JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

# Heart rate-corrected QT interval: A novel diagnostic biomarker for diabetic peripheral neuropathy

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**Keywords**
Diabetes, Diabetic peripheral neuropathy, Diagnosis

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*J Diabetes Investig* 2022; 13: 850–857

doi: 10.1111/jdi.13738

## ABSTRACT

**Aims/Introduction:** To explore the relationship between heart rate-corrected QT (QTc) interval and diabetic peripheral neuropathy (DPN), and whether QTc interval has diagnostic utility for DPN beyond nerve conduction velocity.

**Materials and Methods:** A total of 965 patients with diabetes, including 473 patients with DPN and 492 patients without DPN, underwent standard 12-lead electrocardiography and detailed assessments of peripheral neuropathy.

**Results:** Patients with DPN had longer QTc intervals than those without. Among participants, from the first to fourth quartile of QTc interval, the proportion of patients with DPN appreciably increased and the nerve conduction velocity obviously decreased ($P$ for trend <0.001). The univariate and multivariate analyses showed that prolonged QTc interval was closely associated with increased risk of DPN (univariable odds ratio 1.112, 95% confidence interval 1.097–1.127, $P < 0.001$; multivariable odds ratio 1.118, 95% confidence interval 1.099–1.137, $P < 0.001$). Receiver operating characteristic analysis for the diagnosis of DPN showed a greater area under the curve for QTc interval of 0.894 than the median nerve motor conduction velocity of 0.691, median nerve sensory conduction velocity of 0.664 and peroneal nerve motor conduction velocity of 0.692. The optimal cut-off point of QTc interval for DPN was 428.5 ms with sensitivity of 0.715 and specificity of 0.920 ($P < 0.001$). The combination of QTc interval and nerve conduction testing increased the area under the curve for the diagnosis of DPN (from 0.736 to 0.916; $P < 0.001$).

**Conclusions:** QTc interval with 428.5 ms has more reliable diagnostic utility for DPN than nerve conduction velocity, and prolonged QTc interval is closely associated with an increased risk of DPN.

## INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a common chronic complication of both type 1 and type 2 diabetes, and approximately 50% patients with diabetes develop DPN[1]. The main symptoms of DPN are distressing neuropathic pain and paresthesia, characterized by superficial burning pain and numbness in the lower limbs[2]. However, DPN might be asymptomatic in up to 50% of patients, leading to more difficulties in the timely diagnosis and effective treatment, and contributing to a higher risk of diabetic foot ulceration and non-traumatic lower limb amputation[3]. It is estimated that patients with DPN with or without limb ulceration have a high rehospitalization rate and mortality[3].

The QT interval represents the duration of electrical depolarization and repolarization of the ventricular. As the QT interval is correlated with the heart rate; the higher heart rate, the

†Co-first authors: Ai-jun Jiang and Heng Gu.
Received 27 September 2021; revised 15 December 2021; accepted 17 December 2021



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shorter QT interval and vice versa, heart rate-corrected QT (QTc) interval is usually used clinically[4]. Prolongation of the QTc interval becomes a risk factor for malignant arrhythmia and sudden cardiac death[5]. In addition, it has been shown that the QTc interval in patients with diabetes is longer than those without diabetes[6]. Prolonged QTc interval, even within the normal reference range, has been shown to be associated with diabetic complications and metabolic diseases, including diabetic cardiac autonomic neuropathy[7], diabetic nephropathy[8], diabetic kidney disease[9], insulin sensitivity[10] and non-alcoholic fatty liver disease[11]. Furthermore, prolonged QTc interval was found to be a biomarker for worse prognosis in diabetes patients[12].

However, the role of QTc interval in the pathogenesis of DPN remains totally unclear. The present study explored that the relationship between QTc interval and DPN, and whether QTc interval has diagnostic utility for DPN beyond nerve conduction velocity.

## MATERIALS AND METHODS

### Study design and participants

The present observational study was carried out on total of 965 patients (473 patients with DPN, 492 patients without DPN) in the endocrinology department of the Nanjing First Hospital between January 2020 and December 2020. The inclusion criteria were: (i) diagnosis of diabetes was based on the American Diabetes Association recommendation[13]; (ii) cardiac sinus rhythm; (iii) normal heart rate (60–100 b.p.m.); (iv) normal vital sign; (v) underwent standard resting 12-lead electrocardiograph; and (vi) underwent nerve conduction testing. The exclusion criteria were: (i) taking medications that affect QTc intervals, such as antiarrhythmic drugs, triangular antipsychotic drugs, and α- and β-receptor blockers; (ii) arrhythmia diseases, such as congenital long QT syndrome, tachycardia, bradycardia, pacemaker rhythms, atrial fibrillation, atrial flutter and cardiac conduction; (iii) other diseases affecting the heart rhythm and QT interval, such as hyperthyroidism; (iv) acute diabetic complications, such as diabetic ketoacidosis, hyperglycemic hyperosmolar state and hypoglycemia; and (v) other endocrine disorders might have effect on glucose metabolism, such as polycystic ovary syndrome.

The study protocol was approved by the ethics committee of the Nanjing First Hospital. Written informed consent was obtained from all participants.

### Basic data collection and laboratory examination

Information about demographic characteristics, medical history, physical examinations including height, weight, waist circumference and hip circumference, and blood pressure of all participants was recorded by diabetologists. Body mass index was calculated by weight divided by the square of height (kg/m$^2$) and waist-to-hip ratio (WHR) was calculated by the ratio of waist to hip circumference. After fasting overnight, blood samples were collected on fasting and 2-h postprandial for laboratory parameters. The fasting plasma glucose (FPG) was assessed by glucose oxidase method using an automatic biochemistry analyzer (HITACHI-7180, Tokyo, Japan). Fasting C-peptide and C-peptide 2-h post prandial (2-h C-peptide) were determined using automatic electrochemiluminescence immunoassay (Cobas E601; Roche, Basel, Switzerland). Glycosylated hemoglobinA1c (HbA1c) was measured by high-pressure liquid chromatography (D-10; Bio-Rad, Hercules, CA, USA). Alanine transaminase, aspartate transaminase, blood urea nitrogen, creatinine, uric acid (UA), total cholesterol, triglyceride, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol level were assessed by enzymatic colorimetric assay using an automatic biochemistry analyzer (HITACHI-7180, Tokyo, Japan). Midstream urine samples were obtained in the morning for urine microalbumin-to-creatinine ratio (UACR).

### QTc interval analysis

Resting electrocardiograms (ECGs) were recorded with a standard 12-lead electrocardiograph (FX-8322, Nippon Fukuda Electronics Co, Tokyo, Japan) at a paper speed of 25 mm/s after standardization (10 mm = 1 mV) with filter settings. ECGs were analyzed with computerized automated analysis software imbedded in the electrocardiograph and then were confirmed by a trained cardiologist. The QT, defined as the time from the beginning of the QRS complex wave to the end of the T wave on ECG, and QTc interval was calculated by Bazett's formula: QTc interval = QT interval / square root of the RR interval (QTc = QT / [RR]1 / 2).

### DPN assessment

Participants underwent neurological assessment according to the American Diabetes Association recommendations[13,14]. The diagnostic criteria for DPN are: (i) definite history of diabetes; (ii) neuropathy that occurs at or after the diagnosis of diabetes; (iii) clinical symptoms (such as burning pain, electric shock-like pain, sharp pain, soreness, cold pain, induced pain, itching, numbness and abnormal position perception) and one abnormality among the following five examinations: ankle reflexes, pinprick sensation, vibration perception, temperature perception and pressure perception (or two abnormalities among the of five examinations in diabetic patients without clinical symptoms); and (iv) exclusion of neuropathy of other causes, including neurotoxic drugs (such as chemotherapy drugs), cervical and lumbar diseases (compression, stenosis, degeneration), cerebral infarction, chronic inflammatory demyelinating neuropathy, hereditary neuropathy and vasculitis, infections (such as acquired immune deficiency syndrome) and nerve damage caused by metabolic toxins caused by renal insufficiency. The detailed ways of assessing ankle reflexes, pinprick sensation, vibration perception, temperature perception and pressure perception are described in Appendix S1.

Diabetic patients were divided into two group: (i) with DPN; and (ii) without DPN.

Nerve conduction testing was carried out with surface electrodes and electromyographic digital equipment (E3, Yuanxiang

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Medical Ltd, Hangzhou, China). The patients were relaxed and kept in the supine position with limb skin temperatures of 32–35°C. Bilateral measurements of nerves were carried out, including motor nerve conduction velocity (MNCV) of the median nerve, sensory nerve conduction velocity (SNCV) of the median nerve and MNCV of the peroneal nerve. Median nerve MNCV was recorded at the abductor pollicis brevis with stimulations at the radial side of the wrist and the radial artery of the cubital fossa. The median nerve SNCV was recorded at the root of the middle finger with stimulation at the radial side of the wrist. Peroneal nerve MNCV was recorded at the extensor toe brevis with stimulations at the ankle and the proximal to the fibula. Nerve conduction velocity was assessed by computerized automated analysis software imbedded in the electromyographic digital equipment. The specific normal values are shown in Appendix S1.

### Statistical analysis

Statistical analyses were carried out using the SPSS statistical software 26.0 (IBM Corp., Armonk, NY, USA). In all cases, *P*-values <0.05 ($P < 0.05$) were considered statistically significant. Data were tested for normality using the Shapiro–Wilk test. The mean ± standard deviation, *n* (%) and median (25th and 75th interquartile range) presented continuous variables with normal distributions, categorical variables and continuous variables with skewed distributions, respectively. The differences were compared by the independent *t*-test, Mann–Whitney test and the $\chi^2$-test. Binary logistic regression analysis was carried out to compare the independent influence of the QTc interval and other metabolic parameters on the DPN, and the odds ratio (OR) and 95% confidence interval (95% CI) were determined. Receiver operating characteristic (ROC) analysis and the area under curve (AUC) were used to assess the accuracy and discriminatory ability of QTc in diagnosis of DPN.

## RESULTS

### Baseline characteristics of patients with DPN

The clinical characteristics of two subgroups are shown in Table 1. There was a significant difference in age ($P < 0.001$), sex ($P < 0.001$), diabetes duration ($P < 0.001$), FPG ($P = 0.016$), HbA1c ($P < 0.001$), 2-h C-peptide ($P = 0.002$), alanine transaminase ($P = 0.018$), blood urea nitrogen ($P < 0.001$), UA ($P = 0.036$), TC ($P = 0,49$) and UACR ($P < 0.001$), but no difference in body mass index, waist-to-hip ratio and fasting C-peptide between the two groups. Additionally, patients with DPN had longer QTc interval (436 [426–448] vs 409 [398–419], $P < 0.001$), slower median nerve MNCV (52.80 [48.54–56.18] vs 55.52 [52.92–58.54], $P < 0.001$), slower median nerve SNCV (47.16 [41.98–53.78] vs 52.94 [48.17–58.25], $P < 0.001$) and slower peroneal never MNCV (43.54 [39.09–47.37] vs 46.86 [44.12–49.71], $P < 0.001$) than those without. When age and sex were adjusted by covariance analysis, there were still significant differences between the two groups in QTc interval ($P < 0.001$).

### DPN and neuropathy parameters at different QTc intervals

The neuropathy characteristics of four subgroups according to the QTc interval quartiles are shown in Table 2 and Figure 1. Among participants, from the first to fourth quartile of QTc interval, the proportion of patients with DPN increased (*P* for trend <0.001); inversely, the median nerve MNCV (*P* for trend <0.001), median nerve SNCV (*P* for trend <0.001) and peroneal nerve MNCV (*P* for trend = 0.002) significantly decreased when the QTc interval quartiles increased.

### Relationship between DPN and QTc interval

In Table 3, the univariate and multivariate logistic regression analyses showed that prolonged QTc interval was closely associated with an increased risk of DPN. On average, the risk of developing DPN in the future was 1.112-fold or 1.118-fold higher for each unit increase in the QTc interval (univariable OR 1.112, 95% CI 1.097–1.127, $P < 0.001$; multivariable OR 1.118, 95% CI 1.099–1.137, $P < 0.001$). The univariate analysis also showed that DPN was associated with age (OR 1.047, 95% CI 1.035–1.059, $P < 0.001$), male (OR 0.483, 95% CI 0.371–0.627, $P < 0.001$), diabetes duration (OR 1.006, 95% CI 1.004–1.007, $P < 0.001$), 2 h C-peptide (OR 0.942, 95% CI 0.898–0.988, $P = 0.015$), blood urea nitrogen (OR 1.186, 95% CI 1.106–1.271, $P < 0.001$) and UACR (OR 1.007, 95% CI 1.004–1.011, $P < 0.001$); DPN had no concern with FPG, HbA1c and UA. Multivariate logistic regression analysis showed that age (OR 1.030, 95% CI 1.010–1.050, $P = 0.003$), QTc interval (OR 1.118, 95% CI 1.099–1.137, $P < 0.001$), diabetes duration (OR 1.003, 95% CI 1.001–1.006, $P = 0.010$) and UACR (OR 1.004, 95% CI 1.000–1.008, $P = 0.036$) significantly correlated with DPN (Nagelkerke $R^2 = 0.614$).

### QTc interval and diagnosis of DPN

ROC curve analyses (Figure 2) showed QTc interval had the highest AUC of 0.894 (95% CI 0.874–0.915, $P < 0.001$) among independent indicators; in comparison, the levels of AUC for median nerve MNCV (AUC 0.691, 95% CI 0.657–0.724, $P < 0.001$), median nerve SNCV (AUC 0.664, 95% CI 0.629–0.698, $P < 0.001$) and peroneal nerve MNCV (AUC 0.692, 95% CI 0.658–0.726, $P < 0.001$) were similar. Furthermore, the diagnosis of combined QTc interval and nerve conduction testing parameters performed better with an AUC of 0.916 (95% CI 0.898–0.933, $P < 0.001$) compared with only a combination of nerve conduction testing parameters with an AUC of 0.736 (95% CI 0.704–0.768, $P < 0.001$). Notably, the optimal cut-off point of QTc interval for DPN was 428.5 ms, with sensitivity of 0.715 and specificity of 0.920.

## DISCUSSION

The major findings of the present study are that QTc interval is strongly associated with DPN, and the diagnostic performance of QTc interval in this study was superior to nerve conduction testing. The optimal cut-off point of QTc interval for


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**Table 1** | Baseline characteristics of patients with versus without diabetic peripheral neuropathy

| Variables | Patients without DPN | Patients with DPN | *P*-value |
|---|---|---|---|
| Anthropometric measures | | | |
| Age (years) | 58 (50, 66) | 63 (56, 71) | <0.001 |
| Male, *n* (%) | 155 (68.6) | 230 (51.3) | <0.001 |
| BMI (kg/m$^2$) | 24.04 (21.91, 26.33) | 24.34 (22.03, 27.09) | 0.58 |
| WHR | 0.94 (0.91, 0.96) | 0.94 (0.91, 0.96) | 0.356 |
| Hypertension, *n* (%) | 314 (63.9) | 312 (63.5) | 0.49 |
| Diabetes | | | |
| Diabetes duration, months | 96 (24, 135) | 120 (60, 204) | <0.001 |
| FPG (mmol/L) | 7.43 (5.96, 9.80) | 8.01 (6.34, 10.55) | 0.016 |
| HbA1c (%) | 8.3 (7.0, 9.8) | 9.0 (7.4, 10.5) | <0.001 |
| HbA1c (mmol/mol) | 67 (53, 84) | 75 (57, 91) | <0.001 |
| Fasting C-peptide (ng/mL) | 1.21 (0.67, 1.79) | 1.24 (0.74, 1.85) | 0.779 |
| 2-h C-peptide (ng/mL) | 3.24 (1.72, 4.95) | 2.91 (1.69, 4.38) | 0.002 |
| Biochemistry parameters | | | |
| Alt (U/L) | 22.00 (14.75, 34.00) | 21.00 (14.00, 31.00) | 0.018 |
| Ast (U/L) | 14.00 (11.00, 20.00) | 15.00 (10.00, 20.00) | 0.981 |
| BUN (mmol/L) | 5.77 (4.93, 6.86) | 6.13 (5.15, 7.64) | <0.001 |
| Cr (μmol/L) | 63.25 (51.27, 75.31) | 63.40 (50.75, 79.45) | 0.08 |
| UA (μmol/L) | 282.00 (230.75, 348.50) | 309.00 (236.00, 379.00) | 0.036 |
| UACR (mg/mmol) | 1.93 (0.89, 5.36) | 4.38 (1.50, 14.09) | <0.001 |
| TC (mmol/L) | 14.5 ± 1.05 | 4.35 ± 1.20 | 0.049 |
| TG (mmol/L) | 1.38 (0.92, 2.04) | 1.52 (1.02, 2.38) | 0.794 |
| HDL-C (mmol/L) | 1.37 (0.99, 1.38) | 1.13 (0.99, 1.32) | 0.622 |
| LDL-C (mmol/L) | 1.95 (1.53, 2.40) | 1.87 (1.45, 2.39) | 0.051 |
| $Ca2^+$ (mmol/L) | 2.26 (2.20, 2.32) | 2.26 (2.19, 2.32) | 0.096 |
| ECG parameters | | | |
| HR (b.p.m.) | 72 (66, 79) | 78 (71, 88) | <0.001 |
| QTc interval (ms) | 409 (398, 419) | 436 (426, 448) | <0.001 |
| Nerve conduction velocity | | | |
| L-median nerve MNCV (m/s) | 55.24 (52.36, 58.42) | 52.77 (48.86, 56.76) | <0.001 |
| R-median nerve MNCV (m/s( | 55.68 (52.38, 59.17) | 52.46 (48.42, 56.14) | <0.001 |
| Median nerve MNCV (m/s) | 55.52 (52.92, 58.54) | 52.8 (48.54, 56.18) | <0.001 |
| L-median nerve SNCV (m/s) | 53.11 (47.23, 57.73) | 47.62 (41.63, 54.05) | <0.001 |
| R-median nerve SNCV (m/s) | 53.11 (47.05, 58.25) | 47.10 (41.04, 54.65) | <0.001 |
| Median nerve SNCV (m/s) | 52.94 (48.17, 58.25) | 47.16 (41.98, 53.78) | <0.001 |
| L-peroneal never MNCV (m/s) | 46.34 (43.59, 49.61) | 43.48 (38.70, 46.88) | <0.001 |
| R-peroneal never MNCV (m/s) | 46.53 (43.99, 50.47) | 43.59 (38.41, 47.12) | <0.001 |
| Peroneal never MNCV (m/s) | 46.86 (44.12,49.71) | 43.54 (39.09,47.37) | <0.001 |

Data are expressed as mean ± SD, *n* (%) and median (25th and 75th interquartile). *P*-values were determined by the independent *t*-test, Mann–Whitney test and the $\chi^2$-test. 2-h C-peptide, C-peptide 2-h post-prandial; Alt, alanine transaminase; Ast, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; DPN, diabetic peripheral neuropathy; ECG, electrocardiograms; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; L-median nerve MNCV, left limb median nerve motor nerve conduction velocity; L-median nerve SNCV, left limb median nerve sensory nerve conduction velocity; median nerve SNCV, mean sensory nerve conduction velocity of median nerve of left and right limbs; MNCV, motor nerve conduction velocity; L-peroneal never MNCV, left limb peroneal nerve motor nerve conduction velocity; median nerve MNCV, mean motor nerve conduction velocity of median nerve of left and right limbs; QTc interval, heart-corrected QT interval; R-median nerve MNCV, right limb median nerve motor nerve conduction velocity; R-median nerve SNCV, right limb median nerve sensory nerve conduction velocity; R-peroneal never MNCV, right limb peroneal nerve motor nerve conduction velocity; peroneal nerve MNCV; mean motor nerve conduction velocity of peroneal never of left and right limbs; SNCV, sensory nerve conduction velocity; TC, total cholesterol; TG, triglyceride; UA, uric acid; UACR, urine microalbumin-to-creatinine ratio; WHR, waist-to-hip ratio.

diagnosis of DPN was 428.5 ms. As far as the authors know, this is the first study to comprehensively analyze the relationship between QTc interval and DPN.

Guidelines for the diagnosis of DPN require the presence of symptoms and signs, and nerve conduction testing or small fiber function assessment if patients are asymptomatic[1].

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**Table 2** | Diabetic peripheral neuropathy and nerve conduction parameters at different QTc interval

| | QTc Q1 (*n* = 240) <407 ms | QTc Q2 (*n* = 242) 407–422 ms | QTc Q3 (*n* = 242) 422–438 ms | QTc Q4(*n* = 241) >438 ms | *P* for trend value |
|---|---|---|---|---|---|
| DPN (%) | 9.2 | 25.2 | 66.5 | 94.6 | <0.001 |
| L-median nerve MNCV (m/s) | 54.55 (52.01, 58.04) | 54.08 (51.04, 57.93) | 53.95 (50.72, 56.94) | 52.78 (49.44, 57.18) | 0.007 |
| R-median nerve MNCV (m/s) | 55.12 (51.93, 59.26) | 54.48 (51.04, 58.06) | 53.57 (50.11, 57.14) | 52.83 (49.09, 56.76) | <0.001 |
| Median nerve MNCV (m/s) | 55.05 (52.34, 58.05) | 54.52 (51.22, 57.57) | 54.05 (50.87, 56.91) | 53.07 (49.04, 56.78) | <0.001 |
| L-median nerve SNCV (m/s) | 52.26 (46.07, 56.43) | 51.95 (45.72, 52.29) | 49.63 (43.96, 55.82) | 47.62 (41.67, 54.93) | <0.001 |
| R-median nerve SNCV (m/s) | 51.52 (46.24, 57.67) | 51.75 (45.71, 57.89) | 49.11 (43.17, 55.20) | 47.24 (40.82, 55.05) | <0.001 |
| Median nerve SNCV (m/s) | 52.13 (46.57, 56.57) | 51.88 (45.84, 57.41) | 49.24 (44.08, 55.20) | 47.42 (41.70, 54.26) | <0.001 |
| L-peroneal never MNCV (m/s) | 45.45 (42.46, 48.53) | 45.16 (41.97, 48.67) | 44.61 (41.49, 47.51) | 43.94 (39.29, 47.99) | 0.012 |
| R-peroneal never MNCV (m/s) | 45.68 (43.31, 49.72) | 45.45 (41.99, 49.32) | 45.09 (41.67, 48.68) | 43.59 (37.7, 47.96) | <0.001 |
| Peroneal never MNCV (m/s) | 45.55 (42.94, 48.59) | 45.57 (41.62, 49.02) | 45.40 (40.80, 47.81) | 43.96 (38.86, 48.39) | 0.002 |

Data are expressed *n* (%) and median (25th and 75th interquartile). *P*-values for trend were determined by the liner by liner association. DPN, diabetic peripheral neuropathy; L-median nerve MNCV, left limb median nerve motor nerve conduction velocity; L-median nerve SNCV, left limb median nerve sensory nerve conduction velocity; L-peroneal nerve MNCV, left limb peroneal nerve motor nerve conduction velocity; median nerve MNCV, mean motor nerve conduction velocity of median nerve of left and right limbs; median nerve SNCV, mean sensory nerve conduction velocity of median nerve of left and right limbs; MNCV, motor nerve conduction velocity; Q1, the first quartile; Q2, the second quartile; Q3, the third quartile; Q4, the fourth quartile; QTc interval, heart-corrected QT interval; R-median nerve MNCV, right limb median nerve motor nerve conduction velocity; R-median nerve SNCV, right limb median nerve sensory nerve conduction velocity; R-peroneal nerve MNCV, right limb peroneal nerve motor nerve conduction velocity; peroneal nerve MNCV, mean motor nerve conduction velocity of peroneal never of left and right limbs; SNCV, sensory nerve conduction velocity.


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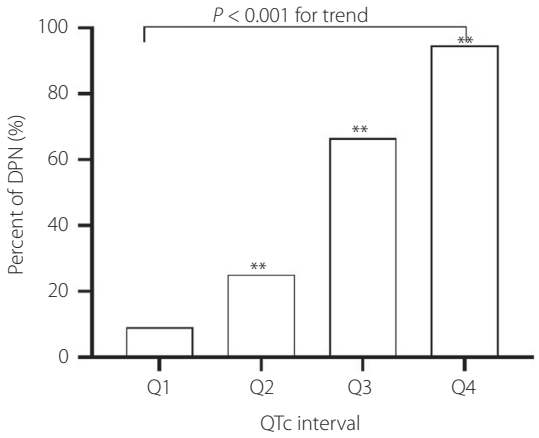


**Figure 1** | The proportion of patients with diabetic peripheral neuropathy (DPN) stratified by QTc interval quartiles. QTc interval, heart-corrected QT interval; Q1, the first quartile; Q2, the second quartile; Q3, the third quartile; Q4, the fourth quartile; $^{**}P < 0.001$.

However, nerve conduction testing is costly, time-consuming and highly technical[15]. In the present study, nerve conduction testing was relatively crude in diagnosing DPN due to its lower AUC. In fact, this is consistent with clinical nerve conduction velocity only detecting large fiber neuropathy[16]. In contrast, we detected too few peripheral nerves, especially only a kind of sensory conduction velocity, which might weaken the diagnostic effect of nerve conduction testing on DPN. With regard to the relationship between age, diabetes duration, UACR and DPN, the Diabetes Control and Complications Trial also reported that older age, longer diabetes duration, macroalbuminuria and sustained albuminuria are most significant risk factors for DPN[17]. Therefore, these risk factors contribute to identifying early DPN. Recently, researchers have tried to discover some more reliable biological markers for DPN. Skin biopsy for intra-epidermal nerve fiber density and corneal confocal microscopy have their own advantages, but the biggest common disadvantage is hard to carry out in various clinical sites[18,19]. The gold biomarker should be accurate, efficient, repeatable, economical, painless, as well as practical and practicable to apply in routine hospitals. To date, researchers have not proposed the ideal biomarker for DPN.

ECG is a rapid and convenient technique, and QTc interval in multiple clinical trials has been shown to play a key role in the assessment of a variety of metabolic disease, including diabetic complications[7], diabetic ketoacidosis[20] and non-alcoholic fatty liver[21]. Subbalakshmi *et al.*[22] found that only female diabetes patients with somatic neuropathy had prolonger QTc intervals compared with healthy controls. The present study expanded the number of participants, adjusted for sex interference, and extended their understanding of the association of QTc interval and DPN to broader diabetes patients. Previous studies have shown that a QTc interval of 440 ms or longer was a risk factor for all-cause and cardiovascular mortality in patients with type 2 diabetes and foot ulcers[23,24]. It has been shown that a QTc interval <440 ms is considered within the normal range[25]. Hashimoto *et al.*[9] reported that a QTc interval of 418 ms was a biomarker for progression of albuminuria. Thus, prolongation of the QTc interval, even within the normal range, could be a biomarker for diseases. In this regard, the diagnosis of a QTc interval of 428.5 ms in the present study was quite clear. Additionally, the QTc interval could boost the sensitivity of nerve conduction testing, meaning the combination of these two measures could further improve diagnostic accuracy.

The mechanism underlying the relationship between QTc interval and DPN is not totally elucidated. Multiple studies have also shown that the QTc interval is associated with age[26], sex[27], hyperglycemia[28] and diabetes duration[29], which are the risk factors for DPN in the present study. Another potential mechanism that contributes to the association between the QTc interval and DPN is ion channel. Hyperglycemic concentration

**Table 3** | Univariate and multivariate analysis to explore relationships between QTc interval and diabetic peripheral neuropathy

| Variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value |
| Age | 1.047 (1.035, 1.059) | <0.001 | 1.030 (1.010, 1.050) | 0.003 |
| Male | 0.483 (0.371, 0.627) | <0.001 | 1.050 (0.678, 1.626) | 0.826 |
| QTc interval | 1.112 (1.097, 1.127) | <0.001 | 1.118 (1.099, 1.137) | <0.001 |
| Diabetes duration | 1.006 (1.004, 1.007) | <0.001 | 1.003 (1.001, 1.006) | 0.010 |
| FPG | 1.000 (0.987, 1.012) | 0.964 | – | – |
| HbA1c | 0.997 (0.979, 1.015) | 0.752 | – | – |
| 2-h C-peptide | 0.942 (0.898, 0.988) | 0.015 | 0.934 (0.860, 1.014) | 0.101 |
| UA | 1.001 (0.999, 1.002) | 0.283 | – | – |
| BUN | 1.186 (1.106, 1.271) | <0.001 | 1.122 (0.991, 1.271) | 0.069 |
| UACR | 1.007 (1.004, 1.011) | <0.001 | 1.004 (1.000, 1.008) | 0.036 |

2-h C-peptide, C-peptide 2-h post-prandial; 95% CI, 95% confidence interval; BUN, blood urea nitrogen; FPG, pasting plasma glucose; HbA1c, Glycosylated hemoglobinA1c; OR, odds ratio; QTc interval, Heart-corrected QT interval; UA, uric acid; UACR, urine microalbumin to creatinine ratio.

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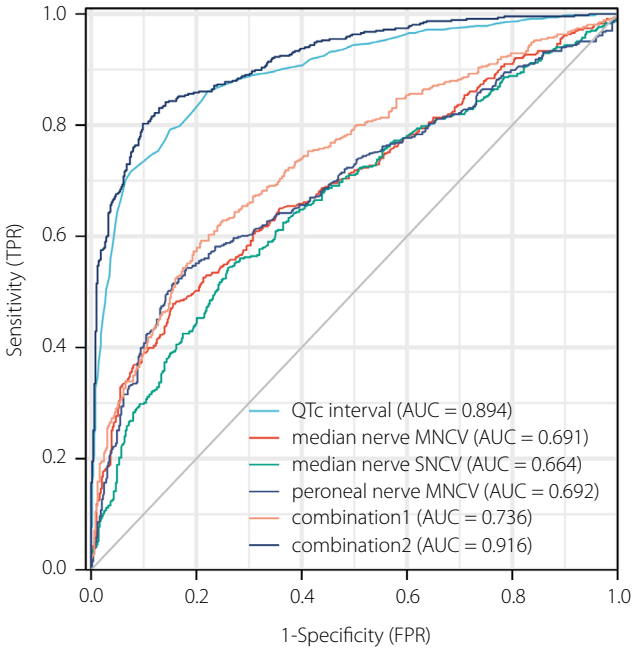


**Figure 2** | Receiver operating characteristic curves for QTc interval and nerve conduction velocity for diagnosis of diabetic peripheral neuropathy. AUC; area under the curve; combination1, a logistic regression model of nerve conduction parameters; combination2, a logistic regression model of QTc and nerve conduction parameters; MNCV, motor nerve conduction velocity; QTc interval, heart-corrected QT interval; SNCV, sensory nerve conduction velocity.

enhances spontaneous sarcoplasmic reticulum $Ca2^{+}$ release events, leading to cardiac mechanical dysfunction and arrhythmias[30]. Finally, the sympathetic nervous excitability has been associated with QTc interval[31]. In a prior study, among 47 diabetes patients, the presence of peripheral sympathetic adrenergic fibers underwent early alterations, even when there are no clinical symptoms of neuropathy[32]. It is regrettable that we did not assess the sympathetic nervous activity.

The present study still had several limitations to improve. First, this was a single-site study and the sample size was relatively small. Second, the majority of DPN was caused by type 2 diabetes in our study; that is, the diagnostic utility between different types of diabetes could not be reflected. Third, as the present study was a cross-sectional study, the cause–effect relationship between QTc interval and DPN cannot be fully proved. Finally, in current clinical practice, the diagnosis of DPN mainly depends on symptoms and signs. It is regrettable we did not separately analyze the diagnostic performance of each symptom and sign.

QTc interval might be a novel biomarker in DPN, and prolonged QTc interval has more reliable diagnostic utility for DPN compared with nerve conduction velocity, which could be assessed easily in various medical facilities. Further longitudinal studies are required to research the relationship between QTc interval and the severity and prognosis of DPN.

## ACKNOWLEDGMENTS

We express our gratitude to all the patients who participated in this study, and thereby made this work possible.

## DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The study protocol was approved by the ethics committee of the Nanjing First Hospital.

Informed consent: Written informed consent was obtained from all participants.

Approval date of registry and the registration no. of the study/-trial: N/A.

Animal studies: N/A.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Supplementary Material** | Methods for five types of peripheral nerve examinations.

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