Congenital Heart Disease

Tech Science Press

DOI: 10.32604/chd.2024.045953

ARTICLE

Comparison of QT Correction Methods in the Pediatric Population of a Community Hospital: A Retrospective Study

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Received: 12 September 2023 Accepted: 01 February 2024 Published: 20 March 2024

ABSTRACT

Objective: Accurate measurement of QT interval, the ventricular action potential from depolarization to repolarization, is important for the early detection of Long QT syndrome. The most effective QT correction (QTc) formula has yet to be determined in the pediatric population, although it has intrinsically greater extremes in heart rate (HR) and is more susceptible to errors in measurement. The authors of this study compare six different QTc methods (Bazett, Fridericia, Framingham, Hodges, Rautaharju, and a computer algorithm utilizing the Bazett formula) for consistency against variations in HR and RR interval. **Methods:** Descriptive Retrospective Study. We included participants from a pediatric cardiology practice of a community hospital who had an ECG performed in 2017. All participants were healthy patients with no past medical history and no regular medications. **Results:** ECGs from 95 participants from one month to 21 years of age (mean 9.7 years) were included with a mean HR of 91 beats per minute (bpm). The two-sample paired *t*-test or Wilcoxon signed-rank test assessed for any difference between QTc methods. A statistically significant difference was observed between every combination of two QTc formulae. The Spearman's rank correlation analysis explored the QTc/HR and QTc/RR relationships for each formula. Fridericia method was most independent of HR and RR with the lowest absolute value of correlation coefficients. Bazett and Computer had moderate correlations, while Framingham and Rautaharju exhibited strong correlations. Correlations were positive for Bazett and Computer, reflecting results from prior studies demonstrating an over-correction of Bazett at higher HRs. In the linear QTc/HR regression analysis, Bazett had the slope closest to zero, although Computer, Hodges, and Fridericia had comparable values. Alternatively, Fridericia had the linear QTc/RR regression coefficient closest to zero. The Bland-Altman method assessed for bias and the limits of agreement between correction formulae. Bazett and Computer exhibited good agreement with minimal bias along with Framingham and Rautaharju. To account for a possible skewed distribution of QT, all the above analyses were also performed excluding the top and bottom 2% of data as sorted by heart rate ranges (N = 90). Results from this data set were consistent with those derived from all participants (N = 95). **Conclusions:** Overall, the Fridericia correction method provided the best rate correction in our pediatric study cohort.

KEYWORDS

Corrected QT interval; QT prolongation; long QT syndrome; electrocardiogram; retrospective study; bazett; fridericia; framingham; hodges; rautaharju; computer algorithm

1 Introduction

The QT interval represents the ventricular action potential from depolarization to repolarization [1]. Long QT Syndrome (LQTS) is both an acquired and inherited arrhythmia disorder characterized by a prolonged QT interval. The disorder can clinically manifest with syncope, palpitations, and in severe cases sudden cardiac arrest due to Torsade de Pointes [2]. Over 17 genes contributing to ion-channel function have been implicated in congenital LQTS [2–4]. Accuracy of QT measurement, therefore, is imperative for the early detection of LQTS and initiation of appropriate therapy to prevent morbidity and mortality. As QT interval is strongly affected by heart rate (HR), several formulae have been proposed to correct for this relationship. The ideal formula would eliminate any relationship between HR (or RR interval on ECG) and the corrected QT interval (QTc).

Bazett and Fridericia describe an exponential relationship between QT *vs*. RR or HR [5,6]. Bazett developed a formula estimating the duration of systole with varying pulse rates from a study of 39 subjects, which was later adapted to relate QT prolongation to acute rheumatic carditis in children [5,7,8]. Fridericia proposed a relationship between the duration of ventricular repolarization (QT) and pulse period (RR) through a study of 50 subjects with a cutoff of 430 milliseconds (ms) as the definition of prolonged [9]. On the other hand, Framingham, Hodges, and Rautaharju suggested a linear relationship between QT *vs*. RR or HR [10]. The Framingham formula integrated data from 5,018 subjects with a median age of 44 years comprising the Framingham Heart Study to create a linear regression model for correcting QT according to RR cycle length [10]. In response to the discrepancies identified with the non-linear Bazett and Fridericia formulae, Hodges developed a linear QTc formula from a study of 607 subjects [11]. Rautaharju, a newer formula, derived from 57,595 patients ranging from five to 89 years of age with a cutoff of 477 ms; Rautaharju additionally introduced a sex coefficient to account for observed differences in QT duration by sex [12].

The parameters of each formula are detailed in Table 1. Across all formulae, QTc is equivalent to QT at a HR of 60 bpm (frequency of 1 Hz) [13].

Table 1: Correction formulae evaluated in our study

Formula	Function of HR	Function of RR
Bazett	$QT\ (HR/60)^{1/2}$	$QT\ (RR)^{-1/2}$
Fridericia	$QT\ (HR/60)^{1/3}$	$QT\ (RR)^{-1/3}$
Framingham	QT + 154 (1 – 60/HR)	QT + 0.154 (1000 – RR)
Hodges	QT + 1.75 (HR – 60)	QT + 105 (1/RR – 1)
Rautaharju	QT – 185 (HR/60 – 1) + k k = 6 ms [male], 0 ms [female]	QT – 0.185 (RR – 1) + k k = 6 ms [male], 0 ms [female]

Both intra-subject [14,15] and inter-subject [16,17] differences in QTc/HR patterns have been demonstrated. Although the robustness of different QTc formulae against intra-subject and inter-subject variations in HR has been well-explored in adults, it has been less examined in the pediatric population that has intrinsically greater extremes of HR and is more susceptible to errors in QT measurement. Our study aims to determine which formula provides the best rate correction within the pediatric population and to assess if the computer-algorithm utilized by our ECG machine is a reliable method of QT correction compared to manual calculation.

2 Methods

This is a descriptive retrospective study. We included patients in the pediatric cardiology practice of a community hospital who had an ECG performed in the year 2017. We reviewed the age, sex, past medical history, and relevant medications of each participant. We excluded all participants with a past medical history (including cardiovascular disease) as well as those on regular medications. Only the first ECG was retained for each participant. The demographic and ECG parameters associated with each participant may be available upon request. We examined the ECGs for rhythm, HR, QT, RR, and QRS intervals. ECGs with missing leads or excessive noise were removed, along with those with a QRS duration above 120 ms and those not in sinus rhythm. Participant demographics were evaluated using mean and standard deviation (SD) for continuous variables, and frequency and percent for categorical variables. We calculated the QTc interval using the Bazett, Fridericia, Framingham, Hodges, and Rautaharju formulae as well as the computer algorithm. The Marquette™ 12SL™ ECG Analysis Program was utilized for the computer calculation of QTc, which reports the Bazett-corrected measurement of QTc [18].

The overall cohort is described through descriptive statistics. Wilcoxon rank sum test compared clinical characteristics and QTc values between male and female participants. Spearman's rank correlation tests evaluated for potential correlations between two variables. Two-sample paired *t*-test or Wilcoxon signed-rank test, as appropriate, assessed for potential differences between every combination of two QTc methods, with *p*-values adjusted according to the Benjamini-Hochberg method. Separate univariate linear regression models determined potential associations between QTc measurements and HR or RR. Bland-Altman Plots evaluated for agreement between two QTc formulae.

All analyses were also performed by excluding the top and bottom 2% of the data as sorted by HR ranges according to the method adopted by Luo et al. [19]. This group adopted the top and bottom 2% of data instead of the traditional mean ± 2 SD to demarcate the upper and lower normal limits of QTc distributions for each formula on the basis that the characteristics of QT distributions are not clear, possibly following a skewed distribution [20].

All *p*-values are two-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were performed in R Version 4.1.2 (The R Foundation for Statistical Computing).

This study was reviewed and approved by the Institutional Review Board at the New York Presbyterian Brooklyn Methodist Hospital (IRB number 1792968).

3 Results

3.1 Descriptive Statistics

A total of 95 participants were eligible for inclusion in our study. Descriptive statistics are presented as mean ± SD. There were no congenital heart defects among these participants. Our participant population included infants and children from ages one month to 21 years, with a mean age of 9.7 years (SD 6.4) (Table 2). Mean HR was 91 bpm (SD 29), mean RR interval was 717 ms (SD 205), and mean QT interval was 349 ms (SD 44) (Table 2).

Bazett and Computer had the highest mean QTc of 418 ± 23 ms (Table 2). Framingham and Rautaharju had the lowest mean of 349 ± 44 ms, which was also equal to the uncorrected QT. Adopting the definition for prolonged QTc as >440 ms in males or >460 ms in females [21], 10 participants in our cohort would have been falsely identified as having a prolonged QTc according to Bazett, compared to nine in Computer and none in the remaining formulae. The HR of individuals identified with a prolonged QTc varied from 75 to 123 bpm. According to literature, Bazett formula is considered to be accurate for HRs between 60 to 100 bpm, with a tendency to over-correct at HRs > 100 bpm and under-correct at HRs < 60 bpm [22]. Computer (SD = 23 ms), Bazett (23 ms), Fridericia (21 ms), and Hodges (18 ms) all led to decreases in SD compared to uncorrected QT (44 ms), indicating a reduced variability in QTc. SD was unchanged for Framingham (44 ms) and Rautaharju (44 ms). If the threshold for QTc prolongation is set as 2 SD from the mean, Computer and Bazett would require a QTc value > 464 ms for the diagnosis of prolonged QT, Hodges > 440 ms, Framingham and Rautaharju > 438 ms, and Fridericia > 435 ms.

Table 2: Mean and SD of participant demographics, ECG parameters, and QTc calculations for all participants and as stratified by sex

Characteristic	N = 95 Mean (SD)	Female, N = 41[1] Mean (SD)	Male, N = 54[1] Mean (SD)	*p*-value[2]
Age (yrs)	9.7 (6.4)	8.9 (6.7)	10.4 (6.2)	0.274
HR (bpm)	91 (29)	98 (28)	86 (28)	0.009
RR (ms)	717 (205)	658 (181)	762 (212)	0.009
QT (ms)	349 (44)	340 (43)	356 (43)	0.048
Computer	418 (23)	424 (22)	413 (24)	0.049
Bazett	418 (23)	424 (22)	414 (24)	0.050
Fridericia	393 (21)	394 (22)	393 (21)	0.991
Framingham	349 (44)	340 (43)	356 (43)	0.051
Hodges	404 (18)	407 (18)	401 (18)	0.127
Rautaharju	349 (44)	340 (43)	356 (43)	0.048

Note: [1]Mean (SD). [2]Wilcoxon rank sum test.

In our study cohort, 43% of participants were female, while 57% were male. Comparisons between females and males were based on a Wilcoxon rank sum test. A statistically significant difference was observed between males and females for the following parameters: HR, RR, uncorrected QT, Computer, and Rautaharju (Table 2). Discrepancies in HR, RR, and uncorrected QT may attribute to the small sample size of our study, differences in the age distribution of females *vs*. males, or physiological differences between the sexes.

3.2 Associations between QTc Formulae

3.2.1 Spearman's Rank Correlation Tests

Spearman's rank correlations between formulae were linear. Spearman's correlation between Computer and Bazett was 0.999 ($p < 0.001$), signifying an extremely strong positive correlation between the formulae (Table 3). A correlation coefficient of 1 was observed between Framingham and Rautaharju ($p < 0.001$). Statistically significant positive correlations were also noted between Computer *vs*. Fridericia and Computer *vs*. Hodges (Table 3).

Table 3: Spearman's rank correlation coefficients (ρ) between two QTc formulae with statistically significant *p*-values

QTc method 1	QTc method 2	ρ	*p*-value
Computer	Bazett	0.999	<0.001
Computer	Fridericia	0.586	<0.001
Computer	Hodges	0.84	<0.001

(Continued)

Table 3 (continued)

QTc method 1	QTc method 2	ρ	*p*-value
Bazett	Fridericia	0.59	<0.001
Bazett	Hodges	0.84	<0.001
Fridericia	Framingham	0.67	<0.001
Fridericia	Hodges	0.43	<0.001
Fridericia	Rautaharju	0.67	<0.001
Framingham	Rautaharju	1.00	<0.001

3.2.2 Two-Sample Paired t-Test or Wilcoxon Signed-Rank Test

Two-sample paired *t*-test or Wilcoxon signed-rank test, as appropriate, examined for any difference in each combination of two QTc values (*p*-value adjusted with fdr method because of multiple comparisons). A statistically significant difference was observed between every combination of two QTc values (Table 4).

Table 4: Two-sample paired *t*-test or Wilcoxon signed-rank test, as appropriate, assessing for the difference between each combination of two QTc methods

QTc method 1	QTc method 2	*t*-value	Adjusted *p*-value
Computer	Bazett	−13.96	<0.001
Computer	Fridericia	12.20	<0.001
Computer	Framingham	4257.50	<0.001
Computer	Hodges	10.10	<0.001
Computer	Rautaharju	4427.00	<0.001
Bazett	Fridericia	12.57	<0.001
Bazett	Framingham	4264.00	<0.001
Bazett	Hodges	10.64	<0.001
Bazett	Rautaharju	4436.00	<0.001
Fridericia	Framingham	4258.00	<0.001
Fridericia	Hodges	−5.00	<0.001
Fridericia	Rautaharju	4430.00	<0.001
Framingham	Hodges	81.00	<0.001
Framingham	Rautaharju	18.00	<0.001
Hodges	Rautaharju	4454.00	<0.001

3.3 Relationship between QTc Formula and Heart Rate

3.3.1 Spearman's Correlation Coefficient

Spearman's rank correlation analysis determined the relationship between each QTc formula and HR. Our null hypothesis (H0) stated that there is no correlation between the two variables, such that the Spearman's correlation coefficient (ρ) is equal to 0, and there is no monotonic association (inclusive of a linear relationship) between the tested variables. The alternative hypothesis (Ha) asserted the presence of a correlation between each QTc formula and HR, such that ρ is not equal to 0. A correlation coefficient approaching ±1 indicates a stronger correlation. A negative correlation coefficient indicates an inverse relationship between variables (i.e., the higher the HR, the lower the QTc), while a positive correlation coefficient signifies a direct relationship between the variables (the higher the HR, the higher the QTc). Framingham and Rautaharju demonstrated the strongest correlation with HR, both with a ρ of −0.89 (*p*-value < 0.001) (Fig. 1, Table 5). Fridericia had the lowest ρ of −0.34 (*p*-value < 0.001). Hodges (ρ = 0.45, *p*-value < 0.001), Bazett, and Computer had positive coefficients. Bazett and Computer had the same coefficient of 0.50 (*p*-value < 0.001), indicating a moderate correlation between the formulae and HR. In other words, QTc calculations by Bazett and Computer were not independent of HR.

3.3.2 Linear Regression

A linear regression analysis of QTc/HR was conducted to evaluate for the robustness of each formula to changes in HR (Table 6). The formula with a slope closest to zero would provide the best rate correction in our population, minimizing the influence of HR on QTc. Bazett, Computer, and Hodges had positive slopes, denoting a tendency to over-correct QTc at higher HRs and under-correct at lower HRs. Fridericia, Framingham, and Rautaharju had negative slope values, signifying a possible under-correction of QTc at higher HRs and an over-correction at lower HRs. Bazett had the lowest absolute value of slope: for every one-unit increase in HR, QTc increases by 0.324 ms (95% confidence interval (CI) 0.171, 0.478, $p < 0.01$). Computer (0.325, 95% CI 0.172, 0.325, $p < 0.01$), Hodges (0.329, 95% CI 0.218, 0.329), and Fridericia (−0.348, 95% CI −0.482, −0.213, $p < 0.01$), however, had comparably low absolute slope values. Framingham and Rautaharju had the highest absolute slope values; for both, QTc decreases by 1.42 ms for every 1 bpm increase in HR.

3.4 Relationship between QTc Formula and RR Interval

3.4.1 Spearman's Correlation Coefficient

Fridericia yielded a ρ closest to 0 (ρ = 0.34, $p = 0.001$), followed by Hodges (ρ = −0.45, $p < 0.001$) (Table 7). Rautaharju had the strongest correlation to RR (both ρ = 0.89, $p < 0.001$). Bazett and Computer had a moderate correlation with RR (both ρ = −0.50, $p < 0.001$). Each QTc/RR correlation coefficient value was the additive inverse of its corresponding QTc/HR correlation coefficient (e.g., QTc Fridericia/HR ρ = −0.34, QTc Fridericia/RR ρ = +0.34), a reflection of the inverse relationship between RR and HR (as RR increases, HR decreases and vice versa).

3.4.2 Linear Regression

The QTc/RR linear regression analysis identified Fridericia as the best rate correction method in our study cohort. Fridericia had the lowest absolute value of slope: for every one-unit increase in RR, QTc increases by 0.033 ms (95% CI 0.013, 0.053, $p < 0.01$) (Table 8). Bazett, Computer, and Hodges had negative slope values. Fridericia, Framingham, and Rautaharju had positive slope values. Hodges had the next lowest absolute value of slope: for every one-unit increase in RR, the QTc decreases by 0.042 ms (95% CI −0.058, −0.026, $p < 0.01$). Bazett and Computer had the same coefficient of −0.062 (both 95% CI −0.082, −0.042, $p < 0.01$). Framingham and Rautaharju were worst performing with the greatest absolute value of slope: both 0.189 (95% CI 0.169, 0.209, $p < 0.01$).

3.5 Bland-Altman Plots

The Bland-Altman method measured for bias and the limits of agreement between QTc formulae. Statistics are presented in Table 9. The plots (Fig. 2) provide a graphical display of bias (mean difference between two formulae) with 95% limits of agreement (2 SD). Y = 0 represents the line of perfect average agreement (i.e., the average of differences is zero). Framingham and Rautaharju showed a bias approaching 0 (bias = −0.012, 95% CI: −0.013, −0.011) with a narrow 95% limits of agreement (−0.025, 0.0002). Computer and Bazett also had a bias close to 0 (bias = −0.742, 95% CI: −1.26, −0.224) with good agreement (−1.7564, 0.2731). Fridericia and Hodges had a low bias (bias = −11.014, 95% CI: −32.501, 10.473), but poor agreement (−53.12819, 31.09945).

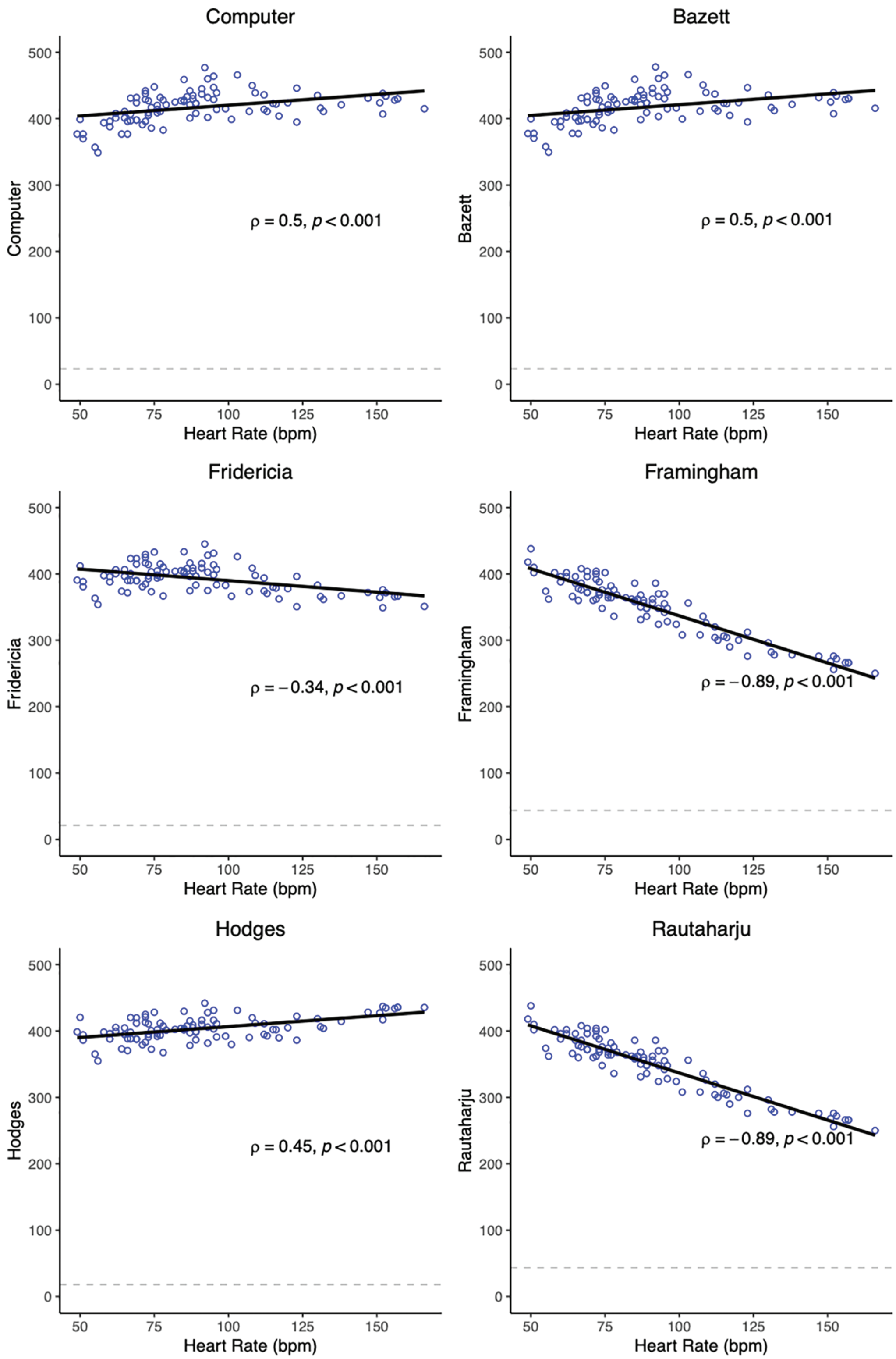

Figure 1: Scatter plots showing QTc/HR relationship with univariate linear regression lines. Spearman's rank correlation coefficient (ρ) and the test *p*-value are also displayed in the plot. The dashed line represents the SD of QTc

Table 5: Spearman's rank correlation coefficient (ρ) for each QTc method *vs*. HR. All correlations were statistically significant

QTc method	HR (bpm)	ρ	*p*-value
Computer	HR	0.50	<0.001
Bazett	HR	0.50	<0.001
Fridericia	HR	–0.34	0.001
Framingham	HR	−0.89	<0.001
Hodges	HR	0.45	<0.001
Rautaharju	HR	−0.89	<0.001

Table 6: Linear regression analyses of different QTc methods *vs.* HR

QTc method	Linear regression coefficient	Lower 95% CI	Upper 95% CI	*p*-value
Bazett	0.324	0.171	0.478	<0.01
Fridericia	−0.348	−0.482	−0.213	<0.01
Framingham	−1.420	−1.531	−1.310	<0.01
Hodges	0.329	0.218	0.439	<0.01
Rautaharju	−1.420	−1.531	−1.310	<0.01
Computer	0.325	0.172	0.478	<0.01

Table 7: Spearman's rank correlation coefficient for each QTc method *vs*. RR. All correlations were statistically significant

QTc method	RR interval (ms)	ρ	*p*-value
Computer	RR	−0.50	<0.001
Bazett	RR	−0.50	<0.001
Fridericia	RR	0.34	0.001
Framingham	RR	0.89	<0.001
Hodges	RR	−0.45	<0.001
Rautaharju	RR	0.89	<0.001

Table 8: Linear regression analyses of different QTc methods *vs*. RR

QTc method	ρ	Lower 95% CI	Upper 95% CI	*p*-value
Bazett	−0.062	−0.082	−0.042	<0.01
Fridericia	0.033	0.013	0.053	<0.01
Framingham	0.189	0.169	0.209	<0.01
Hodges	−0.042	−0.058	−0.026	<0.01
Rautaharju	0.189	0.169	0.209	<0.01
Computer	−0.062	−0.082	−0.042	<0.01

Table 9: Bland-Altman statistics for each combination of two QTc methods

QTc method comparison	Bias	SD of bias	95% limits of agreement
Computer *vs*. Bazett	−0.742	0.518	−1.7564 to 0.2731
Computer *vs*. Fridericia	24.646	19.693	−13.9523 to 63.2442
Computer *vs*. Framingham	68.409	51.766	−33.0529 to 169.871
Computer *vs*. Hodges	13.632	13.155	−12.1519 to 39.4151
Computer *vs*. Rautaharju	68.397	51.761	−33.0542 to 169.8479
Bazett *vs*. Fridericia	25.388	19.689	−13.2022 to 63.9774
Bazett *vs*. Framingham	69.151	51.766	−32.3112 to 170.6126
Bazett *vs*. Hodges	14.373	13.165	−11.4295 to 40.176
Bazett *vs*. Rautaharju	69.139	51.761	−32.3125 to 170.5895
Fridericia *vs*. Framingham	43.763	32.129	−19.2098 to 106.736
Fridericia *vs*. Hodges	−11.014	21.487	−53.1282 to 31.0994
Fridericia *vs*. Rautaharju	43.751	32.123	−19.211 to 106.7129
Framingham *vs*. Hodges	−54.777	50.186	−153.1424 to 43.5874
Framingham *vs*. Rautaharju	−0.012	0.006	−0.0245 to 0.0002
Hodges *vs*. Rautaharju	54.765	50.181	−43.5891 to 153.1197

3.6 Analyses Excluding the Top and Bottom 2% of Data as Sorted by Heart Rate Ranges

Five participants were excluded from the study such that 90 participants were included in the analyses. The new demographics, ECG parameters, and QTc calculations closely resembled the results involving all 95 participants (Table 10).

In the Spearman's rank correlation tests between each combination of two QTc methods, Computer and Bazett as well as Framingham and Rautaharju demonstrated the strongest correlations (Table 11), both with a ρ value of 1.00 ($p < 0.001$).

In the two-sample paired *t*-test or Wilcoxon signed-rank test, as appropriate, to evaluate for potential differences between QTc methods (*p*-value adjusted with fdr method because of multiple comparisons), there was a statistically significant difference ($p < 0.001$) between every two QTc formulae.

In the Spearman's correlation coefficient test for different QT correction methods *vs*. HR, Rautaharju and Framingham maintained the strongest correlation with HR (both $\rho = -0.87$, *p*-value < 0.001) (Table 12). Fridericia continued to demonstrate the weakest correlation with HR ($\rho = -0.28$, *p*-value 0.007).

The linear regression analysis for the new cohort (N = 90) showed Hodges to have the lowest absolute value of slope (0.323, $p < 0.01$), closely followed by Fridericia (0.328, $p < 0.01$), Computer (0.357, $p < 0.01$), and Bazett (0.358, $p < 0.01$ (Table 13). These results differed slightly from those derived from all participants in which Bazett had the lowest absolute value of slope (0.324, $p < 0.01$), followed by Computer (0.325, $p < 0.01$), Hodges (0.329, $p < 0.01$), and Fridericia (0.348, $p < 0.01$).

The results of analyses comparing QTc to RR interval were the additive inverse of their corresponding QTc *vs*. HR calculations, reflecting the inverse relationship between RR and HR.

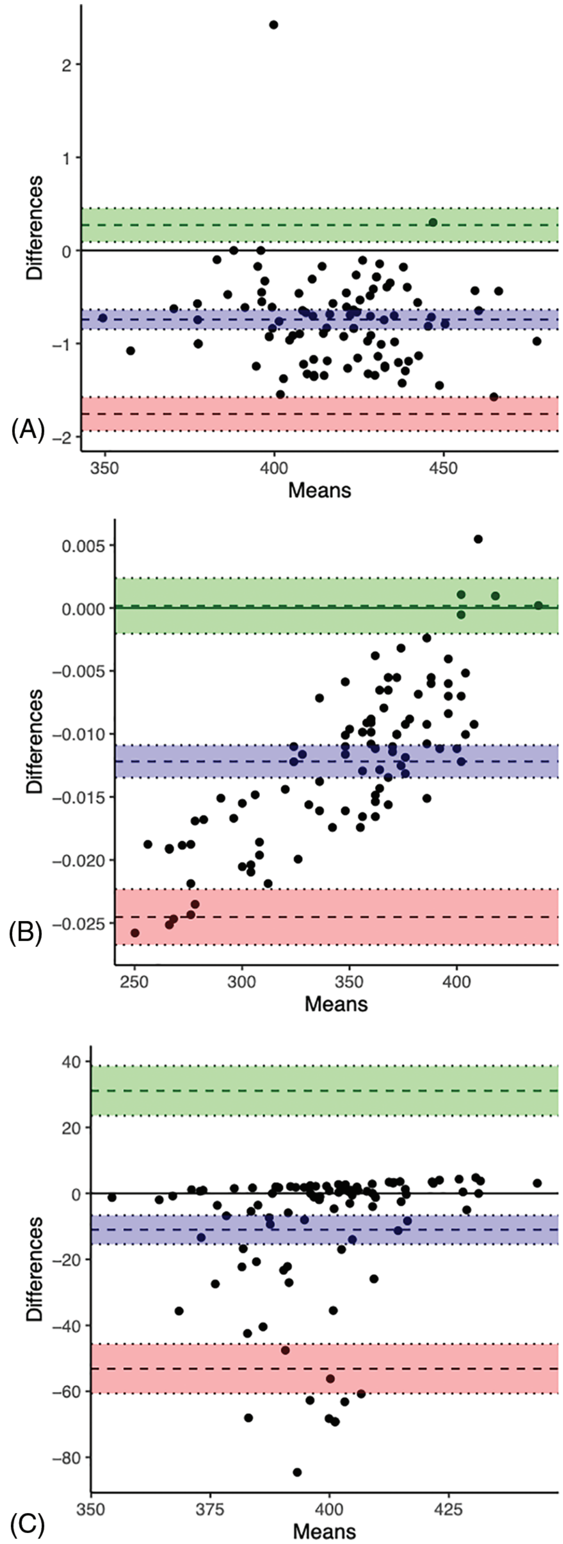

Figure 2: Bland-Altman plots of Computer *vs*. Bazett (A), Framingham *vs*. Rautaharju (B), and Fridericia *vs*. Hodges (C). The dashed line in the center of the green area is the upper 95% limit of agreement. The dashed line in the center of the purple area is the bias (mean difference between the two QTc). The dashed line in the center of the red area is the lower 95% limit of agreement

Table 10: Mean and SD of participant demographics, ECG parameters, and QTc calculations for participants (N = 90) and as stratified by sex

Characteristic	N = 90 Mean (SD)	Female, N = 40[1] Mean (SD)	Male, N = 50[1] Mean (SD)	*p*-value[2]
Age (yrs)	9.9 (6.2)	9.1 (6.6)	10.5 (5.9)	0.307
HR (bpm)	90 (26)	97 (27)	84 (24)	0.009
RR (ms)	717 (187)	665 (178)	759 (185)	0.009
QT (ms)	350 (40)	342 (42)	357 (38)	0.056
Computer	418 (23)	424 (22)	414 (24)	0.084
Bazett	419 (23)	424 (22)	414 (24)	0.087
Fridericia	394 (21)	394 (22)	394 (20)	0.981
Framingham	350 (40)	342 (42)	357 (38)	0.060
Hodges	403 (17)	407 (17)	400 (17)	0.075
Rautaharju	350 (40)	342 (42)	357 (38)	0.056

Note: [1]Mean (SD). [2]Wilcoxon rank sum test.

Table 11: Spearman's rank correlation coefficients (ρ) between two QTc methods with statistically significant *p*-values

QTc method 1	QTc method 2	ρ	*p*-value
Computer	Bazett	1.00	<0.001
Computer	Fridericia	0.65	<0.001
Computer	Hodges	0.89	<0.001
Bazett	Fridericia	0.65	<0.001
Bazett	Hodges	0.89	<0.001
Fridericia	Framingham	0.66	<0.001
Fridericia	Hodges	0.54	<0.001
Fridericia	Rautaharju	0.66	<0.001
Framingham	Rautaharju	1.00	<0.001

Table 12: Spearman's rank correlation coefficient (ρ) for each QTc method *vs*. HR. All correlations were statistically significant

QTc method	HR (bpm)	ρ	*p*-value
Computer	HR	0.48	<0.001
Bazett	HR	0.48	<0.001
Fridericia	HR	−0.28	0.001
Framingham	HR	−0.87	<0.001
Hodges	HR	0.43	<0.001
Rautaharju	HR	−0.87	<0.001

Table 13: Linear regression analyses of different QTc methods *vs.* HR

QTc method	Linear regression coefficient	Lower 95% CI	Upper 95% CI	*p*-value
Bazett	0.358	0.182	0.534	<0.01
Fridericia	−0.328	−0.484	−0.171	<0.01
Framingham	−1.426	−1.552	−1.300	<0.01
Hodges	0.323	0.197	0.449	<0.01
Rautaharju	−1.426	−1.552	−1.300	<0.01
Computer	0.357	0.181	0.533	<0.01

In the Bland-Altman analysis, Framingham and Rautaharju showed a bias approaching 0 (bias = −0.012, 95% CI: −0.018, −0.006) with a narrow 95% limits of agreement (−0.0235, 0.0007). Computer and Bazett also had a bias close to 0 (bias = −0.750, 95% CI: −1.277, −0.223) with good agreement (−1.7834, 0.284). Fridericia and Hodges had a low bias (bias = −8.967, 95% CI: −27.578, 9.644), but poor agreement (−45.4449, 27.5102). These results mirrored that of the entire data set (N = 95).

4 Discussion

Over 25 formulae have been proposed to correct for the HR-dependence of the QT interval, testifying to the controversy surrounding the endeavor towards a universal formula [23]. Existing methods have been repeatedly criticized with numerous attempts to identify more appropriate ones. Studies noting an intra-subject variability in the QT/HR relationship have further complicated the endeavor, suggesting the need for an individual QT correction method derived from subject-specific data [24–26]. Still, other studies recommend accounting for age or sex differences in QT interval [27].

Despite the controversy, Bazett continues to be most widely implemented in clinical practice, including pediatrics. The Schwartz scoring system for the clinical diagnosis of LQTS, for example, integrates the Bazett method to calculate for risk of disease [28]. As Bazett is known to over-correct QT at higher HRs [10], the use of the formula is of especial concern in the pediatric population where the normal HR of neonates ranges from 110 to 160 bpm, and children's HR do not decrease to below 100 bpm until adolescence. In a study of 332 children with a mean age of 10.7 years, Bazett led to a high number of false positives in LTQS screening; results were exacerbated by increases in HR due to postural maneuvering [11]. Additionally, in a study of 54 healthy children with a median age of 9.9 years, Bazett (as well as Hodges) had a positive QTc and HR relationship, resulting in a prolonged QTc at peak exercise; the study recommended the use of Fridericia or Framingham calculated at one minute after maximum exercise for superior congenital LQTS assessment [29]. Our study provides additional evidence that Bazett over-corrects at higher HRs.

Still, other studies support the continued use of Bazett in pediatric cardiology [13,30–34]. In a study of 2,500 randomly selected ECGs from neonates, Bazett provided the most HR independent QT correction and accurately identified neonates affected by LQTS [34]. In a larger scale prospective study of more than 33,000 infants, Bazett successfully identified infants with a prolonged QTc and at significant risk for sudden death [30]. In a review of ECGs from 702 children with 81% less than 2 years of age, Bazett produced the most consistent QTc values across HRs with the support of 460 ms as the best threshold for prolonged QTc [33].

In our study, Fridericia was most independent of HR and RR. This finding supports the conclusion of other studies, which report Fridericia to provide more consistent calculations at faster HRs [24,29,35]. A study on children and adolescents from six to 17 years of age found the ideal HR correction formula to be QTc = QT/($RR^{0.38}$), which most closely resembles the Fridericia formula [36]. Regulatory agencies such as the U.S. Food and Drug Administration recommend the concurrent use of Fridericia and Bazett in clinical trials on drug safety [37,38]. The robustness of Fridericia to changes in HR may attribute to the method of formula development, which studied the QT/HR relationship to identify a coefficient that would minimize the impact of RR on QTc [6,10]. The Bazett formula, alternatively, was not based on such population-based calculations [5].

Framingham and Rautaharju had strong correlations with HR and RR in our study. Our study does not recommend the use of these formulae for QT correction, although the limitations of our study, including its small sample size, must be considered. Hodges had modest performance in the Spearman's rank correlation and linear regression analyses against HR and RR.

Computer-calculated Bazett formula performed equally with a manual calculation of Bazett in our population. Our findings suggest that if Bazett is an appropriate and validated formula for QTc calculation in the pediatric population as seen in other studies, the computer algorithm may be a comparable screening tool to detect QTc prolongation. Computer-derived algorithms and QTc calculators on smart devices may represent valuable point of care resources in settings outside of cardiology practice where health professionals may be less familiar with measuring QT intervals [39]. Moreover, given intrinsic variations in manual QT measurement across health care personnel and facilities, a standardized method of measurement through a computer device may increase both the diagnosis and monitoring of patients with prolonged QTc. Studies on the accuracy and reliability of computer-based algorithms and QTc calculators remain conflicting, however [40,41], with many displaying good precision, but low accuracy [41,42].

Limitations of our study include its retrospective design and small population size consisting of only healthy patients (N = 95). Despite a small sample size, statistically significant differences were observed between formulae. As a community hospital, our population may not be representative of other pediatric populations. Larger scale prospective studies are needed to confirm our findings. Our study assessed the performance of QTc formulae against variations in HR and RR across individuals, while variations in the parameters have also been noted within individuals.

5 Conclusion

Many formulae have been proposed to decrease the impact of HR on QT with conflicting perspectives on the ideal formula for pediatric practice. While Bazett remains most utilized, many have raised concerns regarding the formula's tendency to over-correct at higher HRs. This finding is especially relevant to the pediatric population, which is characterized by extremes of HR, particularly within neonates. Our findings support the use of Fridericia to minimize the influence of HR on QT. Manual and computer algorithm-based calculations of Bazett exhibited moderate linear correlations with HR and RR, while Framingham and Rautaharju had strong correlations. The results of our study must be weighed against its limitations, including a small population size. If Bazett is a reliable and valid method of QT correction as seen in other pediatric study cohorts, our findings suggest that the computer algorithm may be a comparable method for use in clinical practice to standardize QT assessment.

Acknowledgement: None.

Funding Statement: No funding was obtained for this study.

Author Contributions: Study conception and design: KK, IK, YL, ON, BB, MC; data collection: IK, AM, ON, MC; analysis and interpretation of results: KK, IK, YL, WK, AM, ON, BB, MC; draft manuscript preparation: KK, IK, YL, WK, AM, ON, BB, MC. All authors reviewed the results and approved the final version of the manuscript.

Availability of Data and Materials: Statistical data and analyses are available within the text of the article.

Ethics Approval: This study was reviewed and approved by the New York-Presbyterian Brooklyn Methodist Hospital Institutional Review Committee. The study follows the guidelines outlined in the Declaration of Helsinki.

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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