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ORIGINAL RESEARCH

Troponin, A Predictor of Mortality in Methadone Exposure: An Observational Prospective Study

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BACKGROUND: Methadone poisoning/overdose is a global public health problem. We aimed to determine whether methadone poisoning increased cardiac troponin and whether high-sensitivity cardiac troponin I (hs-cTnI) levels predicted the need for intensive care unit admission, intubation, and mortality.

METHODS AND RESULTS: This observational, prospective single-center study was done at Loghman-Hakim Hospital (Tehran, Iran) from June 2018 until February 2019. Patients aged >14 years admitted with a diagnosis of methadone exposure were included. Patients were excluded if they had coexisting conditions associated with elevated hs-cTnI levels. An ECG and hs-cTnI levels were obtained on emergency department presentation. Patients were followed up on their need for intubation, intensive care unit admission, and in-hospital mortality. Of 245 included patients (186 [75.9%] men; median age, 33 years), most referred to loss of consciousness (210 cases, 89%). Nineteen (7.7%) patients had hs-cTnI levels of >0.1 ng/mL (positive), and 41 (16.7%) had borderline levels of 0.019 to 0.1 ng/mL. Twenty-three (9.3%) cases were admitted to the intensive care unit, 21 (8.5%) needed intubation, and 5 (2%) died during hospitalization. An hs-cTnI cutoff value of 0.019 ng/mL independently predicted mortality. For optimal concomitant sensitivity and specificity, receiver operating characteristic curve analysis was conducted and showed that hs-cTnI had an independent significant association with mortality, with a cutoff value of 0.0365 ng/mL (odds ratio, 38.1; 95% CI, 2.3–641.9; $P<0.001$).

CONCLUSIONS: Methadone exposure/toxicity is a newly identified cause of elevated hs-cTnI. Values >0.019 ng/mL, and particularly >0.0365 ng/mL, of hs-cTnI predicted mortality in our sample. Future studies should measure troponin levels in methadone maintenance treatment clients to assess the risk of myocardial injury from long-term exposure.

Key Words: cardiology ■ drug-related deaths ■ opioid ■ overdose ■ prognosis

Methadone is a synthetic opioid agonist used for pain management and as a medication for opioid-use disorder.[1] However, because of its agonist properties, it has the potential for abuse and intoxication.[2] Over the past decade, deaths caused by methadone overdose have significantly increased in Iran and internationally, including in the United States.[3–5]

Importance

Age is considered a major risk factor for methadone-specific deaths,[6,7] and respiratory depression has long been considered the primary mechanism of action.[8] However, more recent data point to the importance of the cardiotoxicity of methadone, especially its effect on QT-interval prolongation and risk of torsades de pointes arrhythmia, which can lead to sudden death.[9,10]

Manini et al showed that the initial cardiac troponin I results were highly associated with drug overdose mortality in a cohort of patients in the emergency department with a drug overdose.[11] Considering 90% specificity and 99% negative predictive value, the mean initial cardiac troponin I results were significantly

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CLINICAL PERSPECTIVE

What Is New?

- Methadone exposure is a newly identified cause of elevated troponin that may predict mortality.
- Values >0.019 ng/mL, and particularly >0.0365 ng/mL, of high-sensitivity cardiac troponin I are suggested to predict mortality

What Are the Clinical Implications?

- In patients with high levels of high-sensitivity troponin of unknown origin, methadone exposure should be considered if the clinical setting is not compatible with myocardial infarction caused by coronary artery disease.
- Practitioners should pay particular attention to patients with methadone poisoning with high high-sensitivity troponin levels, avoid early discharge, and admit these patients in units with close monitoring and supervision.

associated with mortality (1.2 versus 0.06 ng/mL). During our routine practice, we encountered patients with methadone poisoning who had elevated high-sensitivity cardiac troponin I (hs-cTnI) levels without any evidence of myocardial infarction or ischemia on their ECGs. As previously described, hs-cTnI represents a marker of myocardial injury and predicts mortality in several clinical settings.[12,13] However, limited data on cardiac injury and elevated hs-cTnI from methadone intoxication/exposure have been reported in the literature to date.

Goals of This Investigation

We undertook the current study with 2 aims: (1) to determine if methadone poisoning/exposure increases hs-cTnI levels and (2) to assess if hs-cTnI levels predict the need for intubation/intensive care unit (ICU) admission and mortality in patients with methadone poisoning.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

The study was an observational, prospective single-center study of patients presenting to our toxicology emergency department at Loghman-Hakim Hospital (Tehran, Iran) during the study period of June 2018 until February 2019.

Ethics Approval

The study was approved by the research ethics committee of our university (IR.SBMU.RETECH.REC.1398.156). All procedures performed in the study were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All patients provided written informed consent for their data to be included in the study before enrollment. For patients with loss of consciousness, informed consent was obtained from their next of kin. For patients younger than 18 years, the legal age of consent in Iran, written informed consent was obtained from the parents.

Participants

Patients were eligible if they were older than 14 years, presented with a diagnosis of single-substance exposure to methadone confirmed by a urine drug screen and history. Patients were excluded if their urine drug screen was positive for other substances or if they had any medical condition known to be associated with elevated hs-cTnI levels (ie, acute myocardial infarction, rhabdomyolysis, acute decompensated heart failure, renal failure, and sepsis). We also excluded patients with presentation of any of the following: acute chest pain, significant ischemic ST-T change, ejection fraction <45%, or significant regional wall motion abnormality with positive troponin as non–ST-segment–elevation myocardial infarction. Rhabdomyolysis was defined as any on-arrival creatine phosphokinase >1000 U/L.[14,15] Renal failure was defined as glomerular filtration rate <60 mL/min.[16] Corrected QT (QTc) prolongation was defined as a QTc interval of >470 ms for women and 450 ms for men.[17] The Framingham formula was used to correct the QT interval for heart rate extremes.

Procedure

Patients, or in case of loss of consciousness, their relatives, were interviewed by one of the coauthors to collect information on their demographic characteristics, cardiovascular risk factors, and history of cardiovascular or renal disease, and a standardized study instrument was completed. Cardiovascular risk factors were taken for atherosclerotic cardiovascular disease risk evaluation of patients to determine possible candidates for angiography if they had high hs-cTnI.[18] On admission, all patients provided a urine sample for drug screening, an ECG was taken, and hs-cTnI and creatine phosphokinase levels were checked in the emergency department. If the patient had initial high levels of hs-cTnI on admission, a second hs-cTnI measurement and ECG were performed 6 hours after admission to confirm the diagnosis of suspicious myocardial infarction. ECG abnormalities,

including ST-T abnormalities and QT-interval prolongation, were evaluated by a cardiologist (coauthor). Echocardiography was performed for the patients with abnormal ECG and/or high levels of hs-cTnI, considering the 99th percentile as reference value. All hs-cTnI tests were analyzed using bioMerieux VIDAS troponin I ultra-assay. As per instructions of use for the hs-cTnI testing kit, the recommended cutoff for the diagnosis of myocardial infarction has been defined as the 0.019 ng/mL level, corresponding to the 99th percentile of the healthy population. Above this cutoff, any hs-cTnI levels within the range of 0.019 to 0.1 were defined as borderline and values of >0.1 as positive.[19] All patients were followed up for in-hospital mortality, ICU admission, and need for intubation.

Sample Size

Because there was no published study available to determine the prevalence of high hs-cTnI levels in methadone-poisoning cases, we ran a pilot evaluation on our first 30 cases of methadone toxicity through convenience sampling of eligible patients. Six out of these 30 patients (20.0%) had positive troponin (>0.1 ng/mL) in our pilot evaluation. We used the single-population formula $n=z^2\times p\times(1-p)/e^2$ for estimating proportion from the infinite population, with a confidence level of 95% and margin of error of 5%, to determine a target sample size of n=246 methadone-poisoning cases. In consideration of our research strategy, which involved exclusion of patients with other known causes of elevated hs-cTnI levels, we aimed to recruit a higher number of patients (ie, an estimated target sample size of 300 cases).

Measures

We defined our primary outcome as the association between death caused by methadone exposure and hs-cTnI levels. Secondary outcomes were defined as the correlations between intubation, ICU admission, rhabdomyolysis, and prolonged QT interval and cutoffs for elevated hs-cTnI levels, defined as 0.019 ng/mL (ie, 99th percentile reference value, see above) and the new cutoff with optimal sensitivity and specificity, if any.

The frequency of elevated hs-cTnI levels and correlation with in-hospital mortality, ICU admission, need for intubation, and ECG abnormalities were evaluated. Because hs-cTnI levels above 0.019 ng/mL are a possible sign of myocardial injury, a receiver operating characteristic curve analysis was performed to determine the hs-cTnI cutoff value with the highest sensitivity and specificity to predict mortality caused by methadone toxicity compared with the reference value of the 0.019 ng/mL cutoff.

Cases with any other conditions that might cause increased hs-cTnI were excluded from the receiver operating characteristic analysis. The 99th percentile as reference and resulting cutoff values were then used to study the correlation with different outcomes (eg, mortality, ICU admission, intubation, ST abnormality, and QTc prolongation).

Statistical Analysis

A χ^2 test was used to evaluate the association between categorical variables. To compare continuous variables between survivors and nonsurvivors, a Mann-Whitney *U* test was used. Odds ratio (OR) and 95% CI were provided for expressing the strength of associations. For the description of quantitative continuous variables with nonnormal distribution, median and interquartile range were used.

"Enter" logistic model was performed to determine the factors that could independently predict mortality in our series by applying all variables correlated to mortality in a univariate analysis. A *P* value <0.05 was set as the significance level. Statistical Package for Social Sciences version 17.0 (IBM, Armonk, NY, USA) was used for analysis.

RESULTS

Baseline Characteristics of the Study Population

Figure 1 shows the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) diagram of patient recruitment. A total of 54 patients were excluded before the main analysis because they had at least 1 other condition that was considered a probable cause of abnormal hs-cTnI.

Two hundred forty-five patients (186 (75.9%) were men; median age, 33 years) with single-substance exposure to methadone were enrolled in the study. Table 1 shows the patients' demographics and clinical characteristics. Loss of consciousness (210, 89%), vomiting (20, 8.2%), dyspnea (14, 5.7%), dizziness (6, 2.4%), agitation (4, 1.6%), headache (4, 1.6%), tremor, myalgia, hallucination, convulsion, palpitation, and diarrhea (1 each, 0.4%) were presenting clinical manifestations.

Analysis of patients' characteristics and routine laboratory tests shows a significant association between in-hospital mortality and age (*P*=0.014; OR, 1.09; 95% CI, 1.02–1.17) and on-arrival bicarbonate (*P*=0.042; OR, 0.78; 95% CI, 0.61–0.96) (Table 2).

The median age of survivors was 33 years (interquartile range, 24–47; range, 14–78). In total, 19 (7.8%) patients had hs-cTnI levels above 0.1 ng/mL, and 41 (16.7%) had borderline levels of 0.019 to 0.1 ng/mL (Table 2).[19] Five patients (2.0%) died during hospitalization. Twenty-three

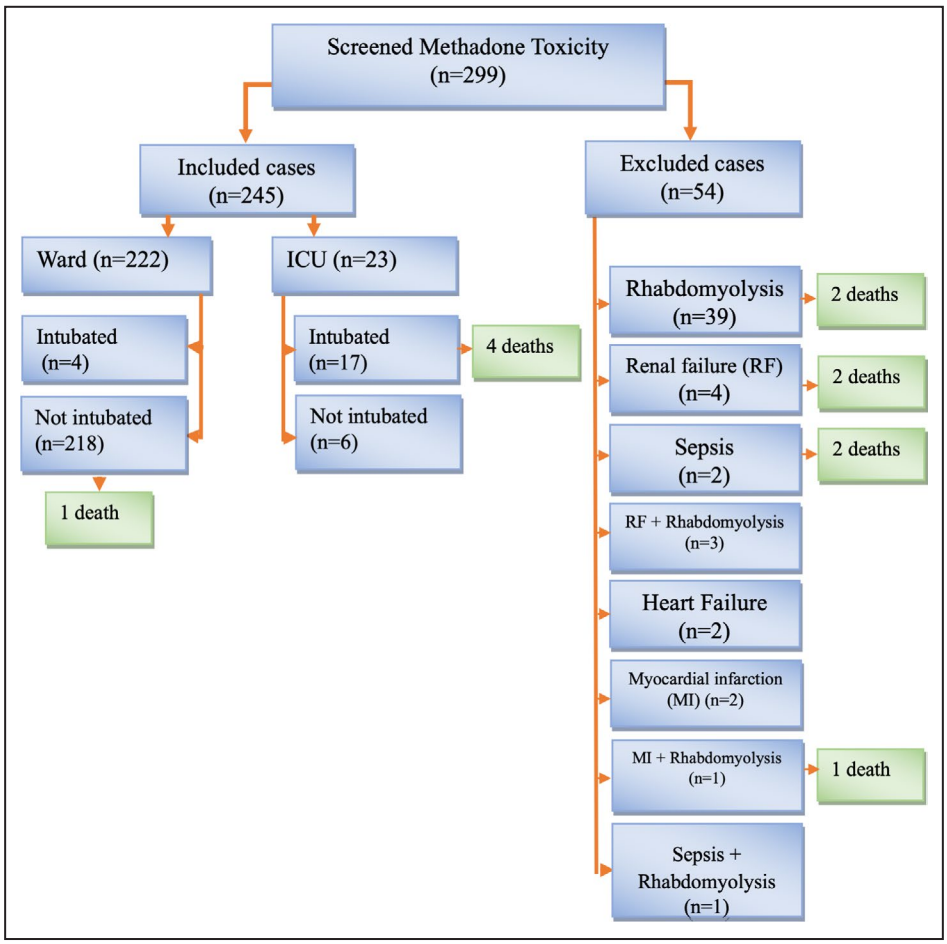

Figure 1. STROBE algorithm (n=299).
ICU indicates intensive care unit; MI, myocardial infarction; and RF, renal failure.

(9.4%) were admitted to the ICU, and 21 (8.6%) needed intubation. Six (2.4%) patients showed prolonged QTc in their ECG, and 1 patient (0.4%) had ST-T wave abnormalities in the ECG (Table 2).

Pooled results of both included and excluded patients showed that in-hospital mortality, ICU admission, need for intubation, QTc prolongation, and rhabdomyolysis were significantly different when 3 standard cutoff values of hs-cTnI were used (Table 2).

The mean ejection fraction was 50%, with normal regional wall motion in all cases.

For the final analysis, we used an hs-cTnI cutoff value of 0.019 ng/mL and determined an hs-cTnI cutoff value of 0.0365 ng/mL using receiver operating characteristic curve analysis to predict mortality in single methadone exposure with the best possible simultaneous sensitivity (80%) and specificity (85.5%) (Table 3 and Figure 2). Sixty (24.5%) and 39 (15.9%) patients had high levels of hs-cTnI, with 0.019 and 0.0365 ng/mL cutoff values, respectively. The hs-cTnI had a significant relationship with mortality with both a 0.0365 ng/mL cutoff (OR, 23.4; 95% CI, 2.5–215.8; P=0.002) and 0.019 ng/mL cutoff (OR, 13.4; 95% CI, 1.4–120.0, P=0.014), although the latter had a lower CI. Admission to the ICU, need for intubation, ST-T abnormalities, and QTc prolongation did not have a significant association with the 0.0365 ng/mL cutoff value (Table 4). The 0.019 ng/mL cutoff was significantly associated with intubation (OR, 2.5; 95% CI, 1.0–6.4; P=0.041). Median [interquartile range] (range) hospital and ICU stay were significantly longer in patients who were deceased (2 [2–3] (1–48) versus 9 days [4–29] (3–47); P=0.001, and 0 (0–44) versus 9 days [3–29] (0–47); P<0.001, respectively). The median [interquartile range] (range) hospital stay was 2 [2–3] (1–16), 2 [2–3] (1–48), and 2 days [2–3] (1–47) in hs-cTnI cutoff <0.019, 0.019–0.1, and >0.1 ng/mL, respectively. It was 6 [4–10] (2–12), 9 [4–13] (4–44), and 9 [5–-] (5–47) in hs-cTnI cutoff <0.019, 0.019–0.1, and >0.1 ng/mL in patients in the ICU, respectively.

There were 3 patients with high atherosclerotic cardiovascular disease risk, of whom 1 died during ICU stay, and 2 others refused angiography.

Table 1. On-Arrival Demographic and Laboratory Characteristics of Included Patients (n=245)

	Survivors (n=240)	Nonsurvivors (n=5)	OR (95% CI)
Male sex, n (%)	182 (75.8)	4 (80.0)	0.78 (0.09–7.16)
Loss of consciousness, n (%)	205 (85.4)	5 (100)	…*
Dyspnea, n (%)	13 (5.4)	1 (20)	0.23 (0.02–2.20)
Agitation, n (%)	4 (1.7)	0	…*
Dizziness, n (%)	6 (2.5)	0	…*
Vomiting, n (%)	20 (8.3)	0	…*
Age, y†	33 [24–46] (14, 78)‡	63 [38–71] (29, 74)‡	1.09 (1.02–1.17)‡
QT, s†	0.39 [0.38–0.41] (0.35, 0.47)	0.38 [0.37–0.42] (0.37, 0.44)	…*
Urea, mg/dL†	30 [23–38] (12, 126)	38 [30–119] (27, 180)	1.03 (1.01–1.06)
Cr, mg/dL†	1.0 [0.9–1.2] (0.4, 3.1)	1.1 [1.0–1.6] (1.0, 1.8)	4.37 (0.66–29.1)
CPK†	140 [92–270] (32, 952)	116 [81–541] (67, 625)	1.00 (1.0–1.0)
CK MB†	18 [13–23] (6, 113)	35 [15–60] (13, 65)	1.00 (1.0–1.06)
WBC, 10^9/L†	10.3 [8.1–14.2] (3.0, 31.0)	10.8 [8.7–14.9] (8.6, 18.2)	1.01 (0.84–1.21)
Hgb, g/dL†	14.2 [12.9–15.7] (6.2, 20.7)	13.8 [11.9–13.9] (11.4, 14.1)	0.79 (0.55–1.14)
Platelet, 10^9/L†	225 [191–273] (98, 581)	217 [148–277] (131, 282)	0.99 (0.98–1.01)
pH†	7.30 [7.25–7.36] (6.97, 7.54)	7.29 [7.20–7.36] (7.19, 7.38)	0.04 (0–1176.6)
pCO2, mEq/L†	51.4 [44.0–61.1] (17.5, 93.5)	40.0 [34.9–60.6] (32.0, 73.0)	0.96 (0.89–1.03)
HCO3, mEq/L†	25.7 [23.1–28.9] (12.7, 45.6)‡	21.0 [17.3–26.0] (15.7, 28.0)‡	0.78 (0.61–0.96)‡

CK MB indicates creatine kinase myocardial band; CPK, creatine phosphokinase; Cr, creatinine; HCO3, bicarbonate; Hgb, hemoglobin; OR, odds ratio; pCo2, partial pressure of carbon dioxide; WBC, white blood cell.

*Not computed.

†Median [interquartile range] (minimum, maximum).

‡Variables have significant *P* values (<0.05).

Regression Analysis

After performing Enter logistic regression applying all on-arrival variables with significant *P* values, including hs-cTnI cutoff >0.0365 ng/mL, age, and HCO3, all 3 factors predicted death independently (OR, 38.1; 95% CI, 2.3–641.9; OR, 0.9; 95% CI, 0.8–0.1; and OR, 1.4; 95% CI, 1.0–1.8, respectively, Nagelkerke R^2, 0.546; P<0.001). Using the cutoff >0.019 ng/mL reduced the odds to 14.2 [1.1–180.1].

Although intubation had an association with hs-cTnI cutoff ≥0.019 in univariate analysis, we performed Enter logistic regression applying significant on-arrival variables for intubation, including Glasgow Coma Scale, age, creatinine, white blood cells, and creatine kinase myocardial band. Analysis showed that creatine kinase myocardial band, age, and Glasgow Coma Scale were factors that could predict intubation independently (OR, 0.98; 95% CI, 0.95–1.0; OR, 0.96; 95% CI, 0.93–0.99; and OR, 1.2; 95% CI, 1.1–1.4, respectively, Nagelkerke R^2, 0.240; P<0.001).

DISCUSSION

Our findings point to high levels of hs-cTnI in methadone deaths and in intubated methadone-poisoning cases, a finding compatible with severe toxicity. Not surprisingly, age was an independent factor predicting mortality. On-arrival low bicarbonate level could indicate end-organ damage leading to lactic acidosis and higher risk of death. No other variables could independently predict mortality in the current study.

Previous studies have been conducted on cardiovascular toxicity of methadone.[3,20] Most of them reported ECG abnormalities, especially QTc prolongation and torsades de pointes arrhythmia.[21–23] Hahn first suggested the possibility of increased troponin attributable to opium toxicity in 2019.[24] The author reported high troponin in an opium-poisoned patient, but no observational study was conducted in this regard. In 2020, Mostafavi et al performed angiography on 87 patients with methadone toxicity and increased troponin, and found no relationship between high troponin levels and significant coronary artery disease. They suggested that increased troponin in patients with methadone poisoning should not be considered as non–ST-segment–elevation myocardial infarction because of atherothrombotic events.[25] We did not perform invasive procedures such as coronary angiography because of a lack of enough evidence for atherothrombotic coronary events in patients' clinical presentations, ECGs, and echocardiography findings.[25] Cardiac troponins are specific biomarkers of myocardial injury,[26,27] and we

Table 2. Outcomes in Excluded and Included Patients Based on Troponin Level

	hs-cTnI Cutoff, n (%)	Rhabdomyolysis, n (%)	Long QT, n (%)	ICU Admission, n (%)	Intubation, n (%)	Mortality, n (%)
Excluded patients, n=54						
>0.1 ng/mL	32 (59)	22 (50)	4 (100)	14 (82)	13 (87)	6 (86)
0.019–0.1 ng/mL	12 (22)	12 (27)	0	2 (12)	2 (13)	1 (14)
<0.019 ng/mL	10 (19)	10 (23)	0	1 (6)	0	0
P value		0.015	0.2	0.06	0.03	0.3
Cramer's V		0.395	0.235	0.3	0.4	0.2
Included patients, n=245						
>0.1 ng/mL	19 (8)	0	1 (17)	14 (61)	3 (14)	2 (40)
0.019–0.1 ng/mL	41 (17)	0	1 (17)	6 (26)	6 (29)	2 (40)
<0.019 ng/mL	185 (76)	0	4 (66)	3 (13)	12 (57)	1 (20)*
P value		…	0.7	0.2	0.1	0.005
Cramer's V		…	0.053	0.111	0.131	0.208
Excluded n=54 vs included n=245 patients						
P value	<0.001	<0.001	0.1	<0.001	<0.001	<0.001
Cramer's V	0.552	0.885	0.106	0.250	0.227	0.214
OR (95% CI)	…	…	0.9–11.8	4.4 (2.2–9.1)	4.1 (2.0–8.7)	7.2 (2.2–23.6)
All patients, n=299						
>0.1 ng/mL	51 (17)	22 (50)*	5 (50)*	17 (42)*	16 (44)*	8 (67)*
0.019–0.1 ng/mL	53 (18)	12 (27)*	1 (10)	8 (20)	8 (22)*	3 (25)
<0.019 ng/mL	195 (76)	10 (23)*	4 (40)	15 (38)*	12 (33)*	1 (8)*
P value		< 0.001	0.019	< 0.001	< 0.001	< 0.001
Cramer's V		0.408	0.163	0.278	0.288	0.287

P values demonstrated in this table show significant difference between groups. hs-cTnI indicates high-sensitivity cardiac troponin I; ICU, intensive care unit; and OR, odds ratio.

*Percentages in parentheses can be used to define the responsible group(s).

suggest that methadone poisoning may cause cardiac injury with a mechanism seemingly unknown to date.

Troponin as a predictor of mortality in poisoning has already been reported by Manini et al[11]. They showed that the initial troponin results were highly associated with drug-overdose mortality. We excluded patients with known causes of elevated troponin, such as acute myocardial infarction, chronic kidney disease, congestive heart failure, sepsis, and rhabdomyolysis.[28,29] Considering normal angiography in Mostafavi et al's study,[25] we believe that myocardial damage may play a role in methadone poisoning because of myocarditis. Several reports of myocardial injury and myocarditis caused by the use of substances including amphetamines,[30] ecstasy,[31] and cocaine[32] have been published in the literature. It needs further evidence for this hypothesis to be reliable.

We observed an in-hospital mortality rate of 4.0% (12 deaths) among all 299 patients. The mortality rate was just 2.0% (5 deaths/245 cases) in included patients (Table 2). Gharehdaghi et al reported a mortality rate of 1.9% in patients with methadone poisoning in 2017 in

Table 3. Diagnostic Measurements of hs-cTnI for Predicting Mortality (n=245)

Variable	Value Cutoff >0.0365 ng/mL	95% CI	Value Cutoff ≥0.019 ng/mL	95% CI
Sensitivity	80.0%	28.3–99.4%	80.0%	28.4–99.5%
Specificity	85.5%	80.3–89.6%	76.7%	70.8–81.9%
Positive likelihood ratio	5.51	3.23–9.40	3.43	2.09–5.62
Negative likelihood ratio	0.23	0.04–1.35	0.26	0.05–1.51
Positive predictive value	10.2%	6.2–16.3%	6.7%	4.2–10.5%
Negative predictive value	99.5%	97.2–99.2%	99.5%	96.9–99.9%
Accuracy	85.3%	80.3–89.5%	76.7%	70.9–81.9%

hs-cTnI indicates high-sensitivity cardiac troponin I.

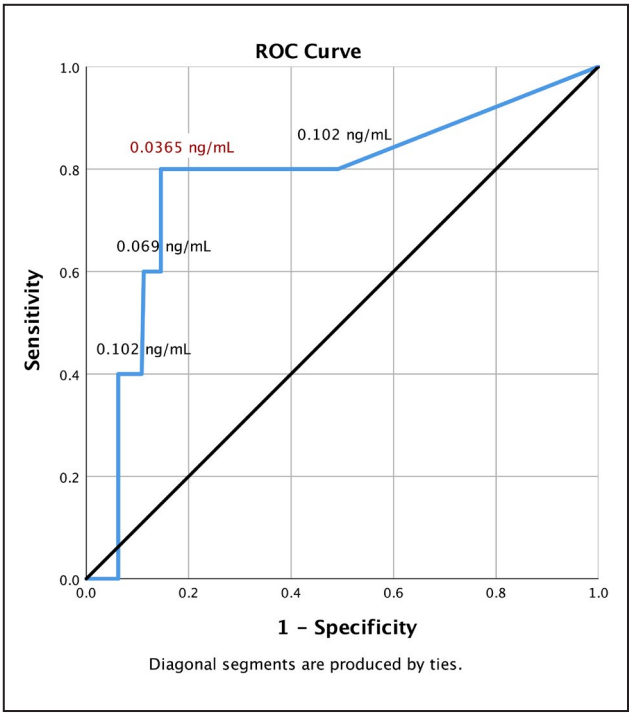

Figure 2. Receiver operating characteristic (ROC) curve for initial troponin and best cutoff correlation to mortality (n=245).

Iran.[33] Soltaninejad and colleagues reported an average 2.5% mortality rate between 2000 and 2010, and showed both an increasing trend of poisoning and increased mortality rate.[34] Our study is in accordance with these results on increased mortality rate during the past 2 decades.

Twenty-one (8.5%) of our patients needed intubation. These results are consistent with the results from our 2016 retrospective study of risk factors for mortality in patients with methadone poisoning, in whom 8.3% required intubation.[35]

The prognostic value of high-sensitivity troponin has been studied in different clinical settings, indicating its relation to worse prognosis.[36] However, before our study, this association had not been studied in patients with methadone poisoning to date. In 2017, evaluating 154 052 participants among the general population by Willeit and colleagues showed that independent of traditional risk factors, high cardiac troponin concentration within the normal range is associated with increased cardiovascular disease risk.[37]

In a median follow-up of 15 years, Jia et al concluded that higher high-sensitivity troponin levels in the general population were also associated with worse long-term (ie, several years) prognosis independent of traditional prior risk factors.[38] Welsh and colleagues demonstrated the predictive value of elevated levels of hs-cTnI in the general population. The hs-cTnI levels of their subjects were all below the 99th percentile of the upper reference limit and were positively associated with cardiovascular events in a 7- to 11-year follow-up study.[39] However, in our current study, increased levels of hs-cTnI were higher than the 99th percentile of the upper reference limit, and we evaluated in-hospital mortality. Considering exclusion of risk factors, in our study, hs-troponin levels were higher, and in-hospital mortality (short term) was evaluated. We believe that the predictive value of hs-cTnI in patients with methadone poisoning is independent of its conventional well-known risk factors in the general population.

In our study, 3.3% of patients (n=10) had QTc prolongation. In 2019, we reported a 39% QTc prolongation in patients who died from methadone poisoning.[9] This high prevalence of QTc prolongation may explain the higher

Table 4. Selected Outcomes Among Troponin Cutoff of 0.0365 ng/mL (n=245)

	Troponin Cutoff > 0.0365 ng/mL		*P* Value	OR	95% CI
	Yes (%)	No (%)			
Mortality	4 (80%)	1 (20%)	0.002	23.4	2.5–215.8
ICU admission	6 (26%)	17 (74%)	0.2	2.0	0.7–5.5
Intubation	6 (29%)	15 (79%)	0.1	2.3	0.8–6.4
ST abnormality	1 (100%)	0 (0 %)	0.2	…	…
QTc prolongation	1 (17%)	5 (83%)	0.9	1.1	0.1–9.3
	Troponin Cutoff ≥0.019 ng/mL				
	Yes (%)	No (%)			
Mortality	4 (80%)	1 (20%)	0.014	13.1	1.4–120.0
ICU admission	9 (39%)	14 (61%)	0.1	2.2	0.9–5.3
Intubation	9 (43%)	12 (57%)	0.041	2.5	1.0–6.4
ST abnormality	1 (100%)	0 (0 %)	0.2	…	…
QTc prolongation	2 (33%)	4 (67%)	0.6	1.6	0.3–8.7

ICU indicates intensive care unit; OR, odds ratio; and QTc, corrected QT.

lethality observed in that study. We did not find a significant relationship between prolonged QTc and mortality in the current study. This finding is inconsistent with the results from a 2014 study by Farsi and colleagues, who reported a significant relationship between QTc prolongation and in-hospital mortality, although it was not an independent association.[40]

To the best of our knowledge, this is the first study to investigate cutoff values of hs-cTnI to predict mortality in patients poisoned with or exposed to methadone. These results may help physicians to identify high-risk patients in the emergency department and provide them with appropriate intensive care. Clearly, patients with elevated hs-cTnI require cardiac and respiratory monitoring and consideration of critical care unit admission. Thus, it might be helpful to avoid early discharge and to use telemetry monitoring. We did not find a significant relationship between hs-cTnI levels and QTc prolongation or between QTc prolongation and mortality. This may reflect that the mechanism by which methadone affects the heart is different in cases of QTc prolongation and abnormal hs-cTnI. Hilal et al reported the predictive role of hs-cTnI, with a cutoff of >1 ng/mL, in patients poisoned with cardiotoxic drugs and toxins. In their study, only 4 (4%) patients were poisoned with opium, and no case of methadone poisoning was reported.[41]

In addition, our findings, along with another recent study,[25] showed that expensive invasive procedures are not necessary to rule out myocardial infarction from atherothrombotic events in methadone poisoning/exposure with elevated hs-cTnI.

Our study had several limitations. First, cardiovascular magnetic resonance imaging was not available to diagnose possible myocarditis cases. Unfortunately, because of the unavailability of cardiovascular magnetic resonance imaging and its high cost, it was not possible for us to investigate the probable myocarditis in patients with increased troponin poisoned with methadone. Cardiovascular magnetic resonance imaging has been shown to be of value in the diagnosis of myocarditis and myocardial infarction with normal or nonobstructive coronary arteries.[42] Second, we had no access to previous ECGs to define if the ECG changes were recent.

Finally, our data are derived from a single-center study; thus, the ability to generalize our findings is limited until our findings are replicated internationally.

Future research should focus on measuring troponin levels in methadone maintenance clients to see if high levels of troponin are a cardiotoxic effect of chronic methadone use or an acute effect of methadone poisoning.

CONCLUSIONS

This study reports elevated hs-cTnI in patients poisoned with or exposed to methadone. Because our findings are based on patients with a diagnosis of methadone poisoning, it is unclear whether high hs-cTnI is a marker of acute poisoning or if its level rises over time because of continuous methadone exposure. Longitudinal designs in methadone maintenance patients may be able to address this question.

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Disclosures

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