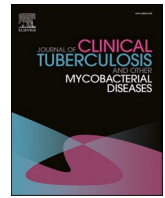




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Monitoring prolongation of QT interval in patients with multidrug-resistant tuberculosis and non-tuberculous mycobacterium using mobile health device AliveCor

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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 patients' 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 QT interval 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

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Mean QTc calculated from AliveCor compared to automated QTc from 12 lead ECG for each patient (n=13)

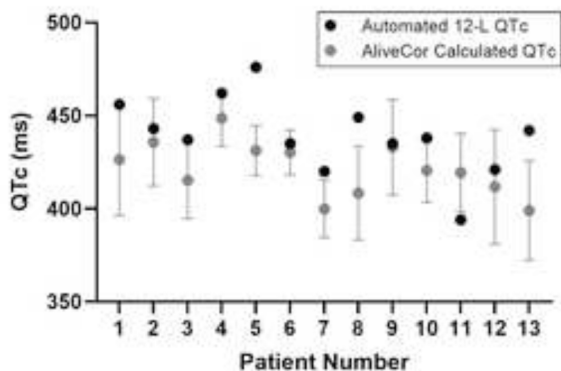


Fig. 1. For each patient, AliveCor tracings were used to manually calculated QTc with the Bazett formula by 3 independent observers. The mean of the 9 readings shown in grey with error bars representing the standard deviation between observers' readings was plotted alongside the automated QTc readout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

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 ($QTc = QT \text{ interval} / \sqrt{RR \text{ interval}}$). 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

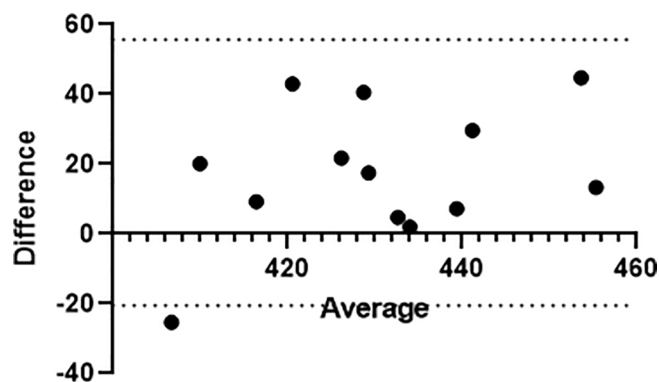


Fig. A1. Agreement between automated QTc readings and manually calculated QTc readings from AliveCor is displayed as a Bland-Altman plot. The values used for manually calculated QTc value is the mean value between the 3 observers (n = 9). The upper and lower 95% confidence intervals are represented as dashed grey lines (---). Bias = 19.43, 95% confidence intervals are from 20.54 to 55.61.

Manually calculated QTc from AliveCor by each observer using the Bazett formula for each patient

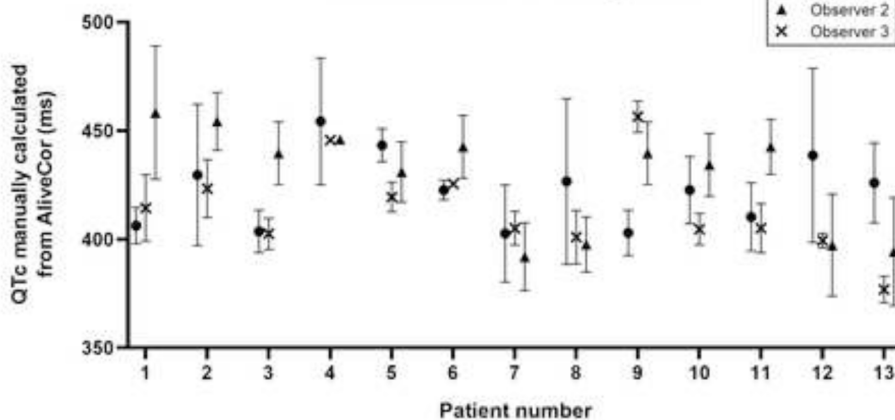


Fig. 2. Graph depicting the intra-observer variation for observer 1,2 and 3. The mean QTc calculated from Lead II of the AliveCor tracing using the Bazett correction formula is plotted for each patient with the SD shown as error bars. The data sets for each observer are shown side by side for each patient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

Table A1

Table to show mean values of manually calculated QTc for each of the AliveCor tracings using the four QTc correction formulae: Bazett, Fridericia, Framingham and Hodges. For each patient 2 observers calculated the QTc three times therefore the mean value is from a total of 6 readings. Standard deviation (SD) values between the 2 observers' readings are also shown in this table.

	MEAN OF THE 6 INTERPRETATIONS OF AliveCor READINGS											
	BAZETT			FRIDERICIA			FRAMINGHAM			HODGES		
	MEAN	SD	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	N
001	424.66	1.89	2	386.98	1.92	2	387.00	1.41	2	399.88	1.59	2
002	450.50	0.24	2	429.46	0.29	2	428.75	0.35	2	425.17	0.24	2
003	441.42	5.54	2	410.24	5.79	2	409.05	5.11	2	412.36	4.67	2
004	444.20	4.66	2	414.05	2.76	2	412.92	2.24	2	414.75	3.18	2
005	425.87	3.48	2	403.56	3.45	2	405.00	3.29	2	402.29	2.89	2
006	460.22	4.09	2	427.20	3.58	2	423.68	2.85	2	427.42	2.95	2
007	466.12	41.89	2	458.72	44.86	2	458.56	43.93	2	455.25	44.90	2
008	416.42	15.44	2	378.03	14.18	2	379.32	11.77	2	393.88	11.84	2
009	414.76	0.60	2	405.97	0.91	2	407.56	0.79	2	403.50	0.71	2
010	467.10	26.73	2	434.06	24.66	2	429.57	21.11	2	432.88	21.39	2
012	435.45	13.98	2	403.94	12.81	2	403.68	11.29	2	407.42	11.20	2
013	453.59	36.65	2	436.08	35.25	2	435.21	32.23	2	431.00	32.53	2
015	422.33	18.62	2	400.95	17.74	2	402.66	16.04	2	400.00	16.26	2
017	391.04	15.02	2	383.74	14.50	2	386.04	14.08	2	382.13	13.97	2

formulae. The observers analysed each anonymous ECG tracings three times, resulting in a total of 9 readings per patient between the 3 observers. The mean QTc values were used. Three of the patients' AliveCor readings were excluded, due to poor tracings or having no 12-Lead to compare to resulting in $n = 13$.

3. Results

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 QTcs 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 carried 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 cardiotoxic 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).

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