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# Sex-differences in short QT syndrome: A systematic literature review and pooled analysis

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Short QT syndrome (SQTS) is an inherited arrhythmic disorder with a risk of sudden cardiac death (SCD).[1,2] Patients may present with symptoms such as palpitations, which could suggest atrial arrhythmias. Several criteria to facilitate the diagnosis of SQTS have been proposed in 2011.[3] The European Society of Cardiology guidelines updated these criteria in 2015.[4] It has been suggested that an implantable cardioverter defibrillator (ICD) is possibly a definitive option to prevent SCD in these patients.[1,5] Some studies have recommended the use of hydroquinidine in high risk SQTS patients including those suffering from recurrent ventricular tachyarrhythmias.[2,6]

Male sex has been associated with a higher penetrance in SQTS. However, the relative lack of large-scale samples and systematic comprehensive analyses has contributed to a limited interpretation of sex differences in SQTS. We conducted a systemic literature review as well as a pooled analysis of 145 patients diagnosed with SQTS between 2000 and 2017. This patient population also included patients diagnosed at our institution. A total of 40 studies were identified through a systematic database analysis (PubMed, Web of Science, Cochrane Library, Cinahl) and their data were analysed according to our model. We used the PICO strategy to identify significant literature by using controlled search items ((Short-QT) AND (syndrome)) related to our clinical question.[7] Three independent researchers did cross-checks on the established database by comparing the collected data. The statistical analysis was performed using SPSS version 25 (IBM, Italy) and the PRISMA-IPD statement checklist was used as guideline to verify the systematic literature review.[8] The data are presented as mean ± SD for continuous variables with a normal distribution, median (interquartile range) for continuous variables with a non-normal distribution, and as frequency (%) for categorical variables. The Kolmogorov–Smirnov test was used to assess normal distribution. Continuous variables with normal and non-normal distributions were compared using Student's *t*-test and the Mann–Whitney *U*-test, respectively. Categorical variables were compared using the Chi-squared-test or Fisher's exact test.

Our analyses suggested that male patients presented more often with syncope as compared with female patients (24% versus 7%; $p = 0.01$) (Table 1). Other presenting symptoms such as palpitations as well as SCD were not significantly different in either group. The median QTc interval recorded in male was 309 ms (257–366) versus 311 ms in the female population (194–379); $p = 0.99$. Although a higher number of female patients underwent ICD implantation (43% versus 33%), this difference was not significant.

We compared the distribution of age between male and female at the time of diagnosis and our analyses suggested no significant difference between the populations (21 (0–67) versus 25.5 (0–70); $p = 0.66$). We also compared the age of the two populations, whilst presenting with an SCD, and this analysis also suggested no significant difference; log-rank $p = 0.36$ (Figure 1). The occurrence of inappropriate and appropriate ICD shocks was similar in both

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**Table 1.** Baseline characteristics of females versus males from 40 studies.

| Study variables | Overall 40 studies $N = 145$ | | $p$-value |
|---|---|---|---|
| Gender, *n* (%) | Male, 101 (70) | Female, 44 (30) | |
| Demographics | | | |
| Age, years, median (IQR) | 25.5 (0–70) | 21 (0–67) | 0.6670 |
| Symptoms at the time of diagnosis (%) | | | |
| Syncope | 24 | 7 | 0.0191 |
| Palpitation | 8 | 14 | 0.4673 |
| Sudden cardiac death | 24 | 25 | 0.9791 |
| Atrial flutter | 3 | 5 | 0.6433 |
| Atrial fibrillation | 11 | 9 | 1.0000 |
| nsVT | 2 | 5 | 0.5868 |
| Asymptomatic | 40 | 43 | 0.8986 |
| ECG data | | | |
| QTc, ms, median (IQR) | 309 (257–366) | 311 (194–379) | 0.9920 |
| Medical treatment (%) | | | |
| Yes | 36 | 49 | 0.2518 |
| ICD-Implantation (%) | | | |
| Yes | 33 | 43 | 0.4937 |
| Genetic screening (%) | | | |
| CaCN2b | 4 | 7 | 0.3921 |
| CaCNA1c | 1 | 5 | 0.2499 |
| CaCNA2D1 | 0 | 2 | 0.3277 |
| KCNH2 | 24 | 30 | 0.3754 |
| KCNQ1 | 8 | 20 | 0.0776 |
| KCNJ5 | 1 | 0 | 1.0000 |
| KCNJ2 | 6 | 5 | 1.0000 |
| SLC22A5 | 1 | 3 | 0.5499 |
| SLC4A3 | 3 | 3 | 1.0000 |
| Electrophysiological study (%) | 72 | 60 | 0.6323 |
| Induced arrhythmia | 46 | 40 | 0.7437 |
| Outcome data | | | |
| Inappropriate shocks over time (%) | 4.4 | 4.6 | 1.0000 |
| Appropriate shocks over time (%) | 3 | 0 | 0.4569 |
| Events – VT or VF and death and aborted sudden cardiac death – during follow-up (%) | 28 | 48 | 0.0384 |
| Aborted sudden cardiac death (%) | 20 | 25 | 0.7223 |
| Not aborted sudden cardiac death (%) | 4 | 7 | 0.6763 |
| Arrhythmic events (nsVT/VT/VF) after discharge (%) | 4 | 16 | 0.0350 |
| Follow-up time, months, median (IQR) | 6 (0–160) | 18 (0–228) | 0.3030 |

ECG: electrocardiogram; IQR: interquartile range; nsVT: non-sustained ventricular tachycardia; VF: ventricular fibrillation; VT: ventricular tachycardia.

groups. Clinical events documented over the follow-up period, including ventricular tachycardia, ventricular fibrillation and/or SCD death were significantly more common among female (48%) as compared with males (28%); $p = 0.03$.

We drew the following conclusions from this pooled analysis: (i) the clinical profile and presenting symptoms among female is comparable to that of male; however, marked with a predominance of syncope among male; (ii) male patients display a lower risk of arrhythmic events and/or SCD than female patients at diagnosis and during follow-up; (iii) there is no significant differences in age when patients presented with SCD.

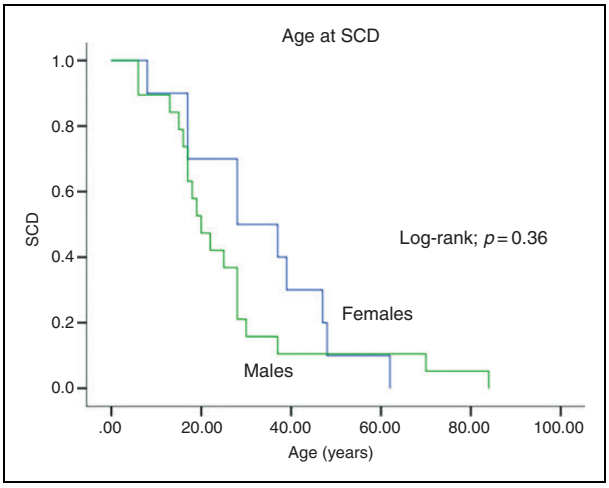


**Figure 1.** Age difference of female versus male at sudden cardiac death (SCD) event.

The present clinical descriptions of SQTS have implied a predominant prevalence of disease among males.[1,2] The lack of prospective randomized trials or specific guidelines has led to the treatment and primary prophylaxis of these SQTS patients being led by expert consensus.[9] Furthermore, very few risk stratification strategies have been elucidated in the literature.[10] It has been previously shown that SQTS is associated with SCD, but there was no significant correlations between QTc interval and presenting symptoms.[11] The present data could support the hypothesis that female SQTS patients also may need frequent follow-ups. Additionally, the use of hydroquinidine combined with an ICD implantation should be evaluated as a therapy option to improve long-term outcome. These data thus stress the need for more prospective studies in large cohort of patients.

Low estradiol levels among females and high testosterone levels among males have been associated with a higher incidence of SCD among patients diagnosed with channelopathies[12,13] and cardiomyopathies.[13] This phenomenon cannot be completely excluded among SQTS patients. Our data from another study, elaborating the use of human cardiomyocytes from induced pluripotent stem cells in Takotsubo syndrome (TTS), patients showed that estradiol had protective effects against catecholamine excess. A reduced level of oestrogen was thus implied to be associated with an increased risk of an acquired long QT syndrome in TTS.[14]

Although we included a total of 145 patients from 40 different studies, whilst also incorporating the original data from our own cohort, there remain limitations in this subgroup analysis. First, the lack of original source data led us to conduct unadjusted estimations and analyses for different conditions, which may impact the authenticity of our findings. Second, the treatment approach was heterogeneous and based on local centre decisions, which could explain the differing rates of ICD implantation among males as compared with females. Third, SQTS has a very low prevalence and this is reflected in the small patient numbers in each individual study. Additionally, the high number of case reports in our pooled analysis means that the assessment of risk of bias is limited.

## Author contribution

IEL, MB, IA contributed to the conception or design of the work. KS, JB, XZ, CW, RS and SL contributed to the acquisition, analysis, or interpretation of data for the work. IA and IEL drafted the manuscript. MB, VL and KO critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

## Declaration of conflicting interests

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