Monitoring prolongation of QT interval in patients with multidrug-resistant tuberculosis and non-tuberculous mycobacterium using mobile health device AliveCor

Shriya Puranik a, Christopher Harlow b, Laura Martin b, Meg Coleman b, Georgina Russell b, Mirae Park c, Onn Min Kon d,*

a Imperial College London, Imperial Clinical Respiratory Research Unit (ICRRU), United Kingdom
b Imperial College Healthcare Trust NHS, United Kingdom
c Imperial College Healthcare Trust NHS, Imperial Clinical Respiratory Research Unit (ICRRU), National Heart and Lung Institute, Imperial College London, United Kingdom
d Imperial College Healthcare Trust NHS, National Heart and Lung Institute, Imperial College London, United Kingdom

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ABSTRACT

Multidrug resistant tuberculosis and non-tuberculous mycobacterium infections present challenges due to complex treatment regimens. Extended treatment regimes expose patients to higher risks of toxic side-effects. A high drug toxicity profile necessitates closer monitoring. One of the more challenging issues is QTc prolongation with non-injectable regimens.

This study investigates the portable AliveCor device to record and measure the QTc on a 6-lead ECG. An automated QTc readout from 12-Lead ECG for each patient (n = 13) and mean QTc value calculated from each patient’s respective AliveCor tracing were compared. The general trend suggests AliveCor underestimates QTc 92% cases calculated the AliveCor QTc as lower than their corresponding 12-Lead QTc readout.

The use of AliveCor could potentially be translated into current clinical practice with caution of percentage variation either side. This could facilitate the use of AliveCor as a promising and convenient screening tool before further evaluation by a 12-Lead ECG is required.

1. Background

Drug-resistant tuberculosis (TB) is a growing concern with approximately half a million new cases of rifampicin-resistant TB recorded, 78% of which were multidrug-resistant TB (MDR-TB) in 2019 [1]. The incidence rate of non-tuberculous mycobacterium (NTM) infections has more than tripled in the United Kingdom (UK) between 1995 and 2006 [2]. A significant challenge presented by MDR-TB and NTM infections is the reliance on second line treatments, which need to be taken by patients for up to 18 months [3]. Extended use of multiple antibiotics exposes patients to a higher risk of toxic side-effects [4,5]. A high drug toxicity profile necessitates closer monitoring to ensure adherence and positive treatment outcomes. With no clear guidance on drug toxicity monitoring for drug-resistant TB and NTM this increases the burden on the healthcare system as clinicians and patients struggle with the complexity of the condition.

Prolongation of the QT interval is a concerning side-effect caused by drugs such as clofazimine, bedaquiline, macrolide and fluoroquinolone antibiotics, which are used as part of MDR-TB and NTM treatment [5,6]. Although rare, this puts the patient at risk of developing polymorphic ventricular tachycardia, Torsades de Pointes, which may be life-threatening [7].

Global expansion in access to medical technology prompted an investigation into the role of mobile health applications in TB drug monitoring [8,9]. This study investigates the use of a portable, handheld device (AliveCor) which records an electrocardiogram (ECG) trace in a minimum of 30 seconds, by establishing three points of contact with electrodes to skin: two thumbs and left ankle or knee [10]. AliveCor is used alongside the Kardia application to record and measure the QTc on a 6-lead ECG, which uses an algorithm for identifying rhythm and has been validated for monitoring atrial fibrillation in patients [11–13]. The Kardia app with AliveCor device has furthermore, since

* Corresponding author at: Chest and Allergy Clinic, St Mary’s Hospital, Imperial College Healthcare NHS Trust, Praed Street, London W2 1NY, United Kingdom.
E-mail address: Onn.kon@nhs.net (O. Min Kon).

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been authorised by the United States (US) Food and Drug Administration (FDA) to monitor prolongation of QT interval in the time of the pandemic because of its ease of use [14]. A unique feature of the AliveCor’s tracing is the presence of lead II, theoretically allowing manual interpretation of QT interval [7]. Therefore, this app could potentially offer remote cardiac monitoring at the convenience of the patient.

2. Method

This pilot study at a tertiary TB centre in London collected preliminary data to assess the accuracy of AliveCor’s corrected QT (QTc) measurements, and its feasibility for use at TB/NTM clinics. As the QT interval differs depending on heart rate, QTc was calculated to allow better comparison between the patient’s readings. A list of MDR-TB and NTM patients on cardiotoxic medications was compiled. Patients volunteered to participate in this feasibility study trialling the AliveCor device and anonymity was maintained throughout. A 6-Lead ECG by AliveCor was recorded for each patient (n = 16) and compared to the gold standard 12-Lead ECG. The ECGs at rest were performed at a convenient time during patients’ routine visit to hospital as these were clinically required for NTM/MDR-TB treatment. Since the default for 12-Lead ECG machines’ QTc calculations used the Bazett formula, this formula was also used to compare the AliveCor QT corrections [15]. The Mortara ELI350 was the 12-Lead ECG machine used in this study and was the only machine used throughout the study. Automated QTc readouts from the 12-Lead and manually calculated QT intervals from lead II of the AliveCor tracing were analysed. Manual calculations involved counting the number of 1 mm squares from the start of the QRS complex to the end of the T wave – to calculate the QT interval - and using a standard formula (QTc = QT interval / \sqrt{(RR interval)}. The end of the T wave was defined as the intercept between the isoelectric line with the tangent through the maximum downwards slope of the T wave [16]. Three clear areas of the AliveCor tracing were selected at random and an average of the QT interval was calculated. The heart rate for each of the AliveCor tracings were also manually calculated from lead II; an average of three R-R was used. An average QTc was calculated by three independent readers from the calculated heart rate and QT interval which was put into an online calculator for each of the correction

![Fig. 1.](image1.png)

**Fig. 1.** For each patient, Alivecor tracings were used to manually calculated QTc with the Bazett formula by 3 independent observers. The mean of the 9 readings shown in grey with error bars representing the standard deviation between observers’ readings was plotted alongside the automated QTc readout from each of the patients’ respective 12-Lead ECG, shown in black.

![Fig. 2.](image2.png)

**Fig. 2.** Graph depicting the intra-observer variation for observer 1,2 and 3. The mean QTc calculated from Lead II of the AliveCor tracing using the Bazett correction formula is plotted for each patient with the SD shown as error bars. The data sets for each observer are shown side by side for each patient for comparison between the three observers.

![Fig. A1.](imageA1.png)

**Fig. A1.** Agreement between automated QTc readings and manually calculated QTc readings from AliveCor is displayed as a Bland-Altman plot. The values used for manually calculated QTc value is the mean value between the 3 observers (n = 9). The upper and lower 95% confidence intervals are represented as dashed grey lines (---). Bias = 19.43, 95% confidence intervals are from 20.54 to 55.61.
The automated QTc readout from the 12-Lead ECG for each patient and mean QTc value calculated from each patient’s respective AliveCor tracings are shown alongside each other in Fig. 1. In 12/13 cases (92%), AliveCor underestimated the QTc in comparison to the corresponding 12-Lead QTc readout. The mean percentage difference between the automated 12-Lead and manually calculated AliveCor readings was 3%. The largest percentage difference between the two readings was 12%. Correlation between the automated QTc and AliveCor QTc was evaluated with Pearson’s correlation coefficient = 0.43, p > 0.05.

For evaluation of AliveCor’s reliability, intra and inter-observer variation were assessed using three observers. Intra-observer variability was evaluated by measuring the mean QTc value and standard deviation averaged from three repeated QTc calculations per patient from their AliveCor ECG trace, for all observers (Fig. 2). The standard deviations and calculated QTc values varied greatly from patient to patient. Bland-Altman analysis comparing the 3 observers’ readings to each other revealed agreement as all but one of the points lay between the limits of agreement. Bias in measurements varied between 6.2 ms and 14.6 ms, standard deviation of bias ranged between 20.3 ms and 30.2 ms. Although Bland-Altman plots suggested agreement, further evaluation to determine the clinical significance of inter-observer variability should be carried out; especially as the sample size in this pilot study was small and therefore inter-observer agreement could not be reliably assessed. A Friedman correlation for inter-observer reliability was also calculated which only showed a p value of 0.2319. We also performed a generalised mixed regression modelling on a sample of 13 patients, with one random effect assigned per patient, to detect potential differences in observation quality between three observers. The average deviation in measurement was lowest in observer 1 (on average 26.2 [95% CI:15.7–36.7]) and largest in observer 3 (on average 34.1 [95% CI:23.6–44.7]), however, differences were not statistically significant.

**4. Discussion**

The larger discrepancies in QTc readings could be due to presence of artefacts, affecting the quality of the AliveCor tracings. Repeat recordings would allow optimal tracings, however, due to curtailment of recruitment as a result of the COVID pandemic, this was not possible. Inter-observer variability presented challenges due to subjectivity of a manually calculated QT interval. Additionally, most patients had a same day comparison of AliveCor with a 12-Lead ECG, however, this was not the case for four out of the 13 patients. This may have accounted for some of the variation in Fig. 1, as the QT interval may have changed between the two readings, and there is known daily variation in QT interval in the same person (up to 75 ms) [17]. Although lead II was used as the lead of choice for interpreting the QTc from it is important to remember that some 12-lead ECG machines use a “global” lead with alterations made considering all 12 leads. This could influence the comparisons between AliveCor and the 12-lead ECG readings. Another limitation may lie with the choice of using the Bazett formula as the comparator. In this case although the Bazett was the default formula used by the 12-lead machine there has been evidence to suggest the Bazett formula can over or under-correct the QT prolongation subject to the heart rate [18,19]. Discrepancies between observers manually calculating the QTc is a well-known problem and reported by Visken et al., where a description of many physiologists including cardiologists were not able to recognise long QT [20].

As this study’s purpose was to provide pilot data and evaluate feasibility; it allowed us to place in context the role for mobile monitoring in modern-day clinical practice. As a pilot study a sample size was not calculated. Moreover, evidence from a recent study by Karacan et al. [21] supported the use of AliveCor for accurately measuring QTc intervals in a paediatric cohort, showing a significant correlation between corrected QT interval from AliveCor reading and 12-Lead ECG (Pearson’s correlation coefficient = 0.57, p < 0.001).

The portability of the AliveCor device would allow a screening tool to identify potential abnormalities in the community and in outreach clinics like homeless shelters, significant for optimising medical care in vulnerable patient groups. These could then be brought for more formal evaluation in a secondary care setting. Furthermore, in light of the recent COVID-19 pandemic, need for remote monitoring has become increasingly relevant. Remote monitoring can aid progression of treatment whilst protecting vulnerable patients from risk of exposure to illness. The AliveCor device overcomes the need for use of personal protective equipment, minimising additional equipment such as ECG pads and contact time with patients.

**5. Conclusion**

In addition to evaluating feasibility this study presents novel data using AliveCor to calculate QTc in patients taking potentially cardiotoxic TB related medications in a real clinical setting. At this stage it
would not be advisable to replace the 12-Lead ECG testing for monitoring the QTc with the AliveCor device as there is not enough evidence to support its reliability. However, there may be opportunity to integrate AliveCor as an accessory in practice - to allow further investigation into practicality of usage in TB and NTM clinics as well as trialling manual interpretation of AliveCor QTc in the same clinics. Provisional use of AliveCor could therefore be cautiously translated into current clinical practice using QTc readings from the device. From Fig. 1 the largest percentage difference was calculated as 12% therefore, if AliveCor QTc were to be used in clinical practice, a threshold allowing for this variation could be factored in. This could facilitate use of AliveCor as a promising screening rather than a definitive diagnostic tool before further evaluation by a 12-Lead ECG if required.

Future studies are required to assess and validate the full potential of AliveCor. Treatment of complex conditions like MDR-TB and NTM remain a clinical challenge with numerous side-effects and compliance issues. Even with enhancement and treatment optimisation, there is huge scope for early identification of side-effects in these medications. With the shift towards personalised medicine, integration of phone apps as a health intervention tool can improve patient experiences, patient care and ultimately patient safety. The implications of this are not necessarily restricted to patient on MDR-TB/NTM medications but all patients on other cardioactive medications requiring monitoring.

Ethical Statement

As a service evaluation and pilot study informed consent was not obtained. AliveCor device has been FDA approved.

Author Contributions Section

OMK, MP, SP conceptualised the manuscript, SP wrote the manuscript with contributions from OMK, MP, CH, CH, MP, SP collected and interpreted data, All authors modified, reviewed and approved manuscript

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Appendix

Difference between automated QTc readings and manually calculated QTc from AliveCor vs. the average AliveCor manual reading (Fig. A1).

Mean manually calculated QTc from AliveCor using four different QTc correction formulae: Bazett, Framingham, Fridericia, Hodges (Table A1).

References

[1] 9789240013131-eng.pdf [Internet]. [cited 2021 May 3]. Available from: https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf.
[2] Ratnatunga CN, Lutzky VP, Kupza A, Doolan DL, Reid IW, Field M, et al. The Rise of Non-Tuberculosis Mycobacterial Lung Disease. Front Immunol 2020 Mar;11:1.
[3] Schnippe K, Firrhabber C, Berhanu R, Page-Shipp L, Sinanovic E. Adverse drug reactions during drug-resistant TB treatment in high HIV prevalence settings: a systematic review and meta-analysis. J Antimicrob Chemother 2017;01;72(7):1871–9.
[4] Prasad R, Singh A, Gupta N. Adverse drug reactions in tuberculosis and management. Indian J Tuberc 2019 Oct 1;66(4):520–32.
[5] Yang TW, Park HO, Jang HN, Yang JH, Kim SH, Moon SH, et al. Side effects associated with the treatment of multidrug-resistant tuberculosis at a tuberculosis referral hospital in South Korea. Medicine (Baltimore). 2017 Jul 14;96(28).
[6] WHO. Global tuberculosis report 2019 [Internet]. WHO. [cited 2020 Feb 20]. Available from: http://www.who.int/tb/publications/global_report/en/.
[7] Salvi V, Karnad DR, Kerkar V, Panicker GK, Manohar D, Natakar M, et al. Choice of an alternative lead for QT interval measurement in serial ECGs when Lead II is not suitable for analysis. Indian Heart J 2012 Nov;64(6):535–40.
[8] Majumder S, Deen MJ. Smartphone Sensors for Health Monitoring and Diagnosis. Sensors. 2019 May 9;19(5).[9] Story A, Garfin RS, Hayward A, Rusovich V, Dadu A, Soltan V, et al. Monitoring Therapy Adherence of Tuberculosis Patients by using Video-Enabled Electronic Devices. Emerg Infect Dis 2016 Mar;22(3):538–40.
[10] AliveCor [Internet]. [cited 2021 May 3]. Available from: https://www.alivecor.com/kardiamobile6l/.
[11] Tu HT, Chen Z, Swift C, Churilov L, Guo R, Liu X, et al. Smartphone electrographic monitoring for atrial fibrillation in acute ischemic stroke and transient ischemic attack. Int J Stroke. 2017 Oct;12(7):786–9.
[12] Li KHC, White FA, Tipoe T, Liu T, Wong MG, Jebusahan A, et al. The Current State of Mobile Phone Apps for Monitoring Heart Rate, Heart Rate Variability, and Atrial Fibrillation: Narrative Review. JMIR MHealth UHealth. 2019 Feb 15;7(2).
[13] Kolotowski L, Balsam P, Glownczyńska R, Rokicki JK, Peller M, Makym J, et al. Kardia Mobile applicability in clinical practice: A comparison of Kardia Mobile and standard 12-lead electrocardiogram records in 100 consecutive patients of a tertiary cardiovascular care center. Cardiol J 2019 Jan 15.
[14] AliveCor [Internet]. [cited 2020 Apr 22]. Available from: https://www.alivecor.com/press/press_release/new-fda-guidance-allows-use-of-kardiamobile-6l-to-measure-qtc-in-covid-19-patients/.
[15] Bazett JC. An analysis of time relations of electrocardiograms. Heart 1920;7:353–67.
[16] Charbit B, Samain E, Merckx P, Panck-Brentano C. QT interval measurement: evaluation of automatic QTc measurement and new simple method to calculate and interpret corrected QT interval. Anesthesiology 2006 Feb;104(2):255–60.
[17] Molnar J, Zhang F, Weiss J, Ehlert FA, Rosenhalt JE. Diurnal pattern of QTc interval: how long is prolonged? Possible relation to circadian triggers of cardiovascular events. J Am Coll Cardiol 1996 Jan;27(1):76–83.
[18] Goldberg I, Moss AJ, Zareba W. QT interval: how to measure it and what is normal? J Cardiovasc Electrophysiol 2006 Mar;17(3):333–6.
[19] Vandenbergh B, Vandael E, Robyns T, Vandenberge J, Garweg C, Foulon V, et al. Which QT Correction Formulas to Use for QT Monitoring? Jun 17 [cited 2021 May 6];5(6). Available from: J Am Heart Assoc Cardiovasc Electrophysiol [Internet]. 2016 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4953726/.
[20] Vinkin S, Rososvky U, Sands AJ, Chen E, Kistler PM, Kalman JM, et al. Inaccurate electrocardiographic interpretation of long QT: The majority of physicians cannot recognize a long QT when they see one. Heart Rhythm 2005 Jun 1;2(6):569–74.
[21] Karacan M, Celik N, Gul EE, Akszen C, Tazvu V. Validation of a smartphone-based electrocardiography in the screening of QT intervals in children. North Clin Istamb 2019 Feb 12;6(1):48–52.