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The Correlation Between Prolonged Corrected QT Interval with the Frequency of Respiratory Arrest, Endotracheal Intubation, and Mortality in Acute Methadone Overdose

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Abstract Corrected QT interval (QTc) prolongation is long considered as a predisposing factor for the occurrence of torsade de pointes (TdP) and sudden cardiac arrest in methadone maintenance treatment. We aimed to elucidate the correlation between QTc prolongation and in-hospital death, respiratory arrest, and endotracheal intubation in acute methadone-intoxicated patients presenting to the emergency department and to assess the value of QTc in predicting these outcomes. A prospective cross-sectional study with a convenience sample of patients with acute methadone overdose was done. Participants were 152 patients aged 15–65 with negative urinary dipstick test for cyclic antidepressants, no history of other QTc-prolonging conditions and co-ingestions, no severe comorbidities affecting the outcomes, and positive urinary dipstick results for methadone. QTc intervals were measured and calculated in triage-time electrocardiogram (ECG). Death was correlated with QTc ($P = 0.014$) and length of ICU admission ($P < 0.001$). In multivariable analysis, death was independently associated only with length of ICU admission [odds ratio (OR) 95 % confidence intervals (95 % CI) 1.36 (1.14–1.61)]. Intubation and respiratory arrest were independently associated with QTc interval [OR (95 % CI) 1.03 (1.02–1.04) and 1.02 (1.01–1.03), respectively]. The receiver operating characteristics curves drawn to show the ability of QTc to predict death, intubation, and respiratory arrest showed thresholds of 470, 447.5, and 450 ms with sensitivity (95 % CI) and specificity (95 % CI) of 87.5 (47.3–99.7), 86.8 (74.7–94.5), and 77.3 (62.2–88.5), respectively. Our study showed that QTc is a potential predictor for adverse outcomes related to acute methadone intoxication. The correlations shown in this study between triage-time QTc and in-hospital respiratory arrest or intubation in methadone overdose may be of clinical value, whether these outcomes are hypothesized to be a reflection of background TdP or intoxication severity.

Keywords Methadone · Opioid-related disorders · Torsades de pointes · Hospital mortality · Apnea

Introduction

Corrected QT interval (QTc) prolongation, whether congenital or acquired, is long considered as a predisposing factor for the occurrence of torsade de pointes (TdP) and sudden cardiac arrest. Some studies have shown the association of QTc prolongation and mortality in intentional organophosphate poisoning, syncope, suspected acute non-specific intoxications, and after ischemic strokes [1–4].

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Others have evaluated QTc prolongation as a well-known complication of methadone consumption in methadone maintenance treatment (MMT) for opioid addiction abstinence compared to other equivalently used agents such as buprenorphine [5]. Some studies have led to development of routine follow-up programs to screen for QTc prolongation and discontinue methadone if critical levels are detected [6–12].

In acute methadone overdose, some risk factors for mortality have been described including female sex, lack of concurrent heroin involvement, overdosing during the weekend, recent leaving of MMT, syrup formulation, and the presence of CYP2B6 and μ-opioid receptor (OPRM1) gene variations [13–16]. In the current literature, however, the main concern in QTc prolongation is its association with TdP and sudden cardiac arrest in MMT programs using methadone on a regular basis, as reviewed by Krantz et al. [7].

In MMT programs, QTc prolongation appears to be related primarily to daily methadone dose, but concomitant administration of CYP3A4 inhibitors, hypokalemia, hepatic failure, administration of other QT-prolonging drugs, and pre-existing heart disease also appear to play a role [6, 16–18]. In one cross-sectional study on 450 patients receiving methadone, the odds ratio for developing syncope was 1.2 times greater with each 50 mg increment in the daily dose [9]. The QTc reaching 470–490 ms or an increase in at least 60 ms from baseline is proposed as a critical level in another study [19]. There is no universal consensus on the QTc cutoff point showing increased incidence of TdP, but most experts mention 500 ms as the alarming value [7].

In this cross-sectional study, a longer QTc interval is hypothesized as a potential indicator of intoxication severity in acute methadone overdose. Therefore, this study is designed to answer the following research question: Can the presence of QTc prolongation at triage predict adverse clinical outcomes such as death, respiratory arrest, or endotracheal intubation in patients with acute methadone intoxication?

Materials and Methods

Study Design and Settings

This was an analytic cross-sectional study conducted in Loghman-Hakim Hospital Poison Center (LHHPC) in Tehran from March 1, 2011, to February 30, 2012. The Loghman-Hakim toxicology unit serves a population in excess of 12.5 million and has an annual ED census of more than 30,000 with about 14,000 hospital admissions. It is the main tertiary hospital for poisoned patients in the capital city and is the largest in the country. This institution has one of the largest and busiest inpatient toxicology facilities in the world [16, 20–22].

This study was approved by Tehran University of Medical Sciences Institutional Review Board.

Selection of Participants

Patients were recruited during 2 days per week (convenience sampling). All patients presenting to ED with a history of methadone intoxication were considered for enrollment. Intoxication or overdose was defined as ingestion of more than 10 mg of methadone in recently non-users (not using methadone within one previous month) or more than usual doses in previous consumers, making them or their companions seek help. A urine dipstick test for methadone for each patient was being done after admission, and patients with negative results were being excluded from the study.

Exclusion criteria were defined as the following: unreliable/unobtainable history, negative urine dipstick results for methadone, presence of significant comorbid illnesses affecting survival or adverse outcomes (e.g., severe heart disease), ages under 15 (excluding pediatric condition, which may be different from adults in several parameters) or over 65 (minimizing the impact of comorbid conditions on results), history of co-ingestions for other known QTc-prolonging drugs or drugs obviously affecting the outcomes (e.g., benzodiazepine overdose makes patients more prone to intubation because of respiratory depression), hypokalemia or hyperkalemia, positive urine dipstick results for cyclic antidepressants, and finally changes in diagnosis during the admission period (Fig. 1). As could be seen in our exclusion criteria, we tried to omit all significant multidrug overdoses from our population based on history and dipstick test results.

Study Protocol

For each patient presenting to ED with the history of methadone overdose or suspicious for this diagnosis, complete vital signs were documented by the emergency physician [resident of emergency medicine, postgraduate year (PGY) 3] and an ECG and other initial laboratory tests [including blood gas, blood sugar (BS), electrolytes, blood urea nitrogen (BUN), creatinine (Cr), and liver function tests] were obtained. From this collection of patients, only those who were visited by one of the investigators (based on availability) were enrolled. In the time of visit, a comprehensive history and physical examination in addition to urinary dipstick tests for methadone (W.H.P.M., Inc, USA, cutoff: 300 ng/mL), cyclic antidepressants (W.H.P.M., Inc, USA, cutoff: 1,000 ng/mL), tramadol

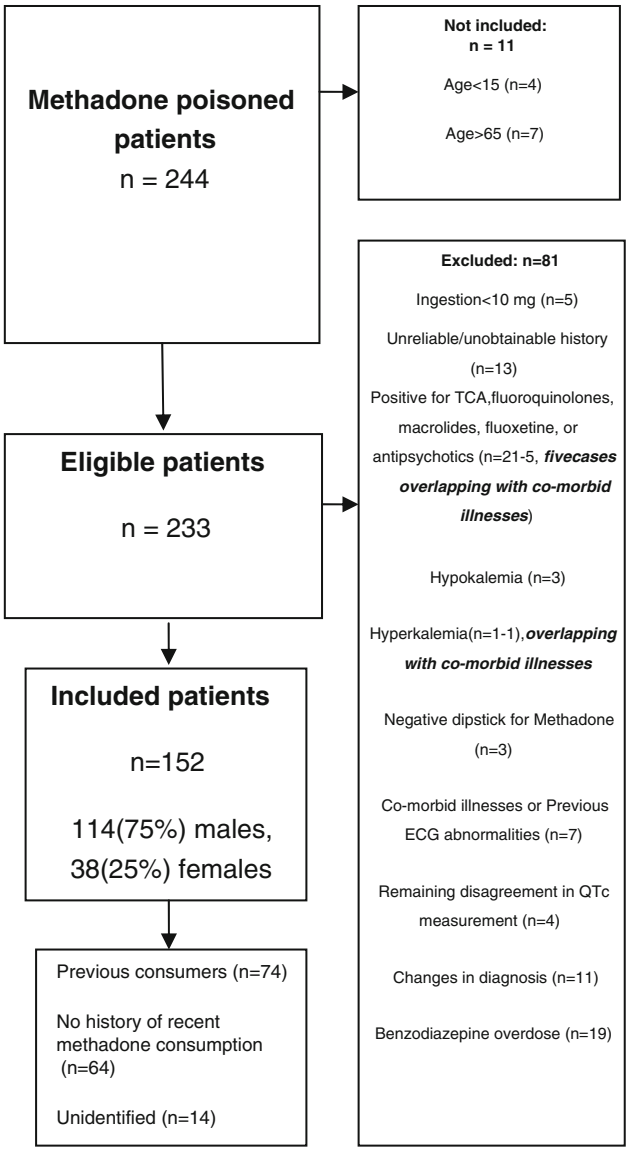

Fig. 1 Step-by-step exclusion of patients to reach the study population

(Rojan®, IRAN, cutoff: 100 ng/mL) morphine (Rojan®, Iran, cutoff: 300 ng/mL), and benzodiazepines (W.H.P.M., Inc, USA, cutoff: 300 ng/mL) were performed to further confirm the diagnosis. The presence or absence of other QTc-prolonging conditions as well as central nervous system (CNS) pathologies and risk factors for respiratory failure (e.g., drugs and pulmonary diseases) were assessed. The data collecting team consisted of a resident of emergency medicine (PGY3), and two medical students directly supervised by an attending physician of clinical toxicology. The research staffs were specifically trained to obtain a comprehensive history, to perform a systematic clinical examination, and to perform and interpret urine dipstick tests. The enrolled patients were visited frequently (every 2–3 h on average) by one of the investigation team members throughout their hospitalization.

Although some patients admitted and discharged with the diagnosis of acute methadone overdose during study period were missed because of lack of 24-h coverage by investigators, this method of data collection was preferred over a retrospective study of all patients for two main reasons: First, performing the history taking, physical examinations, and dipstick tests by researchers and following the hospital course events provide more reliable data over simply reviewing files. Second, most patients with acute methadone overdose and more complicated course were hospitalized long enough to be enrolled by the investigators. Therefore, patients missed by the research team are more likely to have an uncomplicated course and short hospital length of stay.

Electrocardiographic Evaluation

Only those ECGs done in the first few minutes of patientsâ€™ arrival were evaluated. All QT interval readings and QTc calculations were performed by two board-certified emergency medicine specialists experienced in ECG interpretation and blinded to the study protocol and patients. A standard 12 lead ECG was done for each patient, and all standard leads were evaluated by these two physicians [23]. All ECGs were reviewed by both of the readers, and the inter-observer agreements were calculated. The device used to obtain ECG in LHPC ED was not able to calculate QTc automatically, so there were no printed records on strips distracting the ECG evaluators. QTc intervals were calculated by Bazett formula. Disagreements were resolved by consensus, or in a small number of patients, especially in the case of abnormal T waves or T–U wave fusions, by eliminating the unclear lead(s) from evaluation if both of the readers vote for elimination. However, in a few cases, no agreement could be reached, which resulted in exclusion of those patients from the study (see Results).

There is no universal consensus on the limits defining a prolonged QTc interval or a threshold below which there might be no chance for TdP to develop. However, a QTc interval of more than 430 ms for males and 470 ms for females, or independent of sex, above 450 ms is considered as prolonged QTc interval [7].

Patient Management and Disposition

The researching team did not participate in management or disposition of the patients. The decision to intubate a patient in LHHPC ED is made by the emergency medicine residents according to universal indications and hospital protocols under direct supervision of clinical toxicology fellows or

attending physicians (see Study outcomes). Patient disposition follows the same process. In medical toxicology ICUs, the decision making for management and disposition is made directly by toxicology fellows or attending physicians.

Study Outcomes

The primary outcomes of the study were in-hospital mortality, respiratory arrest, and orotracheal intubation. All respiratory depressions with no effective breathing, urging the need for immediate intervention (primarily non-invasive ventilation and intravenous naloxone administration) were categorized under respiratory arrest title. Intubation and mechanical ventilation are mainly performed for patients presenting with respiratory depression refractory to naloxone and non-invasive ventilatory support and those at significant risk of aspiration or impending airway compromise.

Statistical Analysis

Values are reported as mean ± SD for normally distributed continuous variables or median and interquartile range (IQR) for other non-normally distributed continuous variables. Proportions are presented as percentages with 95 % confidence intervals (CI). For univariate analysis, continuous data were analyzed using the Studentâ€™s *t* test if the data were normally distributed (according to the Kolmogorov–Smirnov and Shapiro and Leveneâ€™s tests); otherwise, the adjusted t test was used. Categorical data were compared using Pearson $Ï‡^2$ test. A *P* value less than 0.05 was considered to be statistically significant. To establish the magnitude and direction of the three major outcomes, we calculated the odds ratio (OR and its 95 % CI). The multivariable analysis was performed by constructing a logistic regression model. All variables showing significant correlation with outcomes in univariate analysis were also tested in multivariable analysis. In multivariable model, we entered all variables with *P* value <0.2 in their univariate analysis with our outcomes. We run two separate logistic models for each outcome. One full logistic model with enter method and one model with only significant variables according to forward Wald method. Receiver operating characteristic (ROC) curves were generated to test the ability of QTc in predicting the outcomes of death, intubation, or respiratory arrest. Statistical analysis was performed by Statistical Package for the Social Sciences for Windows version 17.0 (SPSS Inc. Headquarters, Chicago, IL) software program.

Sample Size Analysis

According to the formula of sample size calculation for diagnostic tests, considering a sensitivity of 0.8, a specificity of 0.8, $Î± = 0.05$, and QTc being useful if positive likelihood ratio (PLR) is equal or higher than 2.52, sample size was estimated to be 152 cases.

Results

A total of 152 from 244 methadone-intoxicated patients who presented to ED in the sampling days (2 days a week) were enrolled in the study (92 were excluded, see Fig. 1) from March 1, 2011, to February 30, 2012, with an age range of 15–65 years. Male patients were significantly older (36.3 ± 11.8 vs. 28.7 ± 13.9 years, $P = 0.002$). QTc more than 450 ms was observed in 77 (50.7 %) cases. Basic characteristics of the cases are presented in Table 1.

Two patients were found to develop TdP during hospitalization. The duration of TdP in the first patient was 15 s in ICU, and the second patient developed a 5–10 s episode in ED. Both patients had been intubated before TdPs observed, and the sinus rhythm was recovered before any acute intervention made.

Univariate Analysis

There were 8 deaths, 44 respiratory arrests, and 53 cases which were intubated during admission course. The documented mechanisms of death, diagnosed by physicians in charge of the patients, are shown in Table 2. Death was correlated with QTc interval in presenting ECG ($P = 0.014$) and length of ICU admission ($P < 0.001$). Being intubated during admission course was also correlated with co-ingestions ($P = 0.016$), abnormal respiration ($P < 0.001$), decreased consciousness ($P < 0.001$), QTc intervals more than 450 ms ($P < 0.001$), intoxication dosage ($P = 0.014$), QTc interval in presenting ECG ($P < 0.001$), length of hospitalization ($P < 0.001$), and length of ICU admission ($P < 0.001$). There were also some correlations found for respiratory arrest during admission (Tables 3 and 4). However, because there are multiple comparisons here, an adjusted analysis was done to find independent associations (see below). All variables found to have correlation with outcomes in univariate analysis were also tested in multivariable analysis.

Adjusted Analysis

The most important independent variable for predicting death was the length of ICU admission. For predicting intubation risk, QTc interval on arrival had the highest predictive value, and for predicting respiratory arrest, the QTc interval on arrival and hours from ingestion were shown to be the most important variables (Table 5). The OR of 1.36 (95 %CI 1.14–1.61) means that each additional

Table 1 Basic characteristics of the patients

Signs	Values
Age, mean (SD) (year)	34.4 (12.7)
Male gender, No. (%)	114 (75)
Type of methadone ingestion, No. (%)	
Acute with no history of previous ingestions	64 (42.1)
Acute on chronic, with history for previous ingestions	74 (48.7)
Undetermined	14 (9.2)
QTc interval range (ms)	300–611
QTc, median (IQR) (ms)	450 (54)
Methadone ingestion dosage, median (IQR) (mg)	80 (100)
Arrival time to the emergency from ingestion, median (IQR) (hour)	8 (7)
Pulse rate (mean ± SD)	84 ± 17.6
Respiratory rate (mean ± SD)	21.3 ± 9.2
Systolic blood pressure (mean ± SD)	119.7 ± 18
Glasgow coma score (mean ± SD)	13.5 ± 2.5
Respiratory arrest after disposition from ED, No. (%)	15 (9.9)
Total respiratory arrests, No. (%: 95 % CI)	44 (28.9: 21.6-36.3)
Hospitalization period, median (IQR) (days)	3 (3)
Patients transferred to ICU, No. (%: 95 % CI)	57 (37.5: 30.5-46.5)
length of ICU stay, median (IQR) (days)	5 (5)
Deaths, No. (%: 95 % CI)	8 (5.3: 1.6-8.9)
Tachycardia, No. (%)	26 (17.1)
Tachypnea, No. (%)	13 (8.6)
Bradypnea, No. (%)	3 (2)
Apnea, No. (%)	1 (0.7)
Hypotension, No. (%)	7 (4.6)
Consciousness level at presentation, No. (%)	
15	56 (36.8)
13–14	35 (23)
9–13	24 (15.8)
5–9	22 (14.5)
3–5	12 (7.9)

* Sum of percents do not reach 100 % in some cases because of presenting missing value

IQR inter quartile range, *mg* milligram, *ms* millisecond, *No.* number, *SD* standard deviation

day of staying in ICU increases the risk of death by 14–61 %. Each millisecond increase in QTc interval in arrival-time ECG increases the risk of intubation by 1–3 % and the risk of respiratory arrest by 2–4 %.

To evaluate the diagnostic accuracy of QTc interval for death, we used ROC curves to determine the best cut point with highest simultaneous sensitivity and specificity (Table 6; Fig. 2). According to the table, a threshold of

Table 2 Documented mechanisms of death for expired cases

Patient 1* (pc)**	Patient 2 (*n*)***	Patient 3 (pc)	Patient 4 (pc)	Patient 5 (*n*)	Patient 6 (pc)	Patient 7 (pc)	Patient 8 (pc)
Pneumosepsis	Acute respiratory distress syndrome (ARDS)	Pneumosepsis	Pneumosepsis	Ventricular tachycardia (no TdP was documented)	Acute renal failure (cardiac arrest probably due to acute hyperkalemia)	Ventricular tachycardia (no TdP was documented)	Pneumosepsis + disseminated intravascular coagulation (DIC)

* Patients are numbered according to chronological order

** (pc): previously consuming methadone

*** (*n*): naÄve patient

Table 3 Association between death, respiratory arrest, and intubation with qualitative variables

Dependent variable	Independent variable	Crude OR (95 % CI)
Death ($n = 8$)	Abnormal laboratory test	3.47 (0.82–14.69)
	Syrup form of the drug in comparison with tablet	5.49 (0.62–47.62)
	Co-ingestion	1.51 (0.35–6.56)
	Abnormal pulse rate	0.66 (0.08–5.63)
	Abnormal respiration	1.18 (0.23–6.15)
	Hypotension	0.23 (0.002–675.12)
	Decreased consciousness	4.48 (0.54–37.39)
	Naloxone infusion	32 (0.91–453.83)
	Abnormal ABG	1.22 (0.24–6.30)
	Borderline/prolonged QTc interval	7.4 (0.89–61.69)
	Female gender	1 (0.19–5.18)
	Type of ingestion acute on chronic in comparison with acute	2.25 (0.42–12)
Respiratory arrest ($n = 44$)	Abnormal laboratory test	**2.21 (0.98–4.98)***
	Syrup form of the drug in comparison with tablet	1.12 (0.53–2.40)
	Co-ingestion	1.90 (0.91–3.98)
	Abnormal pulse rate	0.72 (0.27–1.95)
	Abnormal respiration	1.64 (0.72–3.73)
	Hypotension	1.02 (0.19–5.47)
	Decreased consciousness	**5.51 (2.14–14.14)**
	Naloxone infusion	**6.04 (1.55–23.55)**
	Abnormal ABG	1.29 (0.56–2.96)
	Borderline/prolonged QTc interval	**6.11 (2.67–14)**
	Female gender	0.7 (0.3–1.63)
	Type of ingestion acute on chronic in comparison with acute	1.09 (0.52–2.32)
Intubation ($n = 53$)	Abnormal laboratory test	1.85 (0.85–4.06)
	Syrup form of the drug in comparison with tablet	0.62 (0.29–1.33)
	Co-ingestion	**2.36 (1.16–4.77)**
	Abnormal pulse rate	**2.24 (0.95–5.28)**§
	Abnormal respiration	**4.22 (1.88–9.49)**
	Hypotension	2.70 (0.58–12.54)
	Decreased consciousness	**31.40 (7.23–136.41)**
	Naloxone infusion	3.11 (0.54–17.80)
	Abnormal ABG	1.18 (0.54–2.54)
	Borderline/prolonged QTc interval	**14.42 (5.85–35.51)**
	Female gender	0.96 (0.44–2.08)
	Type of ingestion acute on chronic in comparison with acute	0.70 (0.35–1.42)

Bold values indicate statistically significant ($p < 0.05$)

n number

* $P = 0.053$; § $P = 0.062$, these ORs have borderline significance

470 ms can provide a sensitivity of 87.5 % and specificity of 74.3 %, with the area under curve for QTc higher than 470 ms being 0.85 for detecting mortality. The same curve for the diagnostic accuracy of QTc for intubation showed a cutoff of 447.5 ms with a sensitivity of 86.8 % and a specificity of 67.7 %, with the area under curve being 0.80 (Table 4; Fig. 2). ROC curve for QTc in identifying respiratory arrest (Fig. 2) found a cutoff of QTc equal or higher than 450.5 to be associated with sensitivity and specificity of 77.3 and 63 %, respectively, with area under the curve being 0.728.

There was good inter-observer agreement between the two ECG readers (kappa coefficient: 0.81). Four cases with remaining disagreement were discarded.

Table 4 Association between death, arrest, and intubation with quantitative variables

	Death ($n = 8$)		Arrest ($n = 44$)		Intubation ($n = 53$)	
	Yes	No	Yes	No	Yes	No
Age	32.5 (24.4–40.6)	34.5 (32.4–36.7)	36 (31.8–40.1)	33.8 (31.4–36.1)	35.5 (31.6–39.5)	33.8(31.4–36.3)
Intoxication dose	300[a]	139 (100.3–177.6)	174.2 (76.2–272.2)	129.6 (88.7–170.4)	187 (92.9–281.1)	124.5 (83.5–165.5)
Hours from ingestion	9.3 (5.2–13.5)	8.8 (7.9–9.8)	10.3 (8.8–11.9)	8.3 (7.2–9.4)	9.8 (8.3–11.2)	8.5 (7.3–9.6)
QTc interval in presenting ECG	488.5 (454.8–522.2)	447.6 (440.1–455.1)	471.8 (460.9–482.7)	440.8 (431.9–449.7)	479.2 (468.1–490.3)	434 (425.8–442.1)
Length of hospitalization	15 (5–25)[b]	4.3 (3.6–4.9)	8.4 (6.5–10.2)	3.1(2.6–3.6)	8.4(6.9–9.9)	2.5 (2.2–2.9)
Length of ICU admission	15.8 (3.7–27.8)	2.1 (1.5–2.7)	6.8 (4.9–8.7)	0.9 (0.4–1.3)	7.2 (5.7–8.7)	0.2 (0.04–0.3)

Values are mean (95 % CI)

n number

[a] There was only one case

[b] Here, there were two cases, and values are minimum and maximum

Discussion

A large body of literature is dedicated to QTc prolongation in MMT and its association with TdP. The studies done by several researchers showed that there should be a special concern to screen for QTc prolongation in MMT programs, leading to the formation of cardiac safety recommendations for physicians prescribing methadone by Krantz et al. [7]. These recommendations, however, do not include acute intoxications.

ED physicians frequently encounter patients with history of drug overdose for whom a detailed history (type of drug, dose, co-ingestions, etc.) could not be obtained. In such situations, variables that could predict the adverse clinical outcomes could be very helpful. Our study showed that QTc is a potential predictor for adverse outcomes related to methadone intoxication. Prolongation of QTc interval could also be considered an adverse outcome of methadone consumption due to its direct association with TdP. A study in Tehran found acute methadone overdose as the most common cardiotoxic drug, in which QT dispersion was the most specific tool that could successfully predict development of the complications [24].

Our study shows a correlation between QTc interval and in-hospital mortality, intubation risk, and respiratory arrest, but the logistic regression analysis did not show an independent association between QTc interval and mortality. One explanation for this may be a low number of deceased patients in our study, reducing our ability to show any independent association. However, our clinical experience makes us still believe there should be a strong consideration for close observation and monitoring of acute or acute on chronic methadone intoxications with initial QTc more than 450–470 ms, as our findings regarding intubation and respiratory arrest and their independent association with QTc make us more cautious about this matter. The predicting capability of QTc on arrival for respiratory arrest or need for intubation is particularly important for patients developing these complications after disposition from ED (see Results: Basic characteristics). These findings allow us to predict the adverse outcomes early on and take necessary precautions.

The correlation and independent association between QTc prolongation and respiratory arrest may be a point of consideration. Logically, there may not be a direct association between an ECG feature and an outcome such as respiratory arrest, and the occurrence of respiratory arrest may be attributed to co-ingestions or drugs administered for sedation. However, we have found such an association in the absence of any documented confounding factor; there is a strong consideration that the QTc may be a representative of the severity of intoxication, and increases in overdose severity affect the respiratory status of the

Table 5 Logistic regression analysis of important outcomes (death, arrest, and intubation)

Dependent variable	Independent variable	OR (95 % CI)	Model significancy and Nagelkerke R-square
Death ($n = 8$)	Length of ICU admission	1.36 (1.14–1.61)	<0.001, 0.504
Respiratory arrest ($n = 44$)	QTc interval in presenting ECG	1.02 (1.01–1.03)[a]	<0.001, 0.205
	Hours from ingestion	1.11 (1.01–1.22)[a]	
Intubation ($n = 53$)	QTc interval in presenting ECG	1.03 (1.02–1.04)	<0.001, 0.312

[a] Adjusted for intoxication dosage

n number

patient during the admission period. Another hypothesis, however, could be the sequential order of cardiac arrest due to TdPs and the following respiratory arrest which, without intense monitoring, could be indistinguishable from a primary respiratory arrest since TdPs are mostly self-limited. Our study had not been designed to test such a cause and effect hypothesis, and the telemetry data were no longer available for review at the end of the study.

There were found two cases with TdP during hospitalization course. However, these episodes did not result in death. It must be noted that this study was not designed to find TdPs, and we may have some other undetected ones as well.

A number of limitations must be noted. First, the convenience sampling method subjects our study to sampling/spectrum bias, since some patients with less severe intoxications and less complicated hospital course might not have been enrolled. This might artificially inflate the ability of QTc to predict adverse events, as presumably well patients, without adverse outcomes, were primarily missed by these methods. The relatively high percentages of morbidity and mortality in this study could also be explained by this method of sampling and also by the fact that our study has been performed in a large tertiary center which has a naturally higher number of severe intoxications. Second, performing a dipstick test for methadone has its own limitations. The test may only show exposure to this agent in recent days but not serum methadone levels. In addition, false-positive and false-negative results are not uncommon. Third, using the Bazett formula for heart rates more than 100 bpm tends to overcorrect QTc, but since our target was to document QTc at triage, we could not wait for higher rates to be changed over time. In addition, the physicians evaluating ECGs were obligated to evaluate the

Table 6 Diagnostic accuracy of QTc interval for death, intubation, and respiratory arrest

Cut off	Sensitivity	Specificity	PPV	NPV	PLR	NLR	Accuracy	OR
Death								
QTc interval > 470	87.5 (47.3–99.7)	74.3 (66.4–81.2)	15.9 (6.6–30.1)	99.1 (95–99.9)	3.40 (1.4–5.3)	0.17 (.004–0.79)	75	19.5 (2.3–164)
Intubation								
QTc interval > 447.5	86.8 (74.7–94.5)	67.7 (57.6–76.7)	59 (47.2–70)	90.5 (81.5–96.1)	2.67 (1.8–4.1)	0.2 (0.07–0.4)	74.3	13.8 (5.6–33.8)
Respiratory arrest								
QTc interval > 450.5	77.3 (62.2–88.5)	63 (53–72.1)	46 (34.3–57.9)	87.2 (77.7–93.7)	2.1 (1.3–3.2)	0.36 (0.16–0.71)	67.1	5.8 (2.6–12.9)

All values in parenthesis are 95 % CI

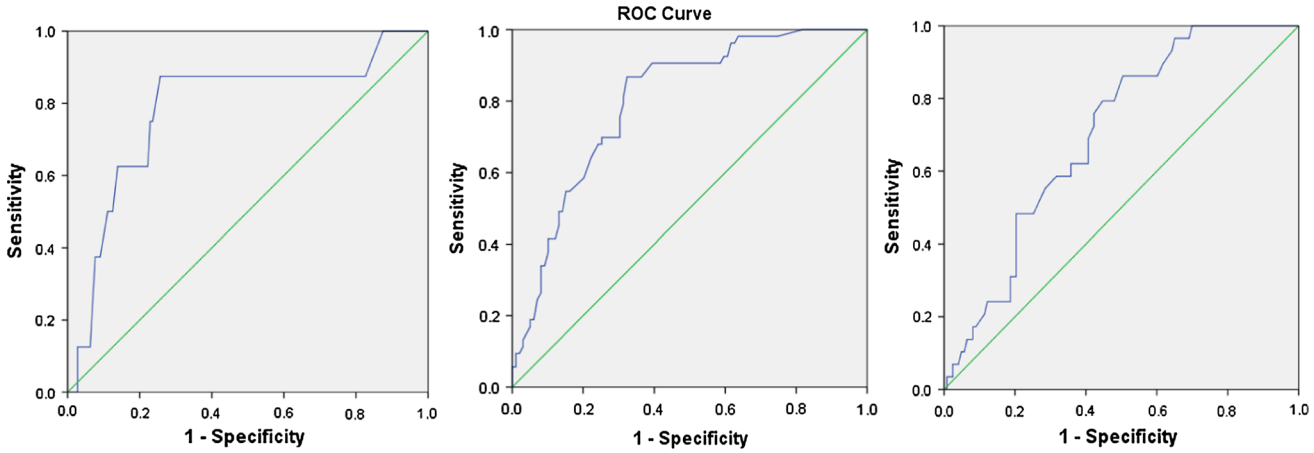

Fig. 2 ROC curve to predict death (*left*), intubation (*middle*), and respiratory arrest (*right*)

leads with more clear T wave morphologies in few cases with abnormal T waves and T–U wave fusions, which may potentially miss the longest QTc interval in 12 leads. Lastly, the number of outcome events (especially death) may not be enough to be included in a logistic regression model and results regarding this point should be interpreted with caution.

Our ROC curves are derived from the univariate analyses. Generally, this is not a confirmatory study in this field because there is no similar publication previously performed. It is an exploratory study, and we have tried to produce some hypotheses for future studies. We are not able to recommend clinicians to implement our results in this step. Further confirmatory studies are needed in this field for being more confident to use these findings in clinical setting. Until such data being provided, our information can be used only as supplementary and auxiliary tool in clinical setting.

Our study presents a different aspect of QTc prolongation, which is the correlation between QTc in triage ECG and some adverse outcomes apparently related to intoxication severity. This may apply to other intoxications as well. A larger study is needed to clarify the association of QTc and mortality.

Conflict of interest None.

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