

Association of QTc Dispersion with Mortality, Intensive Care Unit Admission, Intubation, and Hospital Stay Duration in Acute Methadone Poisoning

Akut Metadon Zehirlenmesinde QTc Dispersiyonunun Mortalite, Yoğun Bakım Ünitesi Kabulü, Entübasyon ve Hastanede Kalış Süresi ile İlişkisi

ABSTRACT

Objective: The objective of this study is to investigate the prognostic significance of QTc dispersion (QTcd) in patients with acute methadone poisoning and its association with critical clinical outcomes, including mortality, Intensive Care Unit (ICU) admission, intubation, and hospital stay duration.

Method: A retrospective cross-sectional analysis was performed using medical records from 311 individuals who presented with acute methadone toxicity to the emergency department of Loghman-Hakim Hospital Poison Center, Tehran, Iran between March 20, 2023 and June 1, 2023. Eligibility was based on a confirmed record of methadone ingestion supported by a positive urine drug screen. To calculate QTcd, the longest and shortest corrected QT (QTc) intervals recorded across the 12-lead electrocardiogram (ECG) were identified, and their difference was taken. The final study population included 100 patients, categorized into prolonged QTcd (QTcd > 60 ms, n = 50) and non-prolonged QTcd (QTcd ≤ 60 ms, n = 50) groups.

Results: This retrospective study included 100 consecutive patients with acute methadone poisoning. The mean QTcd was 64.26 ± 24.55 ms, significantly higher than in the normal population (P < 0.001). Comparison of the two groups revealed no meaningful variation in demographic factors, methadone intake, or time elapsed before Emergency Department (ED) admission (all P > 0.05). Pulse rate was notably higher among individuals with prolonged QTcd (P = 0.03), but there were no significant differences in other vital signs. Hospital stay duration, ICU admission (n = 8), need for intubation (n = 6), and mortality (n = 4) were comparable across both groups.

Conclusion: This study indicates that QTcd did not predict major clinical outcomes such as mortality, ICU admission, or intubation.

Keywords: Methadone, outcome, poisoning, prognosis, QT dispersion, QT interval, QTc dispersion

ÖZET

Amaç: Bu çalışmanın amacı, akut metadon zehirlenmesi olan hastalarda QTc dispersiyonunun (QTcd) prognostik önemini ve mortalite, Yoğun Bakım Ünitesi (YBÜ) kabulü, entübasyon ve hastanede kalış süresi gibi kritik klinik sonuçlarla ilişkisini araştırmaktır.

Yöntem: 20 Mart 2023 ile 1 Haziran 2023 tarihleri arasında [gizlilik nedeniyle çıkarıldı] acil servisine akut metadon toksisitesi ile başvuran 311 kişinin tıbbi kayıtları kullanılarak retrospektif, kesitsel bir analiz gerçekleştirildi. Dahil edilme kriteri, pozitif idrar uyuşturucu taraması ile doğrulanan metadon alımının kayıtlarda bulunmasıydı. QTcd hesaplamak için 12 derivasyonlu elektrokardiyogramda (EKG) kaydedilen en uzun ve en kısa düzeltilmiş QT (QTc) aralıkları belirlenerek aralarındaki fark alındı. Nihai çalışma popülasyonu, QTcd uzamış (QTcd > 60 ms, n = 50) ve QTcd uzamamış (QTcd ≤ 60 ms, n = 50) olarak sınıflandırılan toplam 100 hastadan oluştu.

Bulgular: Bu retrospektif çalışma, akut metadon zehirlenmesi olan ardışık 100 hastayı içermektedir. Ortalama QTcd 64,26 ± 24,55 ms olup normal popülasyona kıyasla anlamlı derecede yüksekti (P < 0.001). İki grup karşılaştırıldığında demografik faktörler, metadon alımı veya acil servise başvuruya kadar geçen süre açısından anlamlı farklılık görülmedi (tüm P > 0.05). Nabız hızı, QTcd uzamış hastalarda belirgin şekilde daha yüksekti (P = 0.03), ancak diğer yaşamsal bulgularda anlamlı fark bulunmadı. Hastanede kalış süresi, YBÜ'ye kabul (n = 8), entübasyon gereksinimi (n = 6) ve mortalite (n = 4) her iki grupta da benzerdi.

ORIGINAL ARTICLE KLİNİK ÇALIŞMA

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Sonuç: Bu çalışma, QTcd'nin mortalite, YBÜ'ye kabul veya entübasyon gibi önemli klinik sonuçları öngörmediğini göstermektedir.

Anahtar Kelimeler: Metadon, sonuç, zehirlenme, prognoz, QT dispersiyonu, QT aralığı, QTc dispersiyonu

Methadone, a synthetic opioid with an extended duration of action, is commonly prescribed for managing chronic pain and assisting in the treatment of opioid addiction.¹ Despite its therapeutic benefits, methadone may contribute to considerable cardiac disturbances, particularly corrected QT interval (QTc) prolongation, predisposing patients to torsades de pointes (TdP), a fatal arrhythmia.^{2,3} Acute methadone overdose, whether intentional or accidental, is a significant public health concern in Iran due to the widespread availability of methadone through methadone maintenance therapy (MMT) clinics. The high prevalence of opioid addiction has led to increased access to methadone, contributing to the risk of overdose.^{2,4} While QTc prolongation has been extensively studied in opioid maintenance therapy, the role of QTc dispersion (QTcd) as a prognostic indicator in cases of acute methadone overdose remains less explored.^{5,6}

QTcd quantifies how unevenly the ventricular muscle returns to its resting state after activation.^{1,7} While the normal range of QTcd remains controversial across studies, most reports suggest a range between 30 and 60 milliseconds (ms).^{1,8,9} Increased QTcd has been linked to heightened arrhythmic risk and adverse cardiac events in various clinical conditions, including cardiotoxic drug poisoning.^{1,5,8,9} Although numerous studies have demonstrated QTcd prolongation in patients undergoing long-term methadone therapy, data on the impact of acute methadone overdose on QTcd remain limited.^{1,6,10}

Excessive opioid ingestion can lead to severe cardiac and systemic complications. Methadone toxicity often necessitates admission to the intensive care unit (ICU), respiratory support via mechanical ventilation, and extended hospitalization.^{3,11} However, the relationship between QTcd and critical outcomes such as mortality, ICU admission, intubation, and length of hospital stay remains unclear. Understanding this association could aid in identifying high-risk individuals and support appropriate clinical actions.

In this retrospective cross-sectional study, we aim to investigate the prognostic significance of QTcd in patients with acute methadone poisoning. By examining its association with mortality, ICU admission, intubation, and hospital stay duration, this study aims to assess the potential of QTcd as an independent prognostic marker for unfavorable clinical events in patients with acute methadone toxicity.

Materials and Methods

Investigative Approach and Patient Enrollment

This study was conducted using a retrospective cross-sectional design. We reviewed the medical records of patients presenting with acute methadone overdose to the emergency department of Loghman-Hakim Hospital Poison Center, Tehran, Iran, one of

ABBREVIATIONS

ACVE	Adverse cardiovascular events
AUC	Area under the curve
ECG	Electrocardiogram
ED	Emergency Department
hERG	Human ether-a-go-go-related gene
ICU	Intensive Care Unit
IQR	Interquartile range
MMT	Methadone maintenance therapy
QTc	Corrected QT
QTcd	QTc dispersion
ROC	Receiver operating characteristic
TdP	Torsades de pointes
TPe	Tpeak-Tend

the busiest poison control centers in the world, between March 20, 2023 and June 1, 2023. Patients were enrolled if they had a history of methadone consumption, either self-reported in conscious individuals or provided by relatives for unconscious patients. Acute methadone overdose was defined as methadone ingestion in non-users or consumption exceeding the usual dose in regular users, leading to a clinical condition that prompted them or their companions to seek medical assistance. Patients who tested negative for methadone in urine analysis or lacked a documented urine toxicology screen were excluded from the study. Other exclusion criteria included age less than 15 or greater than 65 years, incomplete medical records, co-ingestion of medications or substances known to prolong the QTc interval or alter clinical outcomes, electrolyte imbalances (hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia), and preexisting comorbidities. This study was conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent for the use of patient data was obtained from all patients upon hospital admission. The study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (Approval Number: IR.SBMU.RETECH.REC.1404.092, Date: 27.04.2025).

Sample Size Calculation

A priori sample size estimation was performed using the following standard formula for comparison of two independent means:

$$N_{\text{per group}} = \frac{2(Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma^2}{\Delta^2}$$

where $Z_{1-\alpha/2}$ represents the two-sided significance level (α), $Z_{1-\beta}$ corresponds to the desired power ($1-\beta$), σ is the standard deviation of QTc dispersion (in ms), and Δ is the minimal clinically important difference between groups (in ms). Substituting these values into the formula yielded an estimated sample size of 63 patients per group (a total of 126 participants). However, due to institutional limitations on data access, electrocardiographic data were available only for 100 eligible patients.

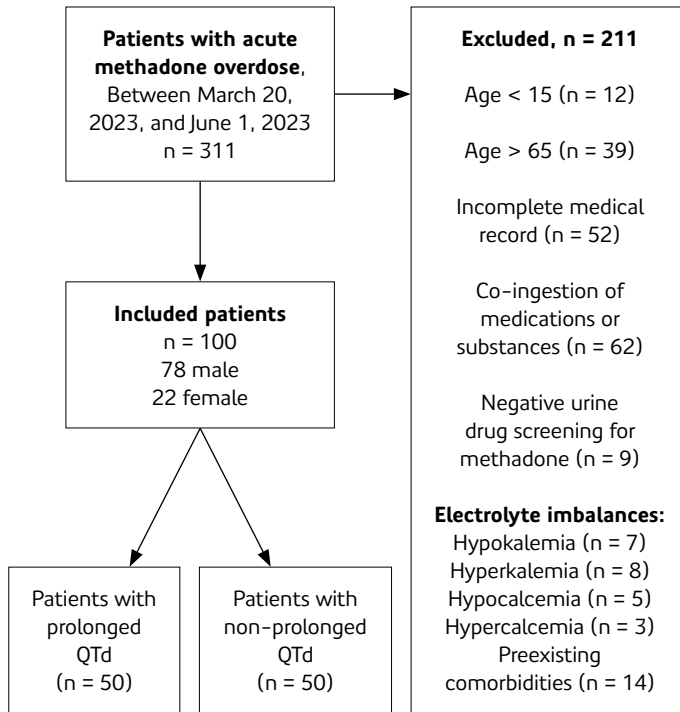


Figure 1. Flowchart of patient selection and inclusion process.

Data Collection

Demographic variables such as age, sex, history of substance use, ingested methadone dose, and the interval between methadone intake and emergency department presentation were collected from patient records by a primary researcher and independently verified by a second researcher. Additionally, vital signs on Emergency Department (ED) admission and primary outcomes were documented, including tracheal intubation, ICU admission, hospitalization duration, and in-hospital mortality.

Electrocardiogram (ECG) Analysis

A researcher, blinded to patient outcomes and clinical characteristics, analyzed the initial ECGs performed in the ED. An attending cardiologist subsequently rechecked each ECG. QT intervals were assessed in all 12 leads from the start of the QRS complex to the termination of the T wave. In the presence of a U wave, the QT measurement was taken to the lowest point between the T and U waves. To account for heart rate variability, the QT interval was adjusted using Bazett's equation, where QTc is obtained by dividing the observed QT duration by the square root of the RR interval ($QTc = QT / \sqrt{RR}$). QTcd was assessed by subtracting the minimum from the maximum QTc interval across all 12 ECG leads, with prolongation defined as a QTcd exceeding 60 ms.^{1,12} Patients were then categorized into prolonged and non-prolonged QTcd groups, and all extracted data were compared between the two groups.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) software, version 27 (IBM Corp., Chicago, IL, USA) was used for statistical analysis. Continuous variables with a normal distribution (determined by Kolmogorov-Smirnov and Shapiro-Wilk tests) are presented as mean $\pm$ SD, and those with a non-normal distribution

are presented as median and interquartile range (IQR). Comparisons between groups were conducted using the independent t-test for normally distributed variables, and the Mann-Whitney U test for non-normally distributed variables. The Chi-square test or Fisher's exact test was applied to analyze categorical data. Statistical significance was defined as a P-value < 0.05 . Receiver operating characteristic (ROC) curves were constructed to evaluate the ability of QTcd dispersion to predict ICU admission, intubation, and in-hospital mortality. The area under the curve (AUC), sensitivity, specificity, and optimal cutoff values were determined. To assess the predictive value of QTcd for major clinical outcomes, we categorized patients based on the occurrence or non-occurrence of each outcome, including death, intubation, and ICU admission. For each outcome, QTcd and other covariates were included in the univariate analysis. In cases where QTcd yielded a p-value under 0.2, QTcd and all other covariates meeting the same threshold underwent multivariate logistic regression to identify those with independent predictive significance. Given the small number of outcome events, Firth's penalized logistic regression was used to reduce small-sample bias.

Results

A total of 311 patients presented to Loghman-Hakim Hospital Poisoning Center with acute methadone overdose between March 20, 2023 and June 1, 2023. Of these, 211 were excluded based on the defined exclusion criteria. The final study population included 100 patients (Figure 1), categorized into two groups: those with QTcd > 60 ms (prolonged QTcd group, $n = 50$) and those with QTcd ≤ 60 ms (non-prolonged QTcd group, $n = 50$). The cohort had a mean age of 34.83 ± 14.16 years, and 78% of participants were male. The baseline characteristics of the patients are presented in Table 1.

The mean QTcd was 64.26 ± 24.55 ms, which was significantly higher than the mean in the normal population (33.4 ± 20.3 ms, $P < 0.001$). There was no significant difference in age ($P = 0.09$) or gender distribution ($P = 0.81$) between the prolonged and non-prolonged QTcd groups. No patients developed TdP during hospitalization. The mean time from methadone consumption to ED admission was 8.45 ± 8.34 hours, and the mean methadone dose was 240.21 ± 296.19 mg, with no significant intergroup differences ($P = 0.72$ and $P = 0.11$, respectively).

On admission to the ED, systolic and diastolic blood pressures, respiratory rates, and oxygen saturation levels were similar between the two groups, with no significant differences detected (all $P > 0.05$). However, the prolonged QTcd group had a significantly higher pulse rate than the non-prolonged QTcd group ($P = 0.03$). Hospitalization duration ranged from 1 to 48 days, without significant differences between groups ($P = 0.83$). There were four deaths, six patients who were intubated during the hospitalization period, and eight patients who required ICU admission. These outcomes did not differ significantly between the two groups (Table 1).

In the univariate analysis, QTcd had a p-value < 0.2 for intubation and ICU admission. Therefore, QTcd and all other covariates with a p-value < 0.2 were included in the multivariate analysis to identify independent predictors of these outcomes. However, the multivariate analysis revealed no significant associations between the covariates and intubation or ICU admission (all $P >$

Table 1. Baseline characteristics, vital signs, electrocardiogram parameters, and clinical outcomes of the patients

Variables	Prolonged QTcd group (n = 50)	Non-prolonged QTcd group (n = 50)	P
Age, mean (SD) (years)	37.38 (14.78)	32.28 (13.18)	0.09
Gender, n (%)			0.81
Male	40 (80)	38 (76)	
Female	10 (20)	12 (24)	
Addiction history, n (%)			0.37
Yes	26 (52)	19 (38)	
No	12 (24)	16 (32)	
Unknown	12 (24)	15 (30)	
Methadone dose, mean (SD) (mg)	245.13 (204.89)	234.55 (378.56)	0.11
Time from methadone consumption to ED, mean (SD) (hours)	7.90 (6.82)	9.03 (9.74)	0.72
Vital signs at admission			
Systolic blood pressure, median (IQR) (mmHg)	115 (24)	110 (20)	0.79
Diastolic blood pressure, median (IQR) (mmHg)	75 (10)	70 (19)	0.87
Pulse rate, median (IQR) (beats/min)	90 (17)	85 (18)	0.03
Respiratory rate, median (IQR) (breaths/min)	16 (4)	16 (4)	0.81
O ₂ saturation, median (IQR) (%)	96 (4)	96 (7)	0.70
ECG parameters			
QTc interval minimum, mean (SD) (ms)	371.32 (27.84)	376.21 (30.35)	0.50
QTc interval maximum, mean (SD) (ms)	454.08 (31.18)	421.99 (32.32)	<0.001
QTcd, mean (SD) (ms)	82.75 (20.61)	45.78 (9.77)	<0.001
Clinical outcomes			
Patients intubated, n (%)	3 (6)	5 (10)	0.71
Patients transferred to ICU, n (%)	1 (2)	5 (10)	0.20
Hospitalization period, median (IQR) (days)	1 (1)	1 (1)	0.83
Death, n (%)	3 (6)	1 (2)	0.61

ECG, Electrocardiogram; IQR, Interquartile range; mg, Milligram; min, Minutes; mmHg, Millimeter Hg; ms, Milliseconds; n, Number; ED, Emergency department; ICU, Intensive care unit; SD, Standard deviation.

Table 2. Association between intubation and Intensive Care Unit admission with clinical features

Dependent variable	Independent variable	OR (95% CI)	P
Intubation	Methadone dose	1.00 (0.99–1.00)	0.97
	O ₂ saturation	0.97 (0.70–1.33)	0.85
	Hospitalization period	0.56 (0.18–1.73)	0.31
	QTcd	0.95 (0.89–1.01)	0.14
ICU admission	O ₂ saturation	1.00 (0.99–1.00)	0.98
	Hospitalization period	1.00 (0.99–1.00)	0.98
	QTcd	1.00 (0.99–1.00)	0.97

ICU, Intensive care unit; CI, Confidence interval; OR, Odds ratio.

0.05). The odds ratios (OR) and 95% confidence intervals (CI) for each variable are presented in Table 2.

To minimize potential bias related to the small number of adverse outcomes, Firth's penalized logistic regression was applied. Separate models were constructed for in-hospital mortality, need for intubation, and ICU admission, including methadone

dose, oxygen saturation on admission, hospitalization period, and QTcd as covariates. None of the variables showed a statistically significant independent association with any of the three outcomes after adjustment (Table 3).

ROC curve analysis demonstrated that QTc dispersion had good discriminative ability for ICU admission (AUC = 0.809; optimal cutoff = 43.6 ms; sensitivity = 85.1%; specificity = 66.7%) but lower performance for intubation (AUC = 0.651) and mortality (AUC = 0.573). The derived cutoff values and diagnostic indices are summarized in Table 4 and Figure 2.

Discussion

This study sought to assess the prognostic significance of QTcd in acute methadone toxicity by investigating its association with major clinical outcomes, including mortality, ICU admission, intubation, and length of hospital stay. Our findings indicate that although patients with acute methadone poisoning had significantly increased QTcd compared to the normal population, there was no significant correlation between QTcd and adverse clinical outcomes. Although QTc dispersion was our primary parameter, we acknowledge that additional electrocardiographic

Table 3. Firth's penalized logistic regression results for predictors of in-hospital mortality, intubation, and Intensive ICU admission

Dependent variable	Independent variable	OR (95% CI)	p
Intubation	Methadone dose	0.99 (0.99–1.00)	0.35
	O ₂ saturation	1.08 (0.87–1.35)	0.44
	Hospitalization period	0.90 (0.33–2.49)	0.85
	QTcd	0.98 (0.87–1.10)	0.75
ICU admission	Methadone dose	0.99 (0.99–1.00)	0.35
	O ₂ saturation	1.08 (0.87–1.35)	0.44
	Hospitalization period	0.90 (0.33–2.49)	0.85
	QTcd	0.98 (0.87–1.10)	0.75
Mortality	Methadone dose	0.99 (0.99–1.00)	0.35
	O ₂ saturation	1.08 (0.87–1.35)	0.44
	Hospitalization period	0.90 (0.33–2.49)	0.85
	QTcd	0.98 (0.87–1.10)	0.75

ICU, Intensive care unit; QTcd, QTc dispersion; OR, Odds ratios; CI, Confidence intervals.

indices such as Tpeak–Tend (TPe) could provide complementary insights into ventricular repolarization heterogeneity.¹³ This study adds to current knowledge on methadone-induced cardiac repolarization changes and their prognostic implications in toxicological emergencies.

Previous studies have consistently shown an association between QT interval prolongation and methadone use. While Krantz et al.¹ found that methadone maintenance therapy is significantly associated with QTc interval prolongation, a study in Japan¹³ reported that QTc increased insignificantly in cancer patients receiving small to modest doses of methadone. However, their study focused on chronic methadone users rather than acute poisoning cases. In contrast, our study specifically examined acute methadone overdose. Manini et al.¹⁴ demonstrated that a prolonged QTc in poisoned patients is a predictor of adverse cardiovascular events, including myocardial injury, dysrhythmias,

Table 4. ROC analysis for corrected QTcd predicting clinical outcomes

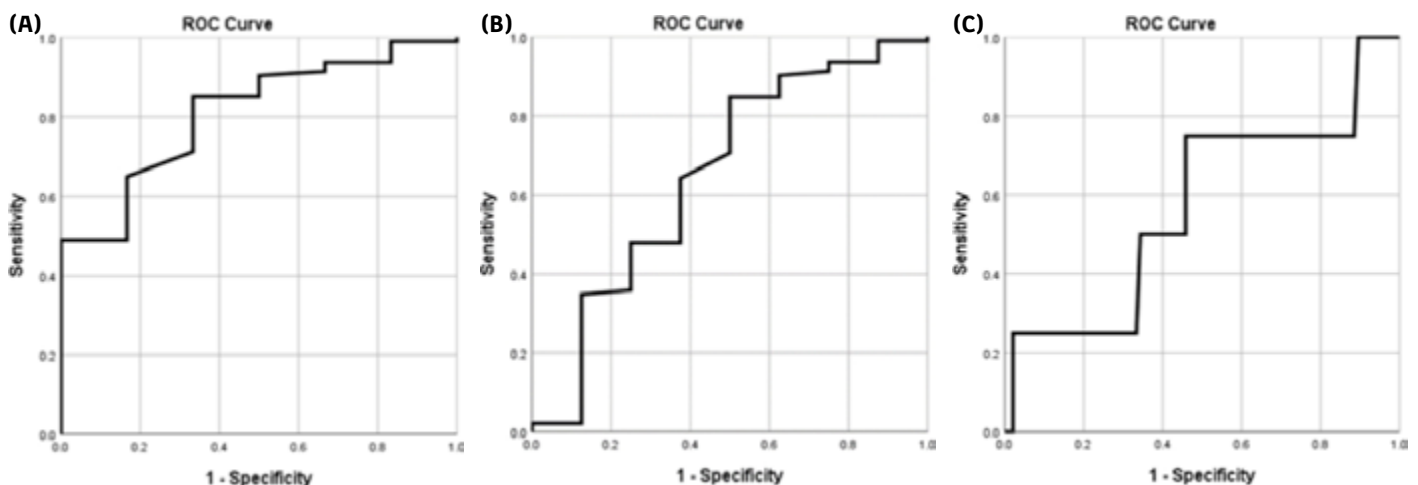
Outcome	AUC	Cut-off (ms)	Sensitivity (%)	Specificity (%)
Intubation	0.651	43.6	84.8	50.0
ICU admission	0.809	43.6	85.1	66.7
Mortality	0.573	62.6	75.0	54.2

ROC, Receiver operating characteristic; QTcd, QT interval dispersion; ICU, Intensive care unit; AUC, Area under the curve.

and cardiac arrest. Farsi et al.³ investigated the association between prolonged QTc and adverse outcomes of methadone overdose, such as death, endotracheal intubation, and respiratory arrest, identifying QTc as a strong predictor of intubation and respiratory arrest. In our study, we examined the association between QTcd and adverse outcomes in cases of acute methadone overdose.

Both increased QTcd and QTc intervals have been reported in association with methadone use.^{1,5} QTcd prolongation has been observed in both acute and chronic methadone exposure.^{1,5} Dorooshi et al.¹⁵ found that QTcd measured at admission did not differ significantly between patients based on long-term methadone use; however, it increased significantly in chronic users 24 hours after hospitalization. QTcd is a non-invasive indicator of myocardial repolarization heterogeneity and can predict the risk of arrhythmia.⁸ In our study, the mean QTc dispersion among methadone-poisoned patients (64.26 ± 24.55 ms) was significantly greater than that reported in the general population (33.4 ± 20.3 ms),^{16,17} supporting the notion that methadone significantly affects ventricular repolarization.

Methadone-induced QT prolongation and abnormal ventricular repolarization primarily result from its inhibitory effects on the human ether-a-go-go-related gene (hERG) potassium channels, which are crucial for the rapid phase of the delayed rectifier potassium current (IKr). By blocking these channels, methadone delays phase 3 of the cardiac action potential, resulting in delayed repolarization and a heightened risk of arrhythmias such as TdP.^{18,19}

**Figure 2. Receiver operating characteristic (ROC) curve for corrected QT interval dispersion (QTcd) to predict intubation (A), Intensive Care Unit (ICU) admission (B), and death (C).**

Methadone's effect on cardiac repolarization has been well established in chronic opioid users, emphasizing the arrhythmogenic risks associated with prolonged QT intervals.^{20,21} However, in our study of acute methadone poisoning, no cases of TdP were observed despite significant QTcd prolongation. This finding aligns with Soroosh et al.,² who observed no cases of TdP in acute methadone overdose, potentially due to the transient nature of repolarization abnormalities in acute settings compared to chronic exposure.

Risk assessment in poisoned patients is both challenging and essential for reducing mortality while optimizing hospital resource allocation.^{5,14} The prognostic role of QTcd in methadone poisoning has been investigated alongside other cardiotoxic agents, such as tricyclic antidepressants, antipsychotics, benzodiazepines, and various toxins.^{5,14} However, our study is novel in its specific focus on methadone. In these toxicities, increased QTcd has been associated with heightened arrhythmic risk and poor clinical outcomes. Consistent with our findings, Hassanian-Moghaddam et al.⁵ demonstrated that QTcd does not appear to be a reliable predictor of death in cases of acute cardiotoxic poisoning. However, they identified an association between QTcd prolongation and the subsequent development of complications, including refractory hypotension and right bundle branch block. Manini et al.¹⁴ showed that QTcd was significantly higher in poisoned patients who experienced at least one adverse cardiovascular event compared to the control group. Nevertheless, QTcd was not identified as an independent predictor of such events. Despite these associations, QTcd remains an inconsistent predictor of adverse outcomes across different toxicological settings. Our findings reinforce this uncertainty, as QTcd in methadone-poisoned patients did not correlate with mortality or ICU admission. Further research is needed to establish standardized QTcd thresholds and validate its utility as a prognostic marker in acute methadone poisoning.

Recent evidence has expanded the understanding of electrocardiographic predictors in acute cardiotoxicities. Lashin et al.²² developed a six-predictor nomogram to estimate the risk of adverse cardiovascular events (ACVE) among patients poisoned with various cardiotoxic agents. Their model incorporated three ECG parameters, including ST-segment changes, prolonged QTc interval, and widened QRS complex, alongside clinical and biochemical variables, achieving 89.2% predictive accuracy for ACVE. Interestingly, despite evaluating several ECG indices, they reported no significant association between ACVE and other ECG abnormalities, such as QT dispersion. Similarly, El-Sarnagawy et al.²³ found that both QTd and QTdc failed to correlate with in-hospital mortality, ICU admission, or ACVE components. Their ROC analysis confirmed the superiority of QTc over QTd for outcome prediction, although the discriminatory power remained limited. Consistent with these findings, our results revealed no independent association between QTc dispersion and major clinical outcomes in acute methadone toxicity. Taken together, these studies suggest that dispersion-based indices may have limited prognostic reliability in acute poisoning, whereas QTc-related measures, especially when combined with clinical and biochemical parameters, may better reflect true cardiac risk.

In our study, a significantly elevated heart rate was observed in the prolonged QTcd group relative to the non-prolonged group,

consistent with existing literature on the interplay between heart rate and ventricular repolarization variability.¹⁶ However, as numerous studies have indicated, the exact relationship between heart rate and QTcd remains unresolved.^{24,25} While heart rate correction formulas such as Bazett's attempt to standardize QT interval measurements, they may introduce inconsistencies when applied to QTc dispersion.^{26,27} In our study, the observed increase in heart rate among patients with prolonged QTcd may reflect underlying autonomic dysregulation or compensatory mechanisms related to methadone toxicity rather than a direct causal relationship between heart rate and QTcd. Future investigations should further explore the role of autonomic function and its impact on QTcd to enhance the clinical utility of this parameter in risk stratification.

In addition, we performed ROC analyses to evaluate the discriminative ability of QTc dispersion for predicting major in-hospital outcomes. The ROC curves demonstrated good discriminative performance for ICU admission (AUC = 0.809), but only modest accuracy for intubation (AUC = 0.651) and poor accuracy for mortality (AUC = 0.573). These findings suggest that, while QTc dispersion may reflect subclinical myocardial repolarization abnormalities that could identify patients at higher risk for intensive care needs, it lacks sufficient discriminatory power to serve as a stand-alone prognostic tool for severe outcomes such as death.

Limitations

It is important to recognize the limitations of this study, particularly the potential for selection bias due to its retrospective design. Since the results are based on hospital-registered files, the accuracy and reliability of the collected data may require careful consideration and review. Additionally, while we used a strict QTcd cutoff (> 60 ms) to define prolongation, other studies have used varying thresholds, which could contribute to differences in reported associations with clinical outcomes. Another limitation was the absence of prior ECGs, which prevented the assessment of QTcd changes from baseline. Furthermore, only baseline ECGs obtained at admission were analyzed, as serial recordings were not consistently available across cases. Another limitation of our study was the unavailability of TPe interval measurements, which have been proposed as additional markers of repolarization heterogeneity. Unfortunately, TPe data were not consistently available in our dataset and therefore could not be analyzed. Some potential prognostic variables, including electrolyte imbalances and concurrent QT-prolonging medications, were unavailable for all patients and therefore not included in regression models. Larger-scale prospective studies are required to clarify the prognostic value of QTcd in methadone overdose.

Conclusion

Our study demonstrates that acute methadone overdose is associated with significantly increased QTcd. However, QTcd did not predict major clinical outcomes such as mortality, ICU admission, or intubation. These findings suggest that although methadone toxicity affects ventricular repolarization, the prognostic utility of QTcd in acute methadone poisoning remains uncertain. Further research is needed to elucidate the clinical relevance of QTcd and its role in risk stratification for patients with acute opioid toxicity.

Ethics Committee Approval: Ethics committee approval was obtained from Ethics Committee of Shahid Beheshti University of Medical Sciences (Approval Number: IR.SBMU.RETECH.REC.1404.092, Date: 27.04.2025).

Informed Consent: Written informed consent for the use of patient data was obtained from all patients upon hospital admission.

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