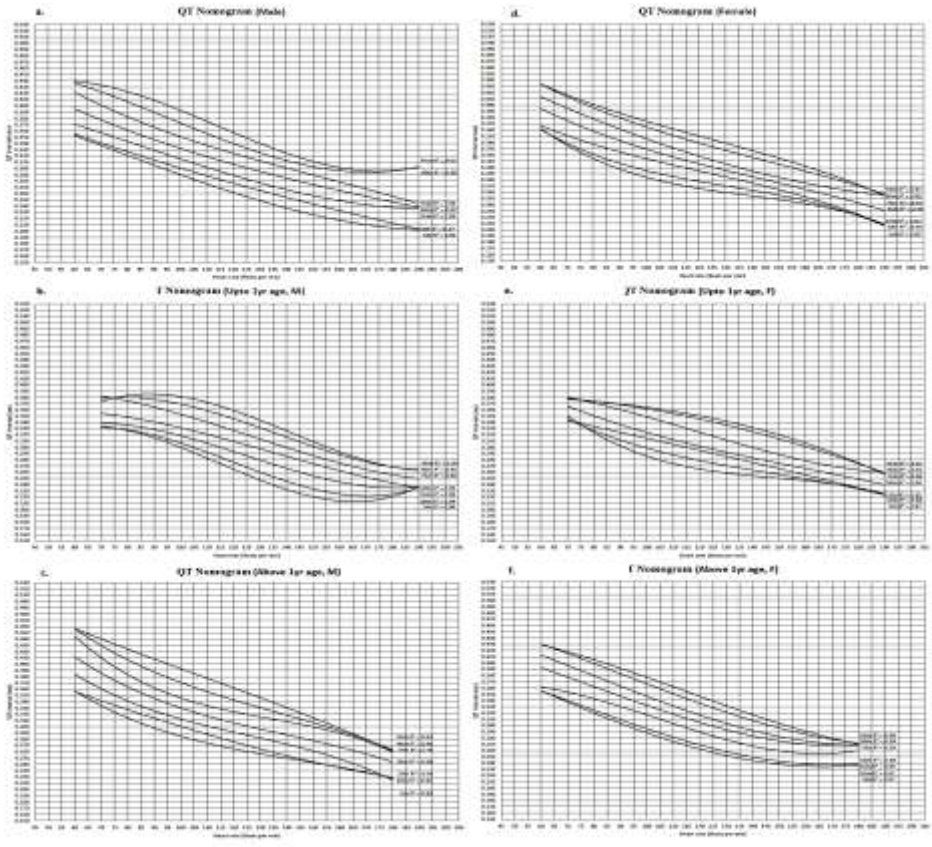

Graph 4: QT interval nomogram for male (a, b, c) and female (d, e, f) children in various age groups (polynomial distribution) male n=647/1205, female n=558/1205

DISCUSSION

Electrocardiography (ECG) is a vector representation of cardiac electrical cycle being clinically used since late 19^{th} century. The ventricular component of this cycle includes ventricular rapid depolarization resulting in ventricular systole and depicted as QRS Complex on ECG. Slower repolarization resulting in ventricular diastole is depicted as T wave. The whole ventricular depolarization-repolarization

sequence depends on cascade of events controlled and modulated by ATP driven ion exchange channels involving NA, K, Ca and Li.[21,22] The whole sequence duration is measured on ECG as QT interval staring from beginning of QRS complex and ending at T wave end. QT interval has long known to be heart rate dependent and various methods to mathematically standardize QT interval at various heart rates has been tried with varying degree of success.

Major interest on actually prolonged QT interval started to appear in early 1990's with genetic recognition of various channelopathies leading to prolonged QT interval, collectively dubbed as long QT interval syndrome (LQTS). Certain modifications were further introduced to demarcate an actual upper limit for "normal" QT interval. Adult population ECGs were reviewed to determine the normal trends. Unfortunately, such data lacked higher heart rates and upper limit for "corrected" QT interval was merely extrapolated from adult data. Hence, when correlated with actual clinical scenarios, a wide grey area range of 40 msec appeared which couldn't be labeled normal or abnormal.

A major limitation arose when the same procedure was adapted for young children who have naturally higher heart rates resulting in false positive prolonged QT interval reports. Such over diagnosis results in undue investigations, physical activity limitation and extreme anxiety for child and parents alike.[23] Our study provides a readily available graphical expression of inter subject QT variability and clear demarcation of values within 2SDs and beyond.

Recently, increasingly emerging reports about Short QT syndrome as one of possible reasons for sudden death has also increased the need for availability of lower limits for QT interval. Another major limitation with QT correction formulae is a lack of information for lower limits of QT interval. Our study highlights importance of nomogram as it provides information about short QT interval with similar ease.

Our study supports the previously documented finding about variation in QT interval with heart rate though correlation was not very high.[6,24] Moreover, it demonstrates a more rapid fall in heart rate during first year of life. Various other studies mention a later age for maximum reduction trend for heart rate.[25] However, they didn't have children younger than 1 yr. This finding requires a nomogram as presented in our study to avoid under as well as over-diagnosis of abnormal QT interval.

Our study showed no gender difference in children. This finding was in accordance with previously published data.[25] Our data showed similar finding as previous reports with male children having slightly shorter QT interval at higher heart rates compared to female children.[25] An interesting finding was the reverse distribution in children less than 1 yr age when compared between the two genders. Male children had a slightly (~10msec) wider dispersion of QT interval rather than just longer QT interval. This finding suggests dynamics of QT interval stability changes variably till older childhood and needs to be considered through plotting each individual against a nomogram rather than any mathematical correction. The adult pattern starts developing in early adolescence.[25] It was also found in Dutch children data where older children between 11-16 yr than our studied age group demonstrating the age of transition into adult pattern of QT interval distribution.[25] As depicted graphically, the QT interval had a wider range for upper as well as lower limits at 2SD at all ages from 1 month to 10 years. This finding suggests that male individuals could be a higher risk of Short QT syndrome which would be missed easily while using Corrected QT values.

Limitation of Study: None

CONCLUSION

Assessing QT interval using 5th and 95th centiles on nomogram can better identify prolonged or short QT interval efficiently. Hence, over and under diagnosis of prolonged or short QT interval, being a possible cause for sudden death can be avoided, preventing unnecessary anxiety and burden of tests for further evaluation on one hand, and readily identifying outliers with actual risk on the other hand among children.

Conflict of interest: None

Disclosures: None.

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