Title: Relationship between a risk score for QT interval prolongation and mortality across rural and urban inpatient facilities

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Highlights

- Length of hospital stays increases with higher risk scores
- Risk of mortality for patients with risk scores ≥ 11 was 11-fold higher than those with risk scores <7
- Among risk factors, sepsis was associated with the highest risk of mortality, whereas hypokalemia and female sex were not associated with increased risk of mortality

Structured Abstract

Objectives

To evaluate the relationship between a modified Tisdale QTc-risk score (QTc-RS) and inpatient mortality and length of stay in a broad inpatient population with an order for a medication with a known risk of torsades de pointes (TdP).

Background

Managing the risk of TdP is challenging due to the number of medications with known risk of TdP and the complexity of precipitating factors. A model to predict risk of mortality may be useful to guide treatment decisions.

Methods

This was a retrospective observational study using inpatient data from 28 healthcare facilities in the western United States. This risk score ranges from zero to 23 with weights applied to each risk factor based on a previous validation study. Logistic regression and a generalized linear model were performed to assess the relationship between QTc-RS and mortality and length of stay.

Results

Between April and December 2020, a QTc-RS was calculated for 92,383 hospitalized patients. Common risk factors were female (55.0%); age>67 years (32.1%); and receiving a medication with known risk of TdP (24.5%). A total of 2770 (3%) patients died during their hospitalization. Relative to patients with QTc-RS<7, the odds ratio for mortality was 4.80 (95%CI:4.42-5.21) for patients with QTc-RS=7-10 and 11.51 (95%CI:10.23-12.94) for those with QTc-RS≥11. Length of hospital stay increased by 0.7 day for every unit increase in the risk score ($p<0.0001$).

Conclusion

There is a strong relationship between increased mortality as well as longer duration of hospitalization with an increasing QTc-RS.

Keywords: Torsades de Pointes, Arrhythmias, Cardiac, Mortality

Introduction

Torsades de pointes (TdP) is a life-threatening ventricular arrhythmia associated with QT interval prolongation.(1) Over 200 cardiac and non-cardiac medications are known to prolong the QTc interval, and 65 of these have a known risk of TdP.(2) Medications with a known risk of TdP are those with substantial evidence linking them to TdP, even when taken as recommended.(3) For example, levofloxacin has a known risk of TdP and studies have found the risk of death to be nearly 2.5 fold higher (HR = 2.49, 95% CI, 1.7-3.64) than the non-QT-prolonging antibiotic amoxicillin.(4) Likewise, the risk of mortality was 2-fold higher for azithromycin, a medication with a known risk of TdP, compared to amoxicillin.(5) In contrast, another study found that in a young adult population, azithromycin was not associated with increased risk of mortality.(6) Moreover, a large nationwide case-control study among patients aged 65 years and older observed an association with increased mortality among patients taking antidepressants with a known risk of TdP (OR = 1.53, 95% CI, 1.51-1.56) compared to antidepressants without a known risk of TdP (OR = 0.99, 95% CI, 0.94-1.05); likewise, antipsychotics with a known risk of TdP were associated with a higher risk of mortality (OR = 4.57, 95% CI, 4.37-4.78) compared to antipsychotics without a known risk of TdP (OR = 2.14, 95% CI, 2.03 – 2.65).(7) While the overall prevalence of TdP is low, it is expected to be highest in hospitalized patients who often have conditions that increase the risk of drug-induced TdP.(1, 8, 9) A patient is not at high risk of TdP can be prescribed a medication with a known risk of TdP and likely not experience negative health outcomes. The American Heart Association (AHA) scientific consensus recommends monitoring of hospitalized patient at risk of drug-induced TdP, that use of QT-prolongation medications should be individualized based on an

analysis of risk vs. benefit and "where benefit clearly outweighs risk, QTc prolongation should not limit necessary therapy".(9) This guideline highlights the need for individualized treatment decisions to limit the use of medications with known risk of TdP in those with high risk of harm, and to encourage the use of these medications among those with low risk of harm whose benefits from the medications outweigh risks.

In clinical practice, to improve patient safety and health outcomes, there is a critical need to identify patients at high risk of TdP and mortality. However, management of the risk of TdP is difficult due to the large number of medications with known risk of TdP and the complexity of precipitating factors. Some examples of the known risk factors for TdP include: admission Bazett's-corrected QTc > 450 milliseconds (ms); age > 67 years; administration of loop diuretics; concurrent use of QTc prolonging medication(s) with a known risk of TdP; female sex; diagnosis of cardiovascular disease; hypokalemia; hypomagnesemia; hypocalcemia; and history of myocardial infarction.(1, 9) Clinicians often have inadequate knowledge of QTc prolonging medications, their consequences, and how to properly manage patients at high risk of TdP.(10-13) In this case, a risk score may be helpful to identify patients with high risk of TdP who would be good candidates for prescribing alternative medications, where feasible, or close monitoring to minimize withholding effective medications.(14)

The assessment of TdP risk can be computed easily and quickly using existing common data elements available from inpatient electronic health records using a validated QTc risk score. This risk score can be used to estimate a patient's risk for QTc prolongation in real-time and assist in mitigating the risk of TdP.(15) Tisdale et al. reported that the prevalence of QTc interval

prolongation in cardiac patients increased from 15% in those with scores < 7 to 73% for those with scores ≥ 11.(15) Incorporation of this risk score into a computer clinical decision support (CDS) alert resulted in a significant reduction in the odds of QTc prolongation and reduction in the use QT interval-prolonging drugs in cardiac care units.(16) Another QTc risk score alerts called pro-QTc score that identifies patients with high risk of mortality.(17) The pro-QTc score includes various known risk factors for QT prolongation, and each factor is considered equal and designated 1 point.(17) In contrast, the Tisdale et al. version assigns weights to each risk factor, based on a logistic regression that predicted that the odds of developing QTc interval prolongation. For example, the odds ratio was 1.5 (95% CI, 1.1-2.0) for female sex, and 2.8 (95% CI, 2.0-4.0) for taking one QTc-prolonging drug.(15)

Although the Tisdale risk score was developed and validated with the purpose of identifying patients at high risk of developing QTc interval prolongation and TdP, there are other potential uses.(18) Because TdP is a rare event, we hypothesized that the risk of mortality would increase as the Tisdale QTc-RS increases, and that a Tisdale QTc-RS threshold of > 11 could be a useful tool to identify patients at high risk of all-cause mortality, similar to the pro-QTc score by the Mayo Clinic. The purpose of this analysis was to evaluate the relationship between a modified Tisdale QTc-RS and inpatient mortality and length of stay in a broad inpatient population who had a prescription order for a medication with a known risk of TdP.

Methods

Study Design: This was a retrospective observational study using inpatient data from a large healthcare system in the western United States.

Study Population: Individuals admitted to one of 28 inpatient facilities between April 1, 2020 and December 31, 2020. Patients were included in the analysis if their prescriber initiated an order for one of the medications with a known risk of TdP as classified by CredibleMeds (www.crediblemeds.org).(2) This study was approved by the University of Arizona and the University of Utah Institutional Review Boards.

Data Source: Data from the period April 1, 2020 through December 31, 2020 were obtained retrospectively from electronic health records (EHR). Data collected from the EHR were elements necessary for the modified Tisdale QTc-RS included: diagnosis of heart failure, myocardial infarction, and sepsis; laboratory data; currently prescribed medications; and patient demographics. Comorbidities were assessed based on *International Classification of Disease, Tenth Revision (ICD-10)* codes and previously validated algorithms using patient physiological status parameters.

A modified Tisdale QTc-RS was used where 4 points were assigned when the most recent ECG had a Fridericia-corrected QT interval (QTcF) > 500 ms, as compared to 2 points in the original version when an admission ECG Bazett's-corrected QTc > 450 ms.(15) This scoring change was implemented because of the ability to obtain QTcF data from the most recent ECG, and the greater risk established with having a QTc > 500 ms. Scores were assigned to risk factors based on their odds ratio of predicting of QTc prolongation as described by Tisdale et al.: female (1 point), age > 67 years (1 point), administration of a loop diuretic (1 point), diagnosis of myocardial infarction (2 points), serum $K^+ \leq 3.5$ mEq/L (2 points), sepsis (3 points), diagnosis of heart failure (3 points), administration of one QT-prolonging medication with known risk of TdP (3 points), administration of two or more QT-prolonging medications with known risk of

TdP (3 points), and a Fridericia-corrected QTc (QTcF) > 500 ms (4 points).(15) The modified QTc-RS ranged from 0 to 23 and was stratified into three risk score categories: low risk (QTc-RS < 7), moderate risk (QTc-RS = 7-10), and high risk (QTc-RS ≥ 11). The modified QTc-RS was calculated each time an order for a medication with known risk of TdP was initiated.(2)

Outcomes: The primary outcomes of interest were inpatient mortality and length of stay.

Statistical Analysis: Descriptive statistics were used to describe frequency distributions for patients' risk factors, QTc-RS, orders for known risk of TdP medication that triggered the QTc-RS calculation, length of stay and mortality. A generalized linear model was used to evaluate the relationship between the length of stay and QTc-RS. Logistic regression was performed to assess the relationship between inpatient mortality and QTc-RS. Statistical tests were performed using SAS 9.4 version (Cary, North Carolina).

Results

Between April 1, 2020, and December 31, 2020, a QTc-RS was calculated for 92,383 unique hospitalized patients (Table 1). The average age was 55 years (SD 21.3). A small number of our population (n = 36, 0.04%) had a diagnosis of long QT syndrome, of which four (11.1%) expired during their hospitalization. Almost 9% (n = 8121) of our study population had COVID-19, and 116 (1.4%) of them died. Less than 1% (n = 65) of the study population had a cardiac or respiratory arrest status, but a majority of these patients expired (n = 54, 83%).

The most common patient risk factors were female sex (55.0%), followed by age > 67 years old (32.1%), being treated with one medication with a known risk of TdP (24.5%), and being treated with two or more medications with known risk of TdP (18.7%). Only 1.1% of patients had a

QTcF > 500 ms, and diagnosis of myocardial infarction was recorded in 0.8% of patients as shown in Table 1. The majority (79%) of patients had low risk (QTc-RS < 7), 18% had moderate risk (QTc-RS = 7-10), and 3% had high risk (QTc-RS ≥ 11). The frequency and proportion of patients who died by individual QTc-RS score is shown in Table 2. A total of 2770 (3%) patients died during their hospitalization. A positive relationship was found between the QTc-RS and mortality. As the score increased, the proportion of deaths increased almost exponentially from 0.5% to 50% (Table 2 & Figure 1). The odds of mortality increased by 32% for every one unit increase in the score (OR = 1.32, 95% CI:1.31 to 1.34). Relative to patients with low risk (QTc-RS < 7), the odds ratio for inpatient mortality was 4.80 (95% CI:4.42 to 5.21) for patients with moderate risk (QTc-RS = 7-10) and 11.51 (95% CI:10.23 to 12.94) for those with high risk (QTc-RS ≥ 11).

Analyses of QTc-RS risk factors showed that the odds ratio for mortality was highest in those with sepsis (OR = 6.41, 95% CI: 5.91 to 6.95), followed by administration of at least 2 medications with a known risk of TdP (OR = 2.91, 95% CI: 2.63 to 3.22) and QTcF > 500 ms (OR = 2.85, 95% CI: 2.34 to 3.46). Overall, almost all Tisdale risk factors were associated with increased risk of mortality except hypokalemia (OR = 0.98, 95% CI: 0.87 to 1.09) and female sex (OR = 0.64, 95% CI: 0.59 to 0.70) (Table 3). In addition, a generalized linear model revealed the length of hospital stay increased by 0.7 day for every one unit increase in the QTc-RS ($p < 0.0001$).

Discussion

The study found that an increasing QTc-RS was associated with increasing risk of inpatient mortality. Our study found an 11-fold increased risk of mortality in those with high-risk scores

(QTc-RS ≥ 11) compared to those with low risk scores (QTc-RS < 7). This finding highlights that a QTc-RS combining and weighting multiple risk factors may be helpful to prevent/mitigate the risk of mortality among those patients being exposed to known risk medications. This finding is supported by another study at the Mayo Clinic by Haugaa et al, that the pro-QTc score predicted all-cause mortality and an increased pro-QTc score was associated with increased risk of all-cause mortality.(17) They found that patients with pro-QTc score ≥ 4 had significantly higher mortality than those with score < 4 (mortality at 6 months was 22% vs. 10%, $p < 0.001$; mortality at 1 year was 27% vs. 13%, $p < 0.001$; and predicted mortality with a hazard ratio of 1.72 (95% CI: 1.11 to 2.66, $p < 0.001$)).(17) The authors commented that this pro-QTc alert may facilitate life-saving intervention by limiting modifiable risk factors contributing to the pro-QTc score.(17)

In addition, our study also showed a longer length of hospital stay for patients with higher QTc-RS. This finding might be explained by the fact that patients with higher scores may have multiple risk factors contributing to more severe disease and longer hospitalization.

Among all QTc-RS risk factors, sepsis was associated with the highest mortality risk. Sepsis patients were severely ill and often had other comorbidities that increased the risk of mortality, therefore the risk score may not add significant new information about the risk of mortality in these patients. Sepsis has been shown to potentially increase the risk of acute organ dysfunction, long-term morbidity, and mortality.(19) Liu et al. reported that sepsis contributed as much as 66% of inpatient deaths.(20)

We also found that the risk of mortality increased as the number of medications with known risk of TdP increased. Compared to those not receiving these medications, the risk of in-hospital mortality was 2-fold higher in patients taking one known risk of TdP medication and 3-fold higher in patients taking two or more medications with known risk of TdP. Bruin et al. demonstrated a 2-fold and 5-fold increased risk of cardiac arrest in patients taking one and two or greater QTc-prolonging medications known to have proarrhythmic risk, respectively.(21) Haugga el al. also reported that use of medications with known risk of TdP was the main contributor to increased pro-QTc scores.(17) The QTcF > 500 ms was associated with a 3-fold increase in risk of hospital mortality, that was very similar to the results published by Pickham et al. who found that the odds for in-hospital mortality are 3-fold higher (OR = 2.99, 95% CI:1.10 to 8.10) for patients with QT prolongation compared to those without QT prolongation (defined as QTc > 500 ms).(8) Haugaa et al. demonstrated even higher mortality rate of almost 4-fold higher in patients with QTc ≥ 500 ms compared to those with QT c < 500 ms.(17) There is also extensive evidence that suggests the link between prolonged QTc and life-threatening TdP, cardiac arrest, cardiovascular death and all-cause mortality.(1, 22-32)

Overall, many of risk factors in the Tisdale risk score have demonstrated an association with mortality.(1, 8, 20-32) Our findings were also aligned with the previous literature showing that almost all of the Tisdale risk factors were associated with increased risk of mortality, except female sex and serum $K^+ \leq 3.5$ mEq. The lack of an association with hypokalemia and mortality may be explained by hypokalemia often being quickly recognized and treated in inpatient settings. Previous studies have also reported a lower mortality rate among females compared to males.(17) Electrolyte abnormalities (calcium < 4.65 mg/dL, potassium < 3.6 mmol/L),

magnesium < 1.7 mg/dL) have also been shown to be a significant predictor of mortality.(17) Thus, it is not clear if sex is a significant predictor of mortality in a generalized inpatient population.

In clinical practice, effective risk stratification may be useful to inform clinical decision making, such as increasing appropriate treatment strategies for high-risk patients and reducing resource utilization for low-risk patients.(14) Moreover, hospitalized patients often have multiple risk factors or comorbidities that put them at risk of mortality, and prescribing medications associated with TdP can induce fatal TdP that further magnified their risk of mortality. Thus, the modified Tisdale QTc-RS that combines important risk factors may be more useful than using an individual risk factor alone because individual risk factors may not reach a threshold that places a patient at a higher risk of mortality. For example, long QTc interval is a marker of critically ill patients. In our study, only 1% and 0.04% of our study population had QTcF > 500 ms and long QTc syndrome, respectively, however 3% of our population died during the hospitalization.

There is controversy about which formula for prolonged QTc is better, Fridericia or Bazett's. While QTcB is widely used in clinical practice, the QTcF > 500 ms was chosen in our study for several reasons. QTcF has better sensitivity/specificity than QTcB for predicting TdP.(33) Also, QTcF is a better predictor of 30-day all-cause mortality, and 1-year all-cause mortality compared to QTcB. (34) Moreover, QTcB tends to over-correct at higher heart rates and under-correct at lower heart rates.(35)Also, Patel et al. reported that Bazett correction formular overestimated the number of patients with prolonged QT (39% by Bazett vs 6.2% by Fridericia) and was not associated with mortality in patients with heart rate > 100 beats/minutes.(36) Vandenberk et al

also found that QTcB overestimated the number of patients with potential dangerous QTc prolongation in adults patients with heart rate < 90 beats per minutes.(34)

Limitations: This study has several limitations inherent to its retrospective design that should be kept in mind when interpreting the findings. It is possible that misclassification bias could occur because the data are derived from EHRs. The medication list for patients may be incomplete because the risk score is calculated based on medications prescribed in the inpatient setting and does not incorporate medications taken prior to admission. In this analysis we did not attempt to take into account medication route of administration or dose. Over the course of a hospitalization both the amount and route of a medication is likely to change, making it challenging to account for these factors. Another limitation of this study was the survival status of the patients was limited to inpatient mortality only, thus the morality rate might be underestimated from the lack of accounting for those who died outside of the hospital. We also did not exclude patients with congenital long QT syndrome, but we anticipate that the number was very small because only 0.04% of our population had been diagnosed with long QT syndrome via ICD-10 code (I45.81). Also, with this ICD-10 code, we were not able to differentiate how many of the patients with long QT syndrome had congenital long QTc syndrome or TdP. For conditions that contribute to the risk score, such as heart failure and myocardial infarction, risk factor points were based on a diagnosis of these conditions. It was not possible to account for stage of heart failure or type of myocardial infarction based on diagnosis coding. In addition, the points assigned to each component of the modified QTc-RS except QTcF > 500 ms were based on the Tisdale QTc risk score that was developed to identify people in a coronary care environment at risk of developing excessive QTc interval prolongation and TdP rather than the risk of mortality. Also, we used

QTcF > 500 ms as a cut-off value that may underestimated those patients at risk for mortality because the best cut-off value of QTcF for predicting TdP may be lower.(33) This study is based on clinical care practice data, which used automated computer ECG software for QTc measurement, thus QTcF values may not be as precise as in the studies where QT intervals are measured manually. It is possible that not all data were collected on all the potential confounders and comorbidities. We did not attempt to include other potential risk factors associated with inpatient mortality such as other abnormal laboratory findings, kidney failure, or other comorbities such as diabetes. Also, our study population maybe sicker than normal because all data were collected within a short period of time (3-months) during the COVID-19 pandemic, and almost 9% of our population had a diagnosis of COVID-19. Future research may be needed to validate the risk stratification.

Conclusion: In a large system our study revealed a correlation between increased risk of mortality and longer hospitalization with an increasing QTc-RS in hospitalized patients whose provider intended to order medications a known risk of TdP. Therefore, utilization of the QTc-RS CDS to identify patients at high risk of mortality could be helpful in guiding treatment and monitoring decisions to mitigate potential harm.

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Figure Legends

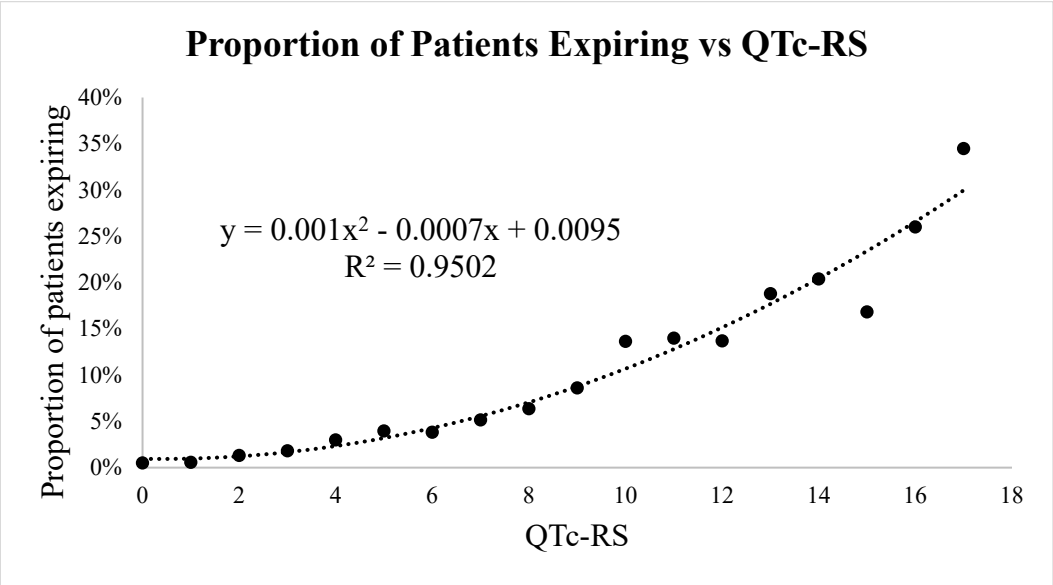

Figure 1: Proportion of patients expiring by QTc-RS score. Scores from18-21 were excluded due to small number (n<10). As the QTc-RS score increased, the proportion of deaths increased almost exponentially.

Table 1: Patient characteristics

Patient characteristic	Frequency n (%)	Proportion of patients who died by each characteristic n (%)
Age (mean ± SD)	54.7 ± 21.3	
Long QT syndrome	36 (0.04)	4 (11.1)
COVID-19 diagnosis	8121 (8.8)	116 (1.4)
Code blue	65 (0.07)	54 (83.1)
Modified Tisdale risk score components		
Female	50,775 (55.0)	1112 (2.2)
Age > 67 years	29,681 (32.1)	1678 (5.65)
No Administration medication with known risk of TdP	52518 (56.9)	696 (1.3)
Administration of one medication with known risk of TdP	22,620 (24.5)	941 (4.2)
Administration of 2 or more medications with known risk of TdP	17,245 (18.7)	1133 (6.6)
Serum $K^+ \leq 3.5$ mEq/L	11,837 (12.8)	391 (3.3)
Sepsis	11,754 (12.7)	1499 (12.8)
Administration of loop diuretic	4,001 (4.3)	348 (8.7)
Diagnosis of heart failure	2,399 (2.6)	225 (9.4)
Most recent QTcF > 500 milliseconds	1,044 (1.1)	152 (14.6)
Diagnosis of myocardial infarction	722 (0.8)	94 (13.0)

Total	92,383 (100)	2770 (3.0)

Table 2: QTc-RS frequency distribution and proportion of patients who died

QTc-RS	Frequency n (%)	Proportion of patients who died n (%)
0	12,984 (14.1)	65 (0.5)
1	23,545 (25.5)	131 (0.6)
2	7,251 (7.9)	94 (1.3)
3	8,653 (9.4)	157 (1.8)
4	10,447 (11.3)	312 (3.0)
5	4,555 (4.9)	180 (4.0)
6	5,862 (6.4)	224 (3.8)
7	7,508 (8.1)	386 (5.1)
8	3,875 (4.2)	246 (6.4)
9	2,613 (2.8)	225 (8.6)
10	2,297 (2.5)	313 (13.6)
11	1,359 (1.5)	190 (14.0)
12	650 (0.7)	89 (13.7)
13	362 (0.4)	68 (18.8)
14	211 (0.2)	43 (20.4)
15	113 (0.1)	19 (16.8)
16	50 (0.1)	13 (26.0)
17	29 (0.0)	10 (34.5)
18	10 (0.0)	2 (20.0)
19	2 (0.0)	1 (50.0)

20	6 (0.0)	2 (33.3)
21	1 (<0.01)	0 (0.0)
Total	92,383 (100%)	2770 (3.0)

Table 3: Multivariable logistic regression analyses of QTc-RS components

Components of the Modified Tisdale Risk Score	OR_{adj} for inpatient mortality
Female	0.64 (0.59-0.70)
Age > 67 years	2.48 (2.29-2.69)
Administration of one medication with known risk of TdP	2.22 (2.01-2.46)
Administration of 2 or more medications with known risk of TdP	2.91 (2.63-3.22)
Serum $K^+ \leq 3.5$ mEq/L	0.98 (0.87-1.09)
Sepsis	6.41 (5.91-6.95)
Loop diuretic	1.37 (1.20-1.56)
Heart failure	1.29 (1.09-1.52)
Most recent QTcF > 500 milliseconds	2.85 (2.34-3.46)
Diagnosis of myocardial infarction	2.17 (1.70-2.76)

OR_{adj}: all components of the modified Tisdale risk score were include in the same model