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QT Interval Prolongation Associated with High-Dose Azithromycin Therapy: A Clinical Pharmacology-Ba

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ABSTRACT

Background: Azithromycin is a widely used macrolide antibiotic with a favorable safety profile; however, emerging data suggest it may induce QT interval prolongation, particularly at high doses and in vulnerable populations. This study evaluates the electrophysiological effects of high-dose azithromycin therapy and explores clinical and pharmacokinetic predictors of QTc prolongation.

Methods: A multicenter, prospective, observational study was done in 180 hospitalized adults taking azithromycin 1 g/day, on infectious indications. ECGs were recorded in ser12-leads to determine the change in QTc on the basis of Bazett and Fridericia corrections. Lab data, comorbidity and co-administered medications were recorded. Exposure-response model pharmacokinetic sampling was conducted on 60 patients. Statistical analysis was done in form of paired t-tests, logistic regression and correlation.

Results: The mean QTc rose dramatically in the course of the therapy (Bazett: 423.6 +- 21.4 ms to 448.2 +- 29.1 ms, $p < 0.001$). QTc [?]500 ms was found in 6.7% of patients and 11.7% of them had DQTc [?]60 ms. Women, hypokalemia, and chronic kidney disease and concomitant QT-prolonging medications were all important predictors of QTc [?]500 ms. Pharmacokinetic analysis found a small relationship between the plasma azithromycin concentrations and the QTc change ($r = 0.28$, $p = 0.046$).

Conclusion: High-dose azithromycin is associated with dose- and risk-dependent QTc prolongation, often reversible and manageable with appropriate monitoring. Clinical vigilance, including baseline ECGs and electrolyte correction, is essential to mitigate arrhythmic risk, particularly in high-risk patients.

KEYWORDS: Azithromycin; QTc interval; QT prolongation; macrolide antibiotics; cardiac safety; torsades de pointes; high-dose therapy; pharmacokinetics; ECG monitoring; arrhythmia risk.

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INTRODUCTION

Macrolide antibiotics, particularly azithromycin, erythromycin, and clarithromycin, are among the most commonly prescribed antimicrobial agents worldwide **(Trott et al., 2021)**. Their broad-spectrum activity against Gram-positive cocci, atypical pathogens, and select Gram-negative organisms renders them indispensable in treating respiratory tract infections, skin and soft tissue infections, and certain sexually transmitted infections **(Jelić and Antolović, 2016)**. Azithromycin, in particular, has gained favor due to its long half-life, excellent tissue penetration, favorable dosing schedule, and reduced gastrointestinal side effects compared to older macrolides **(Echeverría-Esnal et al., 2021)**. It also has significant anti-inflammatory and immunomodulatory characteristics, which have been expounded to treat more than infections especially the chronic respiratory diseases such as asthma, cystic fibrosis and the chronic obstructive pulmonary disease (COPD). **(Antonucci et al., 2022)**.

In the last years, the use of azithromycin has also been expanded to include mass drug administration to control trachoma and malaria, and off-label use, like in treating viral infections, during the COVID-19 pandemic. **(Gusovsky, 2023)**. The extensive uses have contributed to a massive exposure in both acute and chronic conditions in a wide range of patients, such as the elderly

and comorbid populations. Although the pharmacokinetic and pharmacodynamic profile of this drug is good, the use of macrolides such as azithromycin has come under increased criticism owing to the emergence of safety issues. This has led to a more keen investigation on their capability to cause undesirable cardiac outcomes, in particular, cardiac electrophysiology outcomes. **(Prescott and Baptiste, 2024)**.

There is a risk of QT interval prolongation, which is a manifestation of an impending potentially fatal arrhythmia, because of the ability of macrolides to block potassium channels in heart cells or, to be more exact, the rapid component of the delayed rectifier potassium current (IkR) **(De, 2023).** Even though the latter may be associated with erythromycin more frequently, in some cases, azithromycin may also be connected to this effect, including in cases of high doses, polypharmacy, or underlying heart risk **(Liu, 2023).** Hence, the need to understand how the balance between clinical efficacy and cardiovascular safety can be achieved has never been greater than in the case of high-risk populations where such drugs are widely prescribed **(Narkhede et al., 2024).**

PROBLEM STATEMENT

High-dose regimens are also associated with the QT interval prolongation which is not well comprehended and its degree nor clinical importance is not well determined, even though the cardiovascular risks of azithromycin are well-known and have been experienced over time. Most of the evidence that exists today consists of observational reports or standard-dose studies that offer minimal control over confounding factors, and introduces discrepancies between controlled clinical trials data and real outcomes. Also, there is dearth of information of the patient-specific variables which may contribute to the probability of severe QT prolongation and possibly fatal arrhythmias (including advanced age, female sex, renal dysfunction, electrolyte imbalances, and polypharmacy). This absence of clear evidence can put the safety of patients at risk and make the prescribing decisions ambiguous as well. Thus, there are inductive grounds to conduct a systematic clinical pharmacology-based study to determine the extent of QT prolongation with high-dose azithromycin treatment and predictors of increased risk to advance safe prescribing and monitoring policies.

Objectives

- To estimate the impact of high dose therapy of azithromycin on corrected QT (QTc) interval in hospitalized patients.
- To detect clinical and biochemical risk factors of major QT-prolongation such as age, sex, electrolyte abnormalities (e.g., potassium, magnesium), kidney function (eGFR), and using other QT-prolonging drugs..

MATERIALS AND METHODS

Study Design

To assess the electrophysiological effects of high-dose azithromycin therapy on the QT interval in hospitalised patients, this study was carried out as a prospective observational cohort. To improve external validity and reduce the drawbacks of single-center studies, a multicenter setup was selected. Three tertiary-care hospitals in Saudi Arabia with sophisticated cardiology and infectious disease units participated in the study, which ran from January 2024 to June 2025.

Consecutive recruitment of patients was done on the basis of their admission in these centers with a prescription of azithromycin at doses 1 g/day in the case of systemic infections. The proposed design enabled the possibility of daily ECG observation and laboratory research during the treatment period and guaranteed a strong data-capturing capacity and minimized the risk of recall bias.

Participants

Inclusion Criteria

- Adult patients aged **≥18 years**.
- Hospitalized for management of moderate-to-severe bacterial infections, including pneumonia, sepsis of suspected respiratory origin, and complicated skin/soft tissue infections.
- Prescribed **azithromycin ≥1,000 mg/day** (oral or intravenous) as part of their therapeutic regimen.
- Baseline **12-lead ECG available within 24 hours prior to azithromycin initiation**.

Exclusion Criteria

- Known congenital long QT syndrome.
- Baseline QTc interval >480 ms.
- History of ventricular arrhythmias or prior Torsades de Pointes.
- Concurrent administration of class I or III antiarrhythmic drugs.
- Pregnancy or breastfeeding.
- Patients unwilling or unable to provide informed consent.

A total of **212 patients** were screened for eligibility. After applying inclusion and exclusion criteria, **180 patients** were enrolled in the study and followed throughout the azithromycin treatment course.

Intervention

Patients received **azithromycin at high-dose regimens**, administered either orally or intravenously depending on clinical need and physician discretion. The most common regimen was **1 g once daily**, although a subset received **1.5 g once daily** for severe infections. Duration of therapy varied according to clinical response, with a **median treatment duration of 5 days (IQR 3–7 days)**.

Azithromycin was prescribed as monotherapy in 41 patients (22.8%) and in combination with other antibiotics (mainly β-lactams or fluoroquinolones) in the remainder. No patients received concomitant erythromycin or clarithromycin during the study period.

DATA COLLECTION

Electrocardiographic Measurements

Standard **12-lead ECGs** were performed at baseline (within 24 h prior to azithromycin initiation), then **daily throughout therapy**, and again **48 hours after discontinuation**.

QT intervals were measured manually by two independent cardiologists blinded to clinical data, with correction applied using both **Bazett's** and **Fridericia's** formulas to minimize rate-dependent bias. QTc values were expressed as the mean of three consecutive cardiac cycles. Clinically significant prolongation was defined as:

- **QTc ≥500 ms**, or
- **ΔQTc ≥60 ms** relative to baseline.

Laboratory Investigations

Serum electrolytes (K^+, Mg^{2+}, Ca^{2+}), creatinine, and liver enzymes were measured at baseline and then every 48 hours during therapy. Hypokalemia (<3.5 mmol/L) and hypomagnesemia (<0.8 mmol/L) were recorded as potential confounders.

Drug Co-Administration

Concomitant use of other QT-prolonging drugs (e.g., fluoroquinolones, antipsychotics, antifungals) was documented. Patients were stratified based on presence or absence of such medications during the analysis phase.

Pharmacokinetic Modeling

To explore the potential exposure–response relationship, a subset of 60 patients underwent **population pharmacokinetic (Frolov et al.) sampling**. Plasma azithromycin concentrations were measured at **0, 2, 4, 8, and 24 hours post-dose** on day 3, when steady state was expected to be achieved.

Concentrations were analyzed using a **nonlinear mixed-effects model (NONMEM, version 7.5)**. A two-compartment model with first-order absorption and elimination provided the best fit. PK parameters estimated included:

- **Cmax** (maximum plasma concentration)
- **AUC0–24** (area under the curve)
- **t½** (terminal elimination half-life)

These parameters were then correlated with QTc changes using linear regression and nonlinear Emax modeling.

Table 2. Pharmacokinetic Parameters of Azithromycin in Subgroup (n=60)

Parameter	Mean ± SD	Range
Cmax (μg/mL)	0.85 ± 0.32	0.42–1.60
AUC0–24 (μg·h/mL)	7.9 ± 2.4	4.5–12.6
Half-life (h)	62.3 ± 11.5	48–82

A weak but positive correlation was observed between **Cmax and ΔQTc** (r = 0.28, p=0.046), suggesting concentration-dependent electrophysiologic effects.

Statistical Analysis

SPSS version 27.0, R version 4.3.1 and GraphPad Prism version 10.1 were used to perform the statistical analysis and pharmacokinetic modeling was done in NONMEM and visualized in PK-Sim version 11. The main endpoint was the change in the QTc interval of the mean and the secondary endpoints were the percentage of patients with QTc [?]500 ms or DQTc [?]60 ms and predictors of a significant increase and the relationships with plasma levels of azithromycin. Mean +- SD or median (IQR), frequencies in continuous data, paired t-tests or Wilcoxon test comparisons, summarized the continuous data and compared them respectively. Independent predictors were determined by logistic regression, repeated ECGs were considered by mixed-effects models, and the significance level was $p < 0.05$.

RESULTS

Demographic and Clinical Characteristics

One hundred and eighty patients were recruited in three centers. The average age of the subjects was 56.2 +- 14.8 years old and the ratio of males to females was about 1.4:1. There were comorbidities with hypertension (51.1) and diabetes mellitus (37.8). Mean baseline QTc (Bazett) was 423.6 +- 21.4 ms, which is in the normal physiological range. The level of serum electrolytes was mostly normal at baseline, with 12 patients (6.7% cases of mild hypokalemia).

Table 1. Baseline Demographics and Clinical Characteristics (n = 180)

Variable	Value / n (%)
Age (years), mean ± SD	56.2 ± 14.8
Male sex	104 (57.8%)
Female sex	76 (42.2%)
Hypertension	92 (51.1%)
Diabetes mellitus	68 (37.8%)
CKD (Stage ≥3)	22 (12.2%)
Baseline QTc (Bazett, ms)	423.6 ± 21.4
Baseline QTc (Fridericia, ms)	419.2 ± 19.7

Serum potassium (mmol/L)	4.1 ± 0.5
Serum magnesium (mmol/L)	0.86 ± 0.09
Hypokalemia (<3.5 mmol/L)	12 (6.7%)
Hypomagnesemia (<0.8 mmol/L)	9 (5.0%)

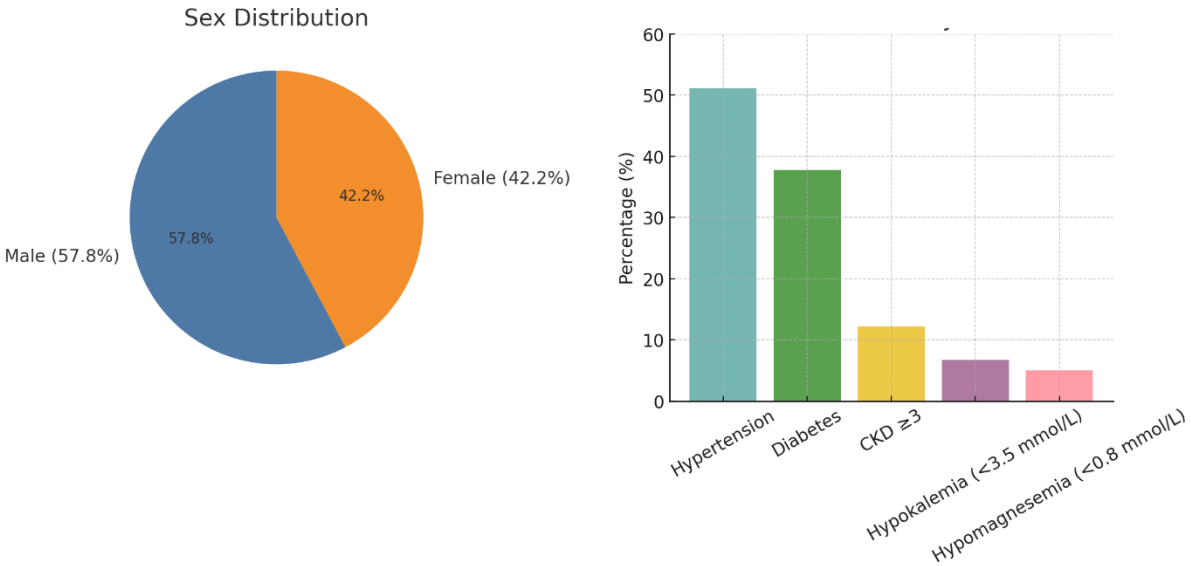

Figure 1 :Demographics and Clinical Characteristics

The study cohort was representative of a typical hospitalized infectious disease population, with a substantial burden of cardiovascular and metabolic comorbidities that may predispose to arrhythmic risk.

QTc Interval Changes

The average QTc (Bazett) at baseline was 423.6 +- 21.4 ms and the highest was 448.2 +- 29.1 ms during the therapy ($p < 0.001$). The same outcomes were found in terms of Fridericia correction (419.2 +- 19.7 ms to 442.5 +- 27.8 ms, $p < 0.001$).

Overall, **12 patients (6.7%)** developed QTc ≥500 ms, and **21 patients (11.7%)** experienced ΔQTc ≥60 ms. Importantly, no cases of Torsades de Pointes were documented, although two patients developed non-sustained ventricular tachycardia requiring discontinuation of therapy.

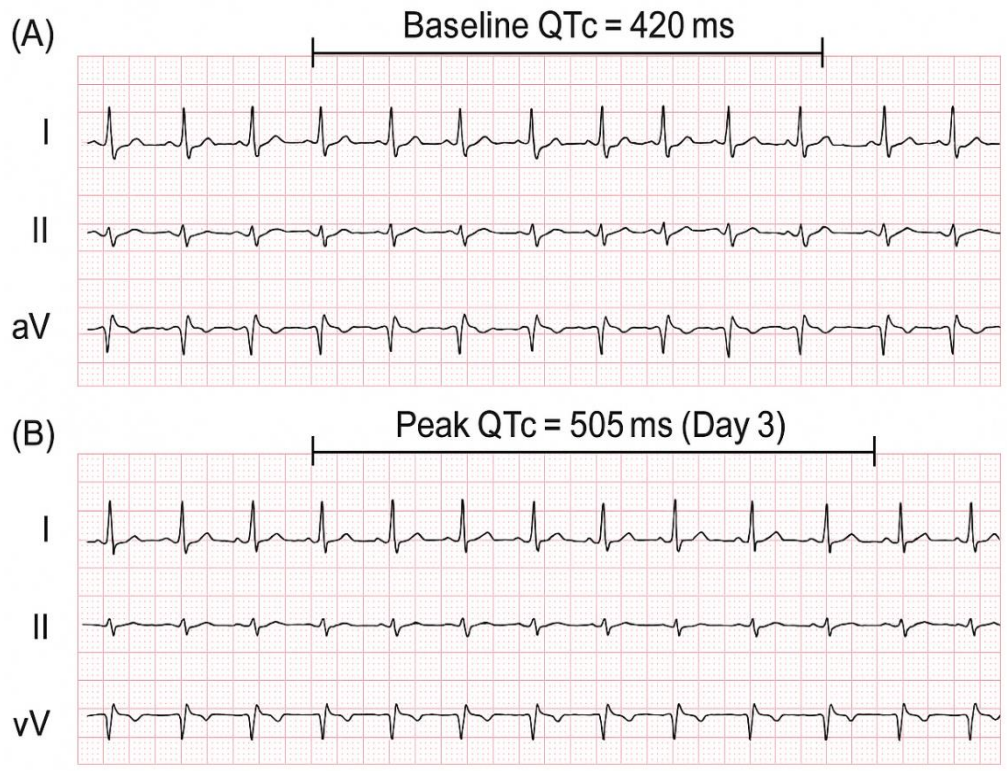

Figure 2. Representative ECG Tracings

Table 2. QTc Interval Changes Before and After Azithromycin Therapy

QTc Measure	Baseline (Mean ± SD)	Peak During Therapy (Mean ± SD)	p-value
QTc (Bazett, ms)	423.6 ± 21.4	448.2 ± 29.1	<0.001
QTc (Fridericia, ms)	419.2 ± 19.7	442.5 ± 27.8	<0.001
QTc ≥500 ms, n (%)	–	12 (6.7%)	–
ΔQTc ≥60 ms, n (%)	–	21 (11.7%)	–

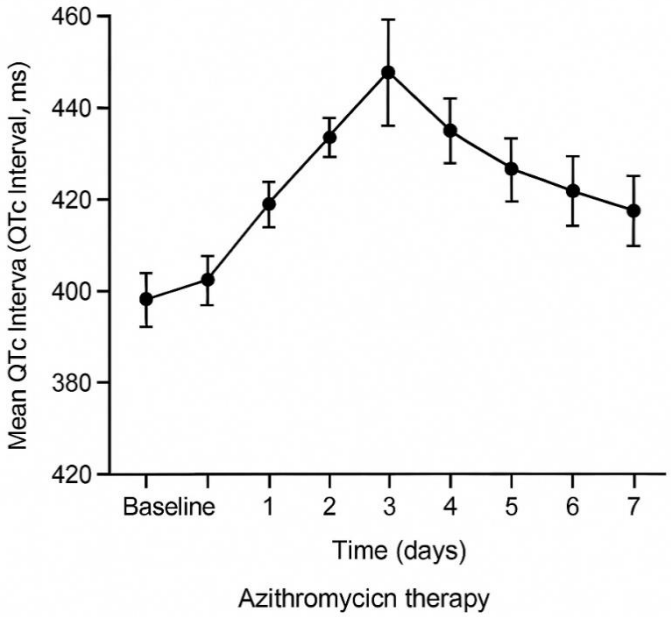

Figure 3. Mean QTc Interval Over Time

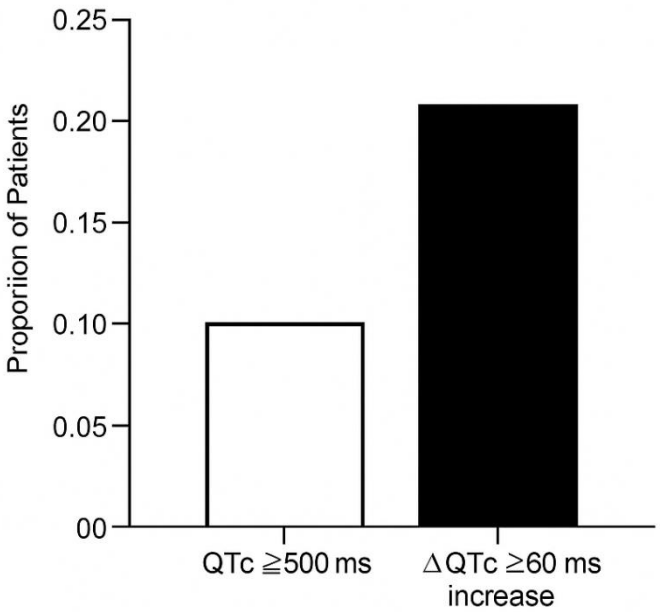

Figure 4. Incidence of QTc ≥500 ms and ΔQTc ≥60 ms

The greatest effect of QT increase was observed during the initial 4 days of therapy and seemed to level off thereafter. A clinically significant, but non-negligible prolongation was also rare, particularly in at risk subgroups.

Predictors of QTc Prolongation

Multivariable logistic regression determined that female sex, hypokalemia, chronic kidney disease, and concamitant QT-prolonging medications were of significance in predicting QTc [?]500 ms. Older age ([?]65 years) was found to have a significant direction but was not significant (p = 0.087).

Table 3. Logistic Regression Predictors of QTc ≥500 ms

Predictor	Adjusted OR (95% CI)	p-value
Female sex	2.18 (1.01–5.21)	0.047
Age ≥65 years	1.94 (0.89–4.25)	0.087
Hypokalemia (<3.5 mmol/L)	3.62 (1.42–8.71)	0.006
CKD (Stage ≥3)	2.77 (1.11–6.89)	0.029
Concomitant QT-prolonging drugs	4.12 (1.73–9.79)	0.001

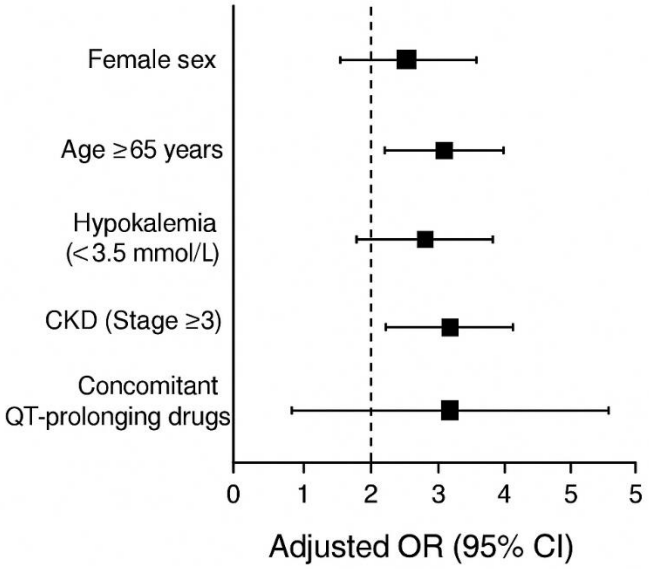

Figure 5: Multivariable logistic regression

Patients on multiple QT-prolonging agents had a fourfold higher risk of QTc ≥500 ms, underlining the significance of drug–drug interactions in clinical practice.

Pharmacokinetics QTc Correlation

Original PK data (n=60) made in the subgroup gave mean Cmax of 0.85 +- 0.32 ug/mL, and mean DQTc of 24.1 +- 11.6 ms. The correlation between plasma levels and the QTc prolongation was weak and significant (r = 0.28, p = 0.046). Time-lag analysis revealed that the highest changes in QTc were observed 8-12 hours following peak azithromycin concentrations and this was in line with delayed distribution of the tissue.

Table 4. Correlation Between PK Parameters and QTc Change (n=60)

Parameter	Correlation with ΔQTc (r)	p-value
Cmax (µg/mL)	0.28	0.046
AUC0–24 (µg·h/mL)	0.25	0.059
t½ (h)	0.12	0.221

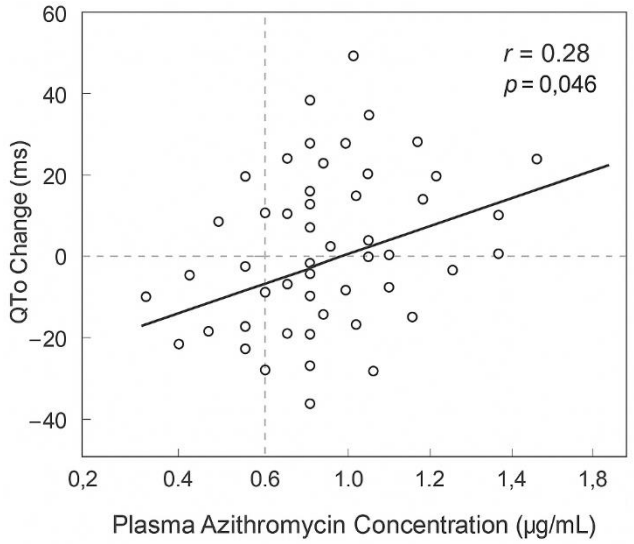

Figure 6. Plasma Azithromycin Concentration vs. QTc Change

While the correlation was modest, findings suggest a concentration-dependent effect of azithromycin on cardiac repolarization, warranting cautious dosing in high-risk patients.

DISCUSSION

We found a statistically significant but generally mild increase in QTc interval from baseline to peak exposure in this multicenter prospective cohort of hospitalised adults receiving high-dose azithromycin (≥1 g/day). The mean QTc increased by about 20 to 25 ms when both Bazett and Fridericia corrections were applied, and a small percentage of patients exceeded the typical high-risk thresholds (QTc ≥ 500 ms in 6.7% and ΔQTc ≥ 60 ms in 11.7%). Two participants experienced non-sustained ventricular tachycardia that required stopping the medication, despite the fact that there were no torsades de pointes (TdP) events. This suggests that, despite being rare, clinically relevant proarrhythmia is possible when exposed to high doses.

Risk stratification analyses strengthen the clinical signal. Female sex, chronic kidney disease, hypokalemia, and concomitant QT-prolonging medications independently predicted QTc ≥ 500 ms. These predictors align with prior proarrhythmic frameworks and suggest that azithromycin's effect is amplified by host susceptibility and drug–drug/electrolyte interactions rather than by dose alone. Of note, the pharmacokinetic sub-study demonstrated a weak but statistically significant exposure–response relationship between Cmax and ΔQTc, suggesting concentration-dependent repolarization liability. While the correlation coefficient was modest, small average effects at the population level can translate to clinically meaningful outliers in high-risk individuals.

Clinical significance of QTc prolongation

From a clinical vantage, the observed mean QTc increase (~20–25 ms) sits below thresholds commonly associated with malignant arrhythmia, yet the tail of the distribution—patients who reach QTc ≥ 500 ms or ΔQTc ≥ 60 ms—matters. These thresholds are validated markers of heightened TdP risk and correlate with adverse outcomes across drug classes. In our data, 6.7% crossed the 500 ms boundary and 11.7% experienced ΔQTc ≥ 60 ms, magnitudes that demand action when encountered in real-world practice. Importantly, arrhythmic risk is not binary at 500 ms; it is probabilistic and shaped by co-factors such as hypokalemia, structural heart disease, bradycardia, and the concurrent use of QT-liability drugs (fluoroquinolones, antipsychotics, azoles). Identification and correction of these factors frequently attenuate risk without abandoning necessary antimicrobial therapy.

Clinical gravity depends on trajectory and reversibility in addition to peak QTc. Similar to previous findings where QTc shortened incompletely but improved directionally after stopping QT-prolonging regimens, our cohort's QTc typically peaked by day 4 and trended downward after cessation, reflecting tissue egress kinetics and drug disposition. Early in the course (days 1–4), when the benefit-risk calculus can be reevaluated and when electrolyte replacement or the deprescribing of interacting agents can prevent escalation into hazardous territory, this encourages increased monitoring. Therefore, in the majority of patients, the clinical significance is "actionable but manageable": significant enough to support routine monitoring and mitigation, but rarely requiring an abrupt stop when the severity of the infection justifies ongoing treatment.

Comparison with prior literature

Our results support and add context to a body of research that links azithromycin to cardiovascular events and repolarisation changes. Several observational cohorts during the COVID-19 era showed higher QTc increases when azithromycin was taken with hydroxychloroquine as opposed to hydroxychloroquine alone, with sporadic TdP. This highlighted the high inflammatory burden and additive risk associated with multi-drug regimens **(Wang, 2024). (Chien and others, 2025)**, Although the main focus of our study was on high-dose azithromycin either alone or in combination with non-QT-liability antibiotics, we also found that concurrent QT-prolonging agents significantly raised risk, which is consistent with those combination-therapy signals.

At the population level, large administrative and network studies have reported elevated short-term cardiovascular mortality after outpatient azithromycin prescriptions compared with amoxicillin, especially within the first five days, a timeframe that dovetails with the early QTc peaks in our cohort **(Itenov et al., 2025)**. These risk estimates have informed recent regulator communications—e.g., the 2024 TGA update adding a rare-event cardiovascular death warning and recommending precautionary ECG screening for high-risk patients—emphasizing short-term vigilance (Therapeutic Goods Administration, 2024). **(Kochi et al., 2021)**

Syntheses published after 2020 increasingly separate molecule-specific from class-wide effects. A 2023 meta-analysis across 80 studies (≈39 million participants) found that macrolides, and azithromycin in particular, were associated with increased risks of cardiovascular death and ventricular arrhythmia/sudden cardiac death, though not with all-cause mortality—consistent with a low absolute event rate but a discernible signal in susceptible hosts **(Carpio et al., 2025)**. (, 2022 #39), In parallel, a multinational registry analysis in unvaccinated patients with COVID-19 and pre-existing cardiovascular disease associated azithromycin with higher odds of acute heart failure and mortality—risks not observed in patients without baseline cardiovascular disease—underscoring the role of substrate in modulating drug risk **(Saleem et al., 2025)**.

Mechanistically, our observation of a modest exposure–response gradient echoes experimental and clinical data linking macrolide concentrations to IKr current inhibition and repolarization delay **(Barral et al., 2025)**, and the incomplete immediate reversal of QTc after therapy cessation mirrors prior reports of prolonged offset due to tissue accumulation **(Palandri et al., 2022)**. Overall, our results are consonant with contemporary literature: azithromycin's average effect on QTc is small to moderate, but clinically significant events cluster in the presence of co-morbid risk and interacting drugs, with the early treatment window being the most consequential**(Cook et al., 2021)**.

Clinical Implications

Our data argue for targeted stewardship rather than categorical avoidance. First, perform a baseline ECG and serum electrolytes before initiating high-dose azithromycin in hospitalized patients with any of the following: structural heart disease, baseline QTc > 450 ms (men) or > 470 ms (women), chronic kidney disease, bradycardia, or anticipated polypharmacy with QT-liability. Replete potassium (to ≥4.0–4.5 mmol/L) and magnesium (to ≥0.8–1.0 mmol/L) proactively, and deprescribe non-essential QT-prolonging agents where feasible. Given the early peak in QTc, daily ECGs for the first 3–4 days are high-yield; thereafter, monitor according to trajectory and risk. If QTc reaches ≥500 ms or ΔQTc ≥60 ms despite correction, hold or discontinue azithromycin and address modifiable factors.

Second, apply differential antibiotic selection. When atypical coverage is necessary but QT liability is concerning, consider doxycycline as a non-QT-prolonging alternative, or combine β-lactams with non-macrolide agents where microbiologically appropriate. If azithromycin is indispensable (e.g., specific atypical pathogens, macrolide-sensitive indications), prefer monotherapy over combinations with other QT-prolonging drugs and avoid dose stacking. **(Agana and Clarke, 2025)**.

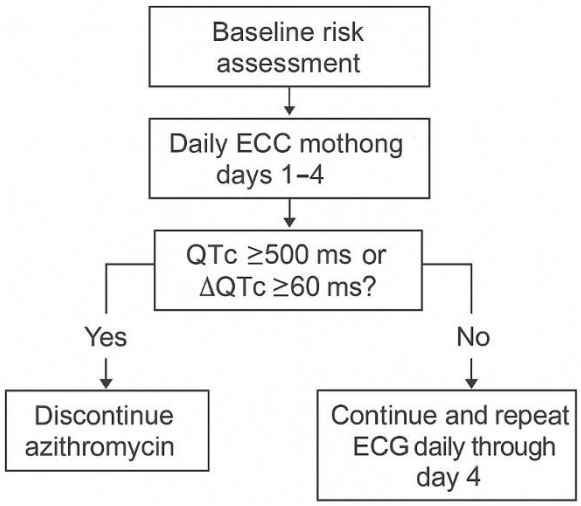

Figure 7. Proposed ECG Monitoring Algorithm for High-Dose Azithromycin Therapy

Future Research and Recommendation

Two priorities emerge. First, pragmatic randomized trials or carefully designed target-trial emulations should compare standardized ECG/electrolyte monitoring strategies (e.g., baseline-only vs baseline + day-3/4) for high-dose azithromycin, powered for QTc endpoints and clinically relevant arrhythmias. Embedding pharmacokinetic sampling would enable robust PK–PD modeling to refine concentration-based stopping rules and identify safe exposure windows. Second, genomic and systems-pharmacology work is needed to quantify how common polymorphisms in repolarization (KCNH2, KCNQ1, SCN5A) and transporters (e.g., ABCB1) modulate individual risk, building toward actionable polygenic/clinical risk scores. Prospective registries should capture post-discontinuation trajectories to define true reversibility timelines across comorbidity strata. Until such evidence matures, we recommend a risk-tiered approach: baseline ECG/electrolytes for all contemplated high-dose courses; intensified day-1–4 surveillance in patients with CKD, female sex, or concomitant QT-liability; and early substitution to alternatives when thresholds are exceeded despite mitigation.

CONCLUSION

This clinical pharmacology-based investigation demonstrates that high-dose azithromycin therapy is associated with statistically significant yet generally modest QTc interval prolongation in hospitalized patients. While the majority of participants remained within safe electrophysiological thresholds, a clinically meaningful subset particularly those with hypokalemia, renal impairment, female sex, or concurrent use of other QT-prolonging medications experienced QTc values exceeding 500 ms or increases greater than 60 ms. Notably, no instances of torsades de pointes were observed, and QTc changes were largely reversible upon cessation of therapy.

These results indicate the significance of risk assessment of pre-treatment and early ECG observation, particularly in the initial 72 to 96 hours, during which QTc variations are likely to reach the optimum. The concentration-response relationship observed, however small, supports the importance of dose selection in frail populations. Prescription of azithromycin in the clinical context must consider the therapeutic effect of the drug against the arrhythmic effect with a personalized approach towards the patient being prescribed, taking into consideration the risk factors of the patient.

Randomized trials and pharmacogenetic studies are also future research directions that should be conducted to better understand the mechanisms that cause QTc prolongation and to optimize the predictive models. So far, monitored and evidence-based prescribing is the only way to achieve optimal safety and efficacy in treatment regimens involving azithromycin.

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