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Effect of Macrolide and Non-Macrolide Therapy on QTc Interval Prolongation in Cardiac Patients with Community-Acquired Pneumonia

Abstract

Introduction. Azithromycin is a macrolide antibiotic widely used to treat various infectious diseases, such as respiratory infections. Several studies have reported an association between azithromycin and QT interval prolongation. QTc prolongation is one of the causes of the life-threatening arrhythmia torsade de pointes (TdP). Torsade de pointes has been reported in approximately 1 % of patients with QT interval prolongation after exposure to azithromycin.

Aim. This study aims to determine the effect of macrolide and non-macrolide regimen therapy on the prolongation of the QTc interval in cardiac patients with community-acquired pneumonia.

Materials and Methods. This is a retrospective cohort study of 33 cardiac patients with community-acquired pneumonia who received macrolide and non-macrolide therapy during hospitalization. Serial electrocardiograms were performed on days 1, 3, 5, and pre-discharge to evaluate the QTc interval.

Outcomes. In the group of heart disease patients with community-acquired pneumonia who received macrolides, there was a significant prolongation of the QTc interval ($p<0.05$) in the independent T-test, Mann-Whitney test, and Friedman test. Risk factors of age, female gender, history of hypertension, and diabetes mellitus had a significant effect ($p<0.05$) in the Friedman test.

Conclusions. This study shows that macrolide therapy in heart disease patients with community-acquired pneumonia significantly and consistently prolongs the QTc interval throughout the treatment period compared with non-macrolide therapy. Risk factors include age, female gender, history of hypertension, and diabetes mellitus.

Keywords: *antibiotics, heart disease, cardiotoxicity, Electrocardiographic changes, drug safety*

Introduction. The macrolide class of antibiotics is widely utilized in clinical settings for a broad range of bacterial infections. Macrolide have been associated with prolongation of the QT interval and development of the polymorphic ventricular tachycardia such as torsades de pointes (TdP) [1]. In a 2020 scientific statement, the American Heart Association (AHA) classified azithromycin, clarithromycin, and erythromycin as QT-prolonging drugs. The mechanism of this risk has been delineated to involve macrolide binding to, and blockade of, delayed rectifier potassium channels that conduct the rapid potassium current Ikr during repolarization, leading to prolonged repolarization and subsequent QT prolongation [2].

Analysis of case reports in which azithromycin has been associated with QT interval prolongation suggests that this occurs in the presence of specific risk factors [3]. Despite these concerns, azithromycin remains recommended due to its high efficacy in controlling infections and its relatively low incidence of other adverse effects.

Community-acquired pneumonia (CAP) refers to infectious inflammation of the lung parenchyma. CAP has a high mortality and morbidity rate worldwide, especially among elderly patients. The increasing burden of CAP

is due to antibiotic resistance, the growth of the elderly population, and underlying comorbidities in older adults [4]. For severe CAP, the Australian Therapeutic Guidelines suggest that azithromycin is recommended [5].

While the relationship between macrolide antibiotics such as azithromycin and QT interval prolongation has been demonstrated to be statistically significant, recent studies have yielded conflicting results. Even though the effects of QT prolongation have been milder in the general population, it may increase the risk of mortality in patients with pre-existing cardiac abnormalities. Patients with diabetes were reported to have a higher prevalence of QTc prolongation. Although the association of QTc prolongation with various risk factors and diabetic complications has been reported in many studies, the findings have been inconsistent. These newer observations suggest that the risk of QT interval prolongation may not be elevated in all patients but may be confined to specific risk groups [5].

Based on these observations, we hypothesized that administration of macrolides could lead to QTc interval prolongation in cardiac patients with community-acquired pneumonia treated at our Integrated Cardiac Center. Therefore, this study aimed to determine the effect of administering macrolides (e.g., azithromycin) and non-macrolides on QTc interval prolongation in cardiac patients with community-acquired pneumonia.

Materials and Methods

Study design and patient characteristics

This study employed an observational retrospective cohort design. Data were collected retrospectively from cardiac patients hospitalized at the Integrated Cardiac Center of Dr. Wahidin Sudirohusodo General Hospital in Makassar. Sampling commenced in April 2024 and continued until the desired sample size was achieved.

The study included cardiac patients aged 18 years or older who were diagnosed with community-acquired pneumonia and received either macrolide or non-macrolide antibiotic regimens. Patients were excluded if they had a history of QT interval prolongation or a baseline ECG showing a QTc interval greater than 450 ms. Additionally, patients receiving medications known to affect the QT interval, such as moxifloxacin, delamanid, digoxin, amiodarone, or azole antifungals, were excluded from the study. Patients with a history of significant cardiovascular arrhythmias, including second- or third-degree atrioventricular block or other clinically significant arrhythmias, were also excluded.

Furthermore, individuals with significant electrolyte disturbances identified through laboratory examinations, those unwilling to participate in the research procedures, or those lost to follow-up were not included in the study.

Patients were monitored, and ECG data were collected on days 1, 3, 5, and at predischarge. Sampling was consecutive and included all patients meeting the inclusion and exclusion criteria until the required sample size was reached.

The research protocol was submitted for approval to the Biomedical Research Ethics Committee of the Faculty of Medicine, Hasanuddin University, and the Integrated Heart Center at Dr. Wahidin Sudirohusodo General Hospital. All procedures were conducted in accordance with ethical standards.

Outcome measure

QT interval prolongation was defined as a QTc interval exceeding 450 ms in men and 470 ms in women, corrected for heart rate on the ECG spectrum. The severity of QTc prolongation was classified into four grades:

- Grade 1: QTc >480 ms and ≤500 ms with a change from baseline >0 ms and ≤30 ms, or QTc ≤480 ms with a change from baseline >30 ms and ≤60 ms.
- Grade 2: QTc >480 ms and ≤500 ms with a change from baseline >30 ms and ≤60 ms, or QTc ≤480 ms with a change from baseline >60 ms.
- Grade 3: QTc >500 ms, or QTc >480 ms with a change from baseline >60 ms.
- Grade 4: Torsade de pointes or other life-threatening ventricular arrhythmias.

Statistical analysis

Data were analyzed using SPSS Statistics version 29.0. Categorical variables were expressed as percentages (%), while numerical data were presented as mean ± standard deviation (SD) for normally distributed data or median (minimum–maximum) for non-normally distributed data, along with 95 % confidence intervals. Normality of data distribution was assessed using the Chi–Square test. For non-normally distributed QTc interval data, serial measurements were analyzed using the Friedman test and the Mann–Whitney U test. Post-hoc multiple comparisons were conducted with Bonferroni correction, considering $p < 0.05$ as statistically significant.

Comparisons between treatment groups at each time point were performed with the Friedman test. Risk factor analyses, including gender, age, hypertension, diabetes mellitus, smoking status, and body mass index (BMI), utilized both the Mann–Whitney U test and the Friedman test as appropriate.

Data visualization included line graphs illustrating trends in QTc interval changes over time, accompanied by 95 % confidence intervals to indicate measurement variability. All statistical analyses accounted for type I error control through appropriate corrections.

Results. The study included 33 patients who met the inclusion criteria. As detailed in Table 1, the majority of respondents were male (63.6 %), aged over 60 years (66.7 %), and had a normal body mass index (72.7 %). Additionally, 63.6 % had a history of smoking, 48.5 % had hypertension, and 27.3 % had diabetes mellitus. Statistical analysis revealed no significant associations between these demographic and clinical characteristics – such as gender, age, BMI, smoking history, hypertension, and diabetes mellitus – and QTc interval prolongation, as all p-values exceeded 0.05. This suggests that these factors did not independently influence the risk of QTc prolongation in the study population.

Significant findings emerged regarding macrolide antibiotic use. Most patients (72.7 %) received macrolides, and among the 17 patients who experienced QTc prolongation, 16 (94.1 %) were macrolide users. Conversely, among the 16 patients without QTc prolongation, only half (50 %) used macrolides. This relationship was statistically significant (p=0.004), indicating a strong association between macrolide use and QTc interval prolongation.

Table 2 presents the changes in QTc intervals during treatment. The mean QTc interval increased from 420.33 ms at baseline (D-1) to 454.06 ms on day 3 (D-3), then decreased slightly to 435.68 ms on day 5 (D-5), followed by a marked decrease to 222.19 ms prior to discharge. The overall difference across these time points was statistically significant (p=0.004). Post-hoc analysis (Table 3) demonstrated significant differences between baseline and subsequent measurements on days 3 (p=0.002), 5 (p=0.043), and predischarge (p=0.001). Significant differences were also observed between days 3 and predischarge (p=0.000) and days 5 and predischarge (p=0.001), while no significant difference was found between days 3 and 5 (p=0.349).

Comparisons of QTc intervals between macrolide and non-macrolide groups are shown in Table 4. At baseline, median QTc intervals were similar (415 ms for macrolide users and 423 ms for non-users). However, by day 3, the macrolide group's median QTc increased to 450 ms com-

Table 1

Baseline Patient Characteristics

		Prolonged QTc interval		
Variables	**Total (n=33)**	**Yes (n=17)**	**No (n=16)**	**p-value**
Gender				0.392[a]
Male	21 (63.6 %)	12 (70.6 %)	9 (56.3 %)	
Female	12 (36.4 %)	5 (29.4 %)	7 (43.8 %)	
Age (years)	60,09 ± 17,51	58,44 ± 20,41	61,65 ± 14,76	0.787[b]
≥60 years	22 (66.7 %)	13 (76.5 %)	9 (56.3 %)	
<60 years	11 (33.3 %)	4 (23.5 %)	7 (43.8 %)	0.218[a]
BMI				
Underweight	3 (9.1 %)	1 (5.9 %)	2 (12.5 %)	0.107[a]
Normal	24 (72.7 %)	15 (88.2 %)	9 (56.3 %)	
Overweight	6 (18.2 %)	1 (5.9 %)	5 (31.3 %)	
Macrolide therapy				
Yes	24 (72.7 %)	16 (94.1 %)	8 (50 %)	**0.004[a]**
No	9 (27.3 %)	1 (5.9 %)	8 (50 %)	
Smoking				
Yes	21 (63.6 %)	12 (70.6 %)	9 (56.3 %)	0.392[a]
No	12 (36.4 %)	5 (29.4 %)	7 (43.8 %)	
Hypertension				
Yes	16 (48.5 %)	7 (41.2 %)	9 (56.3 %)	0.387[a]
No	17 (51.5 %)	10 (58.8 %)	7 (43.8 %)	
Diabetes Mellitus				
Yes	9 (27.3 %)	5 (29.4 %)	4 (25 %)	0.776[a]
No	24 (72.7 %)	12 (70.6 %)	12 (75 %)	

Notes: [a]Chi – square test, [b]Mann – Whitney test

Table 2

Changes in QTc interval during treatment

Time	**Mean ± SD Median (min-max)**	**Mean rank**	**X^2**	**p-value***
Qtc interval D-1 (ms)	420.33 ± 53.43 415 (309 – 568)	2.36	13.304	**0.004**
Qtc interval D-3 (ms)	454.06 ± 63.76 440 (342.9 – 666)	2.95		
Qtc interval D-5 (ms)	435.68 ± 89.66 438 (300 – 538)	2.76		
Qtc interval Predischarged (ms)	222.19 ± 235.53 220 (220 – 518.5)	1.92		

Notes: *Friedman test

pared with 438 ms in the non-macrolide group. On day 5, this difference widened further (460.45 ms vs. 413 ms). At predischarge, the median QTc was 300 ms in the macrolide group and 342 ms in the non-macrolide group. Statistical testing revealed no significant difference at baseline (p=0.943), but significant differences on days 3 (p=0.032) and 5 (p=0.002). No significant difference was observed at predischarge (p=0.647). The Friedman test indicated significant QTc changes over time in the macrolide group (p=0.011) but not in the non-macrolide group (p=0.129).

Further analyses examined QTc prolongation by risk factors, including gender, age, diabetes mellitus, hypertension, smoking, and BMI. Table 5 compares QTc intervals by gender. Among 21 males and 12 females, median QTc values at baseline were 423 ms and 415 ms, respectively. On day 3, females had a slightly higher mean QTc (458.75 ms) than males (451.38 ms), while on day 5, males had a higher mean QTc (448.38 ms) compared with females (413.46 ms). The most pronounced difference occurred at predischarge, with males averaging 284.07 ms and females 113.92 ms. However, no statistically significant differences were found between genders at any time point (all p>0.05). Within-group analysis showed no significant QTc changes over time in males (p=0.299), whereas significant changes were observed in females (p=0.005).

Table 6 shows QTc interval changes by age group, comparing 22 patients aged ≥60 years and 11 patients aged <60 years. Median QTc intervals at baseline were 419 ms and 415 ms, respectively. Both groups showed increases at day 3 (442.5 ms vs. 440 ms). At day 5 and predischarge, the ≥60 years group had medians of 447 ms and 0 ms, while the <60 years group had 424 ms and 391 ms. No significant differences between age groups were found at any time point (all p>0.05). However, within-group analysis revealed significant QTc changes over time in the older group (p=0.047) but not in the younger group (p=0.064).

QTc interval changes by BMI category are detailed in Table 7. At baseline, median QTc was highest in the underweight group (423 ms) compared to the normal (415 ms) and overweight (401 ms) groups. Similar fluctuations were observed at subsequent time points. No significant differences in QTc intervals were found between BMI groups at any measurement (all p>0.05), nor were significant changes observed within BMI groups over time (underweight p=0.134; normal p=0.058; overweight p=0.149).

Table 8 reports QTc changes by smoking status. Median baseline QTc was slightly higher in smokers (423 ms) than in non-smokers (415 ms). On day 3, smokers had a median QTc of 438 ms, while the median QTc in non-smokers increased to 454 ms. On day 5, smokers had a median QTc of 438 ms compared with 442.5 ms in non-smokers. At predischarge, the median QTc was 402 ms in smokers and 300 ms in non-smokers. No significant differences between smokers and non-smokers were found at any time point (all p>0.05). Within-group analysis

Table 3

Post-hoc analysis comparing QTc interval based on timeline

Time	Qtc interval D-3 (ms)	Qtc interval D-5 (ms)	Qtc interval Predischarged (ms)
Qtc interval D-1 (ms)	0.002*	0.043*	0.001*
Qtc interval D-3 (ms)		0.349	0.000*
Qtc interval D-5 (ms)			0.001*

Notes: *Wilcoxon test

Table 4

Changes in QTc interval based on macrolide and non-macrolide groups during treatment

Time	Macrolide (n=24) Median (min-max) Mean ± SD	Non-macrolide (n=9) Median (min-max) Mean ± SD	p-value
Qtc interval D-1 (ms)	415 (309 – 568) 420.74 ± 58.26	423 (357 – 474) 419.22 ± 40.70	0.943[a]
Qtc interval D-3 (ms)	450 (342.9 – 666) 463.95 ± 71.67	438 (391 – 447) 427.67 ± 20.49	**0.032**[a]
Qtc interval D-5 (ms)	460.45 (210 – 538) 446.14 ± 102.49	413 (342 – 438) 407.78 ± 27.45	**0.002**[b]
Qtc interval Predischarged (ms)	300 (220 – 518,5) 220.31 ± 246.26	342 (220 – 461) 227.22 ± 217.98	0.647[b]
P value	**0.011**[c]	0.129[c]	

Notes: [a]independent t-test, [b]Mann-Whitney test, [C]Friedman test

Table 5

Changes in QTc interval based on gender during macrolide and non-macrolide treatment

Time	Male (n=21) Median (min-max) Mean ± SD	Female (n=12) Median (min-max) Mean ± SD	p-value
Qtc interval D-1 (ms)	423 (309 – 568) 426.19 ± 58.43	415 (309 – 464.8) 410.07 ± 43.76	0.413[a]
Qtc interval D-3 (ms)	438 (342.9 – 666) 451.38 ± 67,47	454 (369 – 588) 458.75 ± 59.25	0.536[b]
Qtc interval D-5 (ms)	438 (342 – 538) 448.38 ± 50.11	442.5 (300 – 508) 413.46 ± 134.07	0.896[b]
Qtc interval Predischarged (ms)	402 (300 – 518.5) 284.07 ± 232.92	350 (300 – 491) 113.92 ± 206.49	0.051[b]
P value	0.299[c]	**0.005[c]**	

Notes: [a]independent t-test, [b]Mann-Whitney test, [C]Friedman test

Table 6

Changes in QTc Interval Based on Age During Treatment Period

Time	⩾60 years (n=22) Median (min-max) Mean ± SD	<60 years (n=11) Median (min-max) Mean ± SD	p-value
Qtc interval D-1 (ms)	419 (309 – 568) 425.76 ± 55.23	415 (309 – 491) 409.45 ± 50.33	0.417[a]
Qtc interval D-3 (ms)	442.5 (342.9 – 666) 452.18 ± 69.88	440 (402 – 574) 457.82 ± 52.26	0.759[b]
Qtc interval D-5 (ms)	447 (342 – 538) 452.56 ± 47.94	424 (300 – 496) 401.91 ± 37.90	0.181[b]
Qtc interval Predischarged (ms)	300 (220 – 518,5) 211.75 ± 240.49	391 (300 – 514) 243.09 ± 235.25	0.951[b]
P value	**0.047[c]**	0.064[c]	

Notes: [a]independent t-test, [b]Mann-Whitney test, [C]Friedman test

Table 7

Changes in QTc interval based on BMI during treatment

Time	Underweight (n=3) Median (min-max) Mean ± SD	Normal (n=24) Median (min-max) Mean ± SD	Overweight (n=6) Median (min-max) Mean ± SD	p-value
Qtc interval D-1 (ms)	423 (415 – 433) 423.67 ± 9.01	415 (309 – 568) 425.95 ± 56.06	401 (309 – 452) 396.17 ± 54.02	0.486[a]
Qtc interval D-3 (ms)	438 (433 – 491) 454 ± 32.14	447 (342.9 – 666) 464.25 ± 69.06	408,5 (369 – 465) 413.33 ± 34.27	0.118[b]
Qtc interval D-5 (ms)	413 (413 – 514) 446.67 ± 58.31	453 (402 – 538) 455.98 ± 42.32	431 (220 – 452) 349 ± 175.46	0.250[b]
Qtc interval Predischarged (ms)	300(220 – 413) 137.67 ± 238.45	396.50 (300 – 518.5) 255.81 ± 242.68	300 (220 – 438) 130 ± 203.67	0.283[b]
P value	0.134[c]	0.058[c]	0.149[c]	

Notes: [a]One way Anova, [b]Kruskal Wallis, [C]Friedman test

showed no significant QTc changes over time in smokers (p=0.229), but significant changes were observed in non-smokers (p=0.005).

Table 9 presents QTc changes by diabetes mellitus status. Median QTc at baseline was identical (415 ms) in both groups. At day 3 and day 5, the diabetes group had slightly higher median QTc values (453 ms and 452 ms) than the non-diabetes group (440 ms and 438 ms). At predischarge, both groups had a median QTc of 300 ms. No significant differences were observed between groups at any time point (all p>0.05). However, QTc changes over time were significant in

Table 8

Changes in QTc interval based on smoking history during treatment

Time	Smoking (n=21) Median (min-max) Mean ± SD	No smoking (n=12) Median (min-max) Mean ± SD	p-value
Qtc interval D-1 (ms)	423 (309 – 568) 426.19 ± 58.43	415 (309 – 464.8) 410.07 ± 43.76	0.413[a]
Qtc interval D-3 (ms)	438 (342,9 – 666) 451.38 ± 67.48	454 (369 – 588) 458.75 ± 59.25	0.536[a]
Qtc interval D-5 (ms)	438 (342 – 538) 448.38 ± 50.11	442.5 (220 – 508) 413.46 ± 134.07	0.896[b]
Qtc interval Predischarged (ms)	402 (300 – 518.5) 284.07 ± 32.92	300 (220 – 491) 113.92 ± 206.49	0.051[b]
P value	0.229[c]	**0.005[c]**	

Notes: [a]One way Anova, [b]Kruskal Wallis, [C]Friedman test

Table 9

Changes in QTc interval based on history of diabetes mellitus during treatment

Time	DM (n=9) Median (min-max) Mean ± SD	Non DM (n=24) Median (min-max) Mean ± SD	p-value
Qtc interval D-1 (ms)	415 (361 – 464.8) 418.64 ± 40.12	415 (309 – 568) 420.33 ± 53.43	0.914[a]
Qtc interval D-3 (ms)	453 (369 – 588) 446.78 ± 63.24	440 (342.9 – 666) 454.06 ± 63.76	0.871[b]
Qtc interval D-5 (ms)	452 (342 – 518) 452.94 ± 57.97	438 (300 – 538) 435.68 ± 89.66	0.373[b]
Qtc interval Predischarged (ms)	300 (220 – 518) 150.11 ± 230.10	300 (220 – 518,5) 222.19 ± 235.53	0.338[b]
P value	**0.020[c]**	0.083[c]	

Notes: [a]independent t-test, [b]Mann-Whitney test, [C]Friedman test

the diabetes group (p=0.020) but not in the non-diabetes group (p=0.083).

Table 10 compares QTc intervals by hypertension status. At baseline, the hypertension group had a median QTc of 415 ms, slightly lower than the non-hypertension group (423 ms). At day 3, medians were 426.5 ms and 440 ms, respectively. At day 5, medians were 442.5 ms (hypertension) and 438 ms (non-hypertension). Predischarge medians were 300 ms for the hypertension group and 413 ms for the non-hypertension group. No significant differences were found between groups at any time point (all p>0.05). Within-group analysis revealed significant QTc changes during treatment in the hypertension group (p=0.004) but not in the non-hypertension group (p=0.216).

Discussion. The etiology of CAP is diverse, involving bacteria, viruses, fungi, and protozoa, with gram-positive bacteria commonly implicated. In a more recent systematic review of CAP in adults, the most common causative pathogens were reported to be *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae*.

A global burden of disease study on lower respiratory tract infections (LRTIs) indicated that in 2016, a total of 2,377,697 (2,145,584-2,512,809) deaths occurred from LRTIs in people of all ages, with 1,080,958 deaths (943,749-1,170,638) in adults over 70 years of age. *Streptococcus pneumoniae* was the leading cause of LRTI morbidity and mortality globally, causing more deaths than all other etiologies combined in 2016 (*Haemophilus influenzae* type B, influenza virus, and respiratory syncytial virus). Although progress has been made in reducing the burden of LRTIs, it has not been uniform across regions, and greater efforts are needed, particularly for elderly populations [6].

Early studies suggested that incident cardiac events in patients with CAP were common and associated with increased short-term mortality, especially in older adults, nursing home residents, patients with pre-existing cardiovascular disease, and those with severe pneumonia [6].

This research showed that demographic and clinical risk factors, including gender, age, BMI, diabetes, hypertension, and smoking history, did not significantly contribute to QTc interval prolongation in this cohort. This finding contrasts with previous reports that identified advanced age, female gender, electrolyte disturbances, and concomitant medications as risk factors for QT prolongation [7].

Table 10

Changes in QTc interval based on history of hypertension during treatment

Time	HT (n=16) Median (min-max) Mean ± SD	Non HT (n=17) Median (min-max) Mean ± SD	p-value
Qtc interval D-1 (ms)	415 (357 – 491) 422.62 ± 31.24	423 (309 – 568) 418.16 ± 69.16	0.957[a]
Qtc interval D-3 (ms)	426.5 (369 – 574) 442.44 ± 52.94	440 (342.9 – 666) 464.99 ± 72.39	0.213[a]
Qtc interval D-5 (ms)	442.5 (300 – 514) 418.99 ± 120.29	438 (330 – 538) 451.38 ± 44.40	0.815[a]
Qtc interval Predischarged (ms)	300 (220 – 491) 161.19 ± 217.42	413 (220 – 518.5) 279.62 ± 243.73	0.091[a]
P value	**0.004[b]**	0.216[b]	

Notes: [a]Mann-Whitney test, [b]Friedman test

The QT interval represents ventricular depolarization and repolarization, and its prolongation is a recognized marker for increased risk of life-threatening arrhythmias such as torsade de pointes (TdP). Macrolide antibiotics, including azithromycin, are known to prolong the QT interval by blocking the rapid component of the delayed rectifier potassium current (IKr), encoded by the *hERG* gene, thereby delaying ventricular repolarization [2].

Consistent with prior studies, this investigation found that macrolide use was significantly associated with QTc interval prolongation. The mean QTc interval increased from baseline (420.33 ms) to day 3 (454.06 ms), followed by a slight decrease on day 5 (435.68 ms) and a marked reduction prior to discharge (222.19 ms), with statistically significant differences over time (p=0.004). These findings align with Tanveer et al. [7], who reported a higher risk of QT prolongation with azithromycin in men and elderly patients, and with other studies showing that the risk is particularly elevated in patients with cardiovascular disease or advanced age. However, some recent studies have reported conflicting results regarding the overall risk, suggesting that QT prolongation may not be clinically significant in all patients but primarily in those with predisposing factors [7,8].

The present study also examined QTc interval changes stratified by risk factors. While no significant differences were observed between groups based on gender, age, BMI, smoking, diabetes, or hypertension, within-group analyses revealed significant QTc changes over time in females, older adults (≥60 years), patients with diabetes mellitus, and those with hypertension. These findings suggest that these subgroups may experience more pronounced QTc variability during treatment, which may have clinical implications. The gender differences observed may relate to complex hormonal influences on cardiac repolarization, as supported by Rowe et al. [9], who reported that testosterone modulates QTc in men, whereas progesterone and estrogen ratios influence QTc in women.

Obesity, although recognized as an independent cardiovascular risk factor and associated with QT prolongation in some studies [10], did not demonstrate a significant effect on QTc intervals in this study. Similarly, smoking history did not significantly influence QTc prolongation, consistent with mixed findings in the literature [11]. The lack of significant differences may be due to the relatively small sample size or unmeasured confounders.

Diabetes mellitus was associated with significant QTc changes over time, corroborating previous evidence that diabetic patients have a higher prevalence of QTc prolongation and increased risk of sudden cardiac death, likely due to hyperglycemia-induced myocardial changes [5]. Hypertension was similarly linked to significant QTc changes during treatment, consistent with studies showing increased QT dispersion and elevated cardiovascular risk in hypertensive patients [12].

This study's findings underscore the importance of vigilant cardiac monitoring in patients receiving macrolide therapy, particularly among elderly patients and those with comorbid diabetes or hypertension. Routine ECG surveillance and risk stratification can help mitigate the risk of life-threatening arrhythmias. The study's strengths include real-time ECG monitoring during treatment and a comprehensive assessment of multiple risk factors. However, the relatively small sample size and potential confounding factors limit the generalizability of the results. Future multicenter studies with larger cohorts and detailed electrophysiological analyses are warranted to better elucidate the mechanisms underlying QTc prolongation and to develop predictive risk algorithms.

Conclusion. In conclusion, macrolide therapy in cardiac patients with community-acquired pneumonia is significantly associated with QTc interval prolongation during the treatment period compared to non-macrolide therapy, which does not significantly affect QTc duration. QTc prolongation demonstrated a progressive pattern from treatment initiation, with severity tending to increase over time. Although demographic factors such as age, gender, hypertension, and diabetes mellitus influenced QTc changes within subgroups, they did not in-

dependently predict QTc prolongation across the entire cohort.

Final Statements

Prospects for Further Research. Further multicenter studies involving larger patient cohorts and detailed electrophysiological analyses are required to better understand the mechanisms underlying QTc prolongation and to develop predictive risk algorithms.

Conflicts of interest. The authors declare no conflict of interest.

Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Use of Artificial Intelligence. The authors confirm that no artificial intelligence (AI) tools or large language models were used in the creation of the manuscript, drafting of the text, or generation of figures.

Primary Data and Materials. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Вплив макролідної та немакролідної терапії на подовження інтервалу QTc у пацієнтів з серцевими захворюваннями та позалікарняною пневмонією

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Резюме

Вступ. Азитроміцин – макролідний антибіотик, який широко застосовується для лікування різних інфекційних захворювань, зокрема респіраторних інфекцій. У низці досліджень повідомлялося про зв'язок між азитроміцином і подовженням інтервалу QT. Подовження QTc є однією з причин небезпечної для життя аритмії torsade de pointes (TdP). Torsade de pointes спостерігається приблизно у 1 % пацієнтів із подовженням інтервалу QT після прийому азитроміцину.

Мета. Визначити вплив терапії макролідами та немакролідами на подовження інтервалу QTc у кардіологічних пацієнтів із позалікарняною пневмонією.

Матеріали та методи. Це ретроспективне когортне дослідження 33 кардіологічних пацієнтів із позалікарняною пневмонією, які отримували макролідну та немакролідну терапію під час госпіталізації. Серійні електрокардіограми проводилися на 1-й, 3-й, 5-й день та перед випискою для оцінки інтервалу QTc.

Результати. У групі кардіологічних пацієнтів із позалікарняною пневмонією, які отримували макроліди, було виявлено значне подовження інтервалу QTc ($p<0,05$) за незалежним t-критерієм, критерієм Манна-Уїтні та критерієм Фрідмана. Фактори ризику, такі як вік, жіноча стать, артеріальна гіпертензія в анамнезі та цукровий діабет, мали значний вплив ($p<0,05$) за критерієм Фрідмана.

Висновки. Це дослідження показує, що терапія макролідами у пацієнтів із серцевими захворюваннями та позалікарняною пневмонією значно та послідовно подовжує інтервал QTc протягом усього періоду лікування порівняно з терапією без макролідів. Фактори ризику включають вік, жіночу стать, гіпертонію в анамнезі та цукровий діабет.

Ключові слова: *антибіотики, серцеві захворювання, кардіотоксичність, електрокардіографічні зміни, безпека лікарських засобів*

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