Prevalence and risk factors of acquired long QT syndrome in hospitalized patients with chronic kidney disease

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ABSTRACT

Patients with chronic kidney disease (CKD) have a high risk of fatal arrhythmias. The extended severe corrected QT (QTc) interval is a hallmark of ventricular arrhythmias and sudden cardiac death. The objective of this study was to evaluate the prevalence of acquired long QT syndrome (aLQTS) in hospitalized patients with CKD and search for potential risk factors to improve clinical risk stratification in patients with CKD. Information about patients with CKD was retrospectively collected in our hospital between January 2013 and June 2017. The prevalence of aLQTS in different stages of CKD was evaluated. The common risk factors for QTc prolongation in patients with CKD were compiled, and multivariable logistic regression analysis was used to evaluate how each factor was related to aLQTS in CKD. A total of 804 patients with CKD (299 females, 37.2%) participated in our study. The prevalence of aLQTS among all 804 patients was 56.97%, and the prevalence of QTc prolongation (>500 ms) was 10.07%. Among the elderly, impaired kidney function, hemodialysis, low serum potassium and low left ventricular ejection fraction (LVEF) were associated with QTc prolongation in patients with CKD. The prevalence of aLQTS is much higher and increases with the decline of kidney function in hospitalized patients with CKD, which is related to older age, impaired kidney function, hemodialysis, serum potassium and low LVEF.

Significance of this study

What is already known about this subject?

- An ECG finding of prolonged severe corrected QT (QTc) predicts adverse cardiovascular events.
- Cardiovascular mortality is high in patients with chronic kidney disease (CKD). Little is known about the prevalence and risk factors of QTc prolongation in inpatients with CKD.

What are the new findings?

- As kidney function declined in hospitalized patients with CKD, the prevalence of acquired long QT syndrome (aLQTS) increased significantly.
- There are multiple factors associated with aLQTS in inpatients with CKD.

How might these results change the focus of research or clinical practice?

- They could increase the amount of emphasis that clinicians place on QTc prolongation in hospitalized patients with CKD.

INTRODUCTION

Chronic kidney disease (CKD) is an increasing public issue with an estimated prevalence of 11%–13%.[1] CKD has become one of the leading causes of death.[2] Patients with CKD more frequently succumb to cardiovascular disease-related complications than progress to end-stage renal disease (ESRD).[3] Notably, CKD leads to a large number of coronary events,[4] and a reduced estimated glomerular filtration rate (eGFR) is an independent risk factor for cardiovascular mortality caused by acute myocardial infarction, heart failure, thromboembolic disease and sudden cardiac death (SCD). These events account for 26.5% of all-cause mortality and 64% of cardiac mortality in ESRD.[5 6]

The severe corrected QT (QTc) interval was longer in individuals with CKD than those without it.[7 8] Cardiac repolarization abnormalities are paralleled with the dysfunction of kidney. The QTc interval increases by 2.9 ms with each increased milligram of serum creatinine.[9] The extended QTc interval is a hallmark of ventricular arrhythmias, SCD and all-cause mortality.[10] However, there are limited data on the relationship between CKD and QTc in hospitalized patients with CKD, even though they suffer from commonly recognized risk factors that affect the QTc interval. In this study, we aim to assess the prevalence of acquired long QT syndrome (aLQTS) in hospitalized patients with CKD and search for potential risk factors.

METHODS

Study population

This study is a retrospective analysis of 804 consecutive Chinese inpatients with CKD

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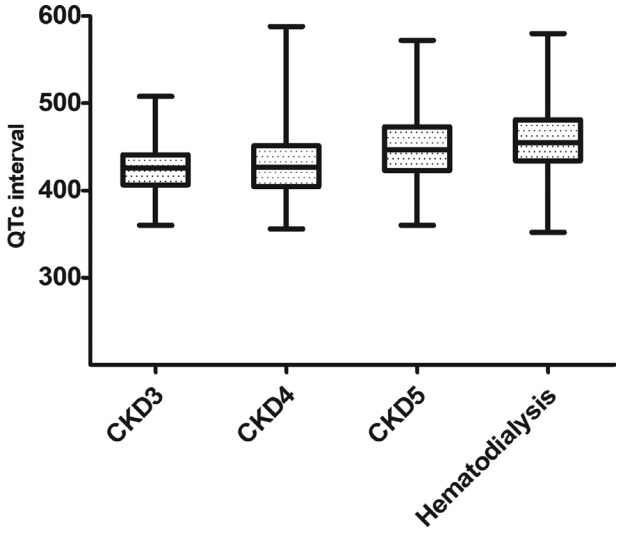

Figure 1 A box and whiskers plot show median, 25th and 75th percentiles and range of QTc in each group.

admitted to the First Affiliated Hospital of Xi'an Jiao Tong University from January 2013 to June 2017. The inclusion criteria were as follows: (1) patients were ≥18 years of age and had been diagnosed with CKD according to the Kidney Disease Improving Global Outcomes 2012 Clinical Practice Guideline for the Evaluation and Management of CKD, which is defined as abnormalities of kidney structure or function that are present for >3 months and impact the health of the patient[11 12]; (2) patients had at least one ECG, which is ordered for every patient that is admitted to our hospital; (3) patients had renal function tests, electrolytes within 48 hours, parathyroid hormone within 3 months and cardiac ultrasound within 6 months. The exclusion criteria were as follows: (1) charted evidence of acute coronary syndromes, cardiac surgery, acute stroke or acute kidney injury; (2) family history of hereditary LQTS; (3) ECG with other cardiac disorders (ie, atrial flutter, atrial fibrillation and atrioventricular block); (4) moderate-to-severe structural heart disease, including valvular stenosis and regurgitation.

The stage of CKD is based on the eGFR and uses the Chronic Kidney Disease Epidemiology Collaboration equation. The stages of CDK are CKD3 (30≤eGFR<60 mL/min), CKD4 (15≤eGFR<30 mL/min) and CKD5 (eGFR<15 mL/min).[13] There were 86 patients with CKD with confirmed pathology reports in the pathology department of our hospital. Hemodialysis patients are those who have begun regular dialysis treatment due to ESDR. The participants include patients who were waiting for a kidney transplant but not kidney transplant recipients. If a patient was admitted to the hospital multiple times over the course of the study period, we only included the admission that had the longest QT interval, compared with the others.

ECG evaluation

Twelve-lead surface ECGs were recorded at a paper speed of 25 mm/s and a voltage of 10 mm/1 mV in the supine position. ECG parameters included heart rate, QT and QTc. The QT intervals were measured in all leads of the ECG, and the longest QT interval was accepted. If a patient was admitted to the hospital multiple times over the course of the study period, we only included the admission ECG that had the longest QT interval. QTc was corrected by the Bazett formula (QTc=QT/(RR interval in seconds)$^{1/2}$). All tracings were studied by two independent investigators, and a consensus was reached in cases where there was a disagreement. Prominent U waves were included in the measurement when they merged into the T wave. The tangent would be drawn in the special type of T wave in order to find the end point of the QT interval.[14] A QTc ≥430 for males and a QTc ≥450 for females was defined as a prolonged QTc.

Clinical data collection

We collected basic information such as age, gender, date of hospitalization, medical insurance, admitting diagnosis and medication history from the electronic medical records. Hemoglobin and serum electrolytes should be tested within 24 hours of the chosen ECG. The parathyroid hormone should be tested within 3 months, and cardiac ultrasound should be completed within 6 months. QT-prolonging drugs refers to drugs listed in the following website: (https://www.crediblemeds.org/med-forms/).

Statistical analysis

IBM SPSS Statistics V.25.0 (IBM Chicago, New York, USA) was used for analysis. Continuous variables were delivered as M±SD and were analyzed using Student's t-test. The Mann-Whitney U test was employed for non-normality distributed variables. The box and whiskers plot shows the median, 25th and 75th percentiles and the range of QTc for each stage of CKD. Numbers and proportions (%) were used for categorical variables and were analyzed by the X^2 test or the Fisher's exact test. The OR and 95% CI were used to express the relationship between the QT interval and the risk factors. The results were considered significant when $p<0.05$. Multivariable logistic regression analysis was used to recognize elements related to aLQTS. Candidate variables in multivariable logistic regression analysis include the factors in which p value is <0.05 in the univariable analysis.

RESULTS

A total of 804 inpatients with CKD participated in this study. The majority of participants (62.8%, 505) were male; the average age of the male patients was 49.37±15.58 years. Females made up 37.2% (299) of the participants, and their average age was 51.30±15.40 years. The proportion of total patients with a prolonged QTc was 56.97% (49.16% in females and 61.58% in males). Severely prolonged (>500 ms) QTc was found in 10.07% of all patients (12.71% in females and 8.51% in males). The prolongation of QTc was made worse by decreased renal function (figure 1). Among patients with CKD stage 3, 4, 5 and patients treated with hemodialysis, the proportion of patients with prolonged QTc and severely prolonged QTc was 32.43% and 1.4%, 40.23% and 6.9%, 59.06% and 10.1% and 64.31% and 12.6%, respectively.

In single factor analysis (table 1), age was not found to be a statistically significant factor between the QTc-prolongation and QTc-normal groups. The proportion of males was greater in the QTc-prolongation group ($p<0.05$), but it did not differ significantly in multiple regression analysis.

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Table 1 Demographic and clinical characteristics of participants

Characteristics	Normal QTc	Prolonged QTc	P values
n	346	458	
Age (year)	49.22±16.141	50.74±15.037	0.168
Male (%)	194 (56.07%)	311 (67.90%)	0.001
Medical insurance			
Basic medical insurance for urban workers (%)	195 (56.36%)	271 (59.17%)	0.726
New rural cooperative medical service (%)	94 (27.17%)	116 (25.33%)	
Self-paying and others	57 (16.47%)	71 (15.50%)	
GFR descriptors and range (%)			
CKD3 (%)	50 (14.45%)	24 (5.24%)	<0.001
CKD4 (%)	52 (15.03%)	35 (7.64%)	
CKD5 (%)	113 (32.66%)	164 (35.81%)	
Hemodialysis (%)	131 (37.86%)	235 (51.31%)	0.352
Diabetes (%)	119 (34.39%)	172 (37.55%)	0.356
Hypertension (%)	143 (41.33%)	214 (46.72%)	0.127
CVD (%)	27 (7.80%)	56 (12.23%)	0.041
Infection of any part (%)	73 (21.10%)	95 (20.74%)	0.902
QT-prolonging antibiotic (%)	49 (14.16%)	84 (18.34%)	0.114
Pathological pattern			
IgA nephropathy (%)	30 (8.67%)	27 (5.90%)	0.775
Lupus nephritis (%)	6 (1.73%)	8 (1.75%)	
Henoch-Schönlein purpura nephritis (%)	7 (2.02%)	8 (1.75%)	
Serum potassium (mmol/L)	4.40±0.83	4.30±0. 80	0.089
Serum calcium (mmol/L)	2.14±0.46	2.00±0.32	<0.001
Hemoglobin (g/L)	97.77±23.78	92.76±21.27	0.002
PTH (pg/mL)	214.46±249.58	280.37±233.64	<0.001
LVEF (%)	64.25±8.77	60.13±10.61	<0.001
Heart rate (bpm)	78.40±15.81	78.59±11.61	0.856

Normal QTc: <430 male, <450 female; prolonged QTc: ≥430 male, ≥450 female.
QTc, corrected QT; GFR, glomerular filtration rate; CVD, cardiovascular diseases; LVEF, left ventricular ejection fraction; PTH, parathyroid hormone; CKD, chronic kidney disease.

Differences in medical insurance were not statistically significant between the QTc-prolongation and QTc-normal groups. The underlying chronic diseases such as hypertension, diabetes and cardiovascular disease (CVD) were more prevalent in the QTc-prolongation group. However, none of them showed a significant difference between the two groups after multiple regression analysis. The presence of infections and the use of QT-prolonging antibiotics did not show significant differences between the two groups. There were 86 patients who had undergone kidney biopsy. The pathological patterns, such as IgA nephropathy (66.28%), lupus nephritis (16.28%) and Henoch-Schönlein purpura nephritis (17.44%), were identified via renal biopsy and showed no significant association with the prolongation of QTc. Patients in the QTc-prolongation group have significantly lower hemoglobin levels and left ventricular ejection fractions. The prevalence of hypokalemia was 11.27% in the QTc-normal group and 12.23% in QTc-prolongation group. The prevalence of hyperkalemia is 12.72% in the QTc-normal group and 8.95% in the QTc-prolongation group (reference value 3.5–5.3 mmol/L). The average potassium level is lower in the QTc-prolongation group, and there is a significant difference between the two groups. The average serum calcium is lower in the QTc-prolongation group, and there is a significant difference between the two groups (reference value 2.11–2.52 mmol/L). Parathyroid hormone levels are higher in the QTc-prolongation group, but there is no significant difference between the two groups.

Factors such as CKD stage, diabetes, hypertension, CVD, age, parathyroid hormone (PTH), serum potassium, serum calcium, hemoglobin, sex and LVEF are included in multivariable logistic regression analysis (table 2). Older age (OR 1.012, 95% CI 1.000 to 1.024), lower serum potassium (OR 0.785, 95% CI 0.649 to 0.949) and lower left ventricular ejection fraction (LVEF) (OR 0.962, 95% CI 0.946 to 0.978) are related to QTc prolongation in patients with CKD. Compared with CKD3, CKD4 (OR 1.20, 95% CI 0.596 to 2.413), CKD5 (OR 2.466, 95% CI 1.329 to 4.577)

Table 2 Risk factors significantly correlated with QTc prolongation in CKD

Characteristics	P values	OR (95% CI)
Age (year)	0.042	1.012 (1.000 to 1.024)
CKD4	0.031	1.200 (1.006 to 2.413)
CKD5	0.004	2.466 (1.329 to 4.577)
Hemodialysis	<0.001	3.345 (1.804 to 6.201)
Serum potassium (mmol/L)	0.013	0.785 (0.649 to 0.949)
LVEF (%)	<0.001	0.962 (0.946 to 0.978)

CKD, chronic kidney disease; LVEF, left ventricular ejection fraction.

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and hemodialysis (OR 3.345, 95% CI 1.804 to 6.201) are more closely associated with QTc prolongation.

DISCUSSION

To analyse the prevalence of and risk factors for QTc-prolongation in patients with CKD, we retrospectively analyzed 804 patients with CKD; 56.97% of patients had aLQTS and 10.07% had severely prolonged QT intervals (QTc >500 ms). The prevalence of QTc prolongation and severe QTc prolongation increased with a decline in kidney function. Multifactor logistic regression was performed to screen for the risk factors for prolonged QTc in all participants. Factors such as age, impaired kidney function, hemodialysis, serum potassium and LVEF are significantly related to aLQTS in patients with CKD.

The prolongation of the QT interval was due to the extended action potential, which is caused by an increased inward current (ie, the sodium or calcium channels) or a decreased outward current (ie, potassium channel). The K^+ currents (I_{Kr} and I_{Ks}) play a key role in myocardial repolarization. A prolonged action potential duration (APD) could lead to early afterdepolarizations that are caused by inward depolarizing currents (L-type Ca^{2+} channels and Na^+-Ca^{2+} exchange currents), which then induce ventricular arrhythmias like torsade de pointes (TdP). Acquired LQTS is affected by a variety of factors and is more prevalent in the elderly population.[15–20] Our research found that the female sex and older age are associated with QTc-prolongation, which is consistent with the findings of previous studies.[21]

The prevalence of LQTS in patients with diabetes is variable, with reported rates ranging from 19% to 44% in different studies.[22 23] The QTc is a significant marker for the progression of albuminuria in people with diabetic nephropathy, and it was related to the severity of diabetic nephropathy.[24] Complications of diabetes, such as hyperglycemia,[25] serum insulin level,[26 27] cardiovascular autonomic neuropathy[25 28] and coronary heart disease[26] were found to be risk factors for QTc prolongation. Diabetes can destroy the human ether-à-go-go-related gene K^+ channels and delay the inactivation of I_{CaL} and I_{BaL}.[29 30] Left ventricular hypertrophy (LVH) reflects the degree of hypertension and is considered to be a manifestation of cardiac myocyte hypertrophy, which is a condition related to 'reduced repolarization reserves'. Hypertension can significantly reduce potassium current densities (I_{peak}, I_{to}, I_{Kur}, I_{ss} and I_{k1}) and increase the L-type calcium channel during the plateau of APD in mice with cardiac hypertrophy.[31 32] Patients with hypertrophic cardiomyopathy often also have QTc-prolongation, which reflects both the severity of the LVH and its prognosis.[33] The prevalence of diabetes and hypertension related to aLQTS are not significantly different between the two groups in our study. Ninkovic *et al* also showed the eGFR had no relationship with the prolongation of QTc in patients with type 2 diabetes.[23] Furthermore, the incidence of LVH gradually increases as GFR falls, and the effect of LVH on QTc interval is impaired when all of the patients with CKD are analyzed together.[34]

The incidence of heart failure increases as renal function decreases.[35] The incidence of aLQTS was from 43% to 72% among patients with heart failure in different clinical trials, and it was approximately 50 ms longer compared with those without heart disease.[36 37] The potential of the dysfunctional I_{Kr}, I_{Ks}, $I_{Ca\text{-}L}$, Na^+/Ca^{2+} exchanger and late INa may contribute to the prolongation of APD in failing hearts.[38 39] The LVEF is lower in the QTc-prolongation group, and the risk of QT prolongation is increased by 0.962 times for every one unit of increased LVEF in multifactor regression analysis.

Hypokalemia and hypocalcemia were found to be strong independent risk factors for QTc prolongation. Hyperkalemia is a well-known complication of CKD, and hypopotassemia is a frequent adverse reaction, especially after a high dosage of diuretics is prescribed. Notably, hypokalemia is almost as common as hyperkalemia in CKD. The prevalence of hyperkalemia is 14%–20%, whereas the prevalence of hypokalemia is 12%–18%.[40–43] Our study showed that the prevalence of hypokalemia was higher than hyperkalemia in both the QT-normal group (11.80% vs 10.56%) and the QT-prolongation group (12.23% vs 8.95%). There was also a significant difference in the levels of serum potassium between the two groups; the risk of QT prolongation increased by 0.785 times for every one unit of increased serum potassium in multifactor regression analysis. Serum calcium is lower in the QTc-prolongation group, which is consistent with the observations of previous studies.[44]

Patients with CKD often take many medications that can cause QT prolongation.[45] Drug pharmacokinetics is complex in patients with CKD. The reduced ability to excrete the drugs increases the sensitivity of CKD patients to these drugs.[46] The QT-prolonging antibiotics were not found to have a significant influence on QTc prolongation in our research. This finding could be influenced by the lack of inclusion of common non-antibiotic QT-prolonging medications in our study (eg, diuretics, antipsychotics, antiarrhythmic and antidepressants).

Secondary hyperparathyroidism is a common complication of CKD. Patch-clamp studies in animal models have demonstrated a modulating effect of PTH on cardiac repolarization through changes in both serum and intracellular calcium concentration.[47] Several studies have shown that the QTc interval was prolonged in patients with secondary hyperparathyroidism; the QTc shortened with treatment as the PTH level came down, although calcium levels did not change.[48] Palmeri *et al* showed that PTH could prolong the plateau of APD, independent of serum calcium levels, both in animals and in patients with coronary artery disease.[49] We analysed the relationship between the QTc interval and PTH levels in patients with CKD. There are no significant differences in PTH levels between the two groups in our study, which suggests that the role of PTH in patients with CKD may be worth further considering.

Renal anemia is a frequent complication found in patients with CKD. The prevalence of QT prolongation in patients with anemia is common.[50 51] Anisocytosis, an early sign of anemia, and macrocytosis are also linked to prolonged QT intervals in hypertensive patients.[52] In patients with ESRD and profound anemia (hemoglobin <90 g/L), each 10 g/L decrease in mean hemoglobin levels was independently associated with increased mortality and cardiac complications.[53] The pathophysiological link between anemia and prolonged QT intervals is, probably, hypoxia, autonomic dysfunction and decreased myocardial oxygen supply. Impairment of delayed rectifier potassium channels and

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calcium channels may explain the changes in repolarization.[54] However, we did not find any literature about renal anemia relating to the QT interval. Hemoglobin levels and the prevalence of anemia are not significantly different between the two groups in our study. The possible reason is that the anemia of CKD is a multifactorial process related to a relative erythropoietin deficiency, uremic-induced inhibition of erythropoiesis, shortened erythrocyte lifespans and disordered iron homeostasis.[55]

Prolonged QTc (as measured by using the Bazett method, where 450 ms was the cut-off for male patients and 460 ms was the cut-off for female patients) is found in 12.9% of the general population, compared with 20.5% of people with CKD.[8] The QTc interval increased by an average of 2.9 ms for each milligram increase in serum creatinine.[9] Our findings are consistent with previous ones. Compared with CKD3, the risk of QTc prolongation is 1.20, 2.47 and 3.35 times in CKD4, CKD5 and hemodialysis patients, respectively. Prolonged QTc is related to unstable myocardial electrical activity and poor cardiovascular outcomes, including TdP and SCD.[56] The prevalence of all-cause and cardiovascular mortality was significantly increased when LQTS was combined with CKD. Hage *et al* observed 280 patients who had been referred for a kidney transplant. Of those, 47% died before having the kidney transplant during the 40-month follow-up period. Patients with a prolonged QTc (39%) had 1-year, 3-year, and 5-year mortality rates of 12%, 36% and 47%, respectively, vs 8%, 24% and 36% for those with a normal QTc.[8 9 57 58] The prolongation of the QT interval is common in patients with CKD. There are numerous factors influencing the QT interval. It is necessary to monitor the QT interval and avoid the factors that can further prolong it in patients with CKD. When TdP is encountered, the QTc interval should be immediately examined before and after the TdP episodes to determine whether it is prolonged. Similarly, we need to distinguish between hereditary LQTS and aLQTS. It is important to distinguish between the two types of LQTS so that CKD can be appropriately managed and clinicians can make the best therapeutic decisions. Further efforts are needed to improve our understanding of the mechanisms by which CKD impacts QTc.

CONCLUSION

The prevalence of aLQTS increases with the decline of kidney function in hospitalized patients with CKD, which correlates with age, impaired kidney function, hemodialysis, serum potassium and LVEF.

LIMITATIONS

This is a single-center retrospective study. Participants were sampled retrospectively by a review of the medical records of inpatients with CKD. We excluded patients who had not had a cardiac ultrasound within 6 months, but only those with some concern for cardiac involvement would have received a cardiac ultrasound during the course of their hospital stays. This may introduce selection bias for eligible participants, and the real prevalence of prolonged QTc may actually be higher. Furthermore, we excluded the patients with unqualified ECGs, and this may also lead to a selection bias. We did not clarify the role of non-antibiotic QT-prolonging medications for the QT prolongation in CKD, and a further study should be done to clarify the role of QT-prolongation drugs. The results are only appropriately applied to inpatients with CKD. We observed a high prevalence of QTc prolongation in CKD, which was related to the LVEF, serum calcium levels and serum potassium levels. We cannot confirm whether QT prolongation is a risk factor for arrhythmias and cardiac death in patients with CKD. Moreover, we did not demonstrate that the management of risk factors for prolonged QTc could decrease the risk of arrhythmias or poor outcomes.

Contributors PL and GL developed the idea for the study. They participated in its design, coordination and data interpretation. They performed the statistical analysis and drafted the manuscript. DH and XS participated in the design of the study and data interpretation. HT, ZW and CL participated in the design of the study and data interpretation. YZ, BL and CS participated in the statistical analysis and data interpretation. PL wrote the paper. All authors have read and approved the final manuscript as submitted.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval This study was approved by the ethics committee of the First Affiliated Hospital of Xi'an Jiao Tong University.

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