Development and Validation of a QTc-Prolongation Risk Score to Optimize Interruptive Medication Alerts

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Abstract

Introduction: Drug-drug interaction (DDI) warnings are employed in many institutions when more than one QTc-prolonging medication is prescribed; however, this leads to alert fatigue where alerts are frequently overridden by clinicians due to patient non-specificity or low risk. This study aimed at reducing alert fatigue through developing a custom alert triggered by a patient-specific QTc-prolongation risk score, and validating it against database-driven DDI warnings for QTc prolongation. Methods and Results: Between November 23, 2019 and January 31, 2020, inpatients with a baseline and a follow-up 12-lead ECG reading within 14 days were identified. Each time a QTc-prolonging medication order was signed or verified, the QTc-prolongation risk score was calculated in the electronic health record (EHR), triggering a custom alert in the background. Follow-up 12-lead ECG readings were used to calculate sensitivity and specificity for both the custom alert and the DDI warning. A total of 100 patients had a risk score calculation and were included in our analysis, representing 521 custom alerts and 449 DDI warnings. The preliminary QTc-prolongation risk score did not achieve a reduction in false positive alerts with a cutoff of 10 points. A multiple logistic regression was performed to re-arrange the components and optimize the risk score. Conclusion: Our adjusted QTc-prolongation risk score, with a cutoff of 5 points, achieved a specificity of 66% and a negative predictive value of 83%. These results will allow us to integrate the risk score into the EHR as a guidance tool to predict QTc-prolongation.

INTRODUCTION

The QT interval is an electrocardiogram (ECG) representation of ventricular depolarization and repolarization.[1]Torsades de pointes (TdP) is a life-threatening polymorphic ventricular tachycardia associated with QT interval prolongation.[1]The risk for TdP increases as the heart-corrected QT (QTc) interval increases, specifically when it exceeds 500 milliseconds (ms).[2] The American Heart Association and the American College of Cardiology Foundation have published a scientific statement to raise awareness on the risk, ECG monitoring, and management of drug-induced QTc interval prolongation and TdP in hospitalized patients.[3] Several risk factors contribute to QTc prolongation including increased age, female gender, QTc-prolonging medications, presence of cardiovascular disease, renal failure and electrolyte abnormalities.[4]

Clinical Decision Support Systems (CDSS) including alert generation for drug-drug interactions (DDIs) are designed to improve clinical decision making. Since QTc prolongation in hospitalized patients increases the risk of TdP, many institutions employ alerts within their prescribing systems when more than one QTc-prolonging medication is prescribed. However, a primary limitation of CDSS is alert desensitization, or alert fatigue, where alerts are frequently overridden by clinicians due to patient non-specificity or low risk.[5]

Multiple investigators have developed methods for risk quantification through a QTc risk score. Tisdale et al.[6] developed a CDSS incorporating a weighted QTc risk score with 67-74% sensitivity and 77-88% specificity that reduced both risk of QTc prolongation and prescribing of non-cardiac medications known to

cause TdP. Similarly, investigators at the Mayo Clinic developed a QTc interval risk score where they found a higher predicted mortality with a score of 4 or greater; however, all risk factors were allocated one point.[7] Given the lacking evidence of how risk factors should be weighed, a systematic analysis was conducted by Vandael et al. to generate an evidence-based list of all risk factors associated with QTc prolongation.[8] Using the evidence per risk factor, a preliminary risk score for QTc prolongation (RISQ-PATH) was developed in an academic tertiary care medical center in Belgium, and points were allocated in accordance with the evidence level in the systematic review. The risk score was found to have a high sensitivity (96.2%) and negative predictive value (NPV; 98%) with a cutoff of 10 points.[9] This score was further optimized and validated in a large patient cohort including 60,208 patients, where the authors reported a sensitivity of ± 87% and a specificity of ± 45%.[5]

Objective

MD Anderson Cancer Center is a university hospital and global leader in cancer care, located in Houston, Texas. MD Anderson's electronic health record (EHR), Epic, currently utilizes DDI warnings provided by First Databank (FDB), one of the major providers of drug databases in the nation. Based on internal assessments, DDI warnings accounted for 47% of all FDB medication warnings from January 2019 through June 2019. Due to limitations in functionality, these DDI warnings do not take patient-specific factors, such as age, cardiovascular history, or electrolytes, into consideration, and alerts generated for QTc-prolonging medications are overridden more than 90% of the time. FDB provides all possible DDI warnings, leaving each institution to determine which warnings to make visible and which ones to filter or keep silent. Filtered warnings determined to be of low priority are turned off by the institution to avoid unnecessary alerts. Replacing the DDI warnings with a custom alert triggered by an accurate QTc-prolongation risk score would be beneficial in reducing overall alert burden and fatigue. The aim of our study is to decrease false positive DDI warnings for QTc-prolonging medications by 20% through triggering a custom alert based on a patient-specific QTc-prolongation risk score at MD Anderson Cancer Center. The accuracy of the QTc-prolongation risk score and its ability to predict the risk for QTc prolongation will be determined based on sensitivity and specificity calculations.

METHODS

Study design and patient selection

This retrospective study was approved by the Quality Improvement Assessment Board (QIAB) at MD Anderson Cancer Center. We initially identified all 12-lead ECGs performed between November 23rd, 2019 and January 31st, 2020. Based on the available ECGs, we included inpatients with a newly signed or verified order for a QTc-prolonging medication, and at least two 12-lead ECG readings: A baseline ECG in sinus rhythm within three days before the QTc-prolonging medication was signed or verified, and a follow-up ECG any time after, up to a maximum of eleven days (i.e., within a fourteen-day time period from the baseline ECG reading). We excluded patients with a pacemaker or with a QRS complex greater than 120 ms. We targeted a sample size of 100 patients and discontinued our ECG screening when we reached this goal.

Risk score development and data collection

Based on sensitivity and specificity results as well as the ability to identify risk factors in the EHR, we built our risk score using the components of the RISQ-PATH model[5] by Vandael and colleagues, with a few modifications to the lookback timeframe and methods of extracting the data. Data extracted from the EHR and added to the risk score included age, sex, body mass index (BMI, kg/m^2), cardiovascular history, liver failure, neurological disorders, thyroid disturbances, potassium (mmol/L), calcium (mmol/L), C-reactive protein (CRP; mg/L), estimated glomerular filtration rate (eGFR; ml/min), and medications associated with a risk of QTc-prolongation and/or TdP (lists 1, 2 and 3 of CredibleMeds). CredibleMeds[10] is an American organization that provides lists of drugs associated with a risk of QTc-prolongation and TdP (list 1: drugs with a known risk for TdP; list 2: drugs with a possible risk for TdP; list 3: drugs with a conditional risk for TdP; list 4: drugs to be avoided by patients with congenital long QT syndrome, including all drugs in lists 1, 2 and 3, in addition to drugs with special risk).

Table 1 lists the components included in our preliminary risk score. Each risk factor is allocated a certain number of points contributing to the total score, with a risk cutoff of 10 points. However, due to limitations in the EHR, the score was unable to automatically extract a previous ECG reading from the patient's chart. This information was collected manually through chart review and was not automatically included in the risk score built in the EHR. The risk score and point allocation were discussed with the cardiology department at MD Anderson Cancer Center, who were in agreement with our methods and risk factors. Details on how we extracted these components from the EHR are listed in table A.1 (Supplementary appendix).

During the validation phase, each time a new QTc-prolonging medication was signed or verified, the modified QTc-prolongation risk score was calculated in the EHR and was saved in an archived file every 12 hours, accessed solely by the investigators. The custom alert associated with the score calculation was not visible during the validation phase. The current DDI warnings that triggered at the time of risk score calculation were saved in a separate file and retrieved by the investigators. A chart review was conducted on patients who met the inclusion criteria to validate the risk score and compare it to the current DDI warnings. QTc intervals were collected manually using baseline and follow-up 12-lead ECG readings, and were corrected using the Fridericia formula (QTcF). We defined a prolonged QTc interval as [?] 450 ms for males, [?] 470 ms for females, or an increase from baseline by [?] 30 ms.

Table 1. Preliminary QTc-prolongation risk score at MD Anderson Cancer Center

Risk factor	**Score**
Age [?] 65 years	3
Female sex	3
BMI [?] 30 kg/m^2	1
(Ischemic) cardiomyopathy and/or hypertension	3
Arrhythmia	3
Thyroid disturbances	3
Liver failure	1
Neurological disorders	0.5
Diabetes	0.5
Potassium [?] 3.5 mmol/L	6
Calcium $<$ 2.15 mmol/L	3
CRP $>$ 5 mg/L	1
eGFR [?] 30 ml/min	0.5
Each list 1 QT-drug CredibleMeds	3 per drug
Each list 2 QT-drug CredibleMeds	0.5 per drug
Each list 3 QT-drug CredibleMeds	0.25 per drug
Prolonged QTc ([?]450()/470()ms) on a previous ECG^{++}	*6*
Maximum risk score	**34.5 points + sum of QT-drugs**
Low risk	**$<$ 10 points**
High risk	**[?] 10 points**

++This component was collected manually through chart review and was not automatically extracted from the EHR. BMI = body mass index; CRP = C-reactive protein; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate based on CKD-EPI; QT-drug = QTc-prolonging drug.

Data analysis

Based on the data collected, we performed sensitivity and specificity analyses to compare the accuracy of the custom alert to the DDI warning. Sensitivity and specificity are properties of diagnostic tests and are not predictive of disease in individual patients. Sensitivity is the ability for a test to correctly determine if a patient has the disease, or its ability to avoid false negatives. Specificity is the ability for a test to correctly

determine if a patient does not have the disease, or its ability to avoid false positives.[10] Sensitivity of the custom alert and the DDI warning was calculated by dividing true positives or the sum of patients with a custom alert or a DDI warning, by the sum of patients with QTc prolongation. Specificity was calculated by dividing true negatives or the sum of patients without a custom alert or a DDI warning, by the sum of patients with no QTc prolongation. The results will help us determine if the risk score is sensitive enough to detect the presence of QTc prolongation risk, and/or specific enough to avoid false positive results.

When evaluating the feasibility or the success of a screening test, we also considered the positive and negative predictive values. A positive predictive value (PPV) is the probability that subjects with a positive screening test truly have the disease, whereas a negative predictive value (NPV) is the probability that subjects with a negative screening test truly do not have the disease.[11] PPV and NPV were calculated for both the custom alert and the DDI warning.

Following data collection, sensitivity and specificity calculations, we performed a multiple logistic regression to analyze the components of the risk score and develop the most optimal prediction model. We used the logworth to determine the contribution of the components to the data model. Components with a p-value of < 0.05 were considered significant, thus contributing to the data model. We used the missing-indicator method rather than the imputation method to deal with missing values.

RESULTS

Patient characteristics

We identified a total of 5,035 12-lead ECGs for inpatients between November 23rd, 2019 and January 31st, 2020. We excluded ECG orders that were duplicated or canceled, those that were not within the fourteen-day timeframe, those with missing follow-up readings, and those not in sinus rhythm (i.e., atrial fibrillation, atrial flutter, sinus tachycardia, and others). This resulted in a total of 324 12-lead ECGs reviewed for a total of 148 unique patients, as shown in figure 1.

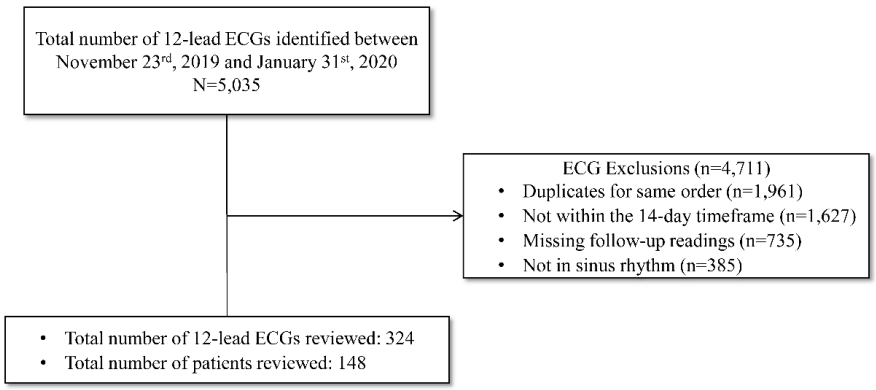

Figure 1. 12-lead ECG readings identified

Of the 148 patients with 12-lead ECG readings we reviewed, 48 patients had neither a custom alert nor a DDI warning. One hundred patients represented a total of 521 custom alerts and 449 DDI warnings, including those which actually triggered and those which were filtered (Figure 2). Eighty out of the 100 patients had both a custom alert and DDI warning trigger, but none of the patients had a DDI warning exclusively without a custom alert.

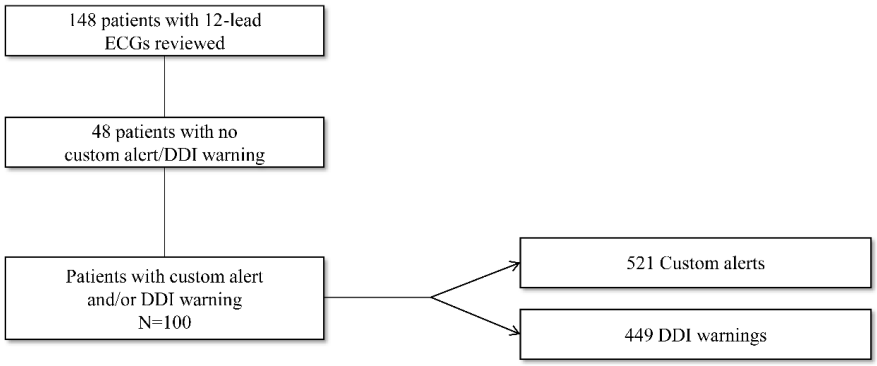

Figure 2. Patient selection based on 12-lead ECG readings

In total, 100 patients (50% females; mean age 61 years) were included in our analysis. The patients' risk factors that were present at the time of score calculation are represented in table 2. Since the risk score calculation was triggered upon signature or verification of a QTc-prolonging medication, the majority of patients had more than one risk score calculation and custom alert at varying times. Therefore, we reported the risk factors as percentages of both total number of patients and total number of custom alerts. Drugs from CredibleMeds list 1, 2 and 3 are not mutually exclusive, and most patients had more than one drug from each list at the time of score calculation. The mean score ± standard deviation was 13 ± 5 with a median (interquartile range) of 12.25 (9-15). Risk scores from the custom alert ranged between 0.5 and 31.75. Baseline 12-lead ECG readings ranged between 346 ms and 519 ms for the custom alert, and between 346 ms and 492 ms for the DDI warning. As for the follow-up 12-lead ECG readings, they ranged between 360 ms and 516 ms for the custom alert, and between 372 ms and 516 ms for the DDI warning.

Table 2. Risk factors and characteristics of patients with a risk score calculation

Risk factor	**Patients (%) N=100**	**Custom alerts (%) N=521**	**Custom alerts with QTc Prolongation* (%)**
Age [?] 65 years	49 (49%) Mean=61, Median=64	240 (46%) Mean=61, Median=64	88 (37%)
Female sex	50 (50%)	269 (52%)	58 (22%)
BMI [?] 30 kg/m^2	34 (34%) Mean=29, Median=28	210 (40%) Mean=29, Median=28	70 (33%)
Ischemic cardiomyopathy and/or hypertension	52 (52%)	297 (57%)	35 (12%)
Arrhythmia	12 (12%)	75 (14%)	27 (36%)
Thyroid disturbances	29 (29%)	152 (29%)	36 (24%)
Liver failure	3 (3%)	17 (3%)	17 (100%) 11 (65%) had higher baseline ECG
Neurological disorders	0 (0%)	0 (0%)	0 (0%)
Diabetes	41 (41%)	221 (41%)	57 (26%)
Potassium [?] 3.5 mmol/L	23 (23%)	83 (16%) Mean=3.75, Median=4	29 (35%)
Calcium < 2.15 mmol/L	21 (21%)	81 (16%) Mean=9, Median=9.1	17 (21%)

Risk factor	Patients (%) N=100	Custom alerts (%) N=521	Custom alerts with QTc Prolongation* (%)
CRP > 5 mg/L	16 (16%)	97 (19%) Mean=89, Median=82 402 missing values	35 (36%)
eGFR [?] 30 ml/min	7 (7%)	48 (9%) Mean=89, Median=90	5 (10%)
List 1 QT-drug CredibleMeds	82 (82%) 1-4 drugs/patient	386 (74%)	105 (27%)
List 2 QT-drug CredibleMeds	62 (62%) 1-3 drugs/patient	235 (45%)	52 (22%)
List 3 QT-drug CredibleMeds	75 (75%) 1-6 drugs/patient	397 (76%)	116 (29%)
Prolonged QTc ([?]450()/470() ms) on previous ECG	15 (15%)	82 (16%)	45 (55%)

*QTc prolongation: QTc [?] 450 ms for males, [?] 470 ms for females, or an increase from baseline ECG by [?] 30 ms.

Custom alert analysis

A variety of drugs triggered a risk score calculation. Table A.2 in the supplementary appendix displays the top drugs triggering risk score calculation stratified by route, risk for TdP based on CredibleMeds list, percentage of all alerts generated, the action that triggered the score calculation, and QTc prolongation associated with each drug. As mentioned earlier, the risk score calculation was generated upon signature or verification of a QTc-prolonging medication from any of the CredibleMeds lists 1, 2 or 3. Intravenous (IV) ondansetron, furosemide and diphenhydramine contributed to 13%, 11%, and 9% of the risk score calculations respectively, and ultimately, custom alerts. Based on follow up ECG review, QTc prolongation was most associated with IV haloperidol (88% of alerts triggered resulted in QTc prolongation), followed by oral methadone (71%), IV metoclopramide (38%), IV promethazine (31%), oral tramadol (25%), and IV ondansetron (25%).

A total of 172 out of 521 (33%) triggering medications were ordered to be administered on an as needed basis (PRN). The top PRN medications including percentage of alerts generated and QTc prolongation are shown in table A.3 in the supplementary appendix. However, data on the number of doses administered was not collected as this was not within the scope and timeline of our project.

Drug-drug interaction warning analysis

Upon analysis of DDI warnings, we identified a variety of drug combinations. It is important to mention, however, that the DDI combinations listed in table A.4 in the supplementary appendix only refer to those that actually triggered and were not filtered. All warnings that triggered were severe and most were overridden, whereas those that were filtered were mostly moderate in nature. The combination of oral amiodarone and IV haloperidol contributed to 13% of all alerts and occurred in only one patient, resulting in QTc prolongation. Another drug combination was IV ondansetron in addition to IV haloperidol, which triggered in two patients and resulted in QTc prolongation 83% of the time. IV ondansetron formed the majority of the remaining DDI warnings in combination with sotalol, methadone, levofloxacin, ciprofloxacin, propofol, promethazine, trazodone, azithromycin, and arsenic trioxide.

Sensitivity and specificity calculations

Sensitivity and specificity were first calculated for the custom alert (Table A.5 in the supplementary appendix). Of all custom alerts, 161 (31%) had a risk score of < 10 points. A score of < 10 indicates low risk for QTc-prolongation, and a custom alert will not fire. This cutoff led to a sensitivity of 81%, a specificity of 35%, a PPV of 32% and an NPV of 84% to predict QTc prolongation.

When factoring in the additional points from manual chart review for patients with QTc prolongation on previous ECG readings, sensitivity was improved by 6%, but the specificity remained the same. The PPV and NPV increased to 33% and 88%, respectively. Nevertheless, this component is not readily available from the chart and the risk score will be unable to automatically include it in the final calculation.

Five out of 100 patients had a follow up ECG that was prolonged per our definition; yet their baseline ECG was more prolonged. This was reflected in 24 risk scores which varied between 8.5 and 18.75 points (median 14.5). We eliminated these scores and recalculated sensitivity and specificity results, however, there was minimal to no change to the values.

In addition to the custom alert sensitivity and specificity calculations, we performed a calculation on the existing DDI warnings (Table A.6 in the supplementary appendix). We found a sensitivity of 54%, a specificity of 65%, a PPV of 42% and an NPV of 75%. The alerts that generated were the alerts that actually triggered for these patients. Alerts not generated refer to those which were filtered at that time, but were archived and identified by the investigators.

Multiple logistic regression

Our preliminary risk score had an area under the Receiver Operating Characteristic (ROC)-curve of 0.848 to predict a QTc [?] 450 ms for males, [?] 470 ms for females, or an increase from baseline ECG by [?] 30 ms. The results of the multiple logistic regression are displayed in table 3. Significant p-values are shown in bold.

Panel A includes the full dataset of all components in our preliminary score, whereas panel B includes the components after exclusion of selected insignificant or unimportant factors.

In the full dataset, significant risk factors included age [?] 65 years, female sex, ischemic cardiomyopathy and/or hypertension, arrhythmia, potassium [?] 3.5 mmol/L, CRP $>$ 5 mg/L, drugs from CredibleMeds list 1 and 2. After excluding BMI [?] 30 kg/m^2, liver failure, diabetes, neurological disease, CRP $>$ 5 mg/L, eGFR [?] 30 ml/min, and drugs from CredibleMeds list 3, panel B logistic regression resulted in similar significant factors, except for arrhythmia which was shown to be no longer significant. However, we decided to keep it in our risk score because we believed it would largely determine the risk for QTc prolongation. Although the CRP component was shown to be significant in our full dataset, we excluded it from panel B after discussions with cardiology, with the notion that most patients at our institution have elevated CRP values. We retained calcium and thyroid disturbances in the updated dataset since many patients with QTc-prolongation had low calcium levels and thyroid disorders.

Table 3. Results of the multiple logistic regression

	Panel A Full (original) dataset
Risk factors	**p-value**
Age [?] 65 years	**< 0.0001**
Female gender	**0.001**
BMI [?] 30 kg/m^2	0.1263
Ischemic cardiomyopathy and/or hypertension	**0.0019**
Arrhythmia	**0.0399**
Thyroid disturbances	0.3354
Liver failure	0.9957
Diabetes	0.6610
Neurological disease	0

	Panel A Full (original) dataset
Potassium [?] 3.5 mmol/L	**0.0223**
Calcium < 2.15 mmol/L	0.8508
CRP > 5 mg/L	**0.0025**
eGFR [?] 30 ml/min	0.9926
Drugs from CredibleMeds List 1 1 drug compared to 0 drug	0.6113 0.3647 0.5437 **0.0141 0.0193** 0.0643 0.9990 0.9990 0.9
2 drugs compared to 0 drug	
2 drugs compared to 1 drug	
3 drugs compared to 0 drug	
3 drugs compared to 1 drug	
3 drugs compared to 2 drugs	
4 drugs compared to 0 drug	
4 drugs compared to 1 drug	
4 drugs compared to 2 drugs	
4 drugs compared to 3 drugs	
Drugs from CredibleMeds List 2 1 drug compared to 0 drug	0.2052 **<0.0001 <0.0001** 0.9960 0.9961 0.9955
2 drugs compared to 0 drug	
2 drugs compared to 1 drug	
3 drugs compared to 0 drug	
3 drugs compared to 1 drug	
3 drugs compared to 2 drugs	
Drugs from CredibleMeds List 3 1 drug compared to 0 drug	0.6860 0.4414 0.2027 0.8340 0.5355 0.6133 0.6551 0.4218 0.89
2 drugs compared to 0 drug	
2 drugs compared to 1 drug	
3 drugs compared to 0 drug	
3 drugs compared to 1 drug	
3 drugs compared to 2 drugs	
4 drugs compared to 0 drug	
4 drugs compared to 1 drug	
4 drugs compared to 2 drugs	
4 drugs compared to 3 drugs	
6 drugs compared to 0 drug	
6 drugs compared to 1 drug	
6 drugs compared to 2 drugs	
6 drugs compared to 3 drugs	
6 drugs compared to 4 drugs	

1.3.6 Risk score adjustments

We performed several adjustments to score points and cutoff values based on the primary regression analysis in panel A, and optimized these adjustments based on results from panel B.

After multiple adjustments, we were able to develop an optimized and balanced QTc-prolongation risk score with a cutoff of 5 points as demonstrated in table 4 below.

Table 4. Optimized risk score

Risk Factor	**Score**	**Custom Alert**	**Custom Alert**
		CredibleMeds list 1, 2 and 3 as trigger	**CredibleMeds list 1 and 2 only as trigger**

Risk Factor	Score	Custom Alert	Custom Alert
Age [?] 65 years	1	Sensitivity: 58% Specificity: 69% PPV: 41% NPV: 82%	Sensitivity: 68% Specificity: 66% PPV: 45% NPV: 83%
Female sex	1		
(Ischemic) cardiomyopathy and/or hypertension	2		
Arrhythmia	2		
Thyroid disturbances	1		
Potassium [?] 3.5mmol/L	1		
Calcium < 2.15mmol/L	1		
Each list 1 QT-drug CredibleMeds	1 per drug		
Each list 2 QT-drug CredibleMeds	0.5 per drug		

Maximum risk score: 9 points + sum of QT-drugs, Low risk: < 5 points, High risk: [?] 5 points

*QTc prolongation: QTc [?] 450 ms for males, [?] 470 ms for females, or an increase from baseline ECG by [?] 30 ms.

A cutoff of 5 points revealed a good balance between sensitivity and specificity (58% and 69% respectively), a PPV of 41% and an NPV of 82%. We also performed our calculation after removal of drugs from CredibleMeds list 3 as a trigger for the risk score. Since these drugs were not shown to be significant and were no longer calculated in the risk score, removing them from the list of triggering medications would help reduce the volume of alerts and make our risk score more accurate. This resulted in a sensitivity of 68%, a specificity of 66%, a PPV of 45% and an NPV of 83%. Compared with the DDI warnings, these values are more balanced and may help detect QTc-prolongation while reducing false positive alerts.

DISCUSSION

In this study, we developed a preliminary QTc-prolongation risk score with a sensitivity of 81%, a specificity of 35%, a PPV of 32%, and an NPV of 84%. Compared with the DDI warnings, our full dataset achieved better sensitivity and NPV, but that resulted in less specificity and PPV. Our multiple logistic regressions allowed us to achieve a sensitivity of 68%, specificity of 66%, a PPV of 45% and an NPV of 83% with an optimized risk score and a cutoff of 5 points. Our aim of reducing false positive alerts by 20% was not achieved, however, many of the DDI warnings were filtered, and those that actually triggered and were included in our calculations were mostly severe, with a high risk of QTc prolongation. On the contrary, medications triggering our risk score calculation and custom alert were based on lists 1, 2 and 3 of CredibleMeds, making it easier to achieve a greater number of custom alerts than DDI warnings. In addition, DDI warnings were only identified in patients who already had the risk score calculated and a custom alert generated. Vandael and colleagues included patients from various hospitals and wards including cardiology, internal medicine and others.[4] Patients at our institution, however, were all cancer patients with different characteristics and risk factors affected by various therapies and comorbidities. Moreover, the study by Vandael and colleagues did not compare the risk score to any existing warning, unlike our study which compared the risk score to an existing DDI warning, aiming to reduce alert burden and fatigue. The study by Tisdale and colleagues included only patients on cardiac units, and did not compare the risk score to another existing warning. However, it had a pre and a post-implementation phase which revealed that incorporating a validated risk score influenced the prescribing of noncardiac QTc interval-prolonging drugs and reduced the risk of QTc-prolongation.[6]

Strengths and limitations

We identified several strengths in our study. First, we performed a thorough review of data and risk factors associated with QTc prolongation, which allowed us to build and evaluate the risk score for all components and their association with QTc prolongation in our patient population. We used the corrected QTcF formula and identified patients in sinus rhythm to better assess QTc prolongation on a follow up ECG reading. Furthermore, the preliminary risk score that was built in the EHR was capable of accurately extracting the data from the patients' charts. The ECG timeframe we set was appropriate to detect medication-related QTc prolongation, eliminating other possible causes. In addition, we compared our custom alert and DDI warning for the same patients and within the same timeframe. This added to the accuracy of our analysis which was based on rigorous data. Performing a multiple logistic regression also helped us identify the risk factors that were mostly associated with QTc prolongation, thus allowing us to re-arrange the score points and increase our sensitivity and specificity results through an optimized risk score. Moreover, using the missing-indicator method in our regression analysis to deal with missing values contributes to a more realistic view and broadens applicability.

Limitations in our study include the inability of the score to automatically extract a QTc interval from the EHR to be included in our risk score or to be used as a reference for clinical decision support. In the future, implementing electronic waveform readings in the EHR would allow for a more accurate assessment of alerts by incorporating this component in the risk score. Additionally, the patients we included already had a baseline ECG reading, which may suggest that these patients were already at high risk for QTc prolongation and were being followed closely by cardiology. Smoking is one of the risk factors for QTc prolongation, however, our score could not reliably extract smoking habits from the chart. As mentioned earlier, the DDI warning is based on the FDB database, whereas the custom alert is based on CredibleMeds list. Most of the DDI warnings were filtered at that time, and the triggering medications were those with the greatest risk for QTc prolongation. This explains the high specificity of the DDI warning compared with the custom alert which included all drugs listed in CredibleMeds lists 1, 2 and 3, regardless of severity. Furthermore, our study was conducted in an oncology setting where patient characteristics and risk factors differ and are affected by various therapies and comorbidities, which makes extrapolating this data to other patient populations challenging.

Future implications

Based on our findings and adjusted score results, we will plan to integrate this risk score into the EHR as a guidance tool. The risk score will be incorporated as a non-interruptive active clinical decision support shown in the work queue or patient list, in addition to an interruptive active clinical decision support linked to a custom alert. We will plan to incorporate this tool for both inpatients and outpatients, and turn off the DDI warnings. We will exclude medications from CredibleMeds list 3 as triggers given their low risk for QTc prolongation and their minimal contribution to our data model. In addition, since ondansetron is very widely used at our institution due to the need for antiemetics in our patient population, and is overridden more than 90% of the time, an option would be to turn off the alerts for IV and oral ondansetron. Another option would be to possibly exclude "as needed" or "once" medications as triggers. Discussions with various departments will be necessary to guarantee the safety and feasibility of this process, while ensuring that the score is accurately extracting the proper information from the EHR. Lastly, it would be ideal to assess the volume of custom alerts a few months later to determine whether it would serve as a replacement clinical decision support for the current DDI warnings for QTc-prolongation in the long term.

1.5 CONCLUSION

Our adjusted QTc-prolongation risk score, with a cutoff of 5 points, predicted a QTc interval [?] 450 ms for males, [?] 470 ms for females, or an increase from baseline ECG by [?] 30 ms with a sensitivity of 68%, a specificity of 66%, a PPV of 45% and an NPV of 83%. These results will allow us to integrate the risk score into the EHR as a guidance tool to predict QTc-prolongation.

AUTHOR CONTRIBUTIONS: All authors have made substantial contributions to the design, analysis,

and interpretation of this work. All authors have contributed to the drafting, reviewing, and approval of this work and agree to be accountable for all aspects of this work's accuracy and integrity.

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