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Review Article

Investigation on Prediction of Life-Threatening Arrhythmia in Long QT Syndrome: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Use of risk stratification tools in Long QT Syndrome (LQTS) will be important to direct treatment strategy on each patient and risk of arrhythmia. There are still other factors that could improve the predictive performance of the risk stratification. **Objective:** This study aims to find a new predictor of Life-Threatening Arrhythmia in the LQTS population. **Method:** Based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA) Protocol 2015, studies extracted from Pubmed, Science Direct, Pubmed Central, EuroPMC, Frontiers with MeSH keywords "Long QT Syndrome AND Predictor AND Life-threatening arrhythmia". The inclusion criteria were cohort studies in LQTS patients (LQT 1, 2, 3) and the endpoint was life-threatening arrhythmia such as aborted cardiac arrest or sudden cardiac death. Study quality assessed with Newcastle-Ottawa Scale and RevMan 5.4 were used to analyse the data with hazard ratio as the measures. **Results:** Six cohort studies (12.343 subjects) fulfilled the inclusion criteria. Male <13 years old (HR = 2.73, 95% CI = 1.72-4.33, p = <0.0001) and female >13 years old (HR = 1.81, 95% CI = 1.36-2.41, p = <0.0001) were significant as predictor of life-threatening arrhythmia. Patients with LQT2 (HR = 1.84, 95% CI = 1.36-2.49, p = <0.0001), LQT3 genotype (HR = 3.88, 95% CI = 2.27-6.62, p = <0.00001), and QTc >530 (HR = 2.45, 95% CI = 1.96-3.06, p <0.00001) were also at increased risk of life-threatening arrhythmia. Syncope occurrence increased the risk (HR = 3.11, 95% CI = 2.47-3.91, p = <0.00001) while beta-blockers usage significantly decreased the risk of life-threatening arrhythmia (HR = 0.46, 95% CI = 0.36-0.60, p = <0.00001). All studies were low risk of bias. **Conclusion:** There were other predictors of life-threatening arrhythmia in LQTS that might be considered to improve the stratification performance.

Highlights:

1. In patients with Long QT Syndrome, life-threatening arrhythmia risk is strongly predicted by age-dependent gender differences, prolonged QTc (>530 ms), prior syncope, genotype (LQT2/3), and mitigated by beta-blocker use—offering a sharper edge for clinical risk stratification.

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Introduction

Long QT Syndrome (LQTS) is one of the syndromes included in cardiac channelopathies that represent a leading cause of sudden death. This syndrome becomes a lethal disorder with a high mortality rate. Symptomatic LQTS population that left without therapy reached a 21% mortality rate within 1 year after first syncope. LQTS also affects the quality of life of patients because they become predisposed with frequent arrhythmogenic syncope along their life. Even asymptomatic patients still have a high risk of sudden cardiac death (SCD).[1-2]

There is some strategy used to manage LQTS on purpose to prevent SCD and treat ventricular arrhythmia that varies from non-pharmacological to pharmacological strategy. Before we choose the modality of treatment, especially the invasive strategy like implantable cardioverter defibrillator (ICD), it is recommended to stratify the risk of life-threatening arrhythmia in the patient. There is a risk stratification tool used to stratify the risk of life-threatening arrhythmia in patients with LQTS named 1-2-3 LQTS risk, but the tools only used QTc interval and LQTS genotype as factor for stratifying the risk.[3-4]

Some studies showed some factors associated with increased risk of life-threatening arrhythmia that result in sudden cardiac death. Not only QTc interval and LQTS genotype as has been used in 1-2-3 LQTS risk, there is another factor that could be considered to have increased the risk like gender, syncope, and usage of beta-blockers. It might help to increase the risk stratifying performance for the LQTS population. Even though there was a similar study done before, that cohort study only included the population in the United States and there still no meta-analysis specifically on this field, therefore we want to do the analysis and include another study with other populations from the international registry.[5-6]

In this meta-analysis, we want to find a new factor that could be a significant predictor for better risk stratifying of life-threatening arrhythmia in the LQTS population.

Material and Methods

The study was conducted based on PRISMA Protocol 2015.[7]

Eligibility Criteria

This systematic review and meta-analysis included cohort studies in patients with LQTS (LQT 1, 2, 3) and the endpoint was life-threatening arrhythmia such as aborted cardiac arrest or sudden cardiac death. The exclusion criteria were case series, case report, and study on patients with other channelopathy comorbidities.

Data Sources and Search Strategy

Data search was conducted on 20 January 2024 in several databases (Pubmed, Science Direct, Pubmed Central, EuroPMC, Frontiers) using the Medical Subject Headings (MeSH) keyword “Long QT Syndrome AND Predictor AND Life-threatening arrhythmia”. The outcome of this study was life-threatening arrhythmia that resulted in sudden cardiac death or aborted cardiac arrest.

Data Extraction and Bias Assessment

Studies in databases screened by the title and abstract for relevancy to this study. After getting full-text of the selected study, we extracted the data independently to review manager and evaluate the characteristics based on inclusion & exclusion criteria. Extracted data includes population characteristics, outcome, and all factors contributed to the outcome.

We measured the quality of included studies using Newcastle-Ottawa Scale (NOS) and resulted in three quality categories “good”, “fair”, and “poor”. We only included study with good quality from NOS measurement.

Statistical Analysis

All data extracted was analysed using Cochrane Collaboration Review Manager version 5.4. We used Hazard Ratio (HR) as outcome measures for all factors related to the outcome with 95% Confidence Interval (CI). To assess the heterogeneity between studies, we test by measuring I^2 where I^2 <50% or the p value of the test > 0.05 can be concluded there is no significant heterogeneity and the analysis will be using a fixed-effects model. Otherwise, the analysis will be using a random-effects model. Results of the analysis will be presented in forest plot and overall effect said to be significant if p value < 0.05 and CI does not reach the vertical line of the plot. Funnel plot presented for significant predictor to evaluate the publication bias by visual identification of asymmetry distribution.[8-9]

Result

As seen in Figure 1, database search found 8099 studies from various countries with 7 duplicate studies. Screening was done and 15 full-texts were eligible for further evaluation. Two studies excluded because the population had other comorbidities other than LQTS. Seven studies with endpoints other

than life-threatening arrhythmia were also excluded from studies.

Table 1 showed characteristics of 6 studies included for analysis with a total 12.343 LQTS population. All of the 6 studies were also categorized in good quality from NOS assessment.

Gender

In Figure 2, two studies (3823 subjects) showed that gender could affect the risk of life-threatening arrhythmia where male had higher risk than female in < 13 years old population (HR = 2.73, 95% CI = 1.72-4.33, I^2 = 14%, p = <0.0001). As compared to > 13 years old population, three studies (6605 subjects) showed female had higher risk than male (HR = 1.81, 95% CI = 1.36-2.41, I^2 = 0%, p = <0.0001).

LQT Genotype

We set LQT1 as a reference for comparison with LQT2 and LQT3. As seen in Figure 2, when compared to LQT1, the population with LQT2 had more risk to develop life-threatening arrhythmia (HR = 1.84, 95% CI = 1.36-2.49, I^2 = 0%, p = <0.0001). Similar results on LQT3 where the risks were higher when compared to LQT1 (HR = 3.88, 95% CI = 2.27-6.62, I^2 = 0%, p = <0.00001).

Time-dependent Beta Blocker

From 4 studies (7906 subjects) included as seen in Figure 2, they included beta-blocker usage as a predictor. The usage of beta-blocker showed to decrease the possibility of life-threatening arrhythmia in the LQTS population (HR = 0.46, 95% CI = 0.36-0.60, I^2 = 0%, p = <0.00001).

Time-dependent Syncope

Figure 2 showed five studies consisting of a total 8957 subjects used to show the effect of syncope occurrence on the life-threatening arrhythmia risk. People who experienced syncope before were at higher risk than people who did not (HR = 3.11, 95% CI = 2.47-3.91, I^2 = 0%, p = <0.00001).

QTc Interval

In this study, we used the QTc border at 530 ms. We found out that LQTS population who had QTc interval more than 530 ms were on higher risk in developing life-threatening arrhythmia that less than 530 ms as seen in Figure 2 (HR = 2.45, 95% CI = 1.96-3.06, I^2 = 0%, p <0.00001).

Figure 3 showed the funnel plot of all significant predictors in this study. The plot showed the symmetrical distribution of the study included in the analysis.

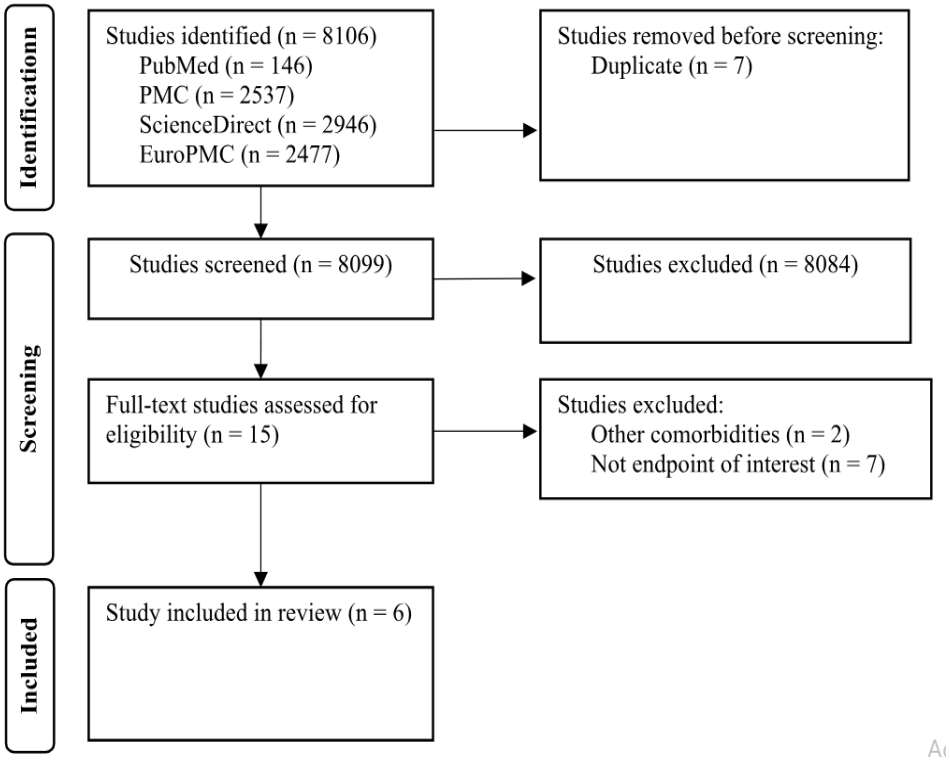
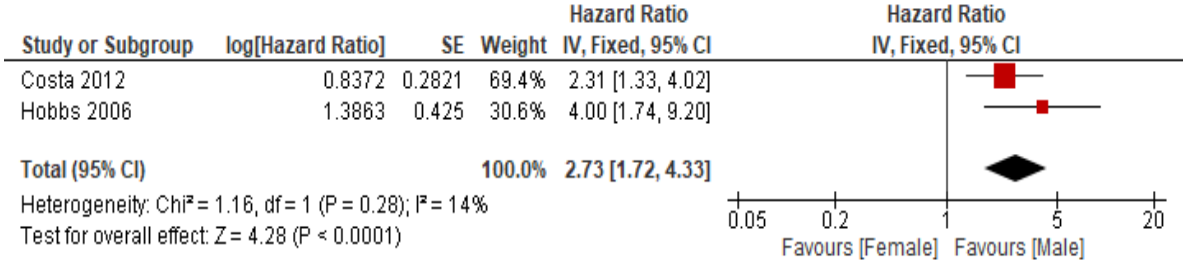


Figure 1. Flow diagram

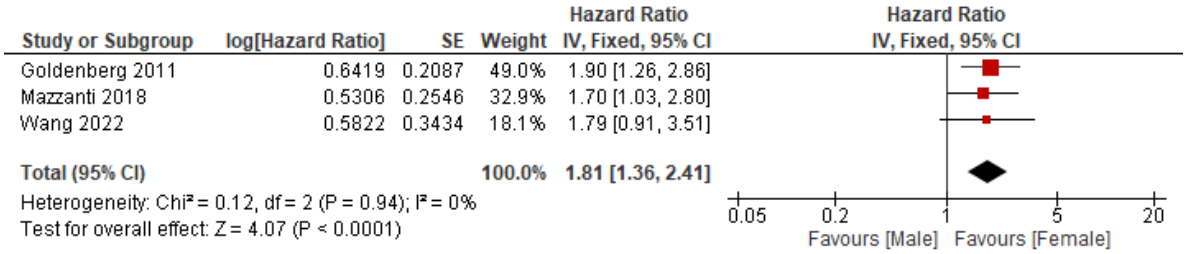
Table 1. Study characteristics

Study	Population (n)	Outcome	Predictor
Mazzanti 2018[10]	1710	Life-threatening arrhythmia (Sudden Cardiac Death, Aborted Cardiac Arrest)	Gender, LQT Genotype, QTc interval, Syncope occurrence, SCD History, beta-blocker
Kaufman 2008[11]	1915	LQT-related Sudden Cardiac Death, Aborted Cardiac Arrest	QTc interval, Syncope occurrence, beta-blocker
Goldenberg 2011[12]	3386	Sudden Cardiac Death, Aborted Cardiac Arrest	Gender, LQT Genotype
Costa 2012[6]	1051	Sudden Cardiac Death, Aborted Cardiac Arrest	Gender, QTc interval, Syncope occurrence
Hobbs 2006[13]	2772	Sudden Cardiac Death	Gender, QTc interval, Syncope occurrence, beta-blocker
Wang 2022[5]	1509	Sudden Cardiac Death, Aborted Cardiac Arrest	Gender, LQT Genotype, Syncope occurrence, Age, beta-blocker

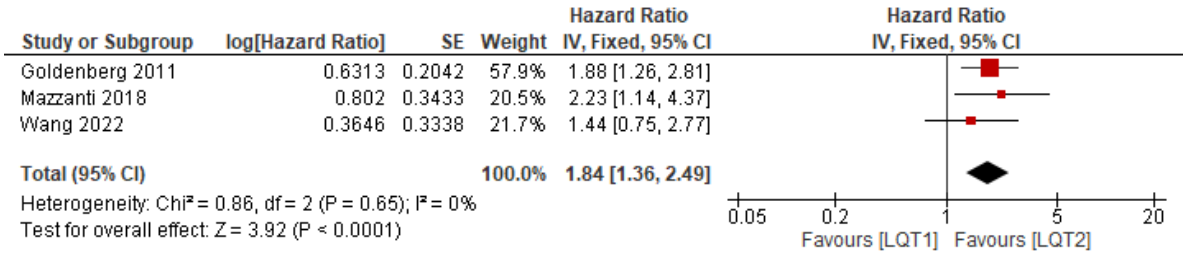
Gender <13 years old



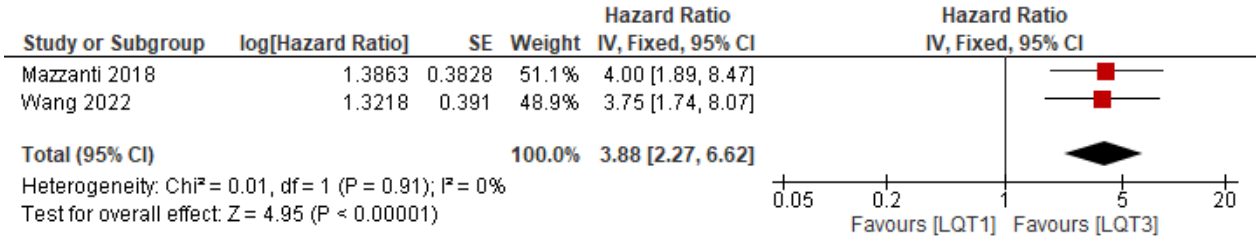
Gender >13 years old



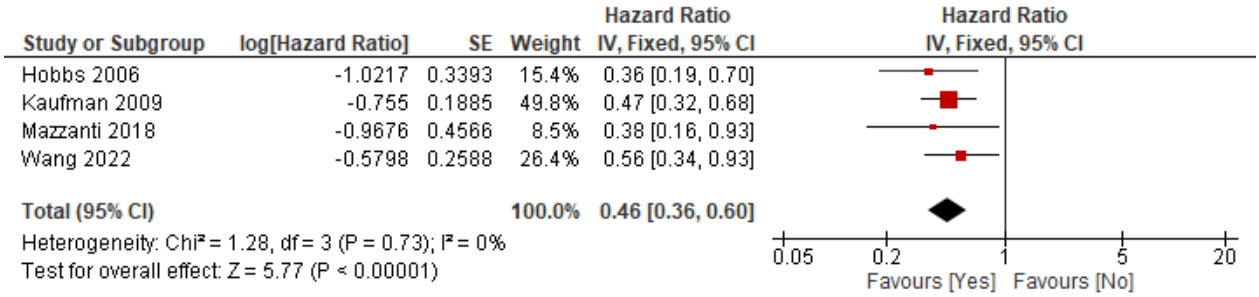
LQT2 Genotype



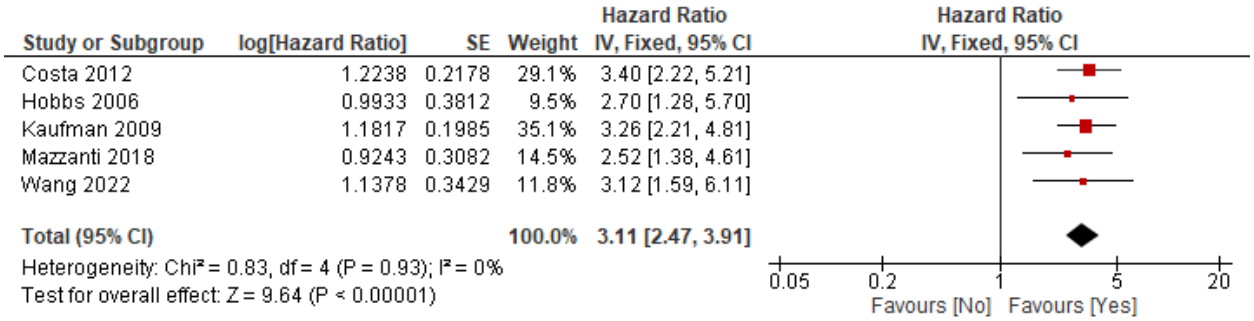
LQT3 Genotype



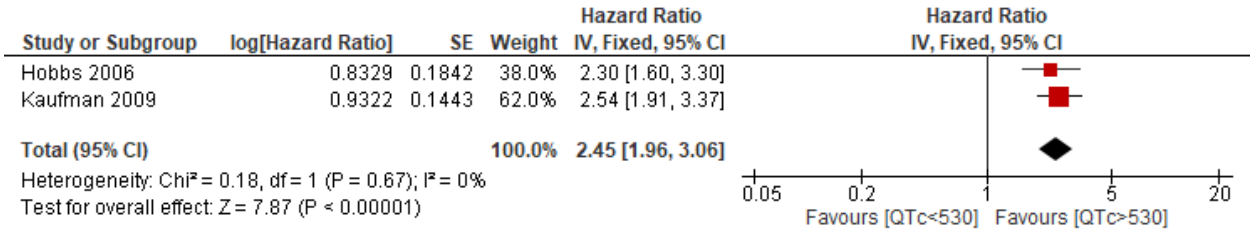
Time-dependent Beta Blocker



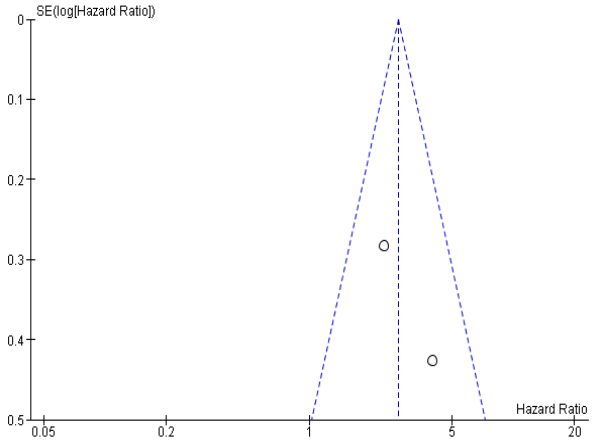
Time-dependent Syncope



QTc Interval

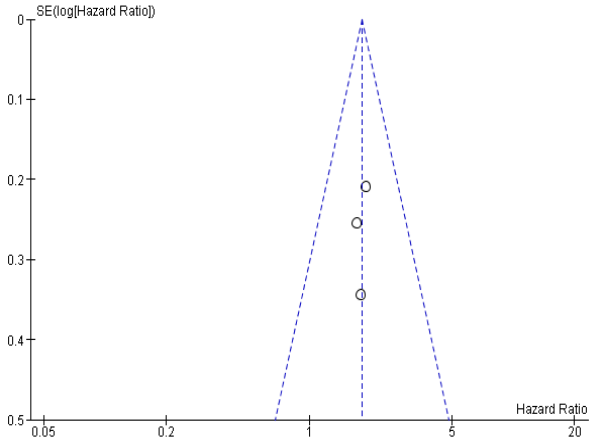


Gender < 13 years old



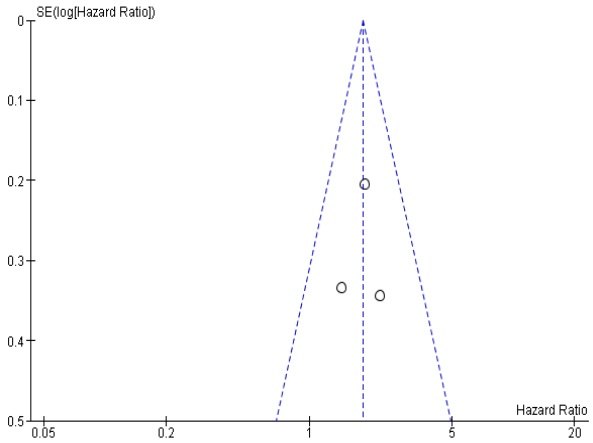
LQT2 Genotype

Gender > 13 years old

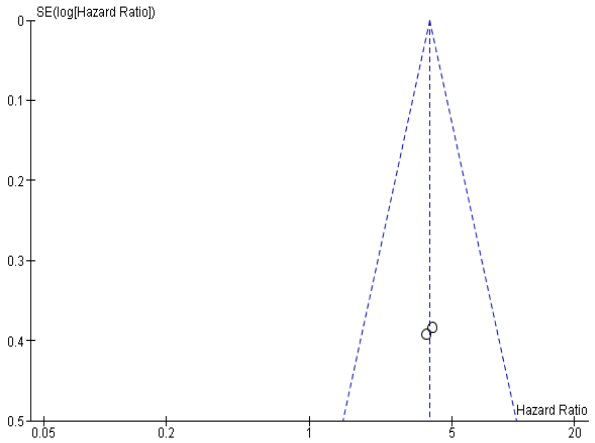


LQT3 Genotype

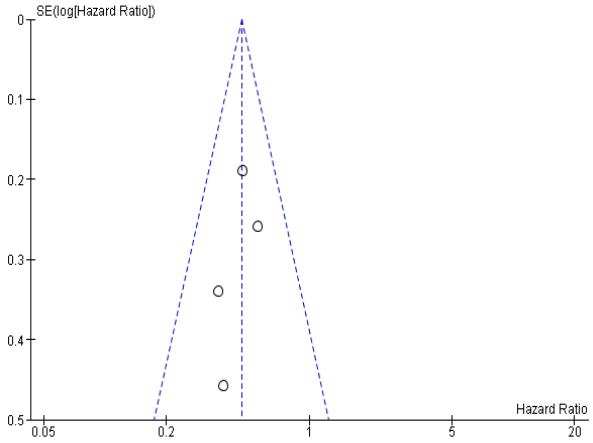
Figure 2. Forest Plot

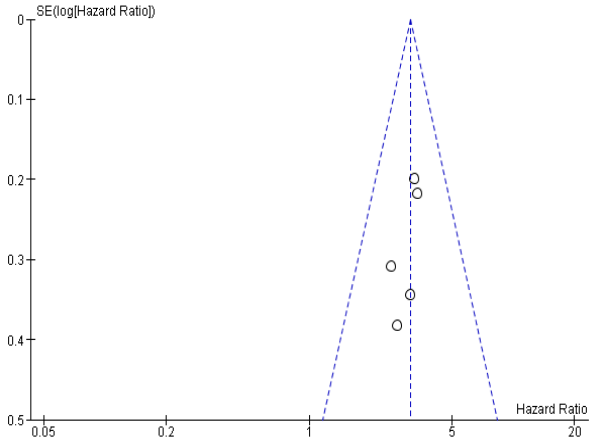


Time-dependent Beta Blocker



Time-dependent Syncope





QTc Interval

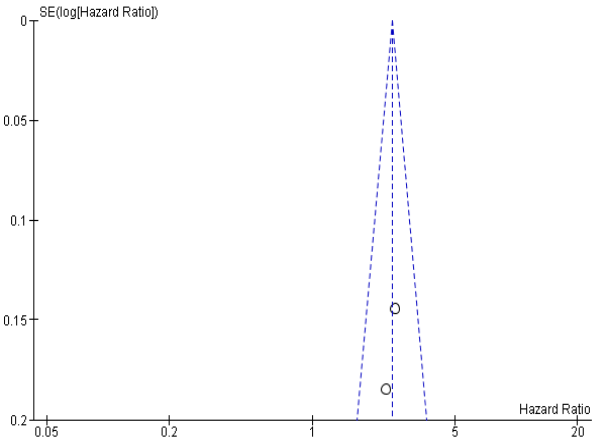


Figure 3. Funnel Plot

Table 2. Newcastle-Ottawa Scale

Studies	Selection	Comparability	Exposure
Mazzanti 2018	★★★★	★	★★★
Kaufman 2008	★★★★	★	★★★
Goldenberg 2011	★★★	★	★★★
Costa 2012	★★★	★	★★★
Hobbs 2006	★★★★	★	★★★
Wang 2022	★★★★	★	★★★

Discussion

From the analysis, we found some factors associated with increased risk of life-threatening arrhythmia. Those factors could be a predictor to the outcome.

Gender was one of them that could predict the risk of life-threatening arrhythmia. The risk in the population <13 years old was higher in male and turned into female in age >13 years. This gender difference along ages was associated with hormones that act on cardiac ion channels. Adult females were exposed to conditions such as menstruation and pregnancy where these hormonal changes favor QT prolongation. Some studies showed estradiol could be a pro-arrhythmic agent in LQTS patients. This hormone interacts with potassium ion currents. On the contrary, Androgen hormones in male were shown to increase potassium channel currents and reduce the QTc interval. This mechanism explained the risk of female above 13 years old were increased and became higher than male.[14][15]

In this study, we found out the outcome difference between LQT genotypes. Populations with LQT1 had lower risk of life-threatening arrhythmia compared to LQT2 and LQT3. We assumed this finding correlate with their specific trigger. LQT1 patients often triggered only when there was vigorous physical activity. On the contrary, life-threatening arrhythmia in LQT2 patients can be triggered just with sudden loud noise or auditory stimuli without any increase of physical activity. Even worse in LQT3 patients, who experience the events without emotional or physical activity such as sleep or rest. Study by Mazzanti et al also showed similar results. Population with LQT2 and LQT3 had higher events than LQT1.[10][16]

Beta-blocker also showed to be a predictor of life-threatening arrhythmia in LQTS patients. Populations who already used beta-blockers had lower risk of the events. Usage of beta-blockers in LQTS is already recommended in some studies to decrease the risk of events such as sudden cardiac death even in asymptomatic patients with confirmed mutation but no QT prolongation. There is a study suggesting a genotype-based approach

when choosing beta-blockers in this population.[3][17]

Syncope is believed to be caused by LQTS-associated arrhythmia and this confirmed those findings. The analysis showed increased risk of life-threatening arrhythmia in the population who already experienced any syncope before. This population is also more susceptible to life-threatening arrhythmia in the time when they experience syncope if it is caused by Torsades De Pointes. This finding similar with study by Liu et al that showed population with higher syncope events also had higher rate of life-threatening arrhythmia in 5-years follow up.[18][19]

In this study, we also included QTc interval to analyze their predictive value of life-threatening arrhythmia. We found out irrespective of genotype, population with longer QTc interval associated with higher risk of the events. This long QTc interval suggests prolonged ventricular repolarization that leads to early after depolarization. This event will result in an ectopic beat that could induce reentrant excitation and create torsades de pointes.[20]

There are some limitations in this study. First, LQTS populations pooled in the same group for analysis were not separated based on genotype. Second, for beta-blockers, there still needs further investigation for more specific types of beta-blockers related to the outcome. In this study, we also did not specify what type of arrhythmia that frequently caused syncope in the LQTS population. Further study is still needed with a more specific population based on genotype with a separate analysis. Population also needed to be more homogenous based on beta-blocker types. Cohort study may be done prospectively to identify the type of arrhythmia that caused syncope and to find out the specific threshold for QTc interval.

Conclusion

In this study, life-threatening arrhythmia in LQTS could be predicted based on gender, LQT genotype, time-dependent beta blocker, syncope occurrence, and QTc interval. These predictors might be considered to be included in the previous risk stratification tools and validated to improve the predictive performance.

Acknowledgement

There is no conflict of interest in this study.

References

1. Schwartz PJ, Crotti L, Insolia R. Long-QT Syndrome. Circulation: Arrhythmia and Electrophysiology [Internet]. 2012 [cited 2024 Mar 24];5(4):868–77. Available from: https://www.ahajournals.org/doi/abs/10.1161/CIRCEP.111.962019.
2. Rohatgi RK, Sugrue A, Bos JM, Cannon BC, Asirvatham SJ, Moir C, et al. Contemporary Outcomes in Patients With Long QT Syndrome. Journal of the American College of Cardiology [Internet]. 2017 Jul 25 [cited 2024 Mar 24];70(4):453–62. Available from: https://www.jacc.org/doi/10.1016/j.jacc.2017.05.046.
3. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. European Heart Journal. 2022 Oct 21;43(40):3997–4126.
4. Mazzanti A, Trancuccio A, Kukavica D, Pagan E, Wang M, Mohsin M, et al. Independent validation and clinical implications of the risk prediction model for long QT syndrome (1-2-3-LQTS-Risk). Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology [Internet]. 2022 Apr 1 [cited 2024 Mar 24];24(4):614–9. Available from: https://pubmed.ncbi.nlm.nih.gov/34505884/.
5. Wang M, Peterson DR, Pagan E, Bagnardi V, Mazzanti A, McNitt S, et al. Assessment of absolute risk of life-threatening cardiac events in long QT syndrome patients. Frontiers in Cardiovascular Medicine. 2022 Oct 7;9:988951.
6. Costa J, Lopes CM, Barsheshet A, Moss AJ, Migdalovich D, Ouellet G, et al. Combined assessment of sex- and mutation-specific information for risk stratification in type 1 long QT syndrome. Heart Rhythm [Internet]. 2012 Jun [cited 2024 Mar 24];9(6):892.
7. PRISMA [Internet]. [cited 2024 Mar 24]. Available from: http://www.prisma-statement.org/PRISMAStatement/FlowDiagram.

8. Higgins, J. P. T., & Thompson, S. G. Quantifying heterogeneity in a meta-analysis. Statistics in Medicine. 2002;21(11):1539–1558. DOI: https://doi.org/10.1002/sim.1186.
9. Dahlan, MS. Pengantar meta analisis (edisi 2). Epidemiologi Indonesia. 2019.
10. Mazzanti A, Maragna R, Vacanti G, Monteforte N, Bloise R, Marino M, et al. Interplay Between Genetic Substrate, QTc Duration, and Arrhythmia Risk in Patients With Long QT Syndrome. Journal of the American College of Cardiology [Internet]. 2018 Apr 17 [cited 2024 Mar 24];71(15):1663–71. Available from: https://pubmed.ncbi.nlm.nih.gov/29650123/.
11. Kaufman ES, McNitt S, Moss AJ, Zareba W, Robinson JL, Hall WJ, et al. Risk of death in the long QT syndrome when a sibling has died. Heart rhythm [Internet]. 2008 Jun [cited 2024 Mar 24];5(6):831–6. Available from: https://pubmed.ncbi.nlm.nih.gov/18534367/.
12. Goldenberg I, Horr S, Moss AJ, Lopes CM, Barsheshet A, McNitt S, et al. Risk for Life-Threatening Cardiac Events in Patients with Genotype-Confirmed Long-QT Syndrome and Normal-Range Corrected QT Intervals. Journal of the American College of Cardiology [Internet]. 2011 Jan 1 [cited 2024 Mar 24];57(1):51. Available from: /pmc/articles/PMC3332533/.
13. Hobbs JB, Peterson DR, Moss AJ, McNitt S, Zareba W, Goldenberg I, et al. Risk of aborted cardiac arrest or sudden cardiac death during adolescence in the long-QT syndrome. JAMA [Internet]. 2006 Sep 13 [cited 2024 Mar 24];296(10):1249–54. Available from: https://pubmed.ncbi.nlm.nih.gov/16968849/.
14. Díez-Escuté N, Arbelo E, Martínez-Barrios E, Cerralbo P, Cesar S, Cruzalegui J, et al. Sex differences in long QT syndrome. Frontiers in Cardiovascular Medicine [Internet]. 2023 [cited 2024 Mar 24];10. Available from: /pmc/articles/PMC10110834/.
15. Locati EH, Zareba W, Moss AJ, Schwartz PJ, Michael Vincent G, Lehmann MH, et al. Age- and Sex-Related Differences in Clinical Manifestations in Patients with Congenital Long-QT Syndrome. Circulation [Internet]. 1998 Jun 9 [cited 2024 Mar 24];97(22):2237–44. Available from: https://www.ahajournals.org/doi/abs/10.1161/01.cir.97.22.2237.
16. Darbar D. Editorial Commentary: Triggers for cardiac events in patients with type 2 long QT syndrome. Heart rhythm : the official journal of the Heart Rhythm Society [Internet]. 2010 [cited 2024 Mar 24];7(12):1806. Available from: /pmc/articles/PMC2997932/.

17. Went TR, Sultan W, Sapkota A, Khurshid H, Qureshi IA, Jahan N, et al. A Systematic Review on the Role of Beta-Blockers in Reducing Cardiac Arrhythmias in Long QT Syndrome Subtypes 1-3. Cureus [Internet]. 2021 Sep 1 [cited 2024 Mar 24];13(9). Available from: /pmc/articles/PMC8485362/.
18. Younis A, Bos JM, Zareba W, Aktas MK, Wilde AAM, Tabaja C, et al. Association Between Syncope Trigger Type and Risk of Subsequent Life-Threatening Events in Patients With Long QT Syndrome. JAMA Cardiology [Internet]. 2023 Aug 1 [cited 2024 Mar 24];8(8):775–83. Available from: https://jamanetwork.com/journals/jamacardiology/fullarticle/2806499.
19. Liu JF, Jons C, Moss AJ, McNitt S, Peterson DR, Qi M, et al. Risk Factors for Recurrent Syncope and Subsequent Fatal or Near-Fatal Events in Children and Adolescents with Long QT Syndrome. Journal of the American College of Cardiology [Internet]. 2011 Feb 2 [cited 2024 Mar 24];57(8):941. Available from: /pmc/articles/PMC3052409/.
20. Nachimuthu S, Assar MD, Schussler JM. Drug-induced QT interval prolongation: mechanisms and clinical management. Therapeutic Advances in Drug Safety [Internet]. 2012 [cited 2024 Mar 24];3(5):241. Available from: /pmc/articles/PMC4110870.