Assessing the Relationship Between Electronic Medical Record (EMR) Generated QTc Alerts and Cancer Patient Mortality

by

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ABSTRACT

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Background: EMR generated drug associated QTc alerts are generated frequently in cancer patient populations and in the last few years their annual frequency has outgrown the number of unique patient visits at our institution. Anecdotally, they are largely ignored by providers, contributing to provider cognitive burnout and alert fatigue. While they may be considered nuisance alerts, the EMR collects rich data on the circumstances underlying the alert, the patients impacted, and their outcomes. By querying the EMR, we aimed to risk stratify patients by cancer site and demographic factors and provide meaning to these alerts allowing providers to incorporate the information we have provided in clinical decision making regarding the care of cancer patients. Our project is the first large-scale analysis of EMR generated QTc prolongation alerts at a tertiary referral center in the United States.

Objective: Acute mortality of cancer patients varies significantly by cancer site and demographic factors following EMR generated drug associated QTc interval prolongation alerts.

Methods: UT-Southwestern's EMR was queried to identify all patients between 10/04/2005 (the date of the 1st recorded alert) and 08/13/2019 over 18-years of age with a diagnosis of cancer and EMR generated drug associated QTc interval prolongation alerts yielding a sample of 19,223 patients. We collected the alert triggering medications, patient demographics, cancer site, and mortality data to identify the time between a patient's 1st alert and recorded death date. Rates of death by age, ethnicity, gender, race, number of alerts, and primary cancer site were identified in the following intervals: within 10 days, 11-180 days, and 181-365 days. Kaplan-Meier Overall Survival Analysis with Cox regression and multinomial multivariable analysis controlling for age, race, ethnicity, and gender, and median survival data analytic methods were used to identify if there were statistically significant differences in mortality at the pre-specified time points based on the above listed variables. Head and neck cancer patients were used as our reference group for comparison when analyzing mortality by primary cancer site. This group was chosen as their rates of within 10-day mortality closely aligned with those predicted by the null hypothesis that there would be no difference in mortality rates within 10-days across primary cancer sites used in our preliminary chi-squared goodness of fit model. Additionally, for patients with EKG's recorded within 10 days of their 1st alert, QTc intervals utilizing Bazett's correction algorithm were collected and the recorded interval of patients with deaths within 10 days was compared

to those who were alive after 10 days, with participants separated by gender.

Results: Analysis of mortality from a patient's 1st QTc alert demonstrated statistically significant ($p<0.05$) higher risk of ≤10-day mortality in: patients with increasing number of QTc alerts, particularly patients with 6-10, HR=1.67 or >11 HR=1.88 alerts. Additionally, increased ≤10-day mortality was demonstrated in cancer patients with male gender, (female patients demonstrated a HR=0.83, compared to a male reference group), African American, HR=1.26, or other/unknown race, HR=1.29, and age >70, hazard ratio (HR)=2.32. Chi-squared goodness of fit testing identified head and neck cancer patients had a ratio of expected (by chance) to observed mortality of 0.98 and given the close concordance with our null model, were used as our reference group in multivariable analysis. Compared to a head and neck cancer patient baseline, significantly increased ≤10-day mortality was seen in: GI, HR=2.16; lung, HR=1.94; blood, HR=1.46; soft tissue, HR=2.26; and female genital, HR=1.55 cancers. Male genital, HR=0.39; breast, HR=0.57; and endocrine, HR=0.48 cancers had significantly decreased ≤10-day mortality. Of patients with EKG's, male patients who died ≤10-days of their 1st alert had significantly longer QTc intervals than males who survived to day 11 (469 vs 450 milliseconds, $p<0.0001$). In patients with any cancer and a QTC alert, 0.01 (male genital)-2.50% (GI) died ≤10 days of their 1st alert. The majority of deaths recorded <1 year after a patient's 1st alert occurred between 11-180 days during which 2.93 (male genital)-23.8% (GI) of the total sample with that primary cancer site diagnosis died. 63.2 (GI)-95.9% (endocrine) of cancer patients were alive >1 year after their 1st alert.

Conclusion: Our research supports the anecdotal suggestion that very few patients die within 10 days of their initial QTc alert, suggesting that in many cases they function as distractions, especially in male genital, breast, and endocrine cancer patients and females or individuals <50 years of age. However, they may also identify patients at imminent risk of death, particularly those with lung, soft tissue, GI, blood, and female genital cancers, or males, African Americans, and individuals >70 years of age. Further, our analysis shows that QTc alerts may be a negative prognostic factor as the patients with more alerts (>5) have greater ≤10-day mortality rates. Additionally, of the patients who die within 365 days of their first alert the vast majority across cancer sites die between 11-180 days.

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PRIOR PUBLICATIONS & PRESENTATIONS

PUBLICATIONS:

Association of electronic medical record generated QTc alerts with acute cancer patient mortality. Bleiberg, BA, Yan J, Xie D, Lightfoot T, Zhu H, Reisch J, Terauchi S, Gerber DE, & Khan SA. Abstract published by the UT-Southwestern Medical Student Research Forum; 2020 Jan 21, Dallas, TX.

PRESENTATIONS AND POSTERS:

Bleiberg BA, Xie D, Lightfoot T, Reisch J, & Khan SA, Electronic Medical Record (EMR) QTc Alerts Are Associated with Higher Mortality Within 10 Days for Patients with Blood, Lung, GI, and Soft Tissue Cancer. Poster presented at the ASCO Quality Care Symposium; 2019 Sep 7, San Diego, CA.

Bleiberg BA, Yan J, Xie D, Lightfoot T, Zhu H, Reisch J, Terauchi S, Gerber DE, Sher DJ, Khan SA. Electronic medical record (EMR) QTc alert associations with acute cancer patient mortality within 10 days by primary malignancy site and demographic factors. Oral presentation at the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN) Young Investigator Symposium; 2019 Oct 24, Fort Lauderdale, FL.

CHAPTER 1: Introduction

Topic: While cancer therapy has developed significantly in recent years, off-target effects of therapy are increasingly managed by supportive medications, which can have serious side effects like QTc interval prolongation (Khan, Ismail, & Khan, 2017). Modern cancer treatment modalities are increasingly targeted and tend to be much less damaging to normal tissues than were their predecessors. However, supportive medications to deal with common side effects remain a mainstay of any chemotherapy regimen. These supportive medications include anti-emetics like ondansetron, narcotics like methadone, and antibiotics like levofloxacin and azithromycin. Some of these widely used medicines, such as those listed above, are associated with a prolongation of the QTc interval, which is one of the most common adverse effects of oral chemotherapy (Khan, Ismail, & Khan, 2017). For instance, in a study of 895 cancer patients undergoing oral chemotherapy, 426 had some form of drug-drug interaction event with 45 having QT interval related adverse events (van Leeuwen et al., 2013). Agents associated with QTc interval prolongation are expected to have a synergistic effect on increasing the interval when taken together, which could further increase the risk of adverse outcomes like torsades de pointes (TdP) (Al-Khatib, LaPointe, Kramer, & Califf, 2003; Ewer & Ewer, 2015). These supportive medications are often co-administered with chemotherapy drugs, which particularly in the case of targeted agents such as vemurafenib, crizotinib, certinib, sorafenib, vandetanib, pazopanib, and others are independently associated with QTc prolongation (Porta-Sánchez et al., 2017).

Topic: The QT interval is an essential part of cardiac monitoring and is the most widely used surrogate marker of predisposition to TdP that can lead to Sudden Cardiac Death

(SCD). The QT interval is measured by the time on surface ECG between the beginning of the QRS complex and the end of the T wave. This period represents the time of ventricular depolarization caused by sodium ion influx into the cardiomyocyte, which has a negatively charged resting potential and subsequent repolarization through the flow of ions between the myocardial cells and extracellular space (Al-Khatib, LaPointe, Kramer, & Califf, 2003; Zhang et. al, 2011). This interval can vary naturally within an individual due to diet, autonomic tone, time of day, and a multitude of other factors. However, an interval greater than 470 milliseconds (msec) in men or 480 msec in women is in the 99th percentile and an interval over 500 msec or drug associated increase in QTc interval greater than 60 msec over baseline is a significant risk factor for the development of TdP (Drew et al., 2010; van Leeuwen et al., 2013). The corrected QT interval is measured by computerized ECG algorithms, which allows for rapid assessment and greater reliability and is known as the QTc. While it has been established that QTc interval prolonging medications can increase the risk of TdP, there is little research indicating how to minimize this risk and its prevalence (Al-Khatib, 2003). Some research suggests that the JT interval may be a better tool to identify patients at significant risk of developing TdP, but the QTc interval remains the standard marker used in clinical practice (Zulgarnain et. al, 2015).

Topic: A prolonged QTc interval has been identified as an independent negative prognostic factor but has not yet been studied specifically in cancer patients. For instance, a study of 1020 patients with type 2 diabetes with long term follow-up (median follow-up of 8.5 years) of up to 13.9 years, demonstrated the relative risk of death was 1.99 (p=.003) in participants with a prolonged QTc interval compared to those with a normal interval less than

450 milliseconds. This relationship was significant after controlling for ethnicity, sex, hypertension, BMI, diabetes duration, A1c level, smoking status, cholesterol, triglyceride levels, eGFR, and baseline cardiovascular disease status (Cox et. al, 2014). This finding was reproduced in non-diabetic patients between ages 55-74 who demonstrated a mortality rate hazard ratio (HR) of 2.02, if they had a prolonged QTc interval (Ziegler et. al, 2008). Meta-analysis of the available data establishes the relative risk in several representative samples between increased QTc interval and total mortality and specifically SCD. When comparing the highest and lowest categories of QT interval length, the pooled relative risk (RR) was identified as 1.35 for total mortality and 1.44 for SCD (Zhang et. al, 2011).

Topic: The proposed mechanism for this increase in death is the association between prolonged QT interval and early afterdepolarization, precipitating re-entrant arrhythmias, which can lead to the development of TdP, which can progress to ventricular fibrillation culminating in SCD (Zhang et. al, 2011). The acute mechanism of death in patients with TdP means that a prolonged QTc interval has been associated with increased short-term mortality, particularly in patients with more acute illnesses. For instance, a study of all-cause mortality following emergency department visits showed a 10-day and 30-day mortality rate of 9% and 13% compared to a rate of 2.1% and 3.7% for patients without a prolonged interval (Anderson et. al, 2018). Patients with recent cardiac surgery and a preoperative prolonged QTc interval and normal left ventricular function had a RR of postoperative mortality of 2.31 at 30 days, 1.73 at 90 days, and 1.52 at 1 year compared to patients with a normal pre-operative QTc ($p<.01$) (Anantasit et. al, 2014).

Topic: The burden of QTc prolongation associated drug morbidity and mortality,

specifically in oncology patient populations is underexplored in the literature, which forces physicians to make clinical decisions regarding prescriptions with incomplete information. While the drug approval process demonstrates that agents approved for the treatment of cancer improve patients' quality and/or duration of life, we do not know how often patients considered at-risk for QTc interval prolongation suffer from adverse reactions, require hospital readmission, or if their risk of mortality in the short or long-term is altered. We also do not know how the prevalence of QTc related adverse outcomes may vary by patient demographics or cancer site. While the Pakistani study conducted by Khan et. al, in 2017 began answering some of these questions, we are the first group to study these trends in an ethnically and racially diverse group of participants with a substantially larger sample size.

Topic: While electronic medical record (EMR) software generates alerts when providers prescribe medications associated with QTc interval prolongation, physicians lack the evidence needed to make fully informed decisions on the risk-benefit of prescribing these medications. As such, healthcare providers are left with the decision to override these alerts and prescribe medications that may put patients at-risk or to heed these alerts and withdraw the prescription of medications that could improve patients' likelihood of recovery or ability to tolerate life-prolonging chemotherapy and enhance their quality of life while undergoing treatment. There is little data indicating the frequency with which physicians make the decision to prescribe or withhold medications once an alert has been generated and what impact these decisions have on patient outcomes (van Leeuwen et al., 2013). More research needs to be done at the intersection of cardiology and oncology to evaluate the risk of patient mortality following the prescription of drugs associated with QTc prolongation.

Topic: By studying the temporal relationship between QTc alerts generated by the EMR and the timing of cancer patient deaths, we can help to classify the potential risks of these medications and what patient populations may be at greatest risk. In this way, we aim to add to the body of evidence that physicians rely on to make informed decisions regarding prescription behavior in the hopes of improving patient care. We hypothesize that QTc alerts are not significantly associated with acute cancer patient mortality but may be a negative prognostic sign and that higher numbers of alerts suggests a worse short and intermediate term prognosis. Further, we hypothesize that some cancers with low mortality rates may have disproportionate numbers of QTc alerts that are not related to prolonged QTc interval associated mortality. Certain medications associated with breast (eribulin) and male genital (abiraterone) cancer treatment are known to generate QTc alerts but are not expected to significantly increase the risk of TdP and SCD. Overall, we predict that within 10-day mortality will differ by primary cancer site in a significant manner. Additionally, we hypothesize that older patients are more likely to have exposure to QTc prolonging medications, potentially prior to their diagnosis of cancer and those who have survived to an advanced age may be more tolerant to drug induced QTc prolongation. Conversely, younger patients may be naïve to these medications and there could be an early weed-out effect of younger patients who are sensetive to this drug interaction leading to more acute mortality following the initiation of a QTc prolongation associated medication. Lastly, we hypothesize that for patients with recorded EKG data, the patients who die within 10 days of their 1st alert will have significantly higher recorded QTc intervals on EKG than those who live beyond day 10.

CHAPTER 2: Methods

Selection of Participants:

Topic: Participants, drawn from UT-Southwestern affiliated hospitals, were included in the study based on a diagnosis of cancer and an EMR alert indicating a potential drug-drug interaction related to risk of QTc interval prolongation, known as a QTc alert. Participants were identified through an EMR query of patients at UT-Southwestern and its affiliated hospitals including Clements University Hospital and Zale Lipshy Hospital. Once identified, participants were included in the study if they had a previous diagnosis of cancer, an EMR alert for a drug-drug interaction associated with additive QTc interval prolongation and were over 18 years of age at the time the alert was generated. All participants were identified between 10/04/2005, which was the date of our EMR's first recorded QTc alert and 08/13/2019, which was the date of our repeat analysis. The demographics of the sample (gender, age, race, ethnicity) are included in table 1 and the raw number of QTc alerts generated annually as well as the number of unique patients with alerts are shown in figure 1.

Topic: Date spans, identifying the duration between a patient's first generated QTc alert and recorded death date were used to sort patients by mortality status. Once participants with QTc alerts who fit our inclusion criteria were identified, we recorded the date of their first generated alert. For deceased patients, we analyzed the duration between their confirmed death date and the date their first alert was generated creating a variable we identified as the patient's "date span." To study patient mortality trends, we separated patients into groups based on the time between their first QTc alert and known death date. The patients were grouped into the following categories: deaths within 10 days of first QTc alert, deaths

between 11-180 days, deaths between 181-365 days, and patients with no recorded death date by day 365.

Topic: The 10-day cutoff was chosen to capture acute worsening of the patients' medical condition requiring multiple medications and is the interval during which QTc prolongation could be one factor contributing to acute mortality. This time frame also extends through the duration of biologic activity of many of the QTc prolongation associated medications widely prescribed to cancer patients including antibiotics like levofloxacin and anti-emetics like ondansetron (Straus et. al, 2005). The 10-day interval has been considered the standard by which all-cause mortality is measured in studies of patient populations with short-term increased mortality such as recent emergency department visits or cardiac surgery, as well as studies investigating the prognostic significance of different QT correction algorithms (Anantasit et al., 2014; Anderson et al., 2018; Vandenberk et al., 2016). We suspect that QTc prolongation may be a contributing factor increasing short term mortality patients with deaths within 10-days of their 1st alert.

Topic: The 180-day mortality cutoff was chosen to assess the hypothesis that patients requiring medicines that prolong the QTc interval have a worsened medical condition and a higher risk of comorbid death. It remains unclear if deaths between 11-180 days are directly related to QTc prolongation effects and it is more likely that QTc prolongation is a marker of poor prognosis and comorbid disease. The 365-day mortality cutoff was chosen, as we felt that deaths between 181 and 365 days were likely unrelated to QTc prolongation and aimed to identify if this population differed from the groups with earlier mortality. We then compared the groups of patients based on the following factors: age, sex, race, ethnicity, and

primary cancer site to identify if these groups varied in statistically significant ways on the variables assessed.

Topic: Agents associated with QTc prolongation were identified as those that triggered drug-drug interaction QTc alerts generated by the EPIC electronic medical record in the charts of our patient population. These flagged agents identified by the pharmaceutical database Lexi-Comp®, include drugs such as arsenic, vemurafenib, and crizotinib, which directly treat cancer and are expected to increase cancer patient survival. The rationale for the inclusion of these medications was our primary interest in the short-term mortality due to cardiac arrhythmias and TdP progressing to SCD, as opposed to long term deaths caused by cancer progression. Since the effect of QTc interval prolonging drugs is suspected to be additive, these drugs, which are known to trigger EMR generated QTc alerts could increase short term risks, despite their overall improvement of cancer patients' expected lifespan. The total number of unique patients and alerts associated with the top 15 most commonly implicated drugs during our study timeframe are illustrated in figure 2.

Topic: Cancer primary sites were grouped according to ICD-10 coding definitions yielding 14 distinct categories of malignancy with no overlap.

Analysis

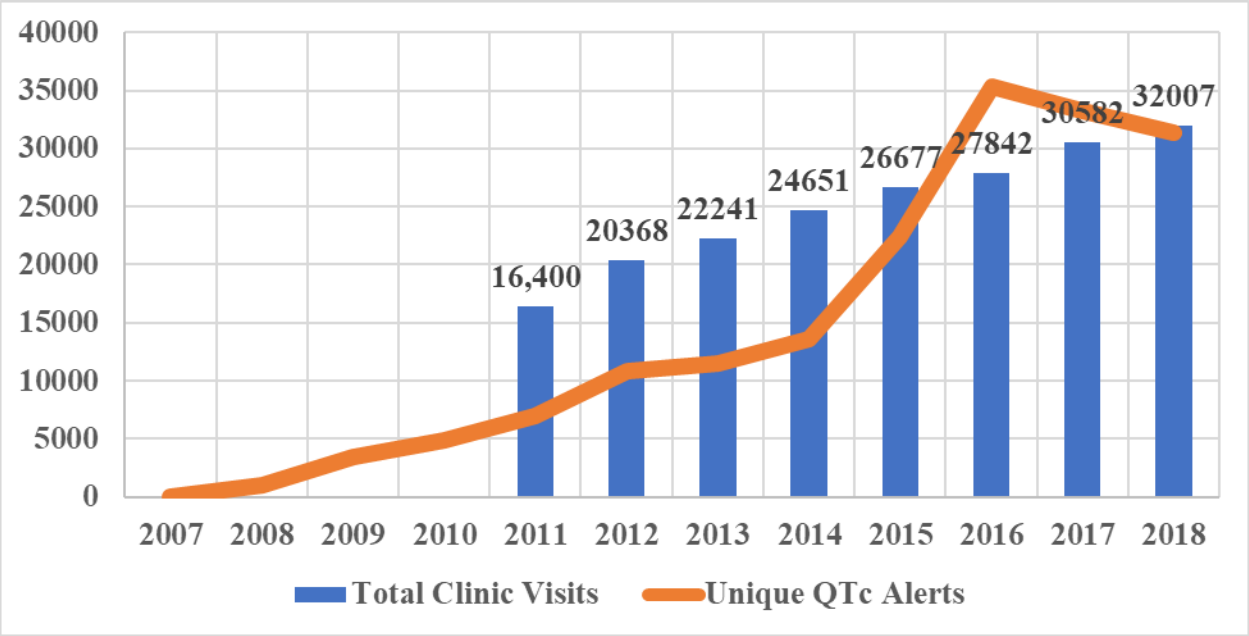
Topic: Figure 1 data on QTc alerts by year was collected by querying the EMR and comparing the number of unique alerts to UT-Southwestern's data on annual follow-up and new patient encounters, which were added to create the composite variable, annual unique patient encounters. Figure 2 data on the frequency of drugs implicated in QTc alerts was acquired by querying the EMR for the drugs associated with EMR generated alerts. Drugs

identified by the EMR were selected based on the Lexi-Comp® drug database. Table 1 describes the demographic and primary cancer site distribution of our sample and the number of patients who were alive and deceased at varying time points. Table 2 data on mortality by demographic data and cancer site at each of the relevant time points was completed by multinomial analysis comparing patients in each group to the specified reference group and in the case of primary site data controls for patient age, race, gender, ethnicity through a multivariable approach. Table 3 and figure 3 data on mortality ≤10 days of patients' 1st alerts and with inclusion of 5-year and median survival data was completed by Kaplan-Meier Overall Survival Analysis with Cox Regression. EKG data on the actual QTc interval of patients ≤10-days of their first QTc alert was identified by querying the EMR to identify the patients who had received EKG's in this time period and comparing the intervals of patients who died ≤10-days to those of patients who were alive after day 10. In this analysis, patients were separated by gender, given the established difference in normal QTc interval length by gender. QT intervals were identified using the GE MUSE automated system, which utilizes the Bazett correction algorithm, the oldest and most widely used correction formula in clinical practice. Notably, the Bazett algorithm is known to be heavily influenced by extreme variations in heart rates due to its closer correlation with heart rate and can lead to higher QTc values than other formula (Kenigsberg, 2007; Muluneh et al, 2019)

Topic: Figure 4 data on the % of patients with deaths recorded at each time interval of interest was collected by dividing the number of deaths at each interval by the total number of patients with that primary cancer site in our sample. The number of patients living greater than 365 days following their final QTc alert was considered the alive group in figure 2.

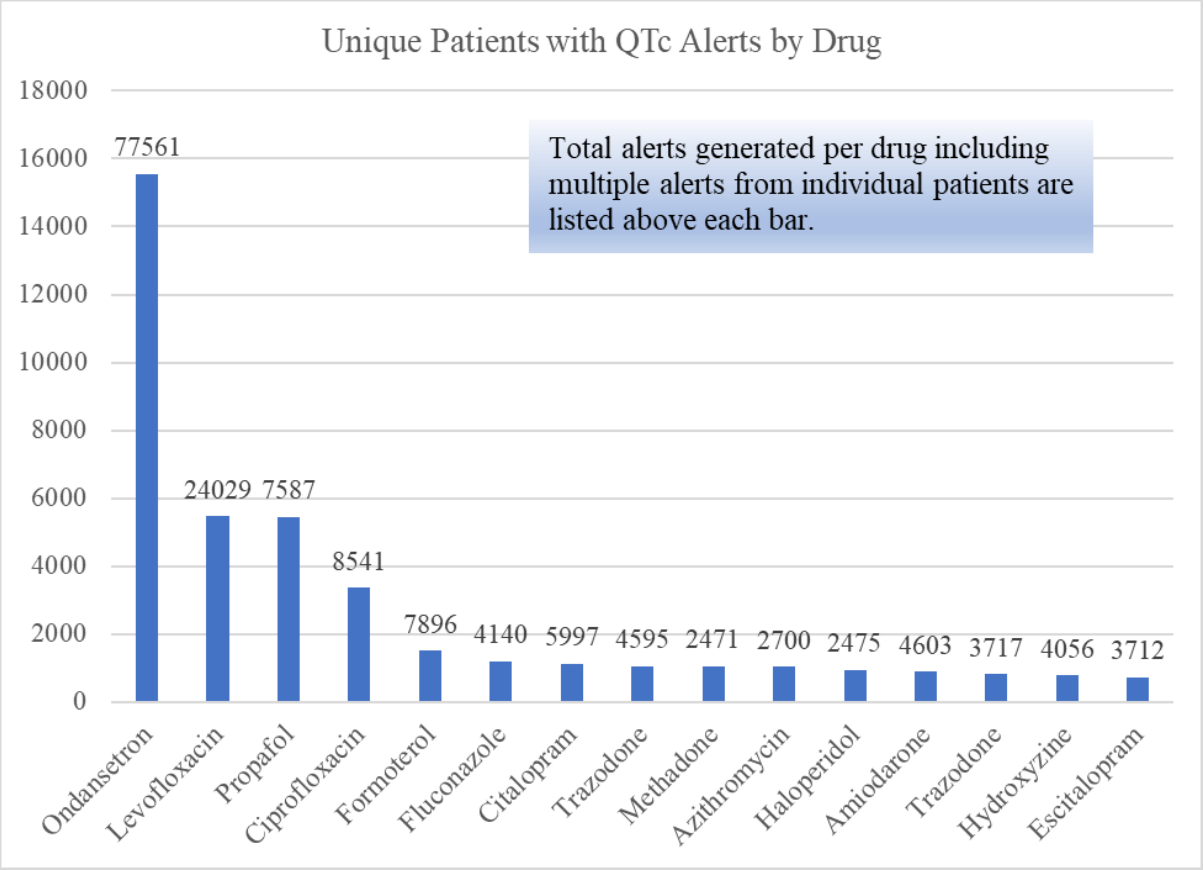
CHAPTER 3: Results

Figure 1. Unique QTc alerts by year compared to combined annual new patient and follow-up encounters



Topic: Analysis of the number of unique QTc alerts generated by the EMR each year from 2008, demonstrated that QTc alerts rose significantly during our study time, particularly between 2014 and 2018 (11,531→31,406 while total patient volume increased less rapidly (24,651→32,007). Alerts increased to the point that there were more alerts than individual patient encounters from 2016-2018. Patient encounter growth was steady over the course of the study period but was outstripped by rapid growth in QTc alerts.

Figure 2. Unique patients impacted by QTc Alerts by specified drug



Topic: Analysis of the drugs most commonly implicated in the generation of QTc alerts by total number of alerts generated and unique patients impacted, generally demonstrated that the number of alerts generated corresponded to the number of patients affected. For instance, figure 1 demonstrates that by far the most QTc alerts were associated with ondansetron, a widely prescribed anti-emetic that impacted the most unique patients. However, propofol, eribulin, dasatinib, formoterol, posaconazole, nilotinib, romidepsin, and arsenic were prominent exceptions to this trend. Propofol generated alerts in the 3rd most patients 5448, but triggered only the 5th most alerts, 7587. Haloperidol (943 patients / 2475 alerts), azithromycin (1023 patients / 2700 alerts), and moxifloxacin (250 patients / 654 alerts) similarly impacted many unique patients, while generating comparatively few alerts. Posaconazole (273 patients / 4668 alerts), eribulin (102 patients / 2004 alerts), romidepsin (28

patients / 931 alerts), nilotinib (33 patients / 498 alerts) dasatinib (59 patients / 762 alerts), and formoterol (1502 patients / 7896 alerts) generated a very high number of alerts relative to the number of unique patients that they affected.

Table 1. Characteristics of cancer patients with QTc alerts and comparison of patients who are deceased versus those who are alive 365 days from first QTc alert.

Patient Characteristics		All patients N (%)	Dead within 10-days	Alive at >10-days	Unknown Vital Status ≤10-days	Dead within 365-days	Alive at >365-days	Unknown Vital Status ≤365-days
Total patients		19223 (100.0%)	143 (0.7%)	18844 (98.0%)	236 (1.2%)	2612 (13.6%)	10474 (54.5%)	6137 (31.9%)
Age at first alert								
	18 - 49	3670 (19.1%)	11 (0.3%)	3624 (98.7%)	35 (1.0%)	307 (8.4%)	2194 (59.8%)	1169 (31.9%)
	50 - 59	4396 (22.9%)	30 (0.7%)	4317 (98.2%)	49 (1.1%)	537 (12.2%)	2491 (56.7%)	1368 (31.1%)
	60 - 69	6010 (31.3%)	46 (0.8%)	5899 (98.2%)	65 (1.1%)	833 (13.9%)	3248 (54.0%)	1929 (32.1%)
	>= 70	5147 (26.8%)	56 (1.1%)	5004 (97.2%)	87 (1.7%)	935 (18.2%)	2541 (49.4%)	1671 (32.5%)
Gender								
	Female	9190 (47.8%)	53 (0.6%)	9019 (98.1%)	118 (1.3%)	1168 (12.7%)	5232 (56.9%)	2790 (30.4%)
	Male	10033 (52.2%)	90 (0.9%)	9825 (97.9%)	118 (1.2%)	1444 (14.4%)	5242 (52.2%)	3347 (33.4%)
Ethnicity								
	Non-Hispanic	16340 (85.0%)	99 (0.6%)	16050 (98.2%)	191 (1.2%)	2021 (12.4%)	9083 (55.6%)	5236 (32.0%)
	Hispanic	1550 (8.1%)	8 (0.5%)	1527 (98.5%)	15 (1.0%)	216 (13.9%)	810 (52.3%)	524 (33.8%)
	Unknown	1333 (6.9%)	36 (2.7%)	1267 (95.0%)	30 (2.3%)	375 (28.1%)	581 (43.6%)	377 (28.3%)
Race								
	White	13899 (72.3%)	79 (0.6%)	13666 (98.3%)	154 (1.1%)	1655 (11.9%)	7793 (56.1%)	4451 (32.0%)
	Black	2270 (11.8%)	18 (0.8%)	2228 (98.1%)	24 (1.1%)	347 (15.3%)	1176 (51.8%)	747 (32.9%)
	Asian	564 (2.9%)	3 (0.5%)	556 (98.6%)	5 (0.9%)	81 (14.4%)	297 (52.7%)	186 (33.0%)
	Other,	2490	43 (1.7%)	2394	53 (2.1%)	529	1208	753

	Unknown	(13.0%)		(96.1%)		(21.2%)	(48.5%)	(30.2%)
Cancer primary site								
	Total sites	20580 (100.0%)	149 (0.7%)	20190 (98.1%)	241 (1.2%)	2765 (13.4%)	11395 (55.4%)	6420 (31.2%)
	Oral cavity	914 (4.4%)	8 (0.9%)	898 (98.3%)	8 (0.9%)	118 (12.9%)	495 (54.2%)	301 (32.9%)
	GI	2425 (11.8%)	44 (1.8%)	2338 (96.4%)	43 (1.8%)	652 (26.9%)	1060 (43.7%)	713 (29.4%)
	Lung	2022 (9.8%)	36 (1.8%)	1963 (97.1%)	23 (1.1%)	538 (26.6%)	921 (45.6%)	563 (27.8%)
	Bone	70 (0.3%)	0 (0%)	67 (95.7%)	3 (4.3%)	8 (11.4%)	38 (54.3%)	24 (34.3%)
	Blood	1313 (6.4%)	8 (0.6%)	1289 (98.2%)	16 (1.2%)	267 (20.3%)	853 (65.0%)	193 (14.7%)
	Skin	617 (3.0%)	4 (0.7%)	597 (96.8%)	16 (2.6%)	76 (12.3%)	324 (52.5%)	217 (35.2%)
	Soft tissue	199 (1.0%)	4 (2.0%)	193 (97.0%)	2 (1.0%)	42 (21.1%)	108 (54.3%)	49 (24.6%)
	Breast	3018 (14.7%)	7 (0.2%)	2989 (99.0%)	22 (0.7%)	173 (5.7%)	2011 (66.6%)	834 (27.6%)
	Female genital	974 (4.7%)	4 (0.4%)	958 (98.4%)	12 (1.2%)	143 (14.7%)	527 (54.1%)	304 (31.2%)
	Male genital	3216 (15.6%)	3 (0.1%)	3182 (98.9%)	31 (1.0%)	142 (4.4%)	1830 (56.9%)	1244 (38.7%)
	Urinary	2738 (13.3%)	17 (0.6%)	2690 (98.3%)	31 (1.1%)	286 (10.5%)	1490 (54.4%)	962 (35.1%)
	CNS/Brain	1268 (6.2%)	5 (0.4%)	1240 (97.8%)	23 (1.8%)	152 (12.0%)	724 (57.1%)	392 (30.9%)
	Endocrine	1116 (5.4%)	1 (0.1%)	1108 (99.3%)	7 (0.6%)	45 (4.0%)	579 (51.9%)	492 (44.1%)
	Unspecified	690 (3.4%)	8 (1.2%)	678 (98.3%)	4 (0.6%)	123 (17.8%)	435 (63.0%)	132 (19.1%)

*Other race and unknown category includes patients identifying in the following categories: Native American, Native Hawaiian or Pacific Islander, Declined to report, and those who left the category blank

Topic: Table 1 demonstrates the overall composition of our sample identifying the demographic and primary cancer site breakdown, with categories based on age of first alert, race, ethnicity, and primary cancer site as well as the population of patients who were alive compared to those who were deceased ≤10 days and ≤365 days from their first QTc alert.

19,224 adult cancer patients with 20,581 distinct primary cancer sites were identified as receiving EMR generated QTc alerts between 2005 and 2019.

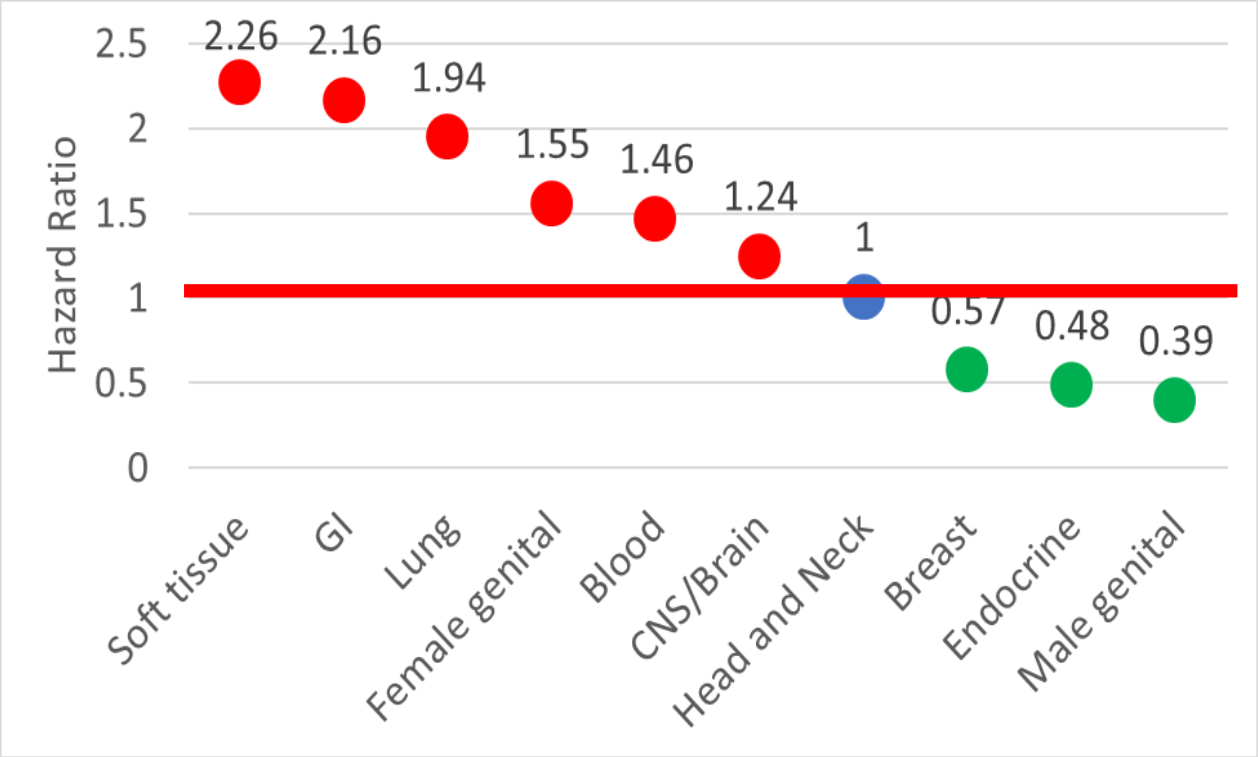
Table 2. Overall survival (Kaplan-Meier Analysis and Cox Regression) two category outcome death ≤10 days of first QTc alert vs no death ≤10 days by demographic factors

Patient Characteristics			# patients	# dead	5-year survival (Std.Err.)	Median survival (y) (95% CI)	Multivariable analysis		
							HR (95% CI)	p	Overall p
Age at first alert									
	18 - 49		3670	574	0.7384 (0.0114)	**** (**** - ****)	Reference		< 0.001
	50 - 59		4396	963	0.6418 (0.0113)	10.21 (8.43 - ****)	1.431 (1.289 - 1.589)	< 0.001	
	60 - 69		6010	1431	0.6097 (0.0099)	8.48 (7.62 - 8.85)	1.621 (1.467 - 1.790)	< 0.001	
	>= 70		5147	1598	0.4885 (0.0117)	4.83 (4.44 - 5.32)	2.326 (2.106 (2.569)	< 0.001	
Gender									
	Male		10033	2501	0.5890 (0.0078)	7.50 (7.00 - 8.01)	Reference		< 0.001
	Female		9190	2065	0.6326 (0.0081)	9.25 (8.27 - 9.88)	0.831 (0.776 - 0.889)	< 0.001	
Ethnicity									
	Non-hispanic		16340	3738	0.6133 (0.0062)	7.66 (7.42 - 8.48)	Reference		< 0.001
	Hispanic		1550	340	0.6255 (0.0205)	9.26 (8.54 - ****)	1.046 (0.930 - 1.176)	0.452	
	Unknown		1333	488	0.5218 (0.0172)	7.61 (3.38 - ****)	1.661 (1.477 - 1.868)	< 0.001	
Race									
	White		13899	3090	0.6269 (0.0066)	8.33 (7.60 - 8.74)	Reference		< 0.001
	Black		2270	593	0.5637 (0.0171)	7.26 (5.95 - 8.64)	1.257 (1.150 - 1.375)	< 0.001	
	Asian		564	127	0.5932 (0.0366)	**** (5.37 - ****)	1.184 (0.990 - 1.415)	0.064	
	Other, Unknown		2490	756	0.5544 (0.0143)	8.58 (6.49 - ****)	1.291 (1.170 - 1.425)	< 0.001	
Total number of alerts									
	1		4259	641	0.7822 (0.0089)	10.71 (10.71 - ****)	Reference		< 0.001
	2 - 5		8072	1495	0.6836 (0.0086)	**** (9.88 - ****)	1.288 (1.173 - 1.414)	< 0.001	
	6 - 10		2975	855	0.5337 (0.0152)	5.72 (5.06 - 6.47)	1.673 (1.507 - 1.858)	< 0.001	
	>= 11		3917	1575	0.4473 (0.0111)	4.12 (3.81 - 4.44)	1.880 (1.706 - 2.071)	< 0.001	

Table 3. Overall survival (Kaplan-Meier Analysis and Cox Regression) two category outcome death ≤10 days of first QTc alert vs no death ≤10 days by cancer primary site

Patient Characteristics		# patients	# dead	5-year survival (Std.Err.)	Median survival (y) (95% CI)	Multivariable analysis		
						HR (95% CI)	p	Overall p
Cancer primary site								
Oral cavity		914	200	0.6526 (0.0242)	9.04 (7.19 - ****)	Reference		
GI		2425	989	0.3764 (0.0159)	2.43 (2.21 - 2.70)	2.157 (1.850 - 2.515)	< 0.001	< 0.001
Lung		2022	856	0.3792 (0.0163)	2.71 (2.30 - 3.02)	1.940 (1.657 - 2.271)	< 0.001	
Bone		70	15	0.6292 (0.0959)	9.26 (3.36 - 9.26)	1.005 (0.593 - 1.702)	0.985	
Blood		1313	571	0.4380 (0.0183)	4.19 (3.61 - 4.50)	1.461 (1.239 - 1.723)	< 0.001	
Skin		617	123	0.6550 (0.0340)	7.09 (5.52 - 8.68)	0.967 (0.771 - 1.214)	0.773	
Soft tissue		199	84	0.2783 (0.0558)	2.59 (1.93 - 3.09)	2.260 (1.749 - 2.920)	< 0.001	
Breast		3018	375	0.7935 (0.0120)	10.71 (10.71 - ****)	0.567 (0.474 - 0.678)	< 0.001	
Female genital		974	272	0.5142 (0.0270)	5.40 (4.21 - 7.34)	1.547 (1.279 - 1.872)	< 0.001	
Male genital		3216	326	0.8128 (0.0112)	**** (**** - ****)	0.394 (0.329 - 0.471)	< 0.001	
Urinary		2738	572	0.6379 (0.0147)	8.33 (7.35 - 9.73)	0.897 (0.763 - 1.055)	0.189	
CNS/Brain		1268	290	0.6087 (0.0226)	8.39 (5.99 - 9.25)	1.242 (1.035 - 1.491)	0.020	
Endocrine		1116	91	0.8107 (0.0243)	9.25 (9.24 - ****)	0.477 (0.372 - 0.613)	< 0.001	
Unspecified		690	207	0.6035 (0.0251)	7.50 (6.38 - ****)	1.187 (0.975 - 1.444)	0.088	

Figure 3. Overall survival (Kaplan-Meier Analysis and Cox Regression) two category outcome death ≤10 days of first QTc alert vs no death ≤10 days by cancer primary site (p<.05 statistically significant sites only)



Topic: In multivariable Kaplan Meier overall survival analysis demographic factors associated with significantly increased ≤10-day mortality included; advancing age, (specifically patients >70 had a non-overlapping 95% Confidence Interval=CI with other age groups), male gender, and Black (HR=1.257) and Other/unknown race (HR=1.661).

Topic: Increasing number of alerts demonstrated a stepwise increase in HR for ≤10-day mortality as compared to a reference group with 1 alert. Patients with 2-5 alerts had a HR for mortality of 1.29, while those with 6-10 alerts had a HR of 1.673 and those with >10 alerts had a HR of 1.88. Notably, patients with >5 alerts (1.51-2.07) had a non-overlapping 95% CI as compared to patients with ≤5 alerts (1-1.41). In comparison to a head and neck cancer reference group, increased ≤10-days mortality was associated with; GI

(HR=2.16), lung (HR=1.94), blood (HR=1.46), soft tissue (HR=2.26), CNS/Brain (HR=1.24) and female genital (HR=1.55) cancer sites. Decreased ≤10-days mortality was associated with female gender (HR=0.83), decreased age, and breast (HR=0.57), male genital (HR=0.39), and endocrine (HR=0.48) cancer sites.

Topic: Median survival analysis demonstrates that males (7.50 years) and non-Hispanic patients (7.66 years) and patients >70 years of age (4.83 years), with 6-10 unique alerts (5.72 years), >11 unique alerts (4.12 years), or GI (2.43 years), lung (2.71 years), and soft tissue (2.59 years) cancers demonstrate significantly decreased median survival times with non-overlapping 95% confidence intervals compared to individuals of other ages, genders, ethnicities, number of alerts, and cancer sites.

Table 4. Mortality at varying time points based on demographics and primary cancer site by multinomial regression

Patient Characteristics		Multivariable analysis								
		Deaths ≤10 days of 1st alert		Deaths 11 - 180 days from 1st alert		Deaths 181 - 365 days from 1st alert		Overall p
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	
Age at first alert								
	18 - 49	Reference		Reference		Reference		< 0.001
	50 - 59	2.057 (1.020 - 4.147)	0.044	1.716 (1.417 - 2.077)	< 0.001	1.055 (0.820 - 1.358)	0.677	
	60 - 69	2.474 (1.264 - 4.841)	0.008	1.899 (1.581 - 2.281)	< 0.001	1.462 (1.162 - 1.840)	0.001	
	>= 70	3.504 (1.802 - 6.814)	< 0.001	2.579 (2.148 - 3.097)	< 0.001	1.898 (1.508 - 2.390)	< 0.001	
Gender								
	Male	Reference		Reference		Reference		0.002
	Female	0.630 (0.432 - 0.919)	0.016	0.860 (0.763 - 0.970)	0.014	0.830 (0.705 - 0.978)	0.027	
Ethnicity								
	Non-hispanic	Reference		Reference		Reference		< 0.001
	Hispanic	0.831 (0.390 - 1.772)	0.633	1.237 (1.014 - 1.508)	0.036	1.100 (0.835 - 1.448)	0.500	
	Unknown	3.217 (1.855 - 5.582)	< 0.001	2.144 (1.753 - 2.622)	< 0.001	1.742 (1.306 - 2.324)	< 0.001	
Race								
	White	Reference		Reference		Reference		< 0.001
	Black	1.538 (0.911 - 2.599)	0.107	1.513 (1.292 - 1.771)	< 0.001	1.095 (0.870 - 1.378)	0.438	
	Asian	1.062 (0.331 - 3.409)	0.919	1.295 (0.942 - 1.779)	0.111	1.491 (1.017 - 2.185)	0.041	
	Other, Unknown	1.872 (1.110 - 3.157)	0.019	1.468 (1.234 - 1.746)	< 0.001	1.201 (0.940 - 1.534)	0.143	
Cancer primary site								
	Oral cavity	Reference		Reference		Reference		< 0.001
	GI	2.645 (1.229 - 5.692)	0.013	2.745 (2.092 - 3.602)	< 0.001	2.145 (1.504 - 3.060)	< 0.001	
	Lung	2.270 (1.035 - 4.980)	0.041	2.433 (1.840 - 3.217)	< 0.001	2.121 (1.475 - 3.049)	< 0.001	
	Bone	####	####	1.292 (0.534 - 3.126)	0.571	0.706 (0.166 - 3.003)	0.637	
	Blood	0.815 (0.302 - 2.196)	0.686	1.889 (1.401 - 2.546)	< 0.001	1.778 (1.207 - 2.620)	0.004	
	Skin	0.770 (0.227 - 2.605)	0.674	0.992 (0.668 - 1.474)	0.968	0.971 (0.582 - 1.619)	0.910	
	Soft tissue	2.991 (0.876 - 10.208)	0.080	2.214 (1.377 - 3.559)	0.001	1.215 (0.575 - 2.566)	0.609	
	Breast	0.399 (0.138 - 1.159)	0.091	0.489 (0.352 - 0.680)	< 0.001	0.528 (0.345 - 0.807)	0.003	
	Female genital	0.776 (0.223 - 2.699)	0.690	1.553 (1.104 - 2.185)	0.011	1.306 (0.827 - 2.062)	0.253	
	Male genital	0.080 (0.021 - 0.304)	< 0.001	0.297 (0.214 - 0.412)	< 0.001	0.288 (0.187 - 0.442)	< 0.001	
	Urinary	0.676 (0.289 - 1.582)	0.367	0.803 (0.600 - 1.076)	0.142	0.753 (0.514 - 1.103)	0.145	
	CNS/Brain	0.618 (0.199 - 1.915)	0.404	1.149 (0.827 - 1.597)	0.407	1.080 (0.705 - 1.654)	0.723	
	Endocrine	0.133 (0.016 - 1.071)	0.058	0.417 (0.271 - 0.642)	< 0.001	0.235 (0.119 - 0.464)	< 0.001	
	Unspecified	1.667 (0.616 - 4.512)	0.314	1.908 (1.358 - 2.680)	< 0.001	1.105 (0.674 - 1.811)	0.692	

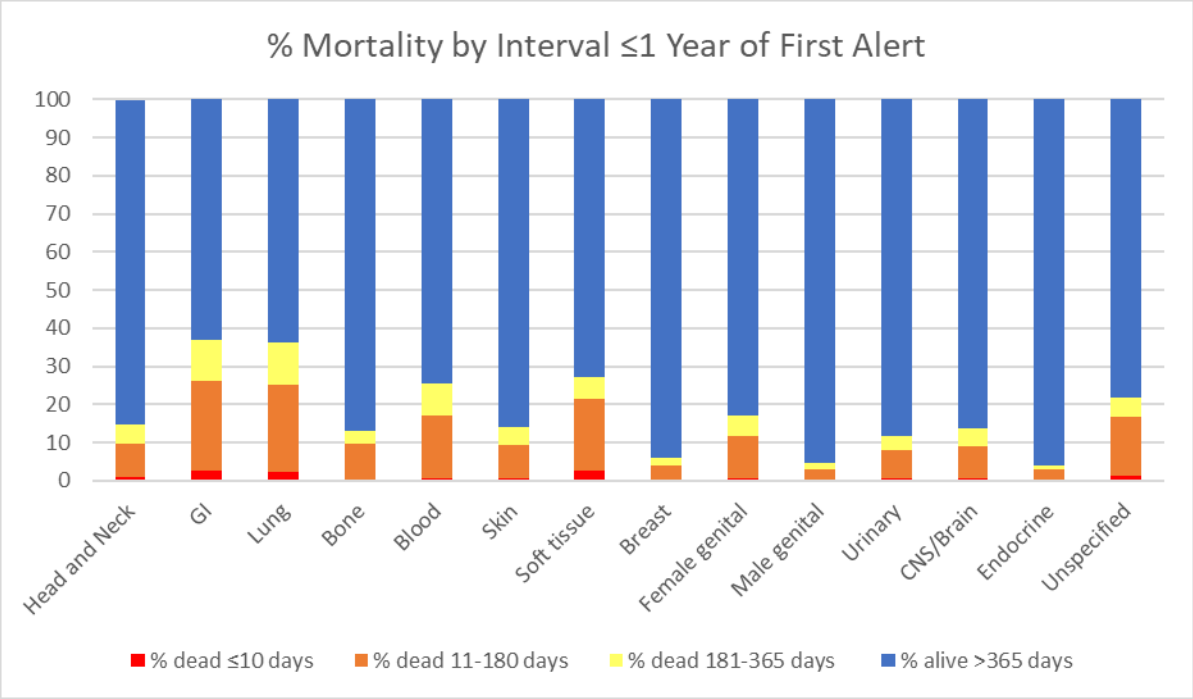
Topic: Multinomial, multivariable analysis controlling for age, race, gender, and ethnicity demonstrated how groups of patients varied in terms of demographics and cancer site based on their mortality status ≤10-days from a patient's 1st QTc alert compared to 11-180 days and 181-365 days.

Topic: ≤10-days of a patients 1st QTc alert significantly increased mortality was associated with patients 50-59 (Odd's Ratio=OR=2.06), 60-69 (OR=2.47), >69 (OR=3.50) years of age, Unknown ethnicity (OR=3.22), Other, Unknown race (OR=1.87), and GI (OR=2.65), and lung (OR=2.27) cancer sites. Decreased mortality was associated with female gender (OR=0.63) and male genital (OR=0.08) cancer site.

Topic: From days 11-180 significantly increased mortality was associated with patients 50-59 (OR=1.72), 60-69 (OR=1.90), and >69 (OR=2.58) years of age (there is a non-overlapping 95% CI between the 50-59 and >69 age groups), Hispanic (OR=1.24) and Unknown (OR=2.14) ethnicity, Black (OR=1.30) and Other, Unknown (OR=1.47) race, GI (OR=2.75), lung (OR=2.43), blood (OR=1.90), soft tissue (OR=2.21), unspecified (OR=1.90) and female genital (OR=1.55) cancer sites. Decreased mortality in this interval was associated with female gender (OR=0.86), breast (OR=0.490), male genital (OR=0.30), endocrine (OR=0.417) cancer sites.

Topic: From days 181-365 significantly increased mortality was associated with patients 60-69 (OR=1.46) and >69 (OR=1.90) years of age, Unknown ethnicity (OR= 1.74), Asian race (OR=1.49), and GI (OR=2.15), lung (OR=2.12), and blood (OR=1.78) cancer sites. Decreased mortality in this interval was associated with female gender (OR=0.83), and breast (OR=0.53), male genital (OR=0.29), and endocrine (OR=0.24) cancer sites.

Figure 4: Mortality by time interval within 365 days of a patient's first QTc alert by cancer site



Topic: proportion of deaths ≤10-days ranged from 0.01% in male genital and endocrine patients to 2.50% in GI and 2.40% in lung cancer patients. Proportion of deaths between 11-180 days was lowest in male genital (2.93%), endocrine (3.08%), and breast (3.62%) and highest in GI (23.8%), and lung (22.8%) cancer patients. The vast majority of patient deaths ≤365-days occurred between 11-180 days and the percentage of mortality events within the total sample population by primary cancer site between 181-365 days was lowest in endocrine (1.03%) and male genital (1.60%) and highest in lung (11.1%) and GI (10.6%) cancer patients. In all cancer sites, most patients were alive after 365 days with proportions ranging from 95.9% in endocrine cancer to 63.8% in lung cancer patients.

Table 5: Measured QTc intervals by EKG ≤10 days of 1st QTc Alert

	# Patients	Mean QTc (milliseconds)	p-value
Males Only			<0.001
Died ≤10 days of 1st QTc Alert	34	469	
Alive	5465	450	
Females Only			p=0.13
Died ≤10 days of 1st QTc Alert	24	455	
Alive	4392	449	

Topic: Table 5 demonstrates that male patients who had an EKG following their first alert and died ≤10-days of their first QTc alert had a statistically significantly (p<.0001) increased QTc interval (469 milliseconds) compared to patients in our sample who had an EKG ≤10-days of their first alert, but who were alive on day 11 (450 milliseconds). There was no significant difference when comparing the QTc intervals of females who received an EKG ≤10-days of their first alert and died during this time interval compared to those who were alive on day 11. Overall our patient cohort demonstrated an elevated QTc interval with no group average below 449 milliseconds.

CHAPTER 4: Conclusions

Topic: Our results in figure 1 demonstrate that within our institution, there is a trend towards significantly increasing numbers of annual QTc alerts. We explain this trend with the following 3 factors: the recent development and increased use of targeted chemotherapeutic drugs that are associated with QTc interval prolongation, increased research establishing the relationship between QTc prolongation and a greater range of drugs, and increased prescription of supportive medications associated with QTc prolongation in efforts to aggressively treat and provide prophylaxis for cancer therapy side effects like pain, nausea, and immunosuppression. The increase in annual QTc alerts greatly outpaces the growth of total cancer patient encounters at our institution.

Topic: While the drugs associated with the largest number of QTc alerts are generally those that impact the greatest number of unique patients, there are significant outliers as shown in figure 2. Given the prevalence of nausea and GI side effects among cancer patients undergoing therapy, it is not surprising that ondansetron is the drug associated with by far the most alerts and that impacts the most unique patients. Other drugs that are widely implicated are prescribed as antibiotic prophylaxis including levofloxacin, ciprofloxacin, azithromycin, posaconazole, and fluconazole or are medications to manage chronic conditions including citalopram, formoterol, amiodarone, trazodone, escitalopram, quetiapine. Certain chemotherapeutic medications like eribulin, dasatinib, nilotinib, romidepsin, arsenic and chronically prescribed drugs like trazodone, and amiodarone generated large numbers of alerts compared to a relatively low number of affected patients demonstrating frequent re-administration. Conversely, drugs including propofol, azithromycin, methadone,

haloperidol, and moxifloxacin are given to many patients, but generate a comparatively low number of alerts suggesting they are often given in short courses.

Topic: Our data demonstrates that EMR generated drug-drug interaction induced QTc prolongation alerts are a growing reality of oncology practice. The annual number of unique alerts generated has outstripped the number of unique cancer patient encounters our center experienced over the last 3 years. While these alerts have traditionally been viewed as a nuisance or distraction contributing to provider burnout and cognitive fatigue, our analysis was aimed at attempting to extract useful data from these alerts by identifying their association with cancer patient mortality. Our primary hypothesis that mortality ≤10-days of a patient's 1st QTc alert varies by primary cancer site was supported by our finding in table 3 that cancer patients with QTc alerts and GI and lung cancers had significantly increased, and male genital cancers had significantly decreased ≤10-day mortality in both multinomial, multivariable and Kaplan-Meier overall survival analysis.

Topic: Part of this trend may be attributed to the overall short-term prognosis associated with these varying cancer sites. Additionally, we believe that patients with these generally more slowly progressive cancers may be prescribed a wide range of QTc prolonging medications that are unlikely to demonstrate within 10-day mortality. In the case of male genital and breast cancer, medications commonly used in therapy such as abiraterone and eribulin respectively, may generate QTc alerts, but are not typically associated with TdP and SCD, potentially contributing to this trend. Our results suggest that patients with lung and GI cancers may represent an at-risk group for which providers should be particularly cautious when prescribing QTc prolonging medications and who may benefit from closer follow-up or

EKG monitoring. Conversely, prescribing these same supportive or therapeutic agents to male genital cancer patients who very rarely die ≤10-days of their first alert likely requires less scrutiny.

Topic: Given that very few patients (<3% of any specified cancer site) die ≤10-days of their first QTc alert as illustrated by figure 4, these EMR generated messages are likely distractions in most instances. Anecdotally, this appears to be the opinion of many of the practicing oncologists we consulted on this project who have noticed few cases of acute mortality following alerts. However, our study has shown that these alerts may be useful tools to identify patients in at-risk groups who have an elevated risk of dying within 10 days based on demographic and cancer primary site factors and about whom oncologists have been warned. This is particularly true in patients who are receiving numerous alerts, given the elevated HR for acute mortality in patients with >5 unique alerts. Further, the statistically significant increase in measured QTc intervals for male patients with EKG data who died ≤10-days of their first alert shown in table 5, could support the possibility that actual QTc interval prolongation by EKG is a negative prognostic factor and may be associated with some instances of acute mortality.

Topic: It is unsurprising that our sample groups averaged relatively long QTc intervals given that they were all prescribed medications associated with QTc interval prolongation. However, the 16 msec increase in QTc intervals of male patients who died within 10 days of their alerts as compared to those who did not is both statistically and clinically significant. However, this difference could potentially be explained by greater severity of illness or a greater number of QTc prolonging medications in the cohort of patients with deaths ≤10-days

of their first alert.

Topic: Our secondary hypothesis was that QTc alerts would not be associated with significant acute, ≤10-day mortality, but are negative prognostic markers. This was supported by our data demonstrating low rates of ≤10-day mortality and a disproportionate number of deaths within 365 days of 1st alerts occurring in the 11-180-day interval across cancer primary sites and demographic factors. While the mechanism underlying this trend and the direct contribution of potential QTc prolongation remains unclear, our results suggest these alerts are a useful prognostic marker. Based on the observed trend that the vast majority of cancer patients with QTc alerts generated do not die ≤10-days of their first alert, and that those who survive 180 days are very unlikely to die within 365 days, we posit that QTc alerts serve as a 180-day warning of increased risk of mortality. Patients that survive this initial period at are low risk of dying within a year, suggesting that within 180 days of a QTc alert, patients may benefit from closer monitoring and follow-up.

Topic: Our additional secondary hypothesis that younger individuals would have higher rates of acute mortality due to a weed-out effect of patients who had been naïve to these medications but are highly sensetive to QTc interval prolongation was not supported. Our data showed that older patients had increased mortality at all time points following their first QTc alert.

Topic: Our overall findings re-demonstrate key aspects of the recently published Pakistani study by Khan et. al, namely that QTc prolonging drugs are widely prescribed to cancer patients and the rates of adverse events associated with drug induced QTc alerts vary significantly by primary cancer type (2017). Given our large-scale, diverse sample, our

results are widely generalizable to other large tertiary or quaternary referral centers in the US. Notably, our sample has a wide distribution of age ranges, including high representation (26.8%) of patients over 70 years of age who are often under-represented or excluded from clinical trials. More broadly, our work shows how EMR's can act as novel research tools to access observational data and supplement traditional research methods not equipped to answer questions such as ours.

Future Directions:

We aim to further study which specific combinations of QTc alert generating medications are more frequently associated with acute, ≤10-day mortality to identify if there are certain combinations of agents that put patients at higher risk of adverse outcomes. We would also like to examine how physicians respond to the EMR generated alerts and identify their impact on prescribing behavior. We encourage other groups to replicate our study design to verify if the associations our group identified are consistent with those found at other large medical centers. Future prospective studies may be able to identify the causal factors that lead to the associations we have identified. We also aim to assess if there are differences in the make-up of patients on whom we have EKG data as compared to those we do not and identify the actual reported cause of death in patients with deaths recorded ≤10-days of their first QTc alert. Lastly, in order to control for cancer site, we feel it would be valuable to use a case matched control approach to see if QTc alerts select for patients with a poor prognosis or if they have any predictive value when patients with similar prognoses, demographics, and cancer sites, but without an alert are compared to those with an EMR generated alert.

Limitations:

This study is based on an association between QTc alerts and cancer patient mortality, we cannot identify definitively if the prescribing physician triggered an override for the alerts and prescribed the implicated medications or if they were taken as prescribed by the patient. Given that we are only studying associations, we are limited to identifying statistically significant trends and cannot assess causality. Our data is also collected from a single site, which may skew the prognosis of our patients based on their cancer site, if for example our center tends to see more early stage breast and male genital cancers due to aggressive screening or is referred particularly advanced lung and GI cancer patients. Further, there are participants in our sample that lack complete demographic information particularly in the race and ethnicity sections. In our analysis of patients by primary cancer site, we included patients with multiple primary cancer site diagnoses. While the vast majority of these instances are genuine separate primary cancer sites and some appear to be secondary malignancies related to the therapy indicated for the initial primary cancer, a minority of these codes are associated with one primary site diagnosis that varies solely on demographic criteria and is not a unique primary malignancy. Additionally, only a subset of patients with QTc alerts had EKG data within 10 days of their first alert so our full sample could not be assessed in our analysis of actual QTc length by EKG for patients that died within 10 days of their first alert as compared to those who did not. Further, we could not stratify patients by severity of illness, cancer stage, or by the number of QTc interval prolonging medications they were prescribed.

LIST OF TABLES

LIST OF FIGURES

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VITAE

Benjamin Bleiberg (May 29th, 1992 to present) was born in Topeka, KS and moved to Houston, TX at age 12. He attended Duke University and graduated with a B.S. in Psychology with minors in Russian Literature in Translation and Biology. He completed a M.S. in Medical Sciences from Boston University and was a research assistant in the Neurological Research Institute of Baylor College of Medicine. He is pursuing a career in Internal Medicine with an interest in Hematology/Oncology.

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