



Prevalence of QT interval prolongation in inflammatory bowel disease

BOWEL

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ABSTRACT

Background/Aims: There is growing evidence linking various cardiac complications with inflammatory bowel disease (IBD). Electrolyte abnormalities, chronic inflammation, and medication use (such as Infliximab) that are associated with IBD are all independent risk factors for QT interval prolongation. Given that malignant ventricular arrhythmias are associated with QT interval prolongation, it is important to risk stratify this subset of patients. Our objective was to evaluate the prevalence of abnormal QT interval prolongation (defined by a QT interval of >450 ms in men and >460 ms in women) in an IBD population.

Materials and Methods: A retrospective chart review of patients with IBD from the Metro Hospital database was performed. Patients' demographic characteristics and laboratory data were abstracted. "RR" and "QT" intervals were measured from the last available electrocardiogram, and corrected QT (QTc) interval was calculated from lead II using Bazett's formula.

Results: Of 142 eligible patients, 42.3% (n=22/52) of males and 48.9% (n=44/90) of females had a prolonged QTc interval. Patients with IBD having a prolonged QTc interval had a higher body mass index than those with a normal QTc interval (29.7±6.9 vs. 26.2±5.9, p=0.005).

Conclusion: Our study demonstrates that patients with IBD are at a higher risk of developing QTc interval prolongation.

Keywords: QT interval, inflammatory bowel disease, Crohn's disease, ulcerative colitis, chronic inflammation

INTRODUCTION

Prolonged QT interval has increased propensity for potential fatal ventricular arrhythmias and is predictive of all-cause and cardiovascular mortality in both healthy individuals and in individuals with cardiac disease (1,2). The prevalence of corrected QT (QTc) interval prolongation in the general population has been reported to be 8.7% in previous studies (3). Patients with prolonged QT interval usually present with dizziness, syncope, or seizures; however, cardiac arrest or sudden death may be the first symptom in as many as 13% of untreated patients (4).

QT interval prolongation can be congenital or acquired. Factors influencing QT interval prolongation includes genetic abnormality, medications (e.g., antiarrhythmics, antihistaminics, psychotropics, and antibiotics), electrolyte abnormalities (i.e., hypokalemia,

hypocalcemia, or hypomagnesemia), and myocardial ischemia (1,5). Bharati et al. (5) also found that QT interval prolongation was associated with chronic inflammation of the ventricular myocardium.

Inflammatory bowel disease (IBD), both Crohn's disease and ulcerative colitis, have been commonly associated with extra-intestinal and systemic manifestations with a frequency of approximately 6%–47% (6-8). Recently, there has been growing evidence of cardiac complications, such as atherosclerosis-related coronary artery disease (CAD), pericarditis, myocarditis, arrhythmias, and conduction defects, associated with patients with IBD (9-13). The pathophysiology behind the cardiac manifestations in patients with IBD is poorly understood, but growing evidence suggests that this could be because of chronic inflammation (10-13).

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Electrolyte abnormalities are often encountered in patients with IBD, which along with cardiotoxic medication use, such as tumor necrosis factor alpha (TNF- α) inhibitors (14,15), and chronic inflammation are all independent risk factors for the development of an abnormal QT interval prolongation. Given the higher incidence of mortality and sudden cardiac death in patients with prolonged QTc interval, it is important to identify and risk stratify these subset of patients with IBD. This forms the basis for our study, and our objective is to evaluate the prevalence of QT interval prolongation in patients with IBD.

MATERIALS AND METHODS

Study population and data collection

This is a single-center retrospective study that was conducted to evaluate the QTc interval in patients with IBD (Figure 1). Patients hospitalized or followed up in the gastroenterology clinic with a diagnosis of IBD (old and new) were identified from the Metro Hospital database. The diagnosis of ulcerative colitis and Crohn's disease was confirmed from the consultant evaluation along with clinical, endoscopic, and histopathological evidence. Patients' characteristics, including age; gender; race; smoking history; and comorbidities, such as hypertension, diabetes, renal failure, and peripheral vascular disease, and laboratory data, including levels of creatinine, cholesterol, calcium, potassium, and magnesium and white cell count, were abstracted from the electronic medical records. Unfortunately, in our patient population, C-reactive protein (CRP) or interleukin (IL) levels were unavailable for further correlation. The ethics committee approval was obtained from the Metro Hospital Institutional Review Board.

Electrocardiographic analysis

Digitally stored 12-lead electrocardiogram (ECG) data in the MUSE system (Marquette Medical Systems; Milwaukee, United

States) was used for analysis. In patients with multiple ECGs, the last available ECG after the diagnosis of IBD was reviewed. Abstracted ECG measurements included the RR and QT interval. The QT interval was measured from the beginning of the QRS complex to the end of the downslope of the T wave (crossing the isoelectric line) from lead II (16). The QTc interval was calculated using Bazett (17) formula (duration of the QT interval in milliseconds divided by the square root of the RR interval in seconds, using the RR interval between the measured and preceding complex). We defined a QT interval as prolonged, if the QTc interval was >460 ms in women or >450 ms in men (as per recommendations from the American Heart Association/American College of Cardiology/Heart Rhythm Society) (16).

Statistical analysis

Categorical variables are reported as counts and percentages, and continuous variables are presented as means \pm standard deviation. Categorical variables were compared using the chi-square test and continuous data using the Student's *t*-test or Wilcoxon nonparametric statistics PASW Statistics version 18 (SPSS Inc; Chicago, United States). All the tests were two tailed, and *p* values of <0.05 were considered statistically significant. Linear regression models were used to correlate the QTc interval with continuous variables. Variables that were statistically significant in univariate models were included in a multivariate logistic regression model after the adjustment for potential confounders.

RESULTS

Patient characteristics

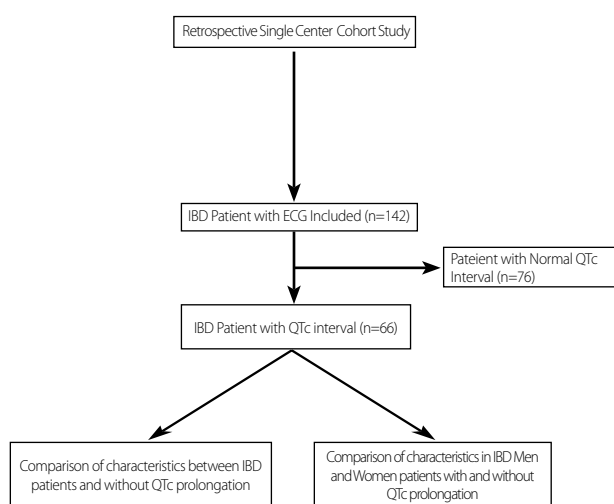
We identified 142 patients with IBD and their standard ECGs were extracted. Of 142 patients with IBD, 63.4% (*n*=90) were

Table 1. Characteristics of a cohort study population with inflammatory bowel disease

Characteristics	IBD cohort (n=142)
Age (mean \pm SD), years	56.4 \pm 15.4
Caucasian (n, %)	119 (83.8%)
Basal Metabolic Index (mean \pm SD)	28.9 \pm 11.8
Coronary Artery Disease (n, %)	22 (15.8%)
Cerebro-Vascular Accident (n, %)	7 (4.9%)
Hypertension (n, %)	38 (26.8%)
Diabetes (n, %)	12 (8.6%)
Smoker (n, %)	65 (45.8%)
WBC (mean \pm SD), 10 ³ / μ L	9.14 \pm 3.94
Potassium (mean \pm SD), mmol/L	4.05 \pm 0.47
Calcium (mean \pm SD), mg/dL	8.92 \pm 0.66
Magnesium (mean \pm SD), mg/dL	2.04 \pm 0.27
Follow-up (mean \pm SD), years	7.4 \pm 3.5

IBD: inflammatory bowel disease; SD: standard deviation; WBC: white blood count; n: number

Study Design:



IBD: inflammatory bowel disease; ECG: electrocardiogram

Figure 1. Study design.

women. Mean age of the study population was 56.4 ± 15.4 years, with a Caucasian predominance (83.8 %). Mean QTc interval of the study population was 459.4 ± 48.8 ms. Mean QTc interval in males was 452.9 ± 43.6 ms, whereas that in women was 463.3 ± 51.4 ms. Mean follow-up period was 7.4 ± 3.5 years. The detailed baseline characteristics of the IBD cohort population is presented in Table 1.

Prevalence of prolonged QTc interval (Table 2)

The overall prevalence of prolonged QTc interval in our IBD population was 46.5%. The mean QTc interval among the patients with a prolonged QTc interval was 495.4 ± 44.4 ms and those without a prolonged QTc interval was 424.5 ± 17.3 ms. Patients with a prolonged QTc interval had a higher body mass index (BMI) than those with a normal QTc interval

Table 2. Characteristics of patients having IBD with and without prolonged QTc interval

	Normal QTc interval 76 (53.5%)	Prolonged QTc interval 66 (46.5%)	p
Age, years	51.3 ± 15.5	54.8 ± 15.9	0.2
Smoker (n, %)	37 (56.9%)	28 (43.1%)	0.2
BMI (kg/m^2), Mean \pm SD	26.2 ± 5.9	29.7 ± 6.9	0.005
Hypertension (n, %)	21 (55.3%)	17 (44.7%)	0.5
Coronary Artery Disease (n, %)	9 (40.9%)	13 (59.1%)	0.3
Diabetes (n, %)	7 (58.3%)	5 (41.7%)	0.6
WBC (mean \pm SD), $10^3/\mu\text{L}$	9.3 ± 3.9	9.1 ± 3.8	0.8
Potassium (mean \pm SD), mmol/L	4.1 ± 0.4	4.0 ± 0.5	0.1
Calcium (mean \pm SD), mg/dL	9.0 ± 0.6	8.8 ± 0.7	0.1
Magnesium (mean \pm SD), mg/dL	2.03 ± 0.3	2.04 ± 0.3	0.8

IBD: inflammatory bowel disease; SD: standard deviation; WBC: white blood count; n: number

(29.7 ± 6.9 vs. 26.2 ± 5.9 , $p=0.005$). Women had 1.3 times [95% Confidence Interval (CI), 0.7–2.6] higher prevalence of having a QTc interval prolongation than males. Comparison and frequency distribution of the QTc interval among men and women is as shown in Figure 2, 3. The prevalence of QTc interval prolongation in different age groups is as follows: ≤ 29 years, 28.6% ($n=2/7$); ≥ 30 to ≤ 60 years, 44.6% ($n=30/59$); and ≥ 60 , 51.9% ($n=27/52$) (Figure 4).

Prevalence of prolonged QTc interval in men

We found that the prevalence of prolonged QTc interval among male patients with IBD was 42.3% ($n=22/52$). Mean age of patients with a QTc interval prolongation was 47.2 ± 15.9 years and those without a QTc interval prolongation was 47.9 ± 15.1 years. Among the QTc interval prolongation group, mean QTc interval was 488 ± 44.7 ms, and among the normal QTc interval group, QTc interval was 427.1 ± 16.7

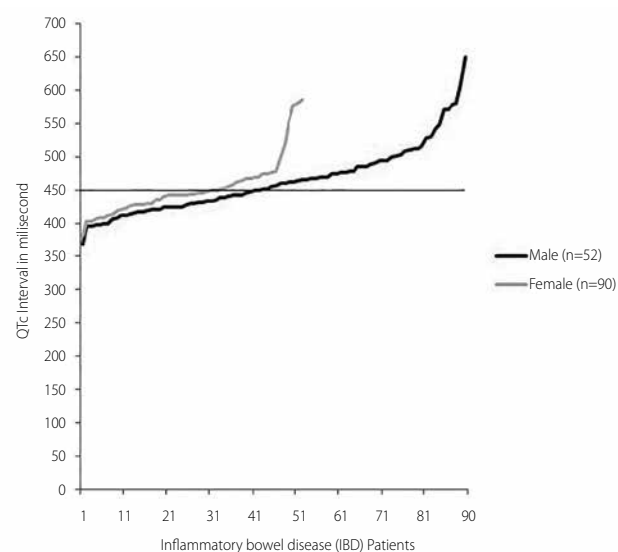


Figure 2. Comparison of prolonged QT interval in men and women.

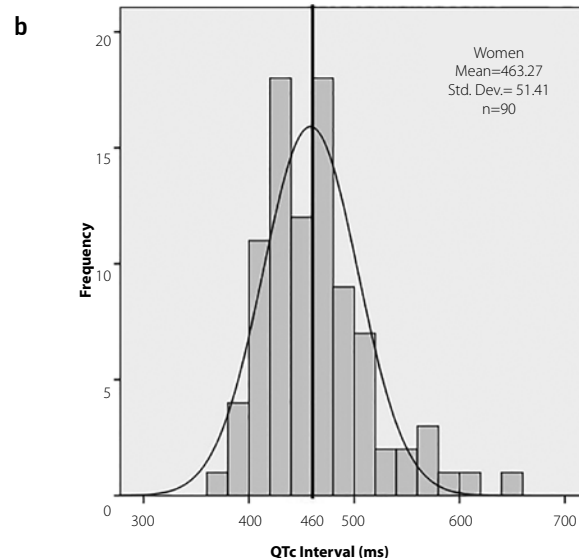
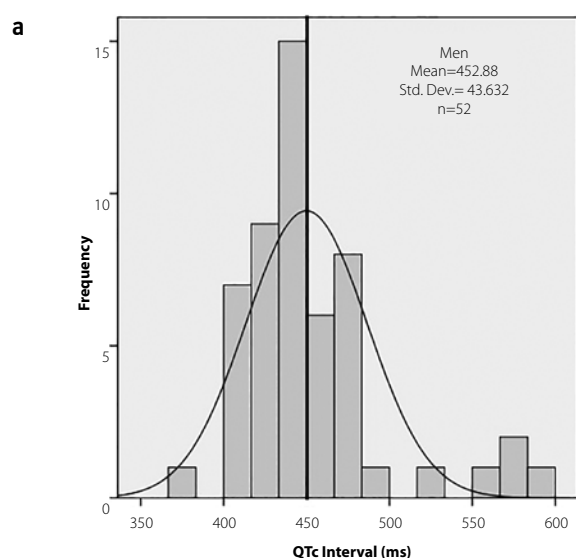


Figure 3. a, b. Frequency distribution of QTc interval among men (a) and women (b).

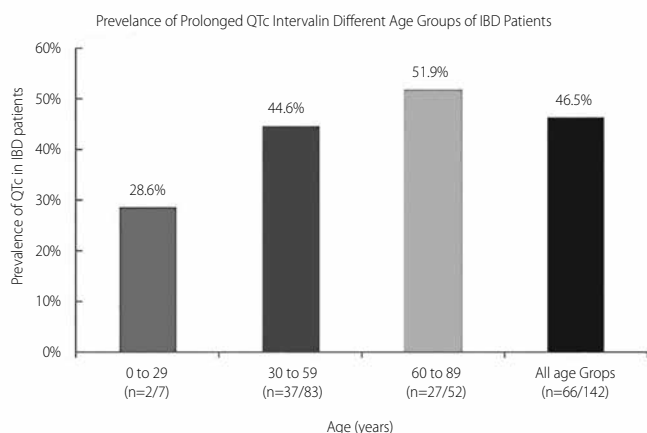


Figure 4. Prevalence of QTc interval prolongation in patients with inflammatory bowel disease (IBD) among different age.

ms. Comorbidities, electrolyte values, and other characteristics among patients having IBD with and without QTc interval prolongation were similar, as shown in Table 3.

Prevalence of prolonged QTc interval in women

The prevalence of prolonged QTc interval among women patients with IBD was similarly high (48.9%). Women with a prolonged QTc interval had a higher BMI than patients with a normal QTc interval (30.1 ± 7.3 vs. 26.3 ± 7.3 , $p=0.03$). Mean QTc interval of patients with a QTc interval prolongation was 502.9 ± 44.1 ms and those without a QTc interval prolongation was 425 ± 19 ms. The characteristics among patients with and without a prolonged QTc interval are shown in Table 4.

DISCUSSION

Extraintestinal manifestations of IBD occur in 42% of patients with colonic disease and 23% of patients with small bowel involvement (18). The main sites of extraintestinal manifestation in patients are the joints (14%–39%), skin (15%), eye (4%), and oral cavity (aphthous stomatitis, 4%) (19,20). Rarely, cardiac complications, such as atherosclerosis/CAD, pericarditis, pericardial effusion, myocarditis, endocarditis, and arrhythmias, can occur, which can be fatal (9-13).

As per our knowledge, there are very few studies evaluating the prevalence of QTc interval prolongation in Caucasian patients with IBD. We found a prolonged QTc interval in nearly 47% of our cohort IBD population, which was clearly higher, than that (8.7%) in the general population published in previous studies (3). A study utilizing the Third National Health and Nutrition Examination Survey demonstrated that the prevalence of QTc interval prolongation in individuals aged >40 years was 6.3% (21). Similarly in the Framingham study Goldberg et al. (22), the prevalence of QTc interval prolongation between the age groups of 30 and 62 years was 5.4%. The Rotterdam Study Hofman et al. (23), which evaluated the prevalence among population aged >55 years, was 11.1%. In comparison with the above studies, in

Table 3. Characteristics of men with and without prolonged QTc interval

	QTc<450 ms n=30 (57.3%)	QTc>450 ms n=22 (42.3%)	p
Age (mean±SD), years	47.9±15.08	47.2±15.9	0.4
Caucasian (n, %)	26 (86.7%)	17 (77.3%)	0.5
Smoking (n, %)	19 (63.3%)	14 (63.6%)	0.98
BMI (mean±SD), kg/m ²	26.5±4.9	29±6.2	0.29
Coronary Artery Disease (n, %)	3 (10%)	2 (9.1%)	0.91
Hypertension (n, %)	6 (20%)	5 (22.7%)	0.81
Diabetes (n, %)	4 (13.3%)	2 (9.1%)	0.63
WBC (mean±SD), 10 ³ /μL	9.6±4.0	8.0±3.4	0.24
Potassium (mean±SD), mmol/L	4.13±0.3	4.02±0.2	0.54
Calcium (mean±SD), mg/dL	8.75±0.7	9.02±0.7	0.1
Magnesium (mean±SD), mg/dL	2.08±0.3	2.11±0.3	0.74
Mean QTc (mean±SD), ms	427.1±16.7	488±44.7	<0.0001

IBD: inflammatory bowel disease; SD: standard deviation; WBC: white blood count; n: number; BMI: body mass index

Table 4. Characteristics of women with and without prolonged QTc interval

	QTc<460 ms n=46 (51.1%)	QTc>460 ms n=44 (48.9%)	p
Age (mean±SD), years	53.7±15.0	58.8±15.1	0.96
Caucasian (n, %)	41 (89.1%)	35 (79.5%)	0.2
Smoking (n, %)	21 (42.9%)	25 (61%)	0.08
BMI (mean±SD), kg/m ²	26.3±7.3	30.1±7.3	0.03
Coronary Artery Disease (n, %)	6 (13 %)	11 (25%)	0.15
Hypertension (n, %)	15 (32.6%)	12 (27.3%)	0.6
Diabetes (n, %)	4 (8.7%)	22 (4.6%)	0.4
WBC (mean±SD), 10 ³ /μL	9.1±3.8	9.7±4.3	0.4
Potassium (mean±SD), mmol/L	4.1±0.4	3.9±0.6	0.2
Calcium (mean±SD), mg/dL	9.2±0.5	8.9±0.7	0.2
Magnesium (mean±SD), mg/dL	1.95±0.27	2.03±0.7	0.8
Mean QTc (mean±SD), ms	425.4±19	502.9±44.1	<0.0001

SD: standard deviation; WBC: white blood count; n: number; BMI: body mass index

our IBD population, the prevalence is much higher among all the age groups (<30 years, 28.6%; 30–60 years, 44.6%; and >60 years, 51.9%).

The main risk factors implicated in QT interval prolongation appear to be hypocalcemia, hyperkalemia, hypomagnesaemia, diabetes, hypertension, female gender, higher BMI, cardiac disease, gene mutations, medications (antiarrhythmics, antibiotics, antipsychotics, and antidepressants) (21,24,25). In our study, except for higher BMI, which was significantly associated with prolonged QTc interval (26.2 ± 5.9 vs. 29.7 ± 6.9 , $p=0.005$), other risk factors, such as female gender, hypertension, CAD,

hypomagnesaemia, hypocalcaemia, and hypokalemia, were not associated with prolonged QTc interval.

Pathophysiology of the cardiac manifestations of IBD is poorly understood. In previous studies involving patients with IBD, cardiac complications, such as CAD, arrhythmias, myocarditis, pericarditis, heart blocks, have been associated with chronic inflammation (5,10,11). In our study, the risk factors except for BMI were similar in patients having IBD with and without prolonged QTc interval. In a study conducted by Bharati et al. (5), QT interval prolongation was associated with chronic inflammation of the ventricle. Patients with IBD are known to have chronic inflammation and elevated inflammatory markers, such as IL-6 and CRP. This inflammation could be the causative factor for abnormal repolarization/depolarization of the ventricle leading to a prolonged QT interval.

Recent studies suggest underlying chronic inflammation leads to interaction between gastrointestinal and cardiovascular autonomic regulation (parasympathetic system) in patients with IBD, particularly during its active phase (26,27). Cardiovascular autonomic dysregulation (cardiac vagal modulation) results in heart rate variability (HRV), prolonged QT interval, and lower baroreflex sensitivity and baroreflex effectiveness (26,27). Similar autonomic imbalance may have a bearing on the pathogenesis of QT interval prolongation in patients with IBD.

The QT interval represents the sum of ventricular depolarization and repolarization. This represents the action potential (AP) duration. The following six sequentially activated currents are responsible in AP: the sodium current, transient outward current, L (long-lasting)-type calcium current (ICaL), rapid component of the delayed rectifier potassium current (IKr), slow component of the delayed rectifier potassium current (IKs), and inward rectifier potassium current. AP is caused by transmembrane flow of ions, including inward depolarizing currents mainly through the sodium and calcium channels and outward repolarizing currents mainly through potassium channels (28). Inflammatory cytokines (particularly TNF- α , IL-6, and IL-1 β) may affect the myocardium either directly by modulating specific ion channels critically involved in AP or indirectly by increasing the central nervous system sympathetic drive on the heart (28).

In a large cohort of 186 patients with myocarditis, it was demonstrated that QTc interval prolongation of >440 ms was frequent (approximately 25% of cases) and predicted a poor clinical outcome, including cardiac death (29). In murine models of the disease, a significant correlation between QTc duration and the degree of cardiac inflammation at the histological examination has been demonstrated. Among systemic inflammation associated with QT interval prolongation, the largest evidence is observed in connective tissue diseases (CTD) (30, 31). Multiple studies demonstrate a significant positive correlation between circulating CRP and IL levels and QTc duration in patients with rheumatoid arthritis having a prevalence of QTc interval pro-

longation anywhere between 7% and 30% (32-36). Moreover, in patients with CTD, elevated IL and CRP levels are independent predictors for the presence of a prolonged QTc interval. Furthermore, Chang et al. (37) found that elevated CRP levels correlated with QTc and independently predicted the presence of QTc interval prolongation.

A number of studies on animal ventricular cells clearly demonstrated the ability of IL-1, IL-6, and TNF- α to prolong AP duration, possibly by enhancing ICaL and inhibiting the potassium channel (38,39). Wang et al. (40) reported that TNF- α downregulates in vitro IKr by impairing the function of the hERG potassium channel via the stimulation of reactive oxygen species. Inflammation can also produce cardiac electrophysiology changes leading to QTc interval prolongation in an indirect manner by inducing autonomic nervous system dysfunction. Inflammatory cytokines increase the sympathetic outflow overdrive, thereby activating the cardiomyocyte β -adrenergic receptor. This in turn affects calcium (ICaL) and potassium (IKs and IKr) conductance with a net effect of an increase in the action potential duration (APD), and thus, cardiac sympathetic denervation can shorten AP duration (41-43).

HRV is a non-invasive method to detect early cardiovascular autonomic impairment by assessing the effects of the sympathetic-vagal balance on the heart (44). In several systemic inflammatory diseases, such as inflammatory arthritis, connective disease disorders, and in various heart inflammatory diseases, there is reduced HRV, indicating an increase in the sympathetic nervous system activity and a decrease in the parasympathetic nervous system activity. HRV parameters are inversely correlated with circulating CRP (and/or inflammatory cytokines) levels in healthy individuals and in patients with cardiovascular diseases (44,45). HRV depression levels are significantly correlated with an increased QTc duration. Autonomic impairment (particularly HRV) is associated with disease duration, disease activity, and inflammatory markers (44,45).

Obesity or increased BMI itself has also been demonstrated to be an independent risk factor for prolonged QT interval (46). Underlying factors could be likely associated with sleep apnea or changes in cardiac morphology because of inappropriate left ventricular mass as suggested by the Losartan Intervention for Endpoint Reduction (LIFE) study (47,48). The mechanistic causes in turn have been postulated to be related to defective calcium inactivation and decreased expression of voltage-gated potassium channels leading to altered myocyte action potentials (49,50). Our results also appear to suggest that obese patients with IBD are at an increased risk for QT interval prolongation.

It is well known that patients with prolonged QT intervals have higher cardiovascular mortality because of life-threatening ventricular arrhythmias and sudden death. With a large group of patients with IBD receiving potentially cardiotoxic drugs, it is important to risk stratify these patients to prevent catastrophic

cardiovascular events. It would appear to be advisable to perform frequent ECG examinations with an accurate measurement of the QT interval and to be more aware regarding the potential risks when using QT-prolonging drugs in patients with IBD. Our findings of QT interval prolongation in patients with IBD also reinforce the requirement to avoid electrolyte abnormalities (such as hypokalemia, hypocalcaemia, and hypomagnesaemia), which are more prevalent in this subset of patients as well.

Study limitations

The study is a retrospective review of the clinical information that was recorded in the patients' medical records. Conditions not recorded in the medical records would have been missed. Because the retrospective design does not permit an estimate of lifelong inflammatory burden, we could only study an association but not a prospective prediction or causation. Similarly, the influence of confounding factors, such as the use of corticosteroids, immunomodulators, and biological agents; IBD activity; malnutrition; and CRP levels, could not be completely evaluated.

In conclusion, our study demonstrated a higher prevalence of QT interval prolongation in patients with IBD than that in the general population. Although we are unable to establish the causative factor, chronic inflammation may be associated with an abnormal depolarization/repolarization of the ventricles. However, the clinical significance of a prolonged QTc interval and whether it is associated with an increased total or cardiovascular mortality in an IBD population remains unclear and requires to be further evaluated.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Metro Hospital, Case Western Reserve University.

Informed Consent: Informed consent was not received due to the nature of the study.

Peer-review: Externally peer-reviewed.

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