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The Best ECG Lead for Predicting the Risk of Drug-Induced Torsade De Pointes Using Corrected QT Interval: A Comparative Prognostic Study

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Abstract: **Introduction:** Torsade de pointes (TdP) is a deadly complication from drug-induced QT prolongation. Each of the 12 lead of an electrocardiogram (ECG) has a different length of QT interval, and thus might have a different performance in TdP prediction. This study aimed to determine the best ECG lead or set of leads in this regard. **Methods:** This is a comparative prognostic accuracy study using a two-gate data gathering design. The population in this study was from two sources, a case group (Patients who had drug-induced TdP, which were identified through a systematic Medline search) and a control group (those who overdosed on QT-prolonging drugs, which included patients who were under the consultation of Medical Toxicology Services). The areas under the receiver operating characteristic curve (AUROC) of heart rate-corrected QT (QTc) in each single ECG lead and of a mean/median QTc from a set of ECG leads (17 index test) in predicting the risk of TdP were calculated and compared with each other, trying to find the best lead for this propose. QTc Interval measurements were done by four investigators (Interrater reliabilities 0.95). **Results:** Finally, we included 136 and 148 ECGs from TdP cases and controls, respectively. V3 lead had the highest frequency of longest QTc interval, among the leads. The lead having the longest QTc yielded the greatest AUROC in predicting TdP regardless of QT correction formulas (QTcFRA=0.9915, QTcRTH=0.9893, QTcBZT=0.9904). The mean QTc of 3 leads (lead II, plus any two of leads V2-V4), and a median QTc of 6 leads (I, II, aVF, V2, V4, V6) provided similar overall performance for TdP prediction (regardless of the type of QTc formula). **Conclusions:** The longest QTc provided the greatest AUROC in predicting drug-induced TdP, however, the longest QTc is not located in a fixed individual lead in any patient. A less time-consuming method with comparable performance to that of the longest QTc was to use a mean QTc from 3 leads (lead II, plus any two of leads V2-V4). The potential clinical impact of this finding needs to be verified in a prospective cohort study.

Keywords: Long QT syndrome; Area under curve; Torsades de pointes; Electrocardiography; Prognosis

1. Introduction

Torsade de pointes (TdP) is a potentially life-threatening ventricular tachydysrhythmia associated with prolonged QT interval (1–4). A number of xenobiotics are known to cause QT interval prolongation, especially antidysrhythmic drugs in classes IA, IC, and III, and they have been found to trigger TdP (5).

Large cohort studies of individuals with congenital long QT syndrome (LQTS) indicate that the risk of TdP increases 5-7% every 10 ms of QTc being prolonged (2). Since QT interval is an important tool for TdP risk prediction, details on how QT intervals on a 12-lead electrocardiogram (ECG) are measured may affect risk stratification for drug-induced QT prolongation and TdP. These various aspects of methods for QT measurement include: 1) which lead, or which sets of leads are measured on the 12-lead ECG, 2) tangent vs. threshold methods to be used, and 3) manual vs. automated measurement. Available data suggest that the QT intervals reported on the ECG printouts from commercial automated 12-lead-ECG machines are unreliable compared to those from manual measurements (6,7). As a result, manual measurement of the QT interval is preferable; however, several factors affect manual QT measurements such as the determination of the origin of the QRS wave, T-wave morphology (such as biphasic T-wave, flat T-wave), the end of the T-wave, tangent vs, threshold methods, ECG lead choice, number of complexes per lead, and inter-/intra-observer variability (7–10). QT correction formulas may not be technically part of QT interval measurement, but they permit comparison of QT intervals obtained at various heart rates, which is an important variable.

QT intervals on the same ECG have different lengths in different leads due to the spatial vector of the starting point of

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the Q wave, the endpoint of the T wave, and also the axis of each ECG. The lead with the axis perpendicular to the spatial vector of either of the aforementioned point has the shortest interval (9,11). The beginning of the Q wave in leads V1-V3 usually precedes that in V4-V6, and in the limb leads, and the difference is due to an asynchronous beginning of the Q wave, which may be up to 20 ms (9,11). In an ECG of normal subjects, the discrepancy between the shortest and the longest QT intervals can reach up to 50-65 ms (11).

Historically, lead II was utilized for QT measurement by Bazett in 1920. Lead II was often used because in the early 1900s, there were no precordial leads, and the vector axes of all waves point to lead II, which makes lead II easily recognized. In addition, lead II was found to have the longest QT interval in congenital long QT syndrome (12). A hundred years later, lead II is still commonly suggested as the lead of choice for QT measurement (7,10,12,13). Isbister et al. suggest measuring QT from more than one lead and using the median (6). Another study suggests choosing the longest QT interval, which is mostly located in lead V2 or V3 (11). A study on QT interval measurement accuracy for predicting arrhythmic death, done in 3 populations (general population, acute myocardial infarction (MI), and remote MI) found that the longest QT interval on the 12-lead ECG provided the highest prognostic accuracy for death or ventricular dysrhythmia. However, the authors recommended using a mean of the three longest QT intervals instead, because of an ability to limit measurement errors from measuring any single individual lead, while the mean of the three longest QT intervals provided similar prognostic accuracy to the longest one (8).

Interestingly, the results of the study also revealed that the QT interval from different leads provided different prognostic accuracies for death or fatal dysrhythmia in their 3 study populations(8). However, such an informative study has not been done in the context of drug-induced QT prolongation, but only in those with pathological cardiac conditions. In this study, we aimed to determine a lead or a set of leads of choice for QT measurement to provide the highest prognostic performance in predicting drug-induced TdP.

2. Methods

2.1. Study design and setting

This is a comparative prognostic accuracy study using a two-gate data gathering design. The population in this study was from two sources, a case group (Patients who had drug-induced TdP, which were identified through a systematic search from a Medline database) and a control group (those who overdosed on QT-prolonging drugs as listed on the CredibleMeds.org website (14) but did not develop TdP, which were chosen from patients under the consultation of Medical Toxicology Services, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand, from the first day of August 2013 to November 18th, 2018).

The areas under the receiver operating characteristic curve

(AUROC) of heart rate-corrected QT (QTc) in each single ECG lead and of a mean/median QTc from a set of ECG leads (17 index tests) in predicting the risk of TdP were calculated and compared with each other, trying to find the best lead or set of leads.

A standard operating procedure was created and clarified to all team members in the data collection process. This study was approved by the hospital Institutional Review Board (certificate of approval: 058/2562).

2.2. Study population and recruitment process

The population in this study was from two sources, a case group (Patients who had drug-induced TdP) and a control group (those who overdosed on QT-prolonging drugs as listed on the CredibleMeds.org website (14) but did not develop TdP).

- All patients in the case group were exposed to QT-prolonging drugs (by ingestion or parenteral administration), and they later developed TdP. Since drug-induced TdP is a rare condition, we gathered cases in this group through a systematic search on Medline database using the terms "torsades de pointes" [MeSH Terms] AND ("loattrfull text"[sb] AND "humans"[MeSH Terms]). The database was searched from 1966 to January 31st, 2021. All titles were screened for relevance (titles with in-vitro, animal, laboratory, chemistry, or genetic tests were all excluded). We included TdP cases who were 15 years old or older and had their cause of TdP determined to be from drugs listed on the CredibleMeds.org website (14). They must have had at least one 12-lead ECG done before the occurrence of TdP, and before receiving any medical treatment to stop or prevent TdP. We excluded cases with TdP deemed to be non-drug-related (such as congenital long QT syndrome, cardiomyopathy, and myocardial infarction). For the full-text review, only cases with a measurable QT (without flat T-wave) in all 12 leads were included.

- Those 15 years old or older who overdosed on QT-prolonging drugs as listed on the CredibleMeds.org website (14) but did not develop TdP were comprised as the control group. We considered overdose when a patient ingested or received a QT-prolonging medication at a higher dose than recommended for therapeutics based on the Micromedex® database. The included overdose patients were under the consultation of Medical Toxicology Services, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand, from the first day of August 2013 to November 18th, 2018. In any 12-lead ECG in this group, all QT intervals must have been measurable (no flat T-wave) in all 12 leads. We excluded patients who had QT prolongation from non-drug-related causes, for example, congenital long QT syndrome, cardiomyopathy, or if they had a ventricular dysrhythmia or a non-sinus rhythm ECG.

As mentioned above, cases and controls having an unmeasurable QT (flat T-wave) in at least one lead were excluded from the main data analysis to calculate AUROC (Figure 1). In patients (44 cases, and 32 controls, Figure 1) who were ex-

cluded due to having an unmeasurable QT (flat T-wave) in at least one lead, we counted the frequency of individual leads with any unmeasurable QT intervals (data shown in Supplement Figure 1).

2.3. Data gathering

We used a two-gate (case-control) design instead of the one-gate (cohort) design for data collection because the outcome of the study, TdP, is relatively rare even though drug-induced QT prolongation is common, especially in medical toxicology settings. This design is often done in the early stage of test evaluation if it is of any use before it can be validated in a cohort study (15). With this case-control design, the accuracy may be inflated (15); however, "absolute accuracy" of our index tests is not the objective of this study. This study aimed to identify an ECG lead or a set of leads that provides the "highest accuracy", which is relative to accuracies from all of the index tests.

We did not match cases and controls due to the following reasons. One must not be confused between the diagnostic/prognostic case-control (also called two-gate) design and the etiologic case-control study. These two are different. Diagnostic/prognostic case-control is descriptive and cross-sectional by nature (16). Unlike the etiologic case-control, this type of study tries to find a causal relationship, and time is needed after exposure for the disease to appear. As a result, in the etiologic case-control, eliminating confounding factors is important to allow assessing the true effect of potential causal exposure. However, these concerns are not transferred to the diagnostic case-control design where causality is often irrelevant as pointed out in a textbook Designing Clinical Research (15) and in a minireview "Case–Control and Two-Gate Designs in Diagnostic Accuracy Studies" (16). In fact, matching in diagnostic case-control can distort the overall accuracy of the test including AUROC, in which mathematical adjustment is needed (17,18).

We also collected patient age, sex, QT drug list of overdoses, and co-ingestion using a standardized data collection form.

2.4. Index tests

Seventeen index tests consisted of QTc from each individual 12 ECG leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6) plus the longest QTc from any lead, the mean QTc from the first three leads having the most frequent counts of longest QTc, the mean QTc from three leads having the least frequent counts of longest QTc, the mean QTc from three leads having the highest AUROC for TdP, and the median QTc of 6 leads (I, II, aVF, V2, V4, V6) were studied. We calculated and compared the AUROCs for all of the 17 index tests. The reasoning behind those 17 index tests will be given below. It was possible that we might have more index tests beyond the first 17 originally proposed index tests when the outcomes of the first 17 tests were evaluated.

2.5. QT measurement and quality control

ECGs in this study were measured by four investigators who were senior emergency resident physicians or certified paramedics. They were trained in this procedure. QT interval was measured from the starting point of the Q wave to the endpoint of the T wave in all 12 leads, two complexes per lead. If there was a U wave, the ending point of the T wave was at the nadir of the T-U waves, or the ending point of the U wave if the nadir was unclear. RR interval was the interval between the two closest R waves corresponding to each QT interval. After training, to test for interrater reliability among 4 measurers, ten ECGs from the cases and controls were obtained. Each of the 4 team members measured RR and QT intervals from 240 ECG leads, independently. The intraclass correlation coefficient was calculated for interrater reliability of continuous data among the four team members before the measurement of the study was started. The intraclass correlation coefficient was analyzed and the results were 0.97 for the RR interval and 0.95 for the QT interval.

2.6. QT drug list

We used the QT drug list on Crediblemeds.org (14) to identify QT-prolonging drugs. The Crediblemeds.org committee classified QT-prolonging drugs into four categories: known risk, possible risk, conditional risk, and drugs to avoid in congenital long QT syndrome (cLQTS). Only the first 3 categories of the list were included since we did not include any patients with cLQTS.

2.7. QT correction formulas

There are several heart-rate (HR) correction formulas but in this study, we only selected 3 different formulas for QT-HR correction including the Framingham (QTcFRA = QT+0.154(1-RR)), Rautaharju (QTcRTH = QT*(120+HR)/180), and Bazett (QTcBZT = QT/RR$^{0.5}$) formulas to determine whether an AUROC from each lead or a set of leads would change when the method for QT correction changed. About the reasons why these 3 formulas were selected, Bazett's is still the most widely used around the world (19), the Rautaharju's method is a relatively new formula and has recently been demonstrated to be one of the most accurate formulas to predict drug-induced TdP in a wide range of heart rates (4), and for the Framingham, it was shown that with a heart rate < 90 beats/min, it provided an accurate QT correction with good 30-day all-cause mortality prediction (20).

2.8. Statistical analysis

The sample size was calculated based on a prior study on the prognostic performance of QT interval from different ECG leads for fatal dysrhythmia by comparing the AUROC of the QT interval (8), using a statistical equation to determine a sample size of the AUROC (21) with 80% power. The alpha is 0.05 to detect the AUROC difference of 0.1 point. The calculated sample size was increased by 20% in an attempt to retain power if some of the cases or controls would later be ex-

cluded due to any other reasons such as poor quality of ECG images, etc. The required sample population was 135 cases and 135 controls. Data were collected in Google Sheets. They were transferred to Microsoft Excel version 2019® to calculate QTc using each of the three formulas and for lead counts. We manually counted the frequency of each lead that had the longest QTc from each case in the study population stratified by three different QT-HR correction formulas. For purposes of data analysis, to compare AUROC from each index test, we also calculated a mean QTc for the following groups of leads in each subject: 1) Mean QTc of the first three leads having the most frequent counts of the longest QTc, 2) Mean QTc from three leads having the least frequent counts of the longest QTc, 3) Mean QTc from three leads that had the highest AUROC for TdP. The median value of QTc was also taken from 6 leads (I, II, aVF, V2, V4, and V6), according to a suggestion from Isbister et al. (6), to compare its AUROC with other index tests.

For continuous data and comparison of two groups, we used the Wilcoxon rank-sum test because the data were not normally distributed. For categorical data, Fisher's exact or Chi-square test was used for comparison where appropriate. Statistical significance is when the P-value is less than 0.05. Stata version 13® (StataCorp LP, College Station, TX, USA) was used in this study for statistical analysis.

3. Results

3.1. Patients' enrollment

In the case group, after applying the search strategy in the Medline database, 1,820 titles were discovered. All titles were screened by TR.

One thousand and eleven titles were not relevant and not included leaving 809 full-text articles for review. Finally, 180 drug-induced TdP cases from 169 articles were included for ECG review (Figure 1).

In the control group, 1,876 cases in the Toxicology logbook were screened. Five hundred fifty-seven cases were not included due to being irrelevant. Medical records of 1,139 cases were manually reviewed by SV, finally, 180 cases were included for being controls (Figure 1).

We required QT interval from all 12 leads for measurement. All ECGs in both groups were further reviewed if any of those ECGs had any unmeasurable QT interval due to having a flat T wave. Forty-four and 32 patients in the case and control groups had unmeasurable QT intervals, respectively, and were further excluded for QT and RR interval measurement and data collection (Figure 1).

For the leads with unmeasurable QT intervals in the 76 (44+32) excluded cases, we sorted these leads by frequency of having unmeasurable QT intervals and placed them in order from most to least frequent as the following: aVL (25) > I (13) > III (10) > V1 (9) > aVR (8) = aVF (8) > V6 (4) > V5 (2) = V4 (2) > V3 (1) > V1 (1). Interestingly, lead II had no unmeasurable QT intervals at all in this study (no flat T wave in any

ECG of both groups in lead II; data shown in the Supplement Figure 1). Note that some ECGs had more than one lead with unmeasurable QT intervals (83 leads from 76 ECGs).

3.2. Baseline characteristics of studied patients and ECGs

Finally, we included 148 and 136 ECGs from controls and cases, respectively (one ECG per case, and one per control). In total, QT and RR intervals from 3,408 leads from 284 ECGs were measured for diagnostic/prognostic accuracy comparison.

Patients in the case group were older, with female predominance, more exposed to the known risk group of QT-prolonging drugs, and had more underlying diseases compared with controls (Table 1). The most frequent medication exposed in the case and control groups were Azithromycin (20 cases) and tramadol (157 cases), respectively.

3.3. Lead with the longest QTc interval

Frequency of individual leads having the longest QT interval from each subject was counted (Figure 2), and the results revealed that V3 had the highest frequency of longest QT corrected by Framingham's method (QTcFRA), which was followed by V2, V4, II, aVR, V5, I, V1, V6, III, aVF, and aVL, respectively. For the QTcRTH (Rautaharju correction method), V3 again had the highest frequency of the longest QTcRTH, and that was followed by V2, V4, II, aVR, I, V5, V1, V6, aVF, III, and aVL. For QTcBZT (Bazett's formula), V3 also had the highest frequency of the longest QTcBZT, followed by V2, V4, II, V5, aVR, I, V1, V6, III, aVF, and aVL as shown in Figure 2. The orders appear to be similar but not the same across the 3 different QT correction formulas.

3.4. AUROCs of QTc interval for predicting the risk of TdP

The AUROCs for predicting the risk of TdP were analyzed from the QTc of individual leads (Figure 3), and a mean QTc of a group of three leads having the most frequent longest QTc and a mean QTc of a group of three leads having the least frequent longest QTc.

When we used the longest QTc from each subject to calculate the AUROC for TdP, it yielded the greatest AUROC regardless of heart rate-corrected formulas (0.9915, 0.9893, and 0.9904 for Framingham's, Rautaharju's, and Bazett's formula, respectively). But for the AUROC of a QTc from individual leads, we found differences in the order of the AUROC from each lead based on different formulas. Lead III, aVL, and I provided the greatest AUROC when using Framingham's formula. Lead aVL, III, and V6; and V3, V6, and V5 provided the greatest AUROC for the Rautaharju's and Bazett's formulas, respectively. We also tested the AUROC from a mean QTc of three leads having the greatest AUROC, and we tested with all three QT correction methods. The results are shown in Figure 4.

In addition, because lead II had no unmeasurable QTc at all; and V2, V3, and V4 often had the highest frequency of the

longest QTc, we tested a mean QTc of lead II plus any two of V2-V4 for the AUROC as well. The results are depicted in Figure 4.

For the statistical comparison of all the AUROCs in Figure 4, we used the longest QTc as the reference as it provided the best predictor for TdP (due to its highest AUROC). We found a few individual leads and a few groups of leads that provided no statistically significant differences from the AUROC of the longest QTc. Overall, there were no fixed individual leads that consistently provided comparable AUROC to the one from the longest QTc using different QT correction formulas. For QTcFRA, lead I, II, III, V6, the mean QTc of three leads with the least frequent counts of the longest QTc, and the mean QTc of three leads with the greatest AUROCs had comparable performances in predicting TdP as the longest QTc.

For QTcRTH, lead V6, and mean QTc of three leads with the greatest AUROCs had comparable performance to the longest QTc for TdP prediction.

For QTcBZT, none of the individual leads had good performance comparable to the lead with the longest QTc.

In all three QT correction methods, the median QTc of 6 leads (lead I, II, aVF, V2, V4, and V6); the mean QTc of lead II, V2, and V3; the mean QTc of lead II, V3, and V4; and the mean QTc of lead II, V2, and V4 provided comparable performance in predicting TdP with the longest QTc (Figure 4).

Finally, we compared the AUROC of the longest QTc among the three QT correction methods in predicting TdP, and we found they were not significantly different (p-value=0.2576). Similar findings were also found when comparing the AUROC from groups of leads among all three QT correction methods (Supplement Table 1).

4. Discussion

The measurement of QT interval in our study began with the exclusion of ECGs that were comprised of any lead with unmeasurable QT intervals (flat T-wave). We found that unmeasurable QT intervals were most commonly found in leads aVL (30.1%), I (15.6%), III (12.0%), V1 (10.8%), aVR (9.6%), and aVF (9.6%) (Supplement Figure 1). These findings were similar to a previous study of 38 healthy volunteers. They mostly found unmeasurable QT intervals in leads III, aVL, aVF, and V1 (22). In contrast, our study demonstrated that unmeasurable QT intervals were less common in leads V3 (1.2%), and V2 (1.2%), and they were not found in lead II at all.

After sorting all individual leads by the frequency of individual leads that had the longest QTc, the two leads that had the highest counts of the longest QTc were leads V2 and V3, which was consistent with the 2009 AHA/ACCF/HRS Scientific Statement that the lead showing the longest QT is usually V2 or V3 (11), because the origin of the QRS complex in leads V2 and V3 began earlier compared with the limb leads in a matter of about 20 ms.

For the AUROC of the individual leads, the order of individual leads according to the AUROC from the largest to the smallest was different by different QT correction methods (Figure 3 and 4.1-4.3). However, there were a few similarities, for example, in both Framingham's and Rautaharju's formulas, the two largest AUROCs of individual leads were from lead aVL, and III, which were consistent with the findings reported in the study by Lund et al. (8). The study found that the lead with the highest accuracy was located in lead II, III or aVL, but was never located in any precordial leads. In contrast to the greatest AUROCs from Framingham's and Rautaharju's formulas, with Bazett's, QTc from many precordial leads such as V3, V5, and V6 were found to have the greatest AUROCs, and not from the limb leads.

Our study also found that the longest QTc in any subject regardless of QT correction formulas always provided the greatest AUROC to predict TdP. This interesting finding was identical to a previous study, even considering that such a study was done in a different setting. The study was done on the prognostic accuracy of different ECG leads for predicting any arrhythmic death and the QT abnormality was noted to be from cardiac conditions, and not due to drugs (8).

To be able to identify an ECG lead that has the longest QTc, one will have to measure the QT interval of all 12 leads because the longest QTc does not fix in a particular lead all the time in any individual. This would be time-consuming, and less satisfying in clinical settings, especially in a situation like working in the ED. As a result, it would not be practical for clinical practice even though the longest QTc provides the best predictive performance for a serious adverse outcome like TdP. A better choice seemed to be finding a QTc from any single fixed lead or a set of leads that provided a similar AUROC with the lead having the longest QTc to be able to predict the deadly outcome, like having TdP, more accurately. At first, we believed a lead that had the most frequent longest QTc (Figure 2: lead V2, V3, V4) would be the one; however, our study demonstrated that was not the case (Figure 4.1-4.3, lead V2, V3, V4). The reason might be that even though leads V2-V4 most often had the longest QTc, they only had the longest QTc ranging from 16-23% (Figure 3) of all subjects. We tried to use the mean QTc from V2-V4, the leads with the most frequent longest QTc, but this still did not give us a comparable performance as the longest QTc (Figure 4.1-4.3: mean QTc of three leads having the most longest QTc).

Surprisingly, we found that a mean QTc from three leads that contained lead II, and any two leads from V2-V4 (II, V2, V3; or II, V2, V4; or II, V3, V4) provided very good performance and was comparable to the AUROC of the longest QTc (Figure 4.1-4.3). This finding was consistent across all QT correction formulas.

Isbister et al. (6) suggested using a median QTc of 6 leads such as from leads I, II, aVF, V2, V4, and V6. Our results found that the AUROC from the median of those 6 leads was also comparable to the AUROC of the QTc from the lead with the longest QTc. Using the median QTc from 6 leads would shorten the time to measure the QT interval from 12 leads to find the longest one by half. At this point, we would say that both the median QTc of 6 leads and the mean QTc from 3

leads (lead II + any two of leads V2-V4) could be used instead of the longest QTc since both of them provided comparable AUROCs for TdP prediction. However, in favor of saving time, we would use the mean QTc from 3 leads (lead II + any two of leads V2-V4), because this consumes less time while maintaining the highest overall test performance to predict TdP. If the QT interval in lead II is unmeasurable, then use the median of 6 leads (It does not matter if one or two leads in the set were unmeasurable, because, for the median, the one in the middle (or average of two numbers in the middle, if the number of data in the set is even) is the representative of the set).

4.1. Limitations

This study had some limitations due to the nature of the disease outcome, TdP. Due to the rare incidence of drug-induced TdP, we used a diagnostic case-control (two-gate) design for this study population, instead of using a cohort (one-gate) design as is recommended for a prognostic/diagnostic study. However, the case-control design is suggested for the early stage of a diagnostic/prognostic study (15). This diagnostic case-control design may have inflated test accuracy in our study; however, as mentioned in the methodology, we did not mean to use the "absolute accuracy" of the index tests as to how accurate those tests predict the main outcome. Instead, we meant to compare which index test was relatively the best (highest accuracy or comparable accuracy, but less time-consuming). Thus, a prospective study is needed to verify the results of this study and to see if it has any clinical impact.

Second, we did not attempt to find any cut-off point for corrected QT intervals. In clinical settings, clinicians use corrected QT interval with a cut-off value to define QT prolongation. This could limit the applicability of this study. It was our purpose to not add complexity to this study and not make this study too long. We see this study as a preliminary one, and we will continue our plan for the next studies to find cut-off values of each index test and to compare among them to see if the cut-off number of the longest QT interval can still predict TdP the best.

5. Conclusion

The longest QTc provided the greatest AUROC in predicting drug-induced TdP; however, the longest QTc is not located in a fixed individual lead in any patient. To identify the longest QTc from a 12-lead-ECG, one must measure the QT interval from all 12 leads, and doing so is time-consuming. Instead, using a mean QTc from three leads containing lead II, plus any two of leads V2-V4 was less time-consuming and it provided comparable overall test accuracy to the longest QTc, regardless of QT correction formulas. However, the potential clinical impact of this finding needs to be verified in a prospective study.

6. Declarations

6.1. Acknowledgments

None.

6.2. Conflicts of interest

The authors declare that they have no conflicts of interest.

6.3. Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Faculty of Medicine Vajira Hospital (certificate of approval number: 058/2562).

6.4. Source of funding

This study was funded by Navamindradhiraj University Research Funds.

6.5. Author contributions

RO conceived the study, designed the trial, and obtained research funding. RO supervised TR and SV the conduct of the trial and data collection. TR performed systematic review and recruited cases from Medline for drug-induced TdP cases. SV reviewed and undertook recruitment of drug-induced QT prolongation cases from the Toxicology logbook of the Medical Toxicology Unit, Department of Emergency Medicine Vajira Hospital, Bangkok, Thailand. TR and SV collected and managed the data. RO managed quality control of the study. RO provided statistical advice on study design and data analysis. TR drafted the manuscript. RO reviewed and revised the manuscript. RO takes responsibility for the paper as a whole. All authors read and approved the final version of manuscript.

6.6. Data availability statements

The data that support the findings of this study are available from the authors but restrictions apply to the availability of these data, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission from Faculty of Medicine Vajira Hospital, Navamindradhiraj University.

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Table 1: Patient characteristics in both groups

Variables	Total (n=284)	Control (n=148)	Case (n=136)
Age (year)			
Median (IQR)	28 (18-58.5)	18 (16-21)	62 (45-72.5)
Gender			
Male	166 (58.5)	121 (81.8)	45 (33.1)
Underlying disease			
Cardiovascular disease	49 (17.3)	0 (0)	49 (36)
Hypertension	58 (20.4)	1 (0.7)	57 (41.9)
Diabetes mellitus	32 (11.3)	0 (0)	32 (23.5)
Renal disease	4 (1.4)	0 (0)	4 (2.9)
Other	33 (11.6)	9 (6.1)	24 (17.7)
Drug category			
Known risk	112 (39.4)	2 (1.4)	110 (80.9)
Possible risk	139 (48.9)	134 (90.5)	5 (3.7)
Conditional risk	32 (11.3)	12 (8.1)	20 (14.7)
Drug to avoid in LQTS	1 (0.4)	0 (0)	1 (0.7)
Heart rate (beats/minute)			
Median (IQR)	80 (62-98)	97 (80-114)	62 (52-77)
Medication exposed*			
Tramadol	158	157	1
Dextromethorphan	34	33	1
Fluoxetine	6	4	2
Azithromycin	20	0	20
Amiodarone	19	0	19
Sotalol	18	0	18
Other	155	20	135

Data are presented as median (IQR) or frequency (%). LQTS: long QT syndrome. *: Top three frequent medications in case and control groups.

Supplement Table 1: Comparison of AUROCs from the groups of leads among all three QT correction methods

Leads	QTcFRA	QTcRTH	QTcBZT	P-value
Mean QTc of 3 leads with the least frequent counts of longest QTc (aVL, III, aVF)	0.9735	0.9694	0.9631	0.162
Mean QTc of 3 leads with the most frequent counts of longest QTc (V3, V2, V4)	0.9786	0.9771	0.9814	0.9094
Median QTc of lead I, II, aVF, V2, V4, V6	0.9791	0.9768	0.9756	0.4586
Mean QTc of lead II, V2, V3	0.9827	0.9837	0.9839	0.9368
Mean QTc of lead II, V3, V4	0.9796	0.9808	0.9812	0.8708
Longest QTc from each subject	0.9915	0.9893	0.9904	0.2576

QTcFRA: QT interval corrected by the Framingham's method; QTcRTH: QT interval corrected by the Rautaharju's method; QTcBZT: QT interval corrected by the Bazett's method; AUROC: Area under the receiver operating characteristic curve.
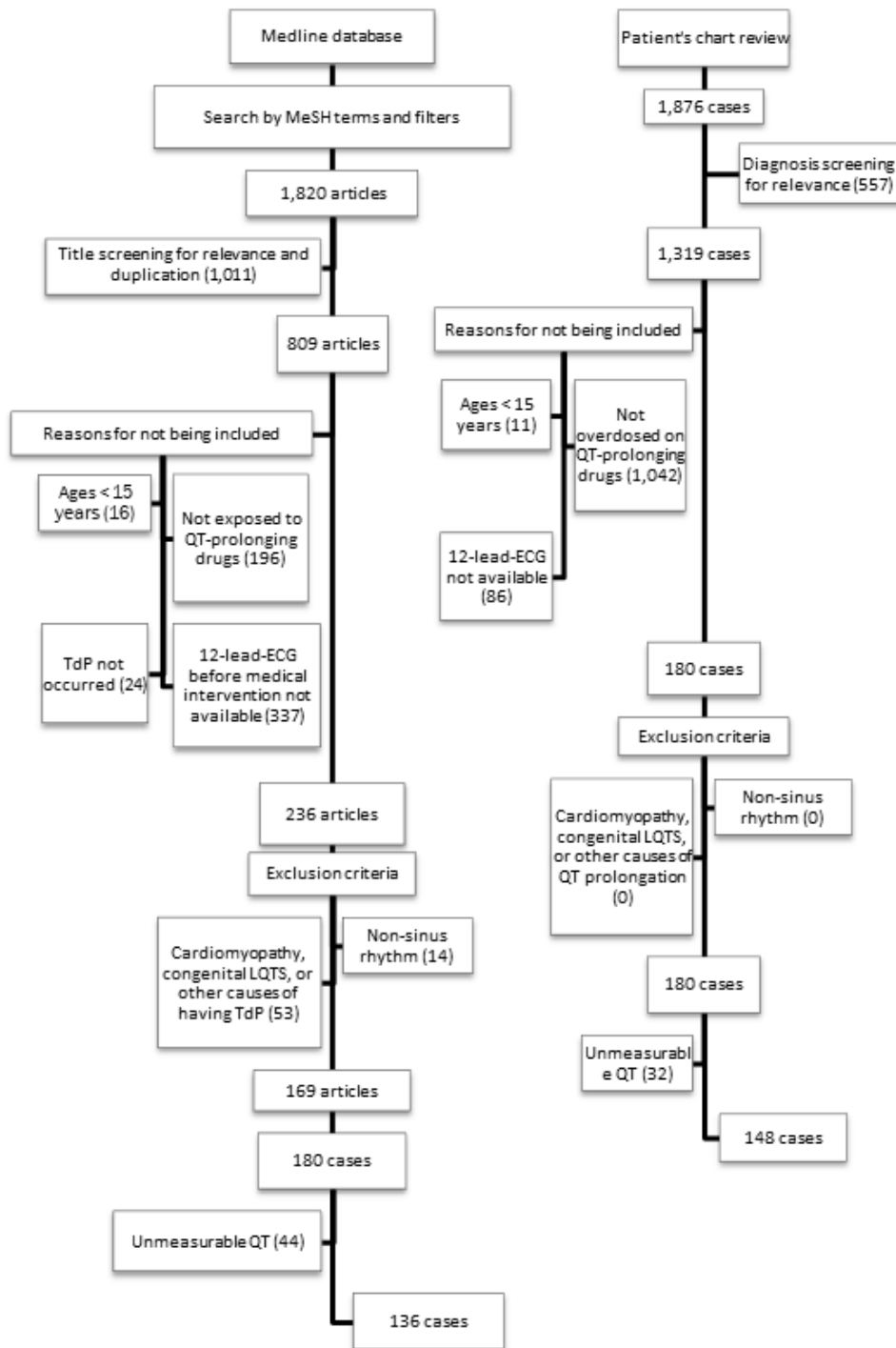
Figure 1: Inclusion and exclusion process in the case and control groups. MeSH: Medical Subjecy Heading; LQTS: long QT syndrome; ECG: electrocardiogram; TdP: Torsade de pointes.
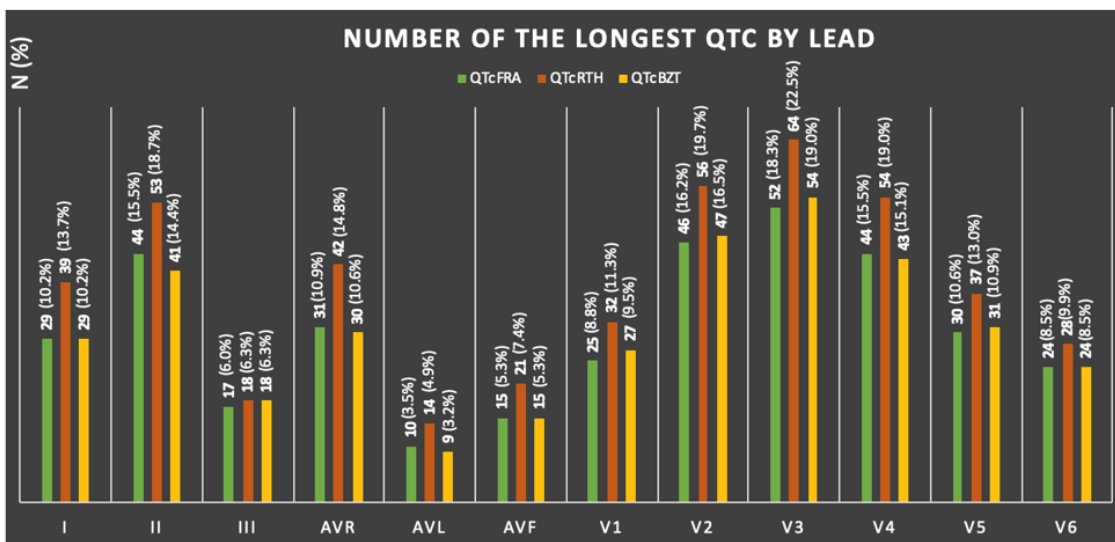
Figure 2: Frequency of the longest QTc by lead and QT correction formula. QTcFRA: QT interval corrected by the Framingham's method; QTcRTH: QT interval corrected by the Rautaharju's method; QTcBZT: QT interval corrected by the Bazett's method; N: number.
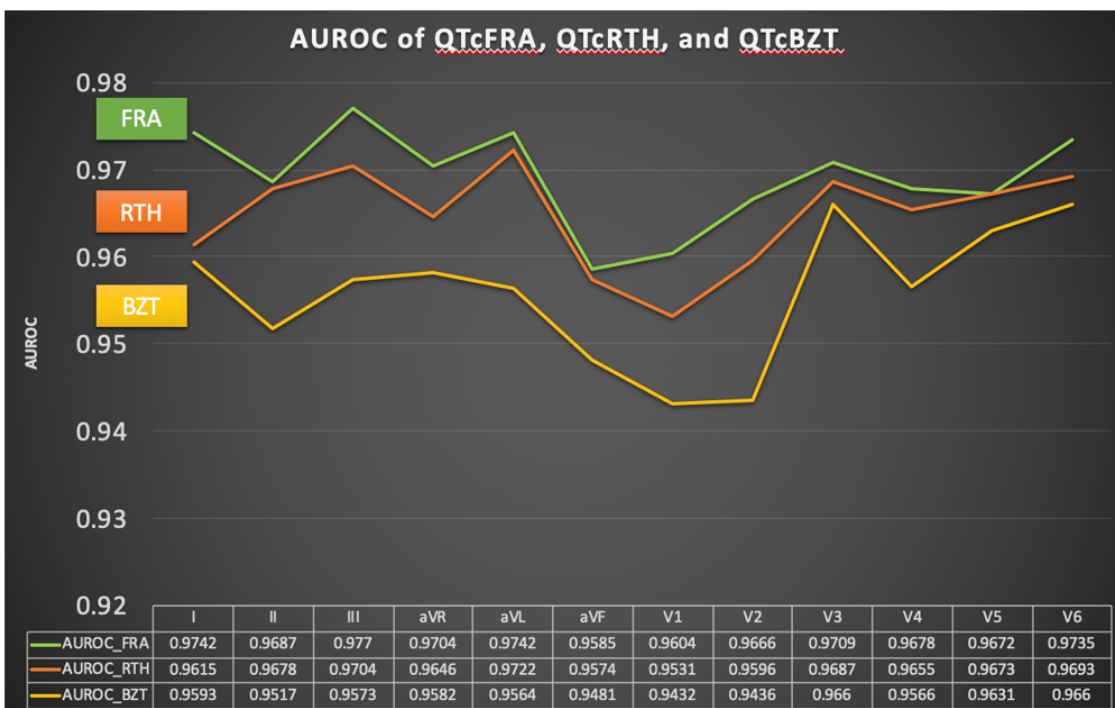

	I	II	III	aVR	aVL	aVF	V1	V2	V3	V4	V5	V6
AUROC_FRA	0.9742	0.9687	0.977	0.9704	0.9742	0.9585	0.9604	0.9666	0.9709	0.9678	0.9672	0.9735
AUROC_RTH	0.9615	0.9678	0.9704	0.9646	0.9722	0.9574	0.9531	0.9596	0.9687	0.9655	0.9673	0.9693
AUROC_BZT	0.9593	0.9517	0.9573	0.9582	0.9564	0.9481	0.9432	0.9436	0.966	0.9566	0.9631	0.966

Figure 3: The AUROCs of QTc (from each lead from QTcFRA, QTcRTH, and QTcBZT) for prediction of TdP. QTcFRA: QT interval corrected by the Framingham's method; QTcRTH: QT interval corrected by the Rautaharju's method; QTcBZT: QT interval corrected by the Bazett's method; AUROC: Area under the receiver operating characteristic curve; TdP: Torsade de pointes.
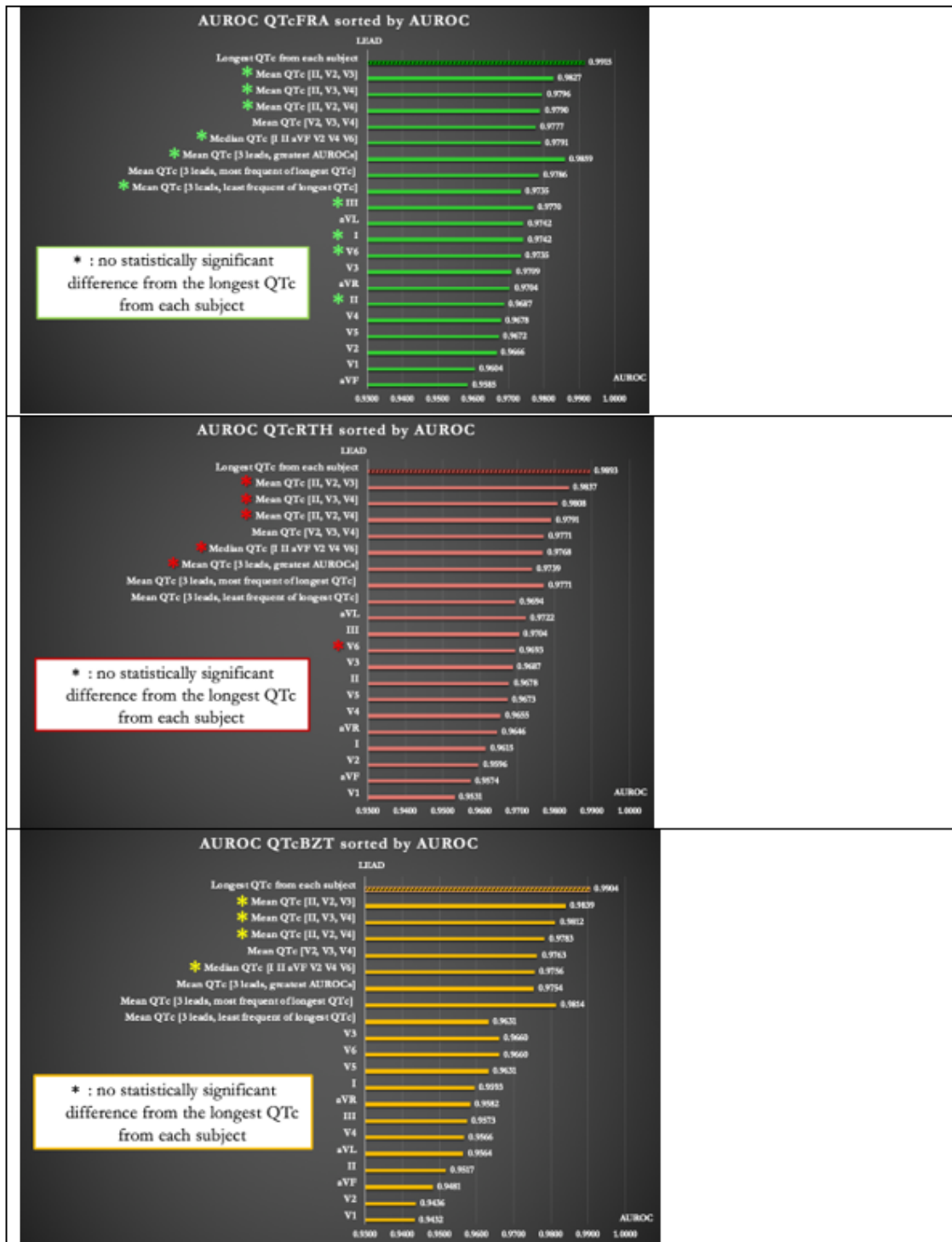
Figure 4: The AUROCs of QTc from individual leads and groups of leads sorted by the size of AUROC in prediction of TdP. QTcFRA: QT interval corrected by the Framingham's method; QTcRTH: QT interval corrected by the Rautaharju's method; QTcBZT: QT interval corrected by the Bazett's method; AUROC: Area under the receiver operating characteristic curve; TdP: Torsade de pointes.
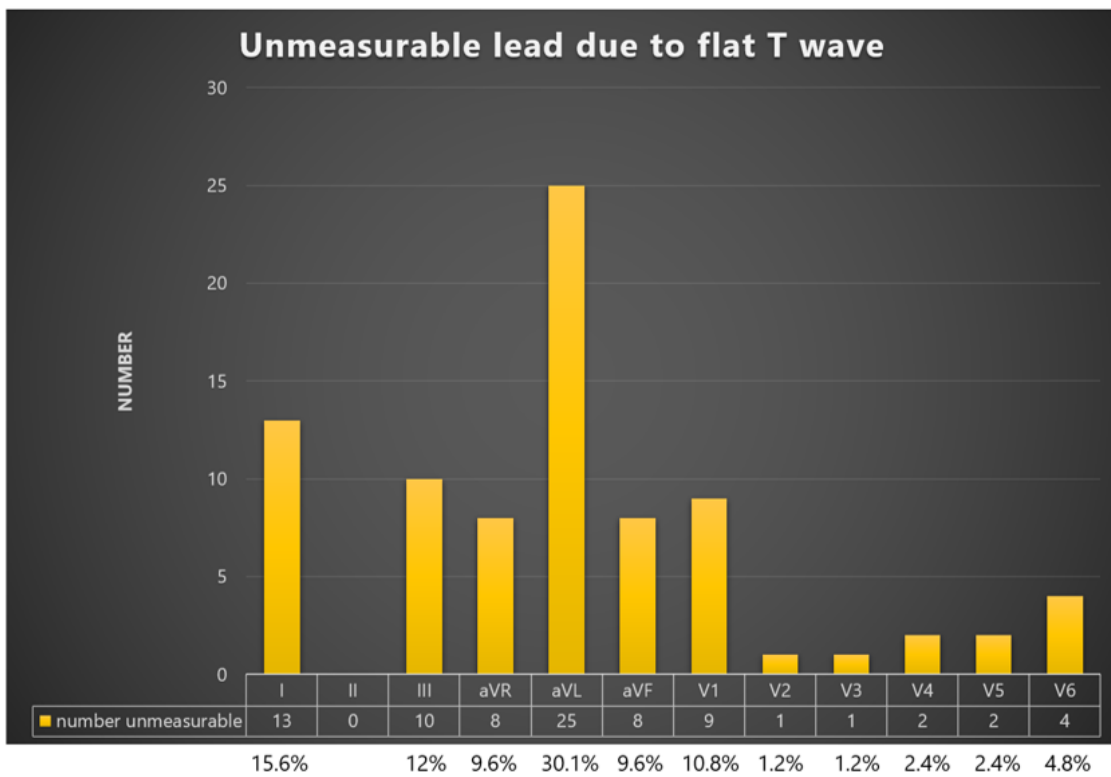
Supplement Figure 1: Frequency of individual leads with unmeasurable QT intervals.